Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from GlaxoSmithKline:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company response**
   a. Clarification Addendum
   b. Post-clarification Addendum

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Peaches Womb Trust

4. **Clinical and Patient expert perspective:**
   a. Dr. Andrew Clamp, Clinical Expert
   b. Dr John McGrane, Clinical Expert

5. **External Assessment Report** prepared by BMJ-TAG
   a. External assessment report – Addendum

6. External Assessment Report – factual accuracy check

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

Document B

Company evidence submission

February 2025

File name	Version	Contains confidential information	Date
ID6145_MMRp_Dostarlimab+PC_EC_Consolidated_ _Final-[REDACTED]	v1.0	Redacted	3rd February

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.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE Health Technology Evaluation Manual.

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

Highlighting in the template (excluding the contents list)

Square brackets and grey 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 [grey highlighting] 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.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

List of tables

List of figures

Abbreviations

AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
AUC	Area under the curve
BIA	Budget impact analysis
BIC	Bayesian information criterion
BICR	Blinded independent central review
BGCS	British Gynaecological Cancer Society
BMI	Body mass index
BNF	British National Formulary
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CP	Carboplatin plus paclitaxel
DCR	Disease control rate
dMMR	Mismatch repair deficient
DOR	Duration of response
DSU	Decision Support Unit
EAG	External assessment group
EAM	Early access to medicine
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life scale, 5-Dimensions, 5-Levels
ESGO/ESTRO/ESP	European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology
ESMO	European Society for Medical Oncology
FDA	Food and Drugs Administration
FIGO	International Federation of Gynaecology and Obstetrics
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IA1	First interim analysis
IA2	Second interim analysis
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
IgG4	Immunoglobulin G4
irAE	Immune-related adverse event

ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LY	Life year
MAA	Managed access agreement
MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Mismatch repair
MMRp	Mismatch repair proficient
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NCRAS	National Cancer Registration and Analysis Service
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMB	Net monetary benefit
NSMP	Non-specific molecular profile
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PCC	Platinum-containing chemotherapy
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival 2
PH	Proportional hazards
POLεmut	DNA polymerase epsilon-mutated
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaires
QLQ-EN24	Endometrial Cancer Module
QoL	Quality of life
RCT	Randomised controlled trial

RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
STA	Single technology appraisal
TA	Technology appraisal
TAP	Cisplatin–doxorubicin–paclitaxel
TEAE	Treatment emergent adverse events
TP53mut	TP53-mutated
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
UK	United Kingdom
US	United States
WTP	Willingness to pay

Executive Summary

Burden of disease

Mismatch repair proficient (MMRp)/microsatellite stable (MSS) primary advanced or recurrent endometrial cancer is an incurable disease that has seen little innovation over the past two decades (1-3). While over 20 years ago, paclitaxel and platinum-based chemotherapy demonstrated modest overall survival (OS) benefits, life expectancy remains poor at 2–3 years (1-6). The current standard of care (SoC) offers only short-lived responses, with most patients requiring subsequent lines of treatment shortly after first-line therapy (1, 2, 7, 8). Later-line options include chemotherapy, hormone therapy, and immunotherapy, such as pembrolizumab with lenvatinib, approved for second-line use after chemotherapy (9-11). This underscores the urgent need for more effective first-line therapies to address the unmet needs of patients with MMRp/MSS disease (12-14).

Clinical efficacy

Dostarlimab, in combination with platinum-based chemotherapy, is the first regimen in decades to significantly improve survival in primary advanced or recurrent endometrial cancer, with benefits observed regardless of mismatch repair status (15, 16). This survival benefit is further supported by improvements in progression-free survival, duration of response, and time to second progression, even after subsequent therapies (15, 16).

Health-economic value

The economic evaluation demonstrates that dostarlimab in the first-line setting slows disease progression, maintains quality of life, and prolongs survival. Cost-effectiveness analysis shows dostarlimab (with PAS price) in addition to the existing SoC, platinum-containing chemotherapy (PCC), to be a cost-effective use of NHS resources, with an incremental cost-effectiveness ratio (ICER) of £[redacted] per quality-adjusted life year (QALY) gained in the base case—well below NICE's willingness to pay (WTP) threshold of £20,000 to £30,000 per QALY. This ICER is also robust across sensitivity analyses.

Without access to dostarlimab, patients often receive costly later-line treatments with limited effectiveness. Making dostarlimab available first-line is crucial to delivering the greatest patient benefit while optimising NHS resource use.

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

Overview of endometrial cancer epidemiology and burden

- In England, approximately 8,200 cases of endometrial cancer are diagnosed annually, making it the most prevalent gynaecological cancer (17). Around 20% of these patients are diagnosed with primary advanced endometrial cancer, and approximately 13% of patients initially treated curatively will experience recurrent disease (17-19).
- Most endometrial cancer is mismatch repair proficient (MMRp)/microsatellite stable (MSS), accounting for approximately 3 out of every 4 cases (17, 19, 20).
- Chemotherapy is the standard of care (SoC) treatment for this group of patients, however, it typically results in short-lived treatment responses and extremely poor survival outcomes with median life expectancy of between 2 and 3 years, thus underscoring the need for more effective therapies to delay disease progression and extend survival (21-25).
- These patients experience a high symptom burden and aggressive disease progression, which can significantly affect their quality of life (QoL), limit their ability to spend time with family, and interfere with daily activities (18, 26-29).
- The limited efficacy of current treatments exacerbates the emotional and physical distress experienced by patients, highlighting the urgent need for new therapeutic options (25, 30-33).

Current clinical pathway of care and unmet need

- The current SoC for the treatment of primary advanced or recurrent endometrial cancer is platinum-containing chemotherapy (PCC), with the most common regimen being carboplatin plus paclitaxel (CP) (9, 10, 34).
- PCC became the SoC in the early 1990s, and there have been few meaningful therapeutic advancements in the first-line treatment of primary advanced or recurrent endometrial cancer since (2, 6, 10).
- In primary advanced or recurrent endometrial cancer, approximately 2 out of every 3 patients have a response to SoC CP, however, long-term survival is limited, with 82% survival at 1 year, reducing sharply to approximately 33% at 3 years (3).
- There remains an urgent need for new, innovative first-line treatment options that can delay treatment progression and improve survival outcomes.

Dostarlimab in combination with PCC

- The addition of dostarlimab in combination with PCC to the treatment pathway for patients with primary advanced or recurrent MMRp/MSS endometrial cancer provides a new treatment option for women in England with significant unmet need. This treatment option can help to extend the time people live without a relapse and ultimately improve OS (21-25, 31).
- While immunotherapies have improved outcomes in patients in the second-line setting, and for first-line patients with mismatch repair deficient/microsatellite instability-high tumours, there has been a lack of innovation for more effective therapies for patients with primary advanced or recurrent MMRp/MSS disease (12-14). Dostarlimab provides a crucial option for patients with limited alternatives, offering renewed hope in the face of significant unmet clinical need (12-14).

1.1. Decision problem

Dostarlimab is currently licensed for use *in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy*. This indication was approved by the MHRA in December 2024. The pre-existing license had restricted the use of dostarlimab to mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) tumours and this biomarker subgroup has been recommended by the National Institute for Health and Care Excellence (NICE) within managed access under the Cancer Drugs Fund (CDF).

This submission focuses on part of the technology's marketing authorisation affected by the broadening of the indication statement, specifically patients with MMRp/MSS endometrial cancer who are candidates for systemic therapy. This HTA evidence submission hopes to extend access of the treatment to patients with primary advanced or recurrent MMRp/MSS endometrial cancer, ensuring equitable access to advancements in care across all patient subgroups.

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	Dostarlimab with PCC followed by dostarlimab maintenance.	As per scope	N/A
Population	People with primary advanced or recurrent endometrial cancer with MMRp/MSS tumours who are candidates for systemic treatment.	As per scope	N/A
Subgroups	If the evidence allows the following subgroups will be considered: • Local vs metastatic recurrence • People who have had primary debulking surgery vs those who have not had surgery • Molecular subgroups (such as NSMP, POLε and p53abn).	Molecular subgroups (POLεmut, TP53mut and NSPM) as per scope. GSK does not believe the subgroups local vs metastatic recurrence and people who had primary debulking surgery vs those who have not had surgery are appropriate for consideration as part of the appraisal.	**Local versus metastatic recurrence**: Within the pivotal RUBY trial which evaluated dostarlimab within the proposed indication, recurrence was captured as a 'yes/no' binary variable and the location of recurrence was not recorded. Subgroup analysis has been performed on patients with recurrent disease but, within this subgroup, further analysis based on the location of the recurrence is not feasible. In addition, guidelines recommend CP for first-line treatment regardless of recurrence location. Therefore, GSK does not believe it is informative for subgroups based on local or metastatic recurrence to be considered as part of this technology appraisal. **People who had primary debulking surgery vs people who have not**: GSK does not believe this to be a subgroup of relevance. All patients typically undergo surgery to debulk primary advanced endometrial cancer unless the patient is insufficiently fit. The RUBY trial recruited patients regardless of prior surgical status, however the majority had undergone prior surgery for MMRp endometrial cancer ([redacted]). The small number of patients not receiving surgery would likely prevent any meaningful conclusions from being drawn from a subgroup analysis. Furthermore, it is also unlikely to be feasible to carry out this analysis given how information relating to surgery was collected as part of the RUBY trial.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Within the clinical study report, prior anti-cancer surgery for endometrial cancer is captured as a binary 'yes/no' variable and therefore the type and/or outcome of surgery is not readily available.
Comparators	• Platinum-based chemotherapy (such as paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide) followed by routine surveillance • Hormone therapy (such as medroxyprogesterone acetate and megestrol) followed by routine surveillance • Durvalumab with platinum-based chemotherapy, followed by durvalumab with or without olaparib maintenance (subject to NICE appraisal) • Pembrolizumab with platinum-based chemotherapy, followed by pembrolizumab maintenance (subject to NICE appraisal)	Platinum-containing chemotherapy	GSK do not believe the comparators outlined in the NICE decision problem—hormone therapy, durvalumab in combination with PCC followed by durvalumab with or without olaparib maintenance, and pembrolizumab in combination with PCC followed by pembrolizumab maintenance —are relevant comparators. Hormone therapy is not an alternative treatment in patients eligible for dostarlimab, and durvalumab and pembrolizumab-based regimens are not currently available through routine commissioning within the NHS, and therefore not established standards of care. See Section 1.3.4.4 for details.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality-of-life.	As per scope, with the addition of PFS2	PFS2 is an additional secondary efficacy outcome evaluated in the RUBY trial.
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.	As per scope	N/A

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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.		
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	MHRA marketing authorisation was received on December 13th, 2024, for the following indication: Jemperli is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy.	N/A

Abbreviations: BGCS, British Gynaecological Cancer Society; CP, carboplatin and paclitaxel; FDA, Food and Drugs Administration; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; MMR, mismatch repair; MMRp, DNA mismatch repair proficient; MSS, microsatellite stability; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSMP: Non-specific molecular profile; PCC; platinum-containing chemotherapy; PFS2, progression-free survival 2; POLε: DNA polymerase epsilon; SmPC, summary of product characteristics; p53abn: TP53mutation.

1.2. Description of the technology

The summary of product characteristics or information for use are provided in Appendix A.

A description of the technology being evaluated is provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Dostarlimab (Jemperli) in combination with platinum-containing chemotherapy (PCC)
Mechanism of action	Dostarlimab is a humanised monoclonal antibody of the IgG4 isotype that binds to and inhibits PD-1 receptors. The interaction of PD-1 with its ligands results in inhibition of T cell proliferation and function, including cytotoxic activity and cytokine production. Dostarlimab blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2, potentiating T-cell responses, including anti-tumour immune-responses (35).
Marketing authorisation/ CE mark status	Jemperli was first granted marketing authorisation by the MHRA on 7th June 2021. On 13th December 2024, following a type 2 variation submission to the MHRA, a label extension was approved for Jemperli, expanding its use in combination with platinum-containing chemotherapy for treating primary advanced or recurrent endometrial cancer to include patients with MMRp/MSS disease in addition to those with dMMR/MSI-H.
Indications and any restriction(s) as described in the summary of product characteristics	Authorised indications: • Dostarlimab is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with advanced or recurrent endometrial cancer and who are candidates for systemic therapy.† Other existing indications include: • Dostarlimab is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen (35).
Method of administration and dosage	Dostarlimab dosage: • Dostarlimab 500 mg IV every 3 weeks for 6 cycles followed by 1000 mg every 6 weeks for all cycles thereafter. Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years. PCC dosage: • When dostarlimab is administered in combination with PCC, healthcare professionals are advised to consult the SmPC of the combination product(s) for further information on administration, safety aspects, and pharmaceutical particulars.

<table>
<tr><td>Additional tests or investigations</td><td>Mismatch repair testing is not required for this indication according to the SmPC (35). However, in line with NICE diagnostics guidance DG42, testing for MMR status should be routinely conducted for all patients with endometrial cancer within the NHS (36).</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The list price of dostarlimab is £5,887.33 per 500 mg vial (37).
Dostarlimab is administered as an add-on to PCC for a maximum of six cycles followed by maintenance treatment with dostarlimab only until progression of disease or unacceptable toxicity, up to a maximum of 3 years.
The acquisition costs per treatment cycle are shown in the table below:
<table>
<tr><th>Cycle (week)</th><th>Posology</th><th>Dostarlimab acquisition cost per treatment cycle (£) (with PAS)</th></tr>
<tr><td>Cycle 1-6</td><td>500 mg (1 vial) Q3W</td><td>[redacted]</td></tr>
<tr><td>Cycle 7+</td><td>1000 mg (2 vials) Q6W</td><td>[redacted]</td></tr>
</table>
Abbreviations: Q3W: every 3 weeks; Q6W: every 6 weeks.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A confidential simple PAS discount application is approved by the PASLU. A PAS discount of [redacted] is applied to the dostarlimab list price. GSK provides dostarlimab at a net price of [redacted] per 500 mg vial.
No PAS discount is applied to carboplatin or paclitaxel.</td></tr>
</table>

†This is an amendment to the MA which restricted use to patients with dMMR/MSI-H status. Removal of this restriction broadened the indication statement to include MMRp/MSS patients.

Abbreviations: FDA, Food and Drug Administration; GSK, GlaxoSmithKline; IgG4, immunoglobulin G4; MHRA, Medicines and Healthcare products Regulatory Agency; MMRp, mismatch repair proficient; MSS, microsatellite stability; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PASLU, Patient Access Scheme Liaison Unit; PCC, platinum-containing chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; UK, United Kingdom.

1.3. Health condition and positioning of the technology in the treatment pathway

1.3.1. Disease overview

Endometrial cancer is a type of uterine cancer that originates in the lining of the womb (uterus), known as the endometrium. The term endometrial cancer is frequently used synonymously with uterine cancer since approximately 96% of uterine cancers are endometrial carcinomas (38). The majority of these are adenocarcinomas, originating in glandular epithelial cells of the endometrium. Other relatively rare subtypes of endometrial tumours include carcinosarcoma and clear cell carcinoma, both of which are aggressive high-grade malignancies (39). These subtypes are more likely to be diagnosed at advanced stages and are associated with poorer prognosis compared with other endometrial cancer subtypes (39-42).

Upon diagnosis, endometrial cancer is generally surgically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) system, which is based on the spread of the tumour from its initial location in the endometrium to other tissues or organs (43-45). Most patients with endometrial cancer (approximately 80%) are symptomatic and diagnosed at an early stage, with a smaller number (approximately 20%) diagnosed with an advanced stage, at which point the disease has spread beyond the uterus (38, 46, 47).

Primary advanced stage endometrial cancer refers to patients diagnosed with Stage III or Stage IV disease at first presentation, which is associated with a significantly increased risk of mortality compared with early stage disease (34, 48). Irrespective of the stage at diagnosis, patients with endometrial cancer can experience disease recurrence, defined as a malignancy that cannot be detected after primary treatment with curative intent but is radiologically or histologically detected at a later point in time (49).

In contrast to patients diagnosed with earlier stage local disease, patients with advanced or recurrent disease are difficult to treat and have extremely poor survival outcomes (18, 26-28). PCC, specifically CP, is the recommended chemotherapy regimen in the first-line setting for patients with primary advanced or recurrent MMRp/MSS endometrial, regardless of histologic subtype (50).

MMRp/MSS tumours develop despite the presence of a functioning mismatch repair (MMR) system and exhibit few mutations in the microsatellite regions of DNA (51, 52). The MMR system consists of proteins that preserve genetic integrity during DNA replication and

recombination by correcting sequencing errors in DNA (52). Among patients with primary advanced or recurrent endometrial cancer, the MMRp/MSS tumour subtype is the most prevalent, accounting for around 75% of cases (19). In contrast, a smaller subgroup of patients have dMMR/MSI-H tumours, characterised by genetic mutations that impair the DNA repair process (34). Treatment with immunotherapy in combination with PCC in the first-line setting for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer is currently licensed and reimbursed, allowing them greater access to innovative therapies, which are not currently available to MMRp/MSS patients (15, 16, 53, 54).

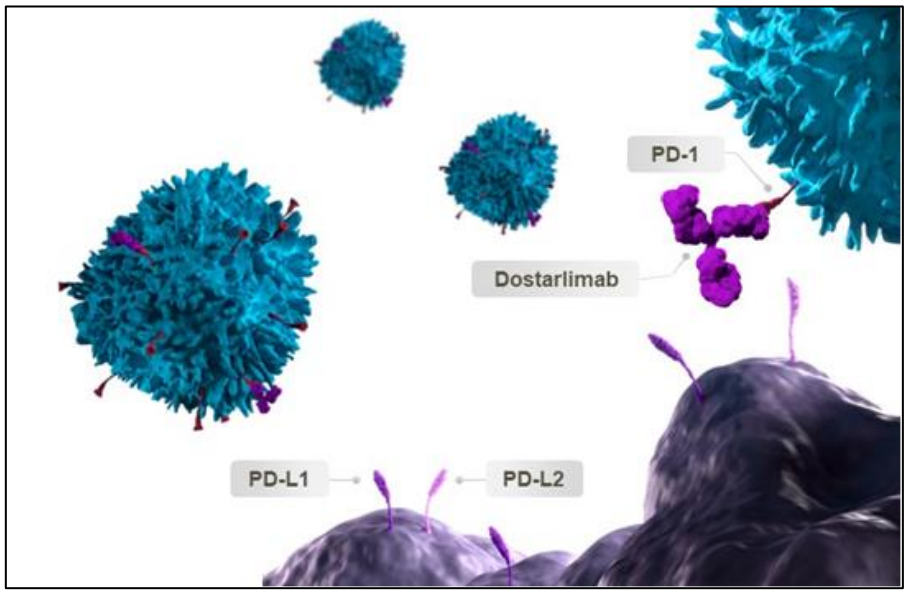
1.3.1.1. Mechanism of action

Dostarlimab is an anti-PD-1 therapy which blocks the binding of PD-1 with its ligands, subsequently preventing immune evasion by the tumour and boosting the anti-tumour immune response (55).

PD-(L)1 inhibition is a well understood mechanism of action and has resulted in a step-change in life expectancy across a number of cancer types such as lung cancers and melanoma. Dostarlimab features an innovative mechanism of action that disrupts T cell-mediated PD-1/PD-L1 signalling, mobilising the adaptive immune system to drive anticancer activity through immune-mediated apoptosis rather than chemotoxicity, resulting in durable responses (56). Unlike anti-PD-L1 immunotherapies, dostarlimab blocks PD-1 interactions with both PD-L1 and PD-L2, offering a broader disruption of PD-1/ligand interactions (57). Furthermore, dostarlimab targets novel binding sites on the PD-1 protein and demonstrates a smaller maximum drop-in time-varying clearance compared with older anti-PD1 treatments. This suggests that dostarlimab offers a differentiated mechanism of action and a more stable pharmacokinetic profile (58).

The mechanism of action for dostarlimab is shown in Figure 1. There is also a growing body of evidence suggesting that the combination of immunotherapy with chemotherapy may have a synergistic effect. Conventional chemotherapy is thought to induce changes in the tumour microenvironment, which may subsequently increase their susceptibility to immunotherapies such as dostarlimab (59-65).

Figure 1: Mechanism of action for dostarlimab



Source: [GSK Data on file] Dostarlimab mechanism of action (MOA) (44)
Abbreviations: PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2.

1.3.2. Epidemiology

Endometrial cancer is the most common gynaecological cancer in England, with reported figures stating around 8,200 new cases diagnosed each year (17). Around 20% of these patients are diagnosed with primary advanced endometrial cancer and approximately 13% of patients that are initially treated curatively will experience recurrent disease (17-19). In terms of MMR status, MMRp/MSS tumours account for approximately 75% of diagnosed endometrial cancer cases (66).

Several risk factors contribute to the development of endometrial cancer. The incidence of endometrial cancer increases with age, with data from 2017 to 2019 indicating that 27% of new endometrial cancer cases occurred in women aged 75 and older (38, 67). A high body mass index is also a notable risk factor, with 34% of uterine cancer cases in the UK linked to obesity (68, 69). Additionally, hormonal risk factors, particularly prolonged or unopposed oestrogen exposure, further elevate the risk (10, 70).

Endometrial cancer is associated with substantial mortality in the UK, with approximately 2,500 uterine cancer deaths annually, equating to around seven patient deaths per day (38). A significant proportion of these deaths are likely attributable to disease progression in patients presenting with primary advanced or recurrent disease (28, 71). Over 90% of patients diagnosed with Stage I endometrial cancer survive for five years or more after

diagnosis, compared with only a 15% survival rate for patients diagnosed with Stage IV disease (28). For patients with recurrent endometrial cancer, five-year survival remains low, at around 20% (72).

1.3.3. Burden of endometrial cancer

1.3.3.1. Clinical and humanistic burden

Primary advanced or recurrent MMRp/MSS endometrial cancer is typically incurable, with a survival expectation of 2–3 years (1-3). Current SoC, chemotherapy, aims to reduce tumour burden, alleviate symptoms, and extend life, but responses are often limited, and relapse is almost inevitable. This form of endometrial cancer is marked by a high symptom burden, aggressive disease progression, and low life expectancy (1-3).

Primary advanced or recurrent endometrial cancer carries a significant humanistic burden, particularly affecting patients' physical functioning, mental wellbeing, and health-related quality of life (HRQoL) (25, 30-33). This burden is especially pronounced in the typical demographic of endometrial cancer patients, most of whom are over the age of 60 (38, 73). At this stage of life, many individuals may already be contending with age-related physical and psychological changes, which are further exacerbated by the disease (74, 75). The impact on their ability to engage in everyday activities, such as household tasks, social interactions, and hobbies, can be profound (74, 75). Although many patients in this age group may be retired, some have caregiving responsibilities or remain employed. These patients often face challenges in fulfilling these roles due to physical limitations, fatigue, and the psychological impact of the disease (29). Endometrial cancer often leads to considerable psychological distress, manifesting as anxiety, depression, and other mental health challenges (30, 32, 33, 76).

At diagnosis or in later palliative stages, primary advanced or recurrent endometrial cancer is characterised by symptoms such as heavy post-menopausal vaginal bleeding, abdominopelvic pain, abdominal distension, and, in some cases, changes in bowel or bladder function, and metastasis-related symptoms like shortness of breath, all of which cause significant discomfort and psychological distress (21, 22, 30, 31, 77). Long-term sequelae following surgery often include menopausal-like symptoms and impaired sexual functioning, such as reduced sexual desire, loss of climax, painful intercourse, and psycho-sexual issues such as anxiety and body image distress, which may strain intimate relationships and contribute to feelings of isolation and emotional distress (30).

The need for innovative treatments that effectively manage cancer while preserving HRQoL is paramount. Historically, chemotherapy alone has often proven insufficient in providing durable relief, leaving patients feeling unsupported and overwhelmed (2, 22). Testimonies from patients with primary advanced or recurrent endometrial cancer highlight feelings of being unprepared for the physical and psychological challenges of the disease, and the limited availability of treatment options often intensifies feelings of hopelessness (78).

Treatment options that provide survival benefits while maintaining HRQoL are essential, as they support more effective disease management and enable patients to pursue personal and professional goals (25, 30, 31). The goal is to ensure that any clinical benefit from emerging therapies is accompanied by a favourable benefit-risk balance, enabling patients to maintain QoL throughout their treatment.

1.3.3.2. Unmet need

Since the 1970s, chemotherapy alone has been the first-line treatment option for patients with primary advanced or recurrent endometrial cancer, with response rates ranging from 50–70% (2, 4-6). However, since the adoption of paclitaxel and PCC as the SoC in this setting over 20 years ago, there have been no further material improvements in duration of response or progression free survival, which remain limited at around 8-13 months (2, 4-6). Disease progression after treatment often necessitates retreatment with anticancer therapies, likely resulting in repeated exposure to chemotherapy and short treatment-free periods (79). Extending PFS would enable patients to maintain stable health for longer, potentially reducing the need for additional treatment and associated healthcare resource use, while allowing them to continue participating in work or family roles.

This limited efficacy of existing chemotherapies underscores a significant unmet need for treatments that can delay recurrence and meaningfully extend life expectancy for patients with MMRp/MSS primary advanced or recurrent endometrial cancer. For these patients with incurable disease, the estimated survival is approximately 2–3 years, contributing to considerable emotional and psychological burdens due to limited treatment options (27). Therapies that extend life expectancy could not only address a critical unmet need but also provide renewed hope to patients diagnosed with this relatively rare but incurable disease.

In contrast, other patient populations have benefited from substantial advancements in cancer care, particularly the introduction of immunotherapies, which have markedly improved survival outcomes (9, 10, 80, 81). The lack of durable treatment options for patients with MMRp/MSS primary advanced or recurrent endometrial cancer is poignantly

emphasized by a patient advocate: “there are simply no alternatives for these women and their outlook is bleak” (82). This “no choice situation” harms both the psychological and physical well-being of patients, fostering feelings of helplessness and limiting options for delaying disease progression (82).

Therefore, there is a critical need for innovative first-line treatment options that can improve survival outcomes for MMRp/MSS patients. It is imperative that an innovative first-line treatment, which extends PFS and/or OS while maintaining HRQoL, becomes available for patients with primary advanced or recurrent endometrial cancer and MMRp/MSS tumour status. Such a treatment would provide a crucial option for patients with limited therapeutic alternatives, offering renewed hope in the face of significant unmet clinical needs (82).

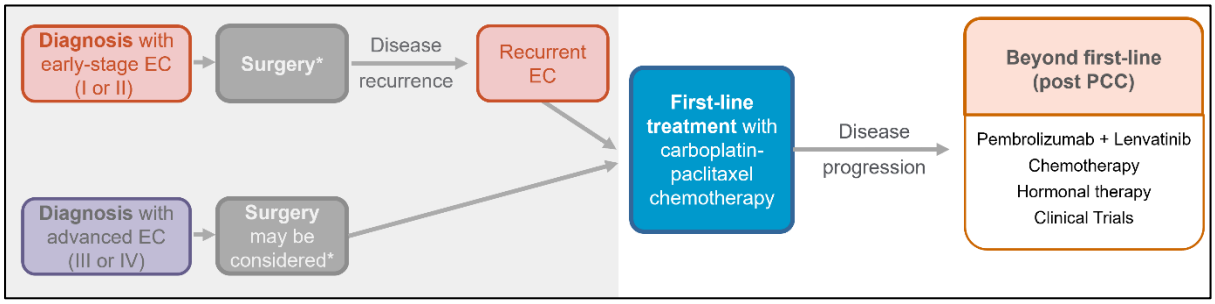
1.3.4. Current NHS care pathway for the management of endometrial cancer

1.3.4.1. Treatment pathway for primary advanced or recurrent MMRp/MSS endometrial cancer

The key clinical guidelines available for the management of endometrial cancer include those from the BGCS, European Society for Medical Oncology (ESMO), and European Society for Gynaecological Oncology/ European Society for Radiation Oncology/ European Society of Pathology (ESGO/ESTRO/ESP) (9, 10, 34). Currently, there are no recently published NICE guidelines outside of laparoscopic hysterectomy for endometrial cancer (83).

Surgical intervention is considered the gold standard initial approach for treating and staging endometrial cancer (9, 10). While often curative in early-stage disease, surgery alone rarely achieves curative outcomes in advanced-stage disease (9, 10). In patients with primary advanced or recurrent MMRp/MSS endometrial cancer, surgery may be performed to reduce tumour burden or alleviate symptoms but is not typically curative in this setting (9, 10). Following surgery, patients with recurrent or primary advanced MMRp/MSS endometrial cancer are treated with first-line systemic therapy (Figure 2) (9, 10). The established SoC is PCC, with the doublet chemotherapy regimen carboplatin in combination with paclitaxel, i.e. CP, being the most predominant and recommended in BGCS guidelines (9, 10).

Figure 2: Current treatment pathway excluding dostarlimab in combination with PCC



Source: ESMO guidelines, NICE TA779, TA904, and TA914 (10, 82, 84, 85).
*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery.
Abbreviations: EC, endometrial cancer; PCC, platinum-containing chemotherapy.

1.3.4.1.1 Platinum-containing chemotherapy (PCC)

Current clinical guidelines recommend the platinum-containing doublet chemotherapy, CP, for the first-line treatment of primary advanced or recurrent endometrial cancer (10). This existing preferred regimen is based on the Phase 3 trial GOG0209 (NCT00063999), which established that CP was not inferior to the cisplatin–doxorubicin–paclitaxel (TAP) regimen with regard to efficacy (median PFS and overall survival [OS] of 13.2 and 37 months with CP, respectively) and was associated with a more favourable toxicity profile (2).

CP treatment may not be suitable for all patients due to comorbidities, patient choice, performance status and treatment burden. In these circumstances, where it is not appropriate to receive doublet chemotherapy, carboplatin monotherapy or hormone therapy might be a preferable and less burdensome option (86).

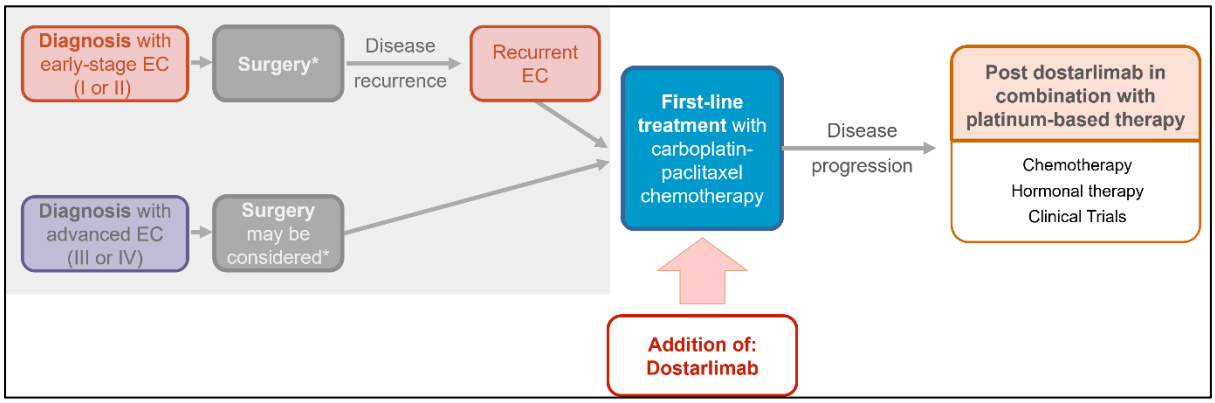
1.3.4.2. Positioning of dostarlimab in combination with PCC in the management of endometrial cancer

Current clinical practice for primary advanced or recurrent MMRp/MSS endometrial cancer is outlined in Figure 3. As dostarlimab is expected to be positioned in addition to PCC, as it is for patients with dMMR/MSI-H, there would be no disruptions to the treatment pathway, as CP is the most commonly used regimen (87). Following completion of the required number of PCC cycles, treatment with dostarlimab is continued until disease progression or unacceptable toxicity or a maximum of three years of treatment (10, 35).

As an addition to established first-line therapy, the combination of dostarlimab with PCC ensures that clinicians have the existing confidence and familiarity with the efficacy and side effects of the chemotherapy regimen when making prescribing decisions. It should be noted that the majority of prescribing clinicians in the NHS will be already familiar with the use of treatment regimen given its availability for dMMR/MSI-H primary advanced or recurrent

endometrial cancer since [redacted] being recommended by NICE in March 2024 (88). Dostarlimab has also been indicated and available in the NHS in the second-line, relapsed setting since 2022 (82).

Figure 3: Proposed treatment pathway including dostarlimab in combination with PCC



Source: ESMO guidelines (10).
*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery.**As per clinical practice and NHS reimbursement, pembrolizumab, an anti-PD-1 therapy, in combination with lenvatinib is not licensed for use following treatment with an anti-PD-(L)1, such as dostarlimab, in the first-line (89-91).
Abbreviations: EC, endometrial cancer; PCC, platinum-containing chemotherapy; PD-1, programmed death protein 1; PD-(L)1, programmed death-ligand 1.

1.3.4.3. Treatment options in the relapsed setting

Systemic treatment options remain limited for MMRp/MSS patients experiencing disease relapse following first-line treatment with PCC. Survival outcomes are particularly poor in this setting, with median OS of approximately 10.3 months in England for those receiving second-line chemotherapy (56). As of May 2023, pembrolizumab with lenvatinib has been recommended by NICE for use in patients with previously treated endometrial cancer whose cancer has progressed on or after PCC (92). This combination therapy has demonstrated an improvement in OS by 5.4 months compared with chemotherapy monotherapy regimens in previously treated MMRp/MSS advanced or recurrent endometrial cancer (14).

However, it is important to note that lenvatinib is associated with a relatively poor adverse event (AE) profile, with 88.9% of patients experiencing Grade 3 or higher AEs when treated with the pembrolizumab-lenvatinib combination (14). In contrast to chemotherapy, which is administered for a limited duration (typically up to six cycles), lenvatinib is a treat-to-progression drug, resulting in ongoing exposure to its associated risks (90). Therefore, careful consideration of the long-term management of adverse effects is essential when evaluating treatment options for this patient population.

It is worth noting that the introduction of dostarlimab would displace pembrolizumab-based regimens from the pathway and preclude its use as a second-line therapy. This is because

these therapies share very similar mechanisms of action, both targeting the PD-1 protein and disrupting the PD-1-ligand interaction (58). Treatment with an anti-PD1 agent in this setting following lack or loss of response to a treatment with the same mechanism of action in the first-line is neither licensed nor reimbursed in England. This is reflected in NHS funding criteria for this regimen (91).

1.3.4.4. NICE scope comparators outlined in the decision problem

The comparators outlined in the NICE decision problem—hormone therapy, durvalumab in combination with PCC followed by durvalumab with or without olaparib maintenance, and pembrolizumab in combination with PCC followed by pembrolizumab maintenance —are not considered appropriate for comparison with dostarlimab in combination with chemotherapy for patients with primary advanced or recurrent endometrial cancer. These treatments are either not established within NHS practice or are unsuitable for the defined patient population (9, 93, 94).

As recognised within national BGCS guidelines, PCC (namely CP doublet) is the SoC treatment for patients with primary advanced or recurrent endometrial cancer (9). Hormone therapy is considered an option for a subset of patients with primary advanced or recurrent endometrial cancer who are likely unsuitable for cytotoxic chemotherapy (9, 93). Therefore, patients requiring hormone therapy are not suitable for dostarlimab in combination with PCC, and so it cannot be considered a relevant comparator. This was also acknowledged in TA963, which recommended dostarlimab in combination with platinum-based chemotherapy for mismatch repair-deficient patients (88).

Durvalumab with PCC, followed by durvalumab with or without olaparib maintenance is an inappropriate comparator, as it is not routinely available nor established SoC in the NHS. As described in the NICE manual under Sections 2.2.12 and 2.6.1, comparators considered at the scoping stage are required to be established practice in the NHS (94). GSK is aware this treatment is undergoing a NICE technology appraisal however a recommendation is not expected until 21st May 2025. GSK are also aware that the licensed indication varies significantly across MHRA/EMA and FDA regulatory jurisdictions which adds further uncertainty to the eventual positioning of this regimen in UK practice (95, 96).

Pembrolizumab with PCC, followed by pembrolizumab maintenance, is not licensed for the treatment of primary advanced or recurrent endometrial cancer and is not routinely available within the NHS and is not part of established NHS practice, as required by NICE methods (94). Including this regimen as a comparator is impractical, as a NICE recommendation is

not expected until at least April 2025 and positioning within UK practice is not yet known. While this treatment is under NICE appraisal and has been investigated in this setting, it cannot currently be considered an appropriate comparator (97).

In summary, the comparators outlined in the NICE decision problem are unsuitable for comparison with dostarlimab in combination with PCC for primary advanced or recurrent MMRp/MSS endometrial cancer. These treatments either lack relevance to the patient population or are not part of established NHS practice (9, 93, 94). This underscores the need to focus on clinically appropriate and established options when evaluating the benefits of dostarlimab in this setting.

1.4. Equality considerations

Endometrial cancer affects women and individuals assigned female at birth, making sex a crucial consideration, particularly given that it is a protected characteristic under the Equality Act 2010 (98). The disease predominantly impacts older women, with incidence rates rising with age, peaking in the 75 to 79 age group (38). Similarly, prostate cancer, which is most prevalent in men over 70, also affects an older demographic. Despite this, prostate cancer therapies addressing a comparable unmet need for men have been valued more than is typical during their corresponding NICE appraisals, resulting in a higher willingness to pay (WTP) thresholds. It is vital that women facing this rare, incurable diagnosis are treated equitably, in accordance with the principles of the Equality Act (38, 73, 98).

GSK is deeply concerned that recent changes to NICE's methods have disproportionately disadvantaged women with endometrial cancer, with the potential to lead to inequitable access to novel treatments compared to their male counterparts. Therapies which have been developed for advanced types of prostate cancer, which affects only men, have previously been afforded special ‘end-of-life’ criteria allowing for a higher decision-making cost-effectiveness threshold of £50,000 per QALY (99, 100). Due to the timing of this particular NICE assessment, relative to those for prostate cancer, women with primary advanced or recurrent endometrial cancer are likely to be disadvantaged despite meeting similar criteria for flexibility: dostarlimab, extends survival by at least three months, is specifically indicated for a small population of fewer than 7,000 patients with a short life expectancy. GSK calls for this same flexibility to be applied to women diagnosed with incurable endometrial cancer, ensuring they have fair and equitable access to novel, effective treatments.

Ethnicity also plays a critical role in survival outcomes in endometrial cancer, with data from the Office for National Statistics revealing that Black Caribbean and Black African women

face higher mortality rates and are more likely to be diagnosed at later stages (101). Additionally, survival outcomes are associated with socio-economic deprivation, with women from middle and most deprived socio-economic groups facing a two-fold and a 53% increased risk of mortality, respectively, compared with less deprived women (102). Addressing these disparities is crucial for ensuring equitable diagnosis and treatment for all demographic groups.

For patients with MMRp/MSS primary advanced or recurrent endometrial cancer, access to innovative treatments such as immunotherapy, which has shown proven survival benefits across several cancer types, is largely reserved for patients who have not responded to first-line therapy or have relapsed (50). The only immunotherapy option available to this patient population, pembrolizumab, is combined with the tyrosine kinase inhibitor, lenvatinib, which has been associated with a notable toxicity burden (11, 90, 103). This limited access not only restricts treatment options but could also further exacerbate inequalities (101, 104). Broadening access to immunotherapies in earlier lines of treatment could help mitigate these disparities and improve survival outcomes across diverse patient populations.

By aligning treatment access with the principles of the Equality Act 2010, healthcare providers can better address the needs of all endometrial cancer patients, ensuring that care is provided equitably and without discrimination based on age, race, or gender (98).

2. Clinical effectiveness

Dostarlimab in combination with platinum-containing chemotherapy (PCC) is the only immunotherapy combination to show a statistically significant overall survival (OS) benefit in the intention-to-treat (ITT) population for primary advanced or recurrent endometrial cancer. Clinically meaningful improvements in survival outcomes were observed regardless of mismatch repair (MMR) status.

RUBY-1 trial design

- Part 1 of the RUBY trial (RUBY-1) (NCT03981796) investigated the addition of dostarlimab to the current standard of care (SoC) carboplatin plus paclitaxel (CP) in patients with primary advanced or recurrent endometrial cancer.
- The RUBY-1 trial was powered to detect improvements in the dual-primary endpoints, progression-free survival (PFS) and overall survival (OS) in the overall ITT population. For the mismatch repair proficient (MMRp)/microsatellite stable (MSS) population, a prespecified analysis of PFS and OS was performed.
- The RUBY trial enrolled a patient population which is generalisable to the UK and provides direct head-to-head evidence against the current SoC treatment in the NHS in this setting.

RUBY-1 PFS, PFS2 and OS for patients with MMRp/MSS primary advanced or recurrent endometrial cancer

- The RUBY-1 trial met its dual-primary endpoints, demonstrating significant improvements in PFS and OS benefit in the ITT population, with the MMRp/MSS subgroup comprising 75% of the overall patient population.
- Within the MMRp/MSS subgroup, the improvement in PFS was maintained across later lines of therapy resulting in improved progression-free survival 2 (PFS2) and OS.
- PFS:
  - Dostarlimab in combination with CP significantly improved PFS in the ITT population compared with the placebo arm (hazard ratio [HR]: 0.64; 95% confidence interval (CI): 0.51, 0.80; p<0.0001) (16).
  - In the prespecified MMRp/MSS subgroup, there was a 24% reduction in risk of progression or death in the dostarlimab arm compared with the placebo arm (HR: 0.76; 95% CI: 0.59, 0.98; nominal p=0.018) (16).
- PFS2:
  - Dostarlimab in combination with CP reduced the risk of progression following the first subsequent anticancer therapy or death in the MMRp/MSS population (HR 0.74; 95% CI: 0.57, 0.97) (15).
  - These results demonstrate the notable improvements in PFS are carried through to later lines of therapy, resulting in ongoing benefits post-progression.
- OS:
  - Dostarlimab in combination with CP demonstrated a statistically significant and clinically meaningful improvement in OS in the ITT population (HR: 0.69; 95% CI 0.54, 0.89; p=0.002) (15).
  - In the prespecified MMRp/MSS subgroup, the median OS was 34 months in the dostarlimab arm compared to 27 months in the placebo arm, an improvement of 7 months. This corresponds to a 21% reduction in the risk of death (HR: 0.79; 95% CI: 0.60, 1.04; nominal p=0.049) (15).

Safety analysis for patients with primary advanced or recurrent endometrial cancer

- Dostarlimab in combination with CP has a generally manageable safety profile consistent with the known profiles of the individual agents.

Conclusion

- The addition of dostarlimab to PCC results in delayed progression of disease at first-line where novel, effective treatments can have their greatest impact. Ultimately this results in improved survival outcomes in a setting where the existing SoC only provides modest and short-lived benefits, and innovative treatment options are lacking. It is therefore paramount that dostarlimab becomes available for these patients.

2.1. Identification and selection of evidence

A systematic literature review (SLR) was conducted on 10 November 2021 (with a refresh on 22 February 2023, 8 August 2023, 26 October 2023 and 16 May 2024) to identify randomised clinical trials (RCT) evidence reporting on the efficacy and safety of dostarlimab in combination with CP and other relevant treatments for primary advanced or recurrent endometrial cancer. Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are provided in Appendix B.

2.2. List of relevant clinical effectiveness evidence

As described in Section 1.3.4, CP is the SoC treatment option in the primary advanced or recurrent endometrial cancer population in England. Fifteen trials were identified to have investigated CP in this population. These trials are summarised in Appendix B. However, aside from RUBY, no RCTs provided direct head-to-head evidence of dostarlimab in combination with CP compared with CP alone, relevant to the decision problem.

The SLR (Appendix B) identified the Phase 3, randomised, double-blind, multicentre RUBY trial as the only RCT that evaluated the efficacy and safety of dostarlimab in combination with CP for female adult patients with primary advanced or recurrent endometrial cancer. Part 1 of the RUBY trial (RUBY-1; ClinicalTrials.gov number: NCT03981796) compared the combination of dostarlimab and CP with SoC, stratified by MMR status, including the MMRp/MSS subgroup. The clinical data and cost-effectiveness analyses are based on this study. Table 3 provides a summary of the clinical evidence supporting the use of this combination in patients with MMRp/MSS primary advanced or recurrent endometrial cancer.

RUBY provides direct head-to-head evidence of dostarlimab in combination with CP compared with placebo in combination with CP, the SoC in England.

Table 3: Clinical effectiveness evidence

Study	Part 1 of the RUBY trial (RUBY-1) (ClinicalTrials.gov number: NCT03981796)
Study design	A multicentre, randomised, double blinded, placebo-controlled Phase 3 study
Population	Female patients with primary Stage III or Stage IV endometrial cancer or first recurrent endometrial cancer, with a low potential for cure by radiation therapy or surgery alone or in combination. (ITT N=494) [MMRp/MSS n=376] †
Intervention(s)	Dostarlimab in combination with CP (N=245) [n=192 MMRp/MSS]
Comparator(s)	Placebo in combination with CP (N=249) [n=184 MMRp/MSS]
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Eligibility criteria	A summary of inclusion and exclusion criteria is provided below. Full details of the eligibility criteria are presented within the study protocol (105) Key inclusion criteria: • Female patient is at least 18 years of age • Patient has an ECOG performance status of 0 or 1 • Patient has histologically or cytologically proven endometrial cancer with advanced or recurrent disease • Patient must provide adequate tumour tissue sample at screening for MMR/MSI status testing • Patient must have primary Stage III or Stage IV disease or first recurrent endometrial cancer, with a low potential for cure by radiation therapy or surgery alone or in combination and meet at least 1 of the following criteria: I. Participant has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumour. II. Participant has primary Stage IIIC1 disease with carcinosarcoma, clear cell, or serous histology, regardless of presence of evaluable or measurable disease on imaging. III. Participant has primary Stage IIIC2 or Stage IV disease, regardless of presence of evaluable or measurable disease.

	IV. Participant has first recurrent disease and is naïve to chemotherapy. V. Participant has received prior neoadjuvant/adjuvant systemic chemotherapy and had a recurrence or progressive disease ≥6 months after completing treatment (first recurrence only). Key exclusion criteria: • Patient has received neoadjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease and one of the following: o Has not had recurrence or progressive disease prior to the first dose in the study Or o Has had a recurrence or progressive disease within 6 months of completing systemic anticancer therapy treatment prior to the first dose on the study • Patient has had >1 recurrence of endometrial cancer • Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent • Patient has received prior anticancer therapy within 21 days or <5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter • Patient has a concomitant malignancy, or a prior non-endometrial invasive malignancy but has been disease-free for <3 years, or received any active treatment in the last 3 years for that malignancy • Patient has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both
Trial drugs and methods of administration	Dostarlimab in combination with CP is administered intravenously. The dosage is as follows: • Dostarlimab 500 mg IV in combination with carboplatin IV AUC 5 mg/ml/min) plus paclitaxel IV (175 mg/m^2) Q3W for six cycles (cycles 1–6), followed by dostarlimab 1,000 mg IV Q6W for all cycles thereafter (cycle 7 onwards) • Treatment with dostarlimab is continued until progression of disease or unacceptable toxicity, up to a maximum of 3 years
Primary outcomes (including scoring methods and timings of assessments)	The dual-primary outcomes were: • PFS assessed by investigator assessment o Initial radiographic scans conducted within 28 days before the first dose were accepted if diagnostic quality was met o Disease extent was assessed radiographically Q6W until Week 25 (±7 days), then Q9W until Week 52 (±7 days)

	○ Subsequent tumour imaging occurred every Q12W until radiographic PD was confirmed, followed by one additional scan 4–6 weeks later or upon starting subsequent anticancer therapy • OS assessed as the time from randomisation to the date of death from any cause. ○ Patients without a documented death at the time of the final analysis were censored at the last date they were confirmed to be alive.
Secondary and exploratory outcomes (including scoring methods and timings of assessments) ‡	• PFS based on BICR assessment • ORR based on BICR and investigator assessment • DOR based on BICR and investigator assessment • DCR based on BICR and investigator assessment • PROs¶ ○ EQ-5D-5L [mapped to EQ-5D-3L] ○ EORTC, QLQ-C30 ○ QLQ-EN24 ○ PROs were assessed at every clinic visit and during every survival follow-up assessment • PFS2 ○ Defined as the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever is earlier • Number of participants with AEs, serious AEs, AEs of special interests, suspected unexpected serious adverse reactions and TEAEs
Post-hoc subgroup analyses	• Exploratory subgroup analyses on the primary endpoints (investigator assessed PFS and OS) were performed on the MMRp/MSS population to explore the homogeneity of the treatment effect across relevant participant subsets: ○ Age (< 65 years or ≥ 65 years) ○ Race (white or other) ○ Region (North America or Europe or Western Europe or Eastern Europe) ○ Histology (endometrioid carcinoma or other) ○ Disease status at baseline (recurrent, primary Stage III, or primary Stage IV), according to the eCRF (source verified classification) ○ Prior external pelvic radiotherapy (yes or no), according to the eCRF (source verified classification)

	○ Patients with “No disease” at baseline

†N refers to the ITT population while n refers to the MMRp/MSS population.
‡Endpoints relating to response assessment (i.e. PFS, ORR, DOR, etc) are based on tumour imaging which were performed as per the statistical analysis plan .
¶[PRO assessments were collected at every clinic visit and during every survival follow-up assessment
Abbreviations: AE, adverse events; AUC, area under curve; BICR, blinded independent central review; CP, carboplatin plus paclitaxel; CSR, clinical study report; DCR, disease control rate; dMMR, DNA mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; ECRF, electronic case report form; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol five dimensions; ITT, intention to treat; IA, interim analysis; IA1, first interim analysis; IA2, second interim analysis; IV, intravenous; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PCC, platinum-based chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; PFS, progression-free survival; PFS2, progression-free survival 2; PRO, patient reported outcomes; QLQ-C30, Quality of Life Questionnaire C30 (Core); QLQ-EN25, Quality of Life Questionnaire Endometrial Cancer Module; QxW, every x weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment emergent adverse event; UK, United Kingdom; US, United States.

2.2.1. UK real-world evidence

A recent retrospective, non-interventional, observational real-world evidence (RWE) study was conducted using anonymised electronic healthcare record-derived data from the UK Arcturis dataset for seven English NHS Trusts between 2000 and 2023 (106). The study identified 731 patients diagnosed with primary advanced or recurrent endometrial cancer, of which 22.7% (n=166) had MMR status noted. Of the patients who had MMR status recorded, 25.3% (n=42) were dMMR/MSI-H and 74.7% (n=124) had MMRp/MSS status, in line with the expected split for this population (36, 106). Patients in the MMRp/MSS population had a mean age of 65.5 years at advanced diagnosis or recurrence, which is similar to the RUBY-1 trial, which forms the basis of the efficacy data for this submission (Section 2.3) (106). Of the patients with MMRp/MSS status that received first-line therapy, median OS was 2.36 years (95% CI: 2.10, 4.05) and median time to next treatment (TTNT) was 1.03 years (95% CI: 0.90, 1.49) (106).

Furthermore, another retrospective, population-based RWE study was conducted using the National Cancer Registration and Analysis Service (NCRAS) data for diagnosis between 2013 and 2019 (8). The study identified 2,376 patients who received first-line systemic treatment for advanced or recurrent endometrial cancer (8). Of these patients, 77.8% (n=1,824) were treated with first-line CP, highlighting that CP is the SoC for these patients (8). The study did not identify patients who were tested for MMR status.

2.2.2. Clinical data presented in the submission

The key RUBY-1 data considered in this submission are from two data cut-off dates: 28 September 2022 (first interim analysis [IA1]) and 22 September 2023 (second interim analysis [IA2]). At IA1, RUBY-1 met the PFS dual-primary endpoint, with statistical significance reached for pre-specified PFS analysis. IA2 was a pre-planned interim analysis for the dual primary endpoint of OS in the intention-to-treat (ITT) population. Table 4 shows the outcome data available for each data cut.

Table 4: Outcome data available for each data cut

Outcome	Data cut-off	Used in economic model
PFS	IA1	Yes
OS	IA2	Yes
PFS2	IA2	No
ORR	IA1	No
DOR	IA1	No
DCR	IA1	No
PROs	IA1	Yes
Subgroup analysis: OS	IA2	No
Subgroup analysis: PFS	IA1	No

Outcome	Data cut-off	Used in economic model
Sensitivity analysis for PFS: PFS (BICR)	IA1	No
Safety	IA2	Yes

Note: The data cut-off for IA1 and IA2 was 28 September 2022 and 22 September 2023, respectively.
Abbreviations: BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; IA1, first interim analysis; IA2, second interim analysis; ORR, objective response rate; OS, overall survival; PFS2, progression free survival 2; PROs, patient reported outcomes.

2.3. Summary of the methodology of the relevant clinical effectiveness evidence

2.3.1. Summary of study methodology

2.3.1.1. Study design

As described in Section 2.2, RUBY-1 is a Phase 3, randomised, double-blind, multicentre study evaluating the efficacy and safety of treatment with dostarlimab in combination with CP followed by dostarlimab versus treatment with placebo and CP followed by placebo. Throughout the remainder of this submission, these arms will be referred to as the dostarlimab arm and the placebo arm, respectively.

The RUBY study consists of a screening period (Day –28 to Day –1), a treatment period, an end of treatment visit, a safety follow-up visit, and a survival assessment period. Following informed consent, patients who met the eligibility criteria for RUBY-1 were randomised 1:1 to the following study arms:

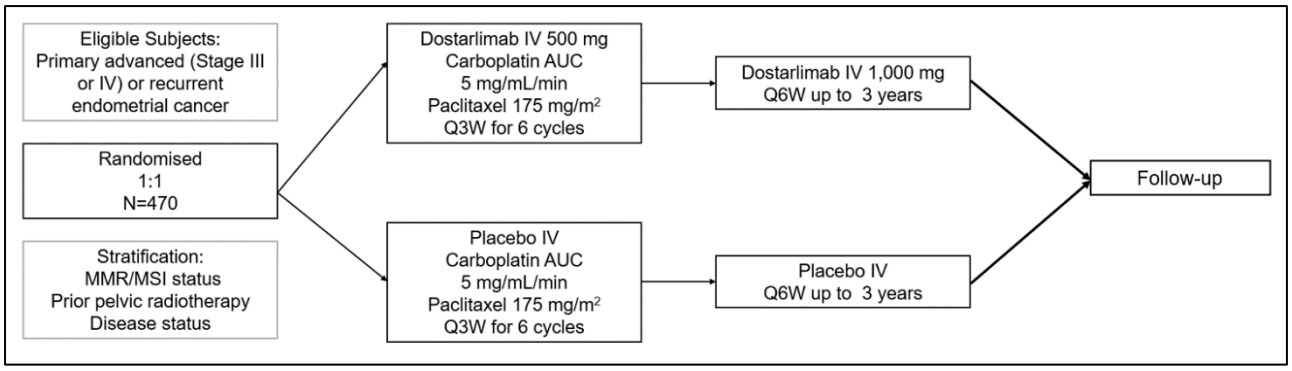
- Dostarlimab arm: Patients received dostarlimab 500 mg intravenous (IV) in combination with CP followed by dostarlimab monotherapy 1,000 mg IV
- Placebo arm: Patients received placebo IV in combination with CP followed by placebo IV.

2.3.1.2. RUBY-1 design

Figure 4 shows the study design for RUBY-1. Following randomisation, eligible patients began cycle one of treatment in the assigned treatment arm. Study intervention administration occurred in 3-week cycles for the first six cycles and in 6-week cycles for all following cycles starting with cycle seven. Study intervention continued for up to 3 years or until progressive disease (PD), unacceptable toxicity, withdrawal of consent, Investigator's decision, or death. Eligibility criteria for RUBY-1 can be found in Section 2.2, Table 3. Patients were stratified by MMR and MSI status as MMRp/MSS or dMMR/MSI-H, prior

external pelvic radiotherapy (yes or no), and disease status (recurrent, primary Stage III, or primary Stage IV). Approximately 470 patients were planned for enrolment in RUBY-1.

Figure 4: RUBY-1 design



Abbreviations: AUC, area under curve; IV, intravenous; MMR, mismatch repair; MSI, microsatellite instability; Q3W, every three weeks; Q6W, every six weeks.

2.3.2. Settings and locations

The study was carried out in 19 countries: the US, UK (including 5 UK sites), Belarus, Belgium, Canada, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Sweden, Turkey and Ukraine.

2.3.3. Trial drugs and concomitant medications

Dostarlimab was administered intravenously at a unit dose of 500 mg Q3W for six cycles (cycles 1–6), then at 1,000 mg Q6W for all cycles thereafter (cycle 7 onwards). Placebo was also administered intravenously Q3W for six cycles (cycles 1–6) and then Q6W for all cycles thereafter (cycle 7 onwards). Both carboplatin and paclitaxel were administered in patients in both treatment arms for the first six cycles only (cycles 1–6). Carboplatin was given IV at a unit dose of area under the plasma or serum concentration-time curve (AUC) 5 mg/mL/min every three weeks. Paclitaxel was given IV (dosed by patient's body surface area) at a unit dose of 175 mg/m^2 Q3W.

2.3.4. Study outcomes

The dual primary endpoints of RUBY-1 were OS and PFS as assessed by the Investigator per RECIST v1.1, and these were statistically powered for the overall population. OS and PFS in the MMRp/MSS population were examined as pre-specified subgroup analyses. The RUBY-1 study population was stratified by MMR status, and all efficacy outcomes were reported for both the MMRp/MSS and dMMR/MSI-H populations. Section 2.2.2 specifies the endpoints that were analysed at IA1 (28 September 2022), and IA2 (22 September 2023). Section 2.2, Table 3 provides a summary of the primary and secondary endpoints.

2.3.5. Patient demographics and clinical baseline characteristics

Table 5 presents a summary of the demographic baseline characteristics of patients in the MMRp/MSS population. There were 192 patients in the dostarlimab arm and 184 patients in the placebo arm. Most patients were White with a median age of [redacted] years and a baseline ECOG performance status (PS) of [redacted]

At study entry, ECOG status was slightly worse in the dostarlimab arm, with fewer patients having a PS of 0 compared with the placebo arm ([redacted]% vs [redacted]%). The baseline characteristics of patients were generally well balanced between treatment arms (107).

Table 5: Summary of demographic characteristics in the MMRp/MSS population

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Age Group, n (%)		
19–64	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Weight (kg)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Height (cm)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BMI (kg/m^2)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BSA (m^2)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
ECOG PS, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.15 (108).
Abbreviations: BMI, body mass index; BSA, body surface area; CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; MMRp, mismatch repair proficient; MSS, microsatellite stability; PS, performance status; SD, standard deviation.

Table 6 presents a summary of the disease history of patients in the MMRp/MSS population, while Table 7 shows a summary of the prognostic stratification factors in these patients. FIGO stage and grade at initial diagnosis, histology, and patient's disease history were similar between the treatment arms (108). Higher risk histologies, like carcinosarcoma, were adequately represented in the trial and evenly distributed across treatment arms.

Table 6: Summary of disease history in MMRp/MSS population

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
FIGO stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at diagnosis		
Carcinosarcoma	[redacted]	[redacted]
Clear cell adenocarcinoma	[redacted]	[redacted]
Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]
Mucinous adenocarcinoma	[redacted]	[redacted]
Other	[redacted]	[redacted]
Serous adenocarcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Most recent grade of disease		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Grade 3	[redacted]	[redacted]
Not accessible	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.17 (108)
Abbreviations: CP, carboplatin plus paclitaxel; FIGO, Federation of Gynaecology and Obstetrics; MMRp, mismatch repair proficient; MSS, microsatellite stability.

Table 7: Prognostic stratification factors in MMRp/MSS population

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Previous external pelvic radiotherapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Disease status		
Primary Stage III	[redacted]	[redacted]
Primary Stage IV	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.10 (108)
Abbreviations: CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable.

A CONSORT diagram showing the patient flow for RUBY-1 is provided in Appendix B.

2.3.6. Disposition of patients

Table 8 shows the summary of participant disposition in the MMRp/MSS population at IA2. [redacted]% of participants in the dostarlimab arm and [redacted]% of participants in the placebo arm remained ongoing in the study at the time of the IA2 data cut.

The most common reason for study discontinuation was death from any cause (dostarlimab arm: [redacted]%; placebo arm: [redacted]%), followed by withdrawal of consent. The most common primary cause of death was disease progression as per RECIST 1.1 (dostarlimab arm: [redacted]%; placebo arm: [redacted]%).

Table 8: Summary of participant disposition in MMRp/MSS population

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Participants' status		
Discontinued from study	[redacted]	[redacted]
Ongoing	[redacted]	[redacted]
On study treatment	[redacted]	[redacted]
In follow-up	[redacted]	[redacted]

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Reason for discontinuation from study		
Withdrawal of consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]
Other	[redacted]	[redacted]
Primary cause of death		
Disease progression	[redacted]	[redacted]
Adverse event†	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]

Source: IA2 CSR Table 14.1.1.5 (109)
†Adverse event as primary cause of death while on study, i.e., death occurring after informed consent and before end of study.
Abbreviations: CP, carboplatin plus paclitaxel; MSS, microsatellite stable; MMRp, mismatch repair proficient.

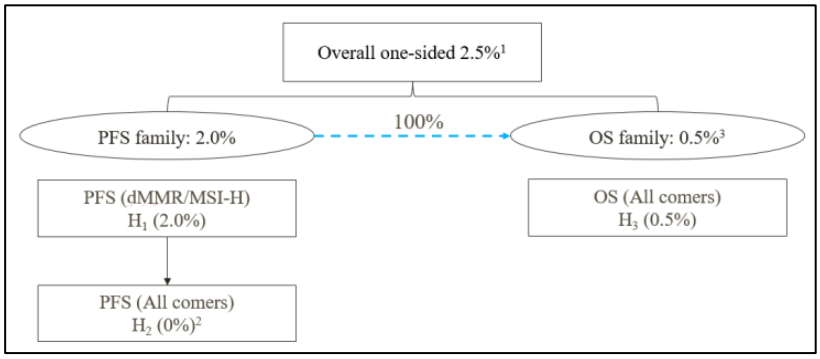
2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of RUBY-1, including a summary of the statistical analyses, are provided in Table 9.

Table 9: Summary of statistical analyses

Study	RUBY-1 (ClinicalTrials.gov number: NCT03981796)
Hypothesis objective	RUBY-1 had three hypotheses: 1. Dostarlimab in combination with CP followed by dostarlimab prolongs PFS (investigator assessment) per RECIST v.1.1 in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo. 2. Dostarlimab in combination with CP followed by dostarlimab prolongs PFS (investigator assessment) per RECIST v.1.1 in patients with primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo in the ITT population. 3. Dostarlimab in combination with CP followed by dostarlimab prolongs OS in patients with primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo in the ITT population.
Statistical analysis	The ITT population for efficacy analyses included all randomised patients (N=494), regardless of treatment received, with 372 patients stratified as MMRp/MSS. The prespecified MMRp/MSS subgroup, determined by source-verified MMR/MSI status, consisted of 192 patients in the dostarlimab arm and 184 in the placebo arm. For the dual-primary efficacy endpoint, PFS (investigator-assessed), the distribution was estimated using the KM method, stratified by MMR/MSI status (dMMR/MSI-H or MMRp/MSS), prior pelvic radiotherapy, and disease status (recurrent, Stage III, or Stage IV). A stratified Cox regression model estimated

<table>
<tr><th>Study</th><th>RUBY-1 (ClinicalTrials.gov number: NCT03981796)</th></tr>
<tr><td></td><td>the PFS hazard ratio (HR) and confidence interval for hypothesis testing. The censoring rule for the primary PFS analysis is summarised below.
<table><tr><th>Situation</th><th>Primary Analysis</th></tr><tr><td>No baseline tumour assessment and no death within 12 weeks</td><td>Censored at randomisation</td></tr><tr><td>No baseline tumour assessment and death within 12 weeks</td><td>Progressed at date of death</td></tr><tr><td>No PD and no death; new anticancer therapy is not initiated</td><td>Censored at last tumour assessment</td></tr><tr><td>No PD and no death; new anticancer therapy is initiated</td><td>Censored at last tumour assessment before new anticancer therapy</td></tr><tr><td>PD or death documented after ≥2 missed disease assessments</td><td>Censored at last tumour assessment prior to the ≥2 missed disease assessment</td></tr></table>
Graphical methods were used to provide strong multiplicity control, with the family-wise type I error controlled at 2.5% (one-sided). Secondary efficacy outcomes were analysed in the ITT and MMRp/MSS populations. Safety analyses were conducted on the safety population (N=487), including 370 MMRp/MSS patients, all of whom received at least one dose of the study intervention.</td></tr>
<tr><td>Sample size, power calculation</td><td>The sample size calculations for the RUBY trial were driven by the primary efficacy endpoint of PFS (investigator assessed using RECIST v1.1). The following assumptions were made for the sample size calculations:
All-comer population (regardless of MMR/MSI status): HR of 0.67, corresponding to an increase in median PFS from 10 months in the placebo arm to 15 months in the dostarlimab arm
Patient distribution by tumour MMR/MSI status: 25% with dMMR/MSI-H and 75% with MMRp/MSS
1:1 randomisation
Alpha = a one-sided alpha of 0.02 was initially allocated to hypotheses regarding IA PFS and an alpha level of 0.005 was initially allocated to hypotheses regarding OS. For IA PFS, hypotheses were hierarchically tested in the dMMR–MSI-H population and then in the overall population; OS was tested in the overall population. If the null hypotheses for IA PFS were all rejected, the 0.02 alpha level would be recycled to the hypothesis of OS, which would be tested at a one-sided alpha level of 0.025; otherwise, OS would be tested only at the initially allocated one-sided alpha level of 0.005
Power = approximately 89% for testing of hypothesis 1
Accrual over a period of 22 months
Assuming an annual dropout rate of 5%
Exponential distribution of PFS
With these assumptions, a total sample size of 470 patients was planned, and approximately 352 patients were expected to be MMRp/MSS.
To maintain the natural distribution of MMRp/MSS (75%) and dMMR/MSI-H (25%) participants in the overall population in this study, the number of</td></tr>
</table>

Study	RUBY-1 (ClinicalTrials.gov number: NCT03981796)
	participants enrolled with MMRp/MSS or dMMR/MSI-H endometrial cancer was capped at approximately 350 and 120, respectively. In addition, the total number of patients with carcinosarcoma was capped at 50 (approximately 10%) to prevent overrepresentation of this patient population.
Data management, patient withdrawals	Patients could be discontinued from the study treatment at any time. Specific reasons for discontinuing study treatment include: • AE • Clinical progression • PD according to RECIST v.1.1 criteria per investigator assessment • Risk to patient, as judged by the investigator, sponsor, or both • Severe noncompliance with the protocol, as judged by the investigator, sponsor or both • Patient becomes pregnant • Withdrawal of consent • Lost to follow-up • Death from any cause • Sponsor decision to terminate study
Summary diagram	 1. The alpha level assigned to a subfamily was rolled over only if the hypotheses within the subfamily were all significant based on the weight for re-allocation presented on the dashed lines connecting subfamilies. Within each subfamily, the weights for re-allocation from each hypothesis to the others are represented on the solid lines connecting hypotheses. 2. Hypothesis testing for PFS in all-comers was only performed if null hypothesis of PFS was rejected in dMMR/MSI-H population. 3. Hypothesis testing for OS started at the time when the hypothesis testing for PFS had completed (i.e., no further hypothesis testing could be performed for PFS), at a re-allocated alpha level (2.5%) if both null hypotheses had been rejected for hypothesis 1 and hypothesis 2; otherwise, OS was tested at the initial alpha level (0.5%).

Abbreviations: AE, adverse events; dMMR, DNA mismatch repair deficient; EC, endometrial cancer; HR, hazard ratio; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; PCC, platinum-containing chemotherapy; PD, progressive disease; PFS, progression-free survival.

2.5. Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for the RUBY-1 trial is provided in Appendix B.

2.6. Clinical effectiveness results of RUBY-1

The following sections present the relevant clinical effectiveness results for both the ITT population and the prespecified subgroup of MMRp/MSS from the RUBY-1 trial. Table 10 shows a summary of the key results from the RUBY-1 trial.

Table 10: Summary of key clinical outcomes from the RUBY-1 trial

Outcome	Subgroup population	Key results	Section
PFS	ITT	Dostarlimab + CP significantly reduced the risk of progression or death by 36% compared with placebo arm (HR: 0.64, 95% CI: 0.51, 0.80, p<0.0001).	2.6.2
	MMRp/MSS	Dostarlimab + CP reduced the risk of progression or death by 24% vs. placebo arm (HR: 0.76, 95% CI: 0.59, 0.98, p= 0.0177)	
OS	ITT	Dostarlimab + CP reduced the risk of death by 31% compared with placebo arm (HR: 0.69, 95% CI: 0.539, 0.890, p=0.002).	2.6.3
	MMRp/MSS	Dostarlimab + CP reduced risk of death by 21% vs. placebo arm (HR: 0.79, 95% CI: 0.602, 1.044, p=0.0493).	
PFS2	MMRp/MSS	Median PFS2 was 24.6 months for the dostarlimab arm vs 15.9 months) for the placebo arm (HR: 0.74, 95% CI: 0.57, 0.97).	2.6.4.1
ORR		ORR was similar: 68.1% (95% CI: 60.4, 75.2) for the dostarlimab arm vs 63.4% (95% CI: 55.4, 70.8) for the placebo arm.	2.6.4.2
DOR		Median DOR was longer for the dostarlimab arm: 8.6 months (95% CI: 6.9, 13.1) vs 6.3 months (95% CI: 4.4, 6.9) for the placebo arm.	
PROs		No significant differences in QoL measures between the dostarlimab and placebo arms.	2.6.4.3

Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; MMRp, mismatch repair proficient; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes.

2.6.1. Duration of follow-up

In the MMRp/MSS population, the median duration of follow-up was [redacted] at the time of the IA1 data cut and 37.5 months at IA2. The median follow-up duration was similar between the dostarlimab arm and placebo arm at [redacted] and [redacted], respectively (109).

2.6.2. Primary endpoint: PFS, investigator-assessed

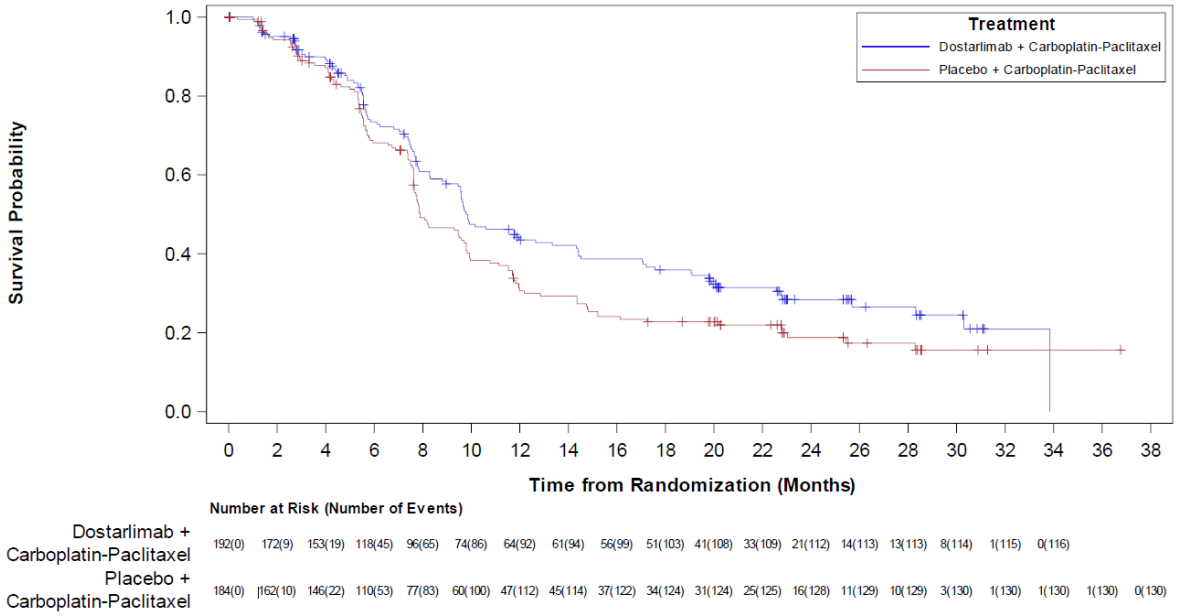
In the ITT population, the dostarlimab arm demonstrated a statistically significant improvement in PFS compared with the placebo arm. Dostarlimab in combination with CP was shown to reduce the risk of progression or death by 36% compared with CP alone with an HR of 0.64 (95% confidence interval [CI]: 0.51, 0.80; p-value <0.0001) (16). The median

PFS was [redacted] months in the dostarlimab arm compared with 7.9 (95% CI: 7.6, 9.5) months in the placebo arm. The KM analysis of PFS in the ITT population can be found in Appendix J.

PFS results in the MMRp/MSS population were broadly consistent with those observed in the ITT population, similarly, demonstrating an improvement in PFS in the dostarlimab arm. Figure 5 shows the KM analysis of PFS in the MMRp/MSS population at IA1. Dostarlimab in combination with CP reduced the risk of progression or death by 24% compared with CP (HR: 0.76, 95% CI: 0.59, 0.98, nominal p-value 0.0177) (16). Median PFS was 9.9 months (95% CI: 9.0, 13.3) in the dostarlimab arm versus 7.7 months (95% CI: 7.6, 9.8) in the placebo arm (Table 11). The PFS curves began to separate in favour of the dostarlimab arm at approximately month 6 and remained separated thereafter.

Additionally, a sensitivity analysis using BICR assessment instead of investigator assessment for PFS similarly showed separation of the curves in favour of the dostarlimab arm (Appendix J). The PFS results as assessed by BICR were consistent with the investigator-assessed PFS results across all populations (Appendix J).

Figure 5: KM curves of PFS (MMRp/MSS patient population)



Source: IA1 CSR Figure 15.1.1. (108).
Data cut off: 28 September 2022.
Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

Table 11: KM analysis of PFS (MMRp/MSS patient population)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS, months (95% CI)	9.9 (9.0, 13.3)	7.9 (7.6, 9.8)
PFS probability (95% CI)		
Month 12	43.5% (35.7%, 51.0%)	30.6% (23.6%, 37.8%)
Month 24	28.4% (21.2%, 36.0%)	18.8% (12.8%, 25.7%)
Hazard ratio (95% CI)	0.76 (0.592, 0.981)	
Nominal p-value of 1-sided stratified log-rank test	0.0177	

Source: IA1 CSR Table 14.2.1.1 (108).
Data cutoff: 28 September 2022
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

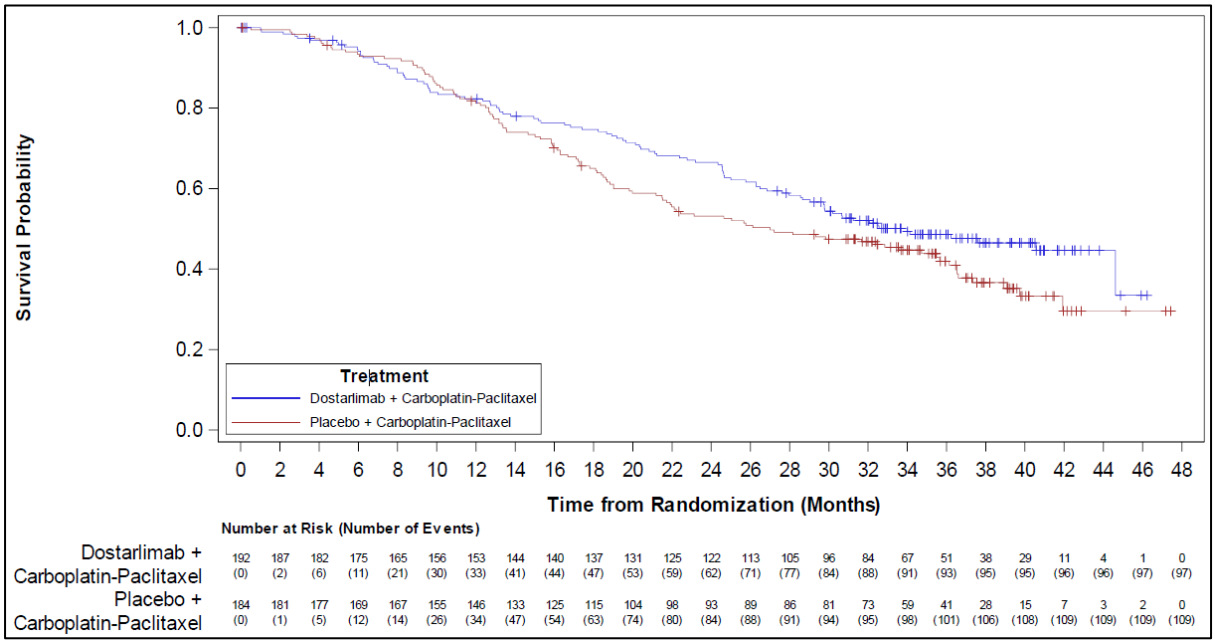
2.6.3. Primary endpoint: OS, investigator assessed

In the ITT population, dostarlimab in combination with CP resulted in a statistically significant improvement in OS compared with CP alone. Dostarlimab in combination with CP was shown to reduce the risk of death by 31% compared with CP alone with an HR of 0.69 (95% CI: 0.539, 0.890; p-value=0.002) (15). The median OS was 44.6 (95% CI: 32.6, NR) months in the dostarlimab arm compared with 28.2 (95% CI: 22.1, 35.6) months in the placebo arm (15, 109). The KM analysis of OS in the ITT population can be found in Appendix J.

OS results in the MMRp/MSS population were broadly consistent with those observed in the ITT population, both demonstrating an improvement in OS in the dostarlimab arm. Figure 6 shows the KM analysis of OS in the MMRp/MSS subgroup at IA2. Dostarlimab in combination with CP reduced the risk of death by 21% compared with CP alone (HR:0.79, 95% CI: 0.602, 1.044; nominal p=0.0493) (16). Median OS for the dostarlimab arm was 34.0 months (95% CI: 28.6, NR) vs 27.0 months (95% CI: 21.5, 35.6) for the placebo arm, corresponding to an improvement in median OS of 7 months.

In the dostarlimab arm, 97 patients (50.5%) experienced an OS event, whilst in the placebo arm 109 patients (59.2%) experienced an OS event (16). A clear and sustained separation of the survival curves can be seen from around 12 months. The KM probability of survival at 24 months was 66.5% (95% CI: 59.2%, 72.8%) and 53.2% (95% CI: 45.6%, 60.2%) in the dostarlimab and placebo arms, respectively (Table 12). After a further 12 months, at month 36, the KM probability of survival was 48.6% (95% CI: 41.0%, 55.7%) in the dostarlimab arm and 41.9% (95% CI: 34.3%, 49.4%) in the placebo arm (15) (Table 12).

Figure 6: KM curves of OS (MMRp/MSS patient population)



Source: IA2 CSR Figure 15.1.8. (109).
Data cutoff: 22 September 2023.
Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; OS, overall survival.

Table 12: KM analysis of OS (MMRp/MSS patient population)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median OS, months (95% CI)	34.0 (28.6, NE)	27.0 (21.5, 35.6)
OS probability (95% CI)		
Month 12	82.3% (76.0%, 87.1%)	81.2% (74.7%, 86.2%)
Month 24	66.5% (59.2%, 72.8%)	53.2% (45.6%, 60.2%)
Month 36	48.6% (41.0%, 55.7%)	41.9% (34.3%, 49.4%)
Hazard ratio (95% CI)	0.79 (0.602, 1.044)	
Nominal p-value of 1-sided stratified log-rank test	0.0493	

Source: IA2 CSR Table 14.2.1.8 (109) and Powell et al. (15).
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival.

2.6.4. Secondary efficacy outcomes

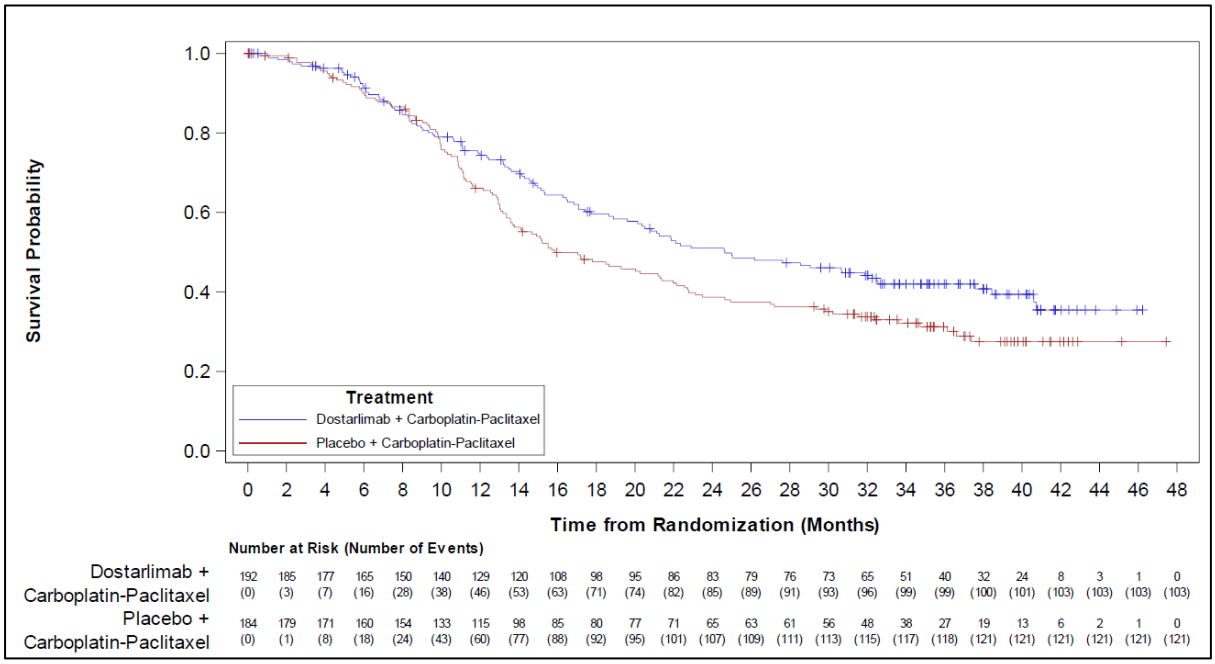
Secondary outcomes are reported below for the MMRp/MSS population only. Full details of results and analyses for each secondary efficacy outcome in the ITT population are available in Appendix J. The clinical benefit of adding dostarlimab to CP was consistently observed across all secondary efficacy endpoints in the MMRp/MSS population, including PFS2, ORR, DCR, DOR, and PFS by BICR (108, 109). Trends in the MMRp/MSS population were generally consistent with those seen in the ITT population.

2.6.4.1. PFS2

At the data cutoff of 22 September 2023, dostarlimab in combination with CP demonstrated a reduction in the risk of progression following the first subsequent anticancer therapy or death (PFS2) among patients with MMRp/MSS disease. This corresponded to a median improvement of 8.7 months in the time to a second progression event for patients in the dostarlimab arm. Specifically, the median PFS2 was 24.6 months (95% CI: 20.1 to 32.6) in the dostarlimab arm, compared with 15.9 months (95% CI: 13.6 to 22.0) in the placebo arm (HR of 0.74 [95% CI: 0.57 to 0.97]), as presented in Table 13 (15).

Figure 7 shows the KM curves for PFS2 in the MMRp/MSS population, where separation in favour of the dostarlimab arm began at approximately month 10 and was maintained throughout the follow-up period. The probability of remaining alive and free of a second progression event was consistently higher in the dostarlimab arm compared with the placebo arm. These findings demonstrate that first-line dostarlimab treatment prolongs the time to second progression or death, even with subsequent immunotherapy use in the placebo arm (Section 2.7). Overall, the PFS2 results indicate that the benefits of dostarlimab in combination with CP are sustained beyond the first progression event and improve post-progression outcomes.

Figure 7: IA2: KM curves of PFS2 (MMRp/MSS patient population)



Source: IA2 CSR Figure 15.1.11. (109).
Data cutoff: 22 September 2023.
Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression free survival 2.

Table 13: IA2: Summary of KM of PFS2 (MMRp/MSS patient population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=65)
Hazard ratio (95% CI)	0.74 (0.571, 0.970)	
Median PFS2, months (95% CI)	24.6 (20.1, 32.6)	15.9 (13.6, 22.0)
PFS2 Probability at 24 months (95% CI)	51.0% (43.3%, 58.2%)	38.7% (31.4%, 45.8%)
PFS2 Probability at 36 months (95% CI)	42.0% (34.4%. 49.4%)	31.2% (24.3, 38.4)

Source: CSR Table 14.2.1.39 (109) and Powell et al. (15).
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression-free survival 2.

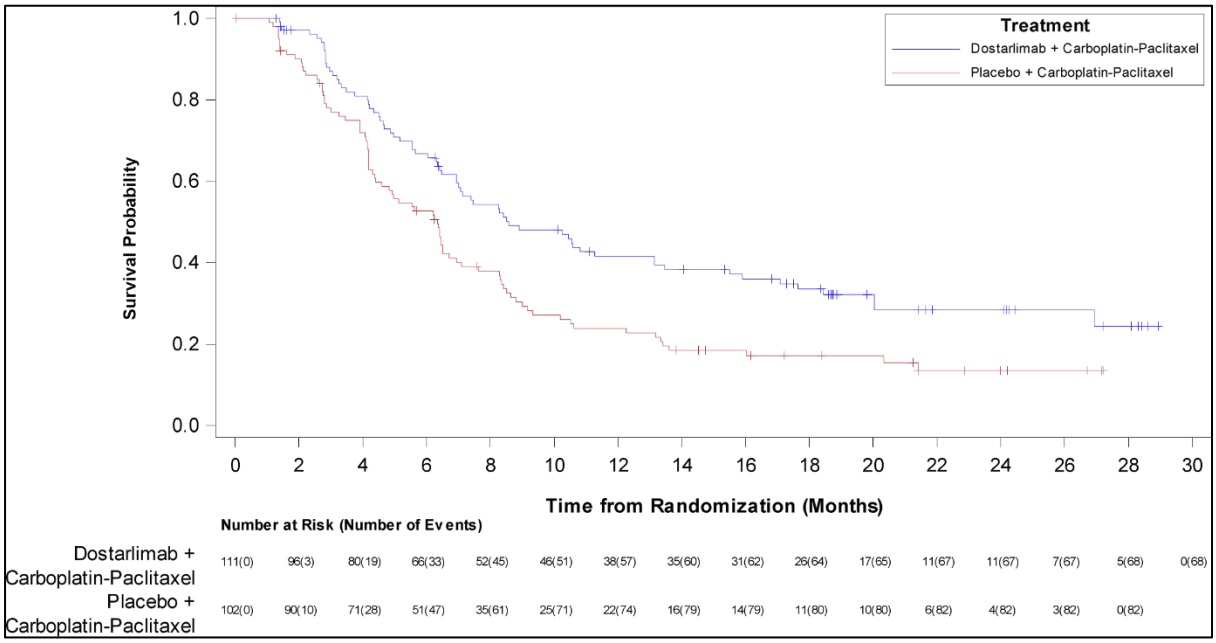
2.6.4.2. Objective response rate (ORR) and duration of response (DOR)

In the MMRp/MSS population, the ORR assessed by investigator per RECIST v1.1 was similar in the dostarlimab arm and in the placebo arm, at 68.1% (95% CI: 60.4, 75.2) versus 63.4%, respectively (95% CI: 55.4, 70.8) (Appendix J) (16).

Figure 8 shows the KM curves of DOR in the MMRp/MSS population at IA1. A longer DOR was observed in the dostarlimab arm with a median DOR of 8.6 (95% CI: 6.9, 13.1) months

compared with 6.3 (95% CI: 4.4, 6.9) months in the placebo arm (Table 14). The 24-month probability of remaining in response was more than 2-fold higher in the dostarlimab arm, 28.4% (95% CI: 19.1, 38.4) compared with 13.5% (95% CI: 7.1, 22.0) in the placebo arm (16).

Figure 8 KM curves of DOR, RECIST v.1.1. based on investigator assessment and primary censoring rule, Interim Analysis (MMRp/MSS patient population)



Source: Adapted from IA1 CSR Table 15.1.9 (108).
Data cutoff: 28 September 2022.
Abbreviations: CI, confidence intervals; DOR, duration of response; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable.

Table 14: KM analysis of DOR, RECIST v.1.1. based on investigator assessment and primary censoring rule, Interim Analysis (MMRp/MSS patient population)

Variable [n (%)]	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Number of responders		
n	111	102
Estimates for DOR (months) Quartile (95% CI)		
50%	8.6 (6.9, 13.1)	6.3 (4.4, 6.9)
Probability of DOR (95% CI)		
Month 12	41.6% (31.7%, 51.2%)	23.8% (15.8%, 32.8%)
Month 24	28.4% (19.1%, 38.4%)	13.5% (7.1%, 22.0%)

Source: IA1 CSR Table 14.2.1.15 (108).
Data cutoff: 28 September 2022.
Abbreviations: CI, confidence intervals; CP, carboplatin plus paclitaxel; DOR, duration of response; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; NR, not reached.

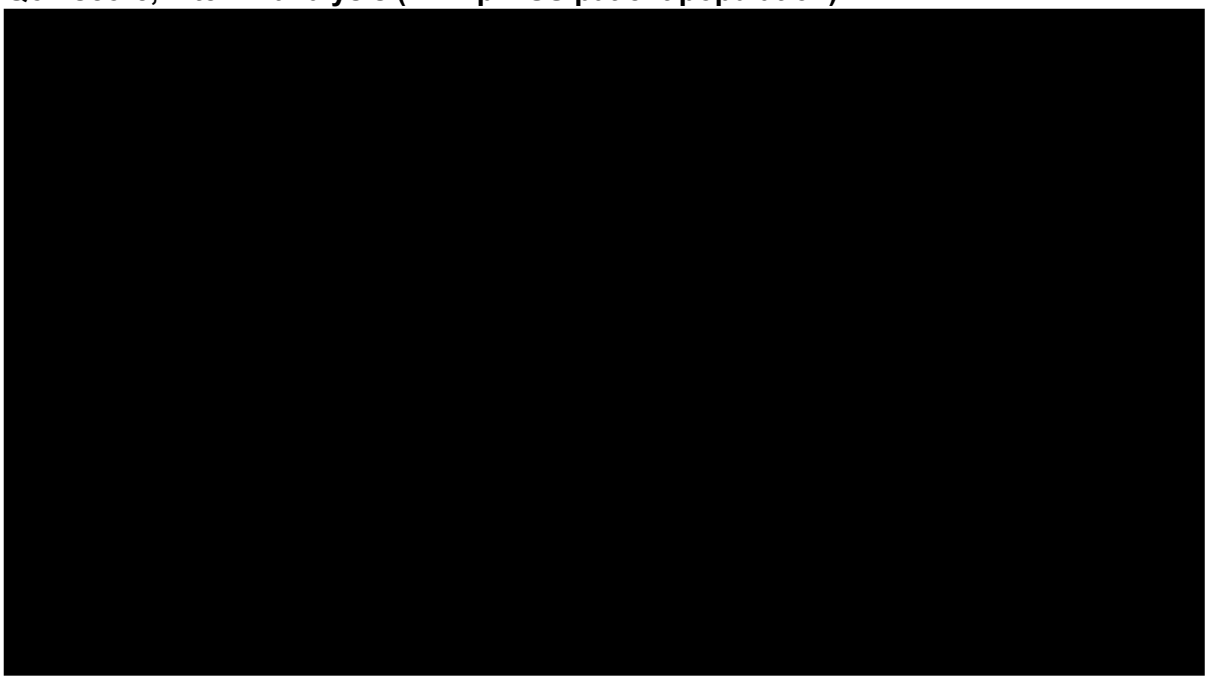
2.6.4.3. Patient reported outcomes (PROs)

The improved PFS outcomes seen within the dostarlimab arm were not associated with a decrease in patient HRQoL. There were no significant differences in QoL measures between

the dostarlimab and placebo arms, indicating that MMRp/MSS patients in the dostarlimab arm experienced clinically similar QoL compared with those in the placebo arm.

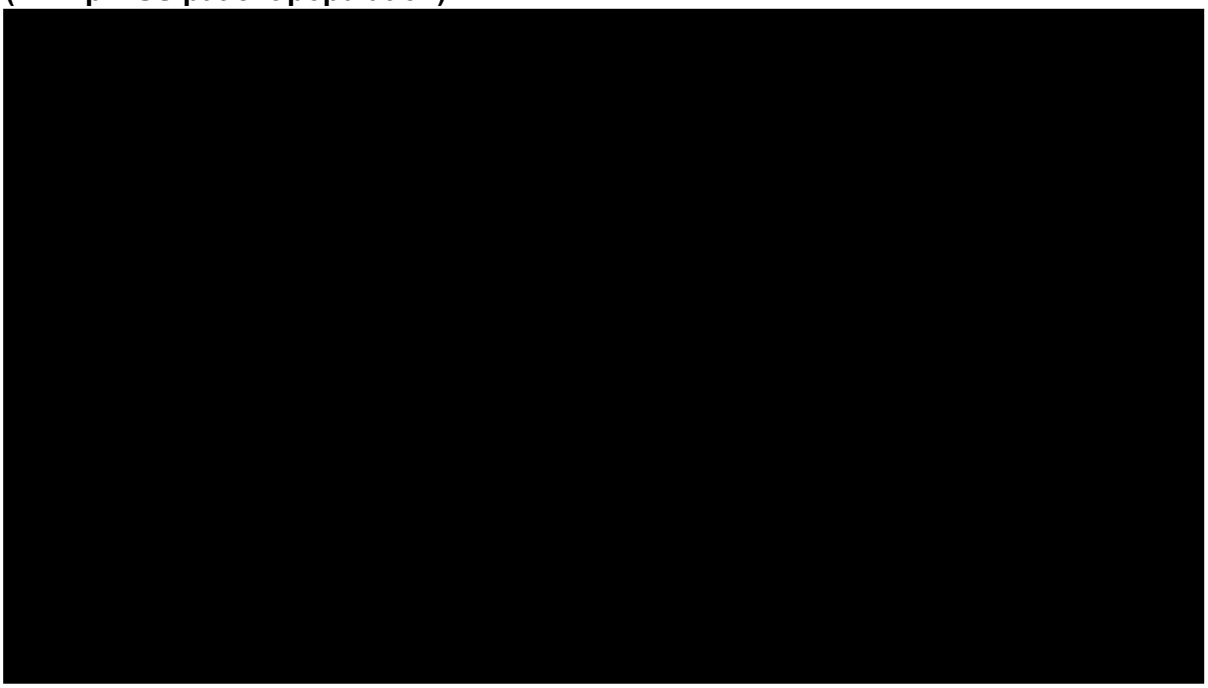
Results were consistent across all analyses, with changes from baseline in both the EORTC QLQ-C30 global (Figure 9 and Appendix J) and EQ-5D-5L VAS score (Figure 10 and Appendix J) showing no substantial differences between treatment arms. Furthermore, EORTC QLQ-C30 global scores were similar or higher in the dostarlimab arm compared with the placebo arm. Overall, these findings suggest that the introduction of dostarlimab to CP has no negative impact on QoL.

Figure 9: Changes from baseline and confidence intervals in EORTC QLQ-C30 global QoL score, interim analysis (MMRp/MSS patient population)



Source: IA1 CSR Figure 15.4.2 (108).
Data cutoff: 28 September 2022.
Abbreviations: BSLN, baseline; Cx, cycle X; EOT, end of treatment; MMRp, mismatch repair proficient; MSS, microsatellite stable; QoL, quality of life; SFU, safety follow-up visit; SVFU, survival follow-up visit; WPB, worst post-baseline.

Figure 10: Changes from baseline and CIs in EQ-5D-5L VAS, interim analysis (MMRp/MSS patient population)



Source: IA1 CSR Figure 15.4.2 (108).
Data cutoff: 28 September 2022.
Abbreviations: BSLN, baseline; CI, confidence interval; Cx, cycle X; EOT, end of treatment; MMRp, mismatch repair proficient; MSS, microsatellite stable; QOL, quality of life; SFU, safety follow-up visit; SVFU, survival follow-up visit; VAS, Visual Analogue Score; WPB, worst post-baseline.

2.7. Subsequent treatments used in RUBY-1

In the ITT population, a higher proportion of patients (173 of 249 patients, 69.5%) in the placebo arm received subsequent anticancer therapy than patients in the dostarlimab arm (120 of 245 patients, 49.0%; Appendix J) (15).

In the MMRp/MSS population, 63.6% of patients received a subsequent treatment. A higher proportion of patients in the placebo arm (72.8%) received a subsequent therapy compared with the dostarlimab arm (54.7%) (15). A list of treatments received by [redacted]% of patients in either arm is reported in Table 15. The most common class of therapy received across both arms was [redacted] ([redacted]%) followed by immunotherapy (27.1%), [redacted] ([redacted]%) and [redacted] ([redacted]%) (15).

Table 15: Subsequent treatment given to [redacted]% of patients in either arm (MMRp/MSS patient population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Any follow-up anticancer therapy, n (%)	105 (54.7)	134 (72.8)	239 (63.6%)
Chemotherapy	[redacted]	[redacted]	[redacted]

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Doxorubicin	[redacted]	[redacted]	[redacted]
Paclitaxel/carboplatin	[redacted]	[redacted]	[redacted]
Pegylated liposomal doxorubicin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Immunotherapy	34 (17.7%)	68 (37.0%)	102 (27.1%)
Pembrolizumab/lenvatinib	22 (11.5%)	43 (23.4%)	65 (17.3%)
Pembrolizumab	9 (4.7%)	20 (10.9%)	29 (7.7%)
Radiation therapy	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
External beam radiation	[redacted]	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]	[redacted]
Megestrol acetate	[redacted]	[redacted]	[redacted]
Everolimus/letrozole	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]

Source: IA2 CSR Table 14.1.1.32 (109) and Powell et al. (15).
Abbreviations: CP, carboplatin plus paclitaxel; MSS, microsatellite stable; MMRp, mismatch repair proficient.

2.8. Subgroup analysis and sensitivity analyses

To explore the homogeneity of the treatment effect across relevant participant subsets, subgroup analyses of PFS and OS were performed (Figure 11 and Figure 12). PFS outcomes across subgroups are largely consistent with the overall MMRp/MSS population. Despite subgroups with relatively small sample sizes, almost all HR estimates remain <1 and none deviate significantly from the overall MMRp/MSS population. Those with Stage III primary disease status and no disease at baseline have hazard ratios >1 with wide confidence intervals, reflective of the better prognosis for these populations and relatively immature data.

2.8.1. Subgroup analysis of PFS

A forest plot of PFS at IA1 in the MMRp/MSS population showed favourable HRs (<1) across most subgroups (Figure 11). Subgroups with the highest HRs included Eastern Europe ([redacted]) and no disease at baseline ([redacted]). Both subgroups had small sample size and wide confidence intervals, likely contributing to variability in these estimates. Additionally, the no disease at baseline

subgroup represented a better prognosis with relatively few events. Overall, all subgroups were generally consistent with the overall treatment effect estimate, with no significant differences based on overlapping 95% CIs.

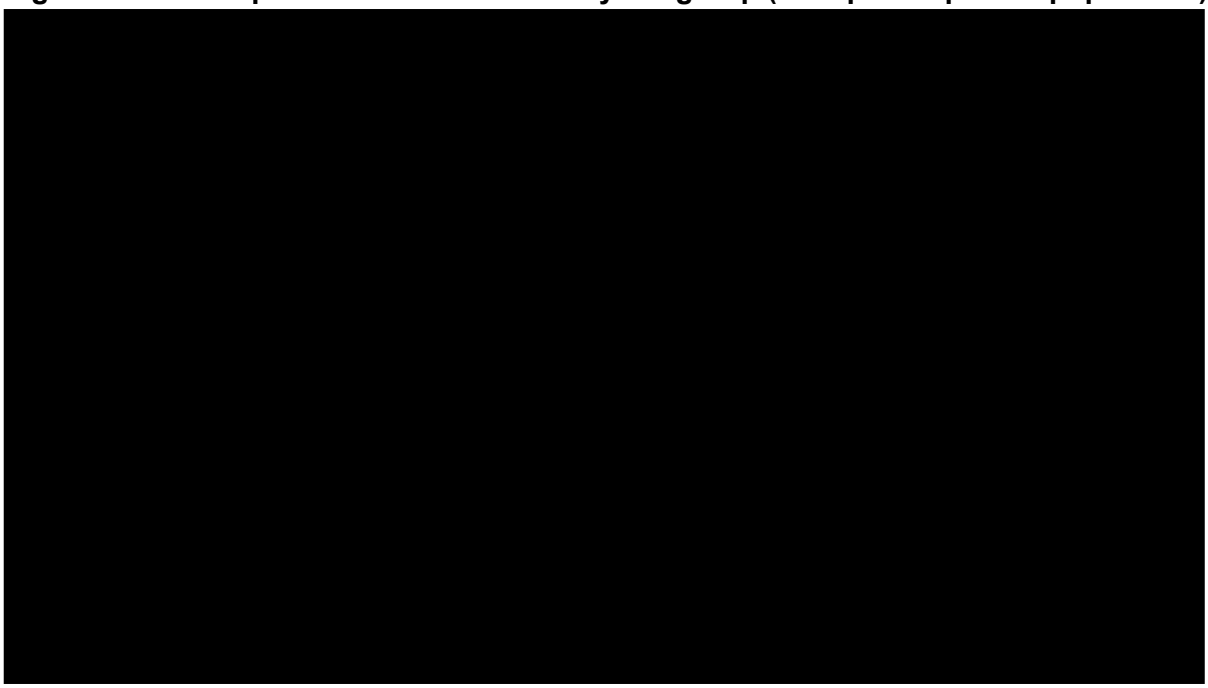
Figure 11: Forest plot of PFS and 95% CIs by subgroup (MMRp/MSS patient population)

Source: IA1 CSR Figure 15.2.1 (108).
Data cutoff: 28 September 2022.
Note: HRs presented are from unstratified Cox regression model.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; PFS, progression-free survival.

2.8.2. Subgroup analysis of OS

A forest plot of OS at IA2 in the MMRp/MSS population showed favourable HRs (<1) across most subgroups (Figure 12). While OS results were generally consistent with PFS findings, confidence intervals were wider due to lower data maturity. Overlapping CIs indicate no significant variation from the overall treatment effect estimate for the MMRp/MSS population. RUBY-1 included a range of histologies, with high-risk subtypes such as carcinosarcoma and mixed carcinosarcoma represented in the 'other' category in Figure 12. This category comprised [redacted] in the dostarlimab arm and [redacted] in the placebo arm. Importantly, outcomes for these higher-risk, non-endometrioid subtypes were consistent with the overall population.

Figure 12: Forest plot of OS and 95% CIs by subgroup (MMRp/MSS patient population)



Source: IA2 CSR Figure 15.2.2. (109).
Data cutoff: 22 September 2023.
Note: HRs presented are from unstratified Cox regression model.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival.

2.8.3. Molecular subgroup analyses

To explore the treatment effect across recognised molecular subgroups of endometrial cancer, exploratory post-hoc subgroup analyses were performed (Table 16). Given the post hoc nature of these analyses, they should be interpreted with caution. Of the 494 patients enrolled and randomised, mutational data were available for 400 (81.0%), categorised as follows: 5 (1.3%) DNA polymerase epsilon-mutated (POLεmut), 88 (22.0%) dMMR/MSI-H, 88 (22.0%) TP53-mutated (TP53mut), and 216 (54.0%) non-specific molecular profile (NSMP) (110). Importantly, approximately 20% of the trial population (94 patients) lacked sequencing data, and subgroup classification was based on sequencing rather than immunohistochemistry, which differs from standard clinical practice (10).

PFS and OS favoured the dostarlimab arm in the TP53mut and NSMP subgroups, with the greatest benefit observed in the TP53mut group (Table 16). Notably, efficacy within the POLεmut population was not available given the extremely small sample size and absence of events in either arm (110). Efficacy across subgroups appears broadly consistent with the overall MMRp/MSS population with HR estimates consistently <1 for PFS and OS outcomes.

Table 16: KM analysis of PFS and OS by molecular subgroup

Molecular subgroup	Dostarlimab in combination with CP (N=152)	Placebo in combination with CP (N=157)
POLεmut, n	2	3
PFS (IA), HR (95% CI)	NA†	
OS, HR (95% CI)	NA†	
TP53mut	47	41
PFS (IA), HR (95% CI)	0.55 (0.30, 0.99)	
OS, HR (95% CI)	0.59 (0.33,1.03)	
NSMP, n	103	113
PFS (IA), HR (95% CI)	0.77 (0.55, 1.07)	
OS, HR (95% CI)	0.89 (0.61, 1.29)	

Source: PFS- Mirza et al. 2023 (110). OS- Powell et al. 2024. (111)
Data cutoff: 28 September 2022.OS Data cutoff: 23 September 2023
†No PFS events were observed for patients classified as POLεmut in either arm.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; IA, investigator-assessed; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; NSMP, non-specific molecular profile; NR, not reached; PFS, progression-free survival; POLεmut, DNA polymerase epsilon-mutated; TP53mut, TP53-mutated.

2.9. Meta-analysis

As outlined in Section 1, the comparator in scope for this appraisal is PCC, with CP being the most commonly used platinum-containing regimen used in this setting in the NHS. RUBY-1 is the only RCT identified evaluating dostarlimab in combination with CP compared with CP alone in patients with MMRp/MSS primary advanced or recurrent endometrial cancer. As such, no meta-analysis or indirect treatment comparison is required (Section 2.2).

2.10. Indirect and mixed treatment comparisons

RUBY-1 is a robust RCT directly comparing dostarlimab in combination with CP and placebo with CP, a comparator outlined in the NICE scope. It provides direct comparative data for an MMRp/MSS primary advanced or recurrent endometrial cancer population, with baseline characteristics broadly aligned between arms (Section 2.3.5). Other comparators listed in the scope, including durvalumab with PCC followed by maintenance durvalumab with or without olaparib, and pembrolizumab with PCC, are not considered relevant for this appraisal as they are not established as SoC in the NHS at the time of this appraisal, in accordance with the NICE HTA manual (94). Consequently, an indirect treatment comparison is not required to support this submission.

2.11. Adverse reactions

The safety population consists of all 487 patients who received at least one dose of study intervention, with 241 patients in the dostarlimab arm. Of these, 370 were stratified as MMRp/MSS, including 189 patients in the dostarlimab arm. Safety data are presented for the full RUBY-1 ITT population. MMRp/MSS safety data are consistent with the ITT population results and are reported in Appendix D.

Overall, the safety profile of the dostarlimab arm was generally consistent with the known safety profiles of the individual agents and demonstrated acceptable, manageable toxicities in the indicated population (Table 17). The safety profile in the dostarlimab arm at IA2 was consistent with that seen at IA1 (15, 16).

2.11.1. Summary of treatment emergent adverse events (TEAEs)

In the ITT population, a total of 241 patients had received at least one dose of dostarlimab in combination with CP and were included in the safety analysis, while 246 patients in the placebo arm were included. All patients (100%) experienced at least one TEAE across both arms.

The overall summary of TEAEs experienced by patients in the ITT population can be found in Table 17. Incidences of participants experiencing any Grade ≥3 TEAEs and serious adverse events (SAE) were >10% higher in the dostarlimab arm compared with the placebo arm. TEAEs leading to death were reported in five participants, all in the dostarlimab arm. [redacted] of these TEAEs were assessed by the Investigator as related to the study treatment (Table 17).

Notably, treatment emergent immune-related AEs related to dostarlimab or placebo were 24.4% higher in participants in the dostarlimab arm compared with the placebo arm.

Table 17: Overall summary of TEAEs (ITT population)

Adverse event category, n (%)	Dostarlimab in combination with CP (N=241)	Placebo in combination with CP (N=246)	Total (N=487)
Any TEAE	241 (100%)	246 (100%)	487 (100%)
Treatment-related TEAEs	236 (97.9%)	243 (98.8%)	479 (98.4%)
Any Grade ≥3 TEAEs	174 (72.2%)	148 (60.2%)	322 (66.1%)
Treatment-related Grade ≥3 TEAEs	128 (53.1%)	115 (46.7%)	243 (49.9%)
Any TEAE with outcome of death	5 (2.1%)	0	5 (1.0%)
Treatment-related TEAE leading to death	2 (0.8%)	0	2 (0.4%)

Any SAEs	96 (39.8%)	69 (28.0%)	165 (33.9%)
Treatment-related SAEs	47 (19.5%)	30 (12.2%)	77 (15.8%)
Any TEAEs leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to infusion interruption	[redacted]	[redacted]	[redacted]
Any TEAE leading to infusion delay	[redacted]	[redacted]	[redacted]
Any TEAE leading to dose reduction	68 (28.2%)	68 (27.6%)	136 (27.9%)
Any immune-related TEAEs	[redacted]	[redacted]	[redacted]
Any dostarlimab- or placebo-related immune-related TEAEs	98 (40.7%)	40 (16.3%)	138 (28.3%)
Any infusion-related reactions	[redacted]	[redacted]	[redacted]

Source: IA2 CSR Table 14.3.1.1. (109) and Powell et al. (15)
Data cutoff: 22 September 2023.
Abbreviations: CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable; TEAE, treatment emergent adverse event; SAE, serious adverse event.

2.11.2. Any grade TEAEs

In the ITT population, the most frequently reported TEAEs (>40%) in both the dostarlimab and placebo arms were nausea (54.4% vs 46.3%), fatigue (52.3% vs 54.9%), alopecia (53.9% vs 50.0%), and peripheral neuropathy (44.0% vs 41.9%); and anaemia (37.8% vs 42.7%) in the placebo arm. A complete list of all TEAEs observed in each treatment arm is provided in Appendix D (15). Overall, the incidences of TEAEs were comparable between the two arms (≤10% difference), with the exception of a higher incidence of maculo-papular rash in the dostarlimab arm [redacted].

2.11.3. Grade ≥3 TEAEs

In the ITT population, Grade ≥3 TEAEs were 12% higher in participants in the dostarlimab arm compared with the placebo arm (72.2% vs 60.2%). The most frequently reported Grade ≥3 TEAEs (>7%) in both arms were anaemia (14.9% vs 16.7%), neutrophil count decreased (8.3%, 13.8%), neutropenia (9.5% vs 9.3%), hypertension (7.1% vs 3.3%), and decreased lymphocyte count (5.4% vs 7.3%). The most frequently reported Grade 4 TEAEs (≥2%) in both arms were neutropenia and decreased neutrophil count (15). Grade 5 TEAEs were reported in [redacted], all in the dostarlimab arm and [redacted] of which were deemed related to study treatment.

2.11.4. Grade ≥3 treatment-related TEAEs

In the ITT population, the incidence of Grade ≥3 treatment-related TEAEs was generally comparable (<5% difference) between the treatment arms, with the exception of decreased neutrophil count which was higher in the placebo arm (8.3% vs 13.8%) (15). As expected, Grade ≥3 treatment-related TEAEs related only to dostarlimab or placebo (and not CP) were higher in patients in the dostarlimab arm ([redacted]% versus [redacted]%). The system organ classes with

the largest differences between arms included investigations ([redacted]% vs [redacted]%) and skin and subcutaneous tissue disorders ([redacted]% vs [redacted]%). For a more comprehensive list of Grade ≥3 treatment related TEAEs, refer to Appendix D.

2.11.5. Deaths and serious AE

In the ITT population, five patients had a TEAE leading to death, all in the dostarlimab arm. TEAEs leading to death included general physical health deterioration, severe acute respiratory syndrome coronavirus 2, opiate overdose, myelosuppression and hypovolemic shock. Of these, the investigator assessed myelosuppression as related to dostarlimab, carboplatin and paclitaxel, and hypovolaemic shock as related to dostarlimab. None of the other TEAEs leading to death were considered related to study treatment. An additional [redacted] had an AE or other cause of death that was not treatment-emergent, occurring more than 90 days after the last dose of study treatment.

A summary of SAEs experienced by patients in the ITT population is provided in Appendix D. The overall incidence of SAEs was approximately 12% higher in the dostarlimab arm compared with the placebo arm (39.8% vs 28.0%) (15). The most frequently reported SAEs (≥2%) that were higher in patients in the dostarlimab arm versus the placebo arm were sepsis (3.3% vs 0.4%), pulmonary embolism (3.3% vs 2.0%), pyrexia (2.9% vs 0.8%), dyspnoea (2.1% vs 0.4%), vomiting (2.1% vs 1.2%), and muscular weakness (2.1% vs 0.4%). In the placebo arm, the more common SAEs were asthenia (0.8% vs 2.4%), anaemia (1.2% vs 2.4%) and urinary tract infection ([redacted]% vs [redacted]%) (15).

2.11.6. Immune-related AEs

As dostarlimab is an immune checkpoint inhibitor, immune-related adverse events (irAE) are of special interest in the RUBY-1 trial and were evaluated. For the class of PD-1 inhibitors, a number of irAEs are known. Based on this information, irAEs were identified as any Grade ≥2 AEs that met the pre-specified criteria based on a pre-defined list of preferred terms and MedDRA Version 26.0.

IrAEs occurred in 58.5% of patients in the dostarlimab arm and 37.0% of patients in the placebo arm. Dostarlimab- or placebo-related irAEs were reported in 40.7% of patients in the dostarlimab arm and 16.3% in the placebo arm (112). The most frequently reported dostarlimab or placebo-related irAE was hypothyroidism in the dostarlimab arm and arthralgia in the placebo arm.

2.12. Ongoing studies

RUBY-1 is an ongoing study with no additional interim analysis data cuts expected. The study is expected to complete in Q3 2026. No further hypothesis testing will be undertaken as the RUBY trial has met the relevant endpoints within the first and second interim analyses.

2.13. Interpretation of clinical effectiveness and safety evidence

Patients with MMRp/MSS primary advanced or recurrent endometrial cancer have limited treatment options. Conventional chemotherapy has been the SoC in this treatment setting for over 40 years, with no significant advancements in first-line treatment which have meaningfully improved survival outcomes (113, 114). This patient population experiences poor long-term treatment outcomes, with a median OS of approximately 1.4–2.4 years in England, despite a number of studies suggesting response rate to SoC CP of 50–60% (1-3, 7, 8).

The RUBY-1 trial represents a landmark study, being the first in decades to demonstrate a statistically significant OS benefit following the addition of dostarlimab to the existing SoC in the first-line setting for patients with primary advanced or recurrent endometrial cancer (2, 6, 16). In the MMRp/MSS population, representing 76.1% of the RUBY-1 trial population, adding dostarlimab to CP reduced the mortality rate by 21%, resulting in a 7 month improvement in median OS compared with those treated with CP alone (Section 2.6.3) (16). Treating physicians, during a clinical advisory board held on 19 April 2024, confirmed this 7-month increase in OS as highly clinically meaningful, emphasising its potential to positively impact patient outcomes and inform treatment strategies (115). Notably, this median OS benefit is more than twice the survival benefit which established the existing chemotherapy SoC (2, 116).

Furthermore, the RUBY-1 trial has demonstrated that adding dostarlimab to CP reduces the rate at which primary advanced or recurrent endometrial cancer progresses (Section 2.6.2) (16). This enables patients to live longer without disease progression, a decline in QoL, or the need for additional lines of anticancer therapy. After two years, patients in the dostarlimab arm were more than twice as likely to remain in response with no evidence of disease progression compared with those in the placebo arm (Section 2.6.4.2) (16). Consequently, for patients with MMRp/MSS primary advanced or recurrent endometrial cancer, adding dostarlimab to the SoC results in a meaningful improvement in outcomes by prolonging PFS and enhancing overall treatment efficacy.

In recent years, immunotherapy regimens have demonstrated improvements in PFS and, consequently, OS when used in the second-line relapsed setting (14, 16, 84). However, the robust PFS2 evidence from the RUBY-1 trial indicates that these therapies are most effective when administered upfront in the first-line setting (16). Despite 37.0% of patients in the placebo arm of the MMRp/MSS population receiving immunotherapy in second-line, the improvement in PFS2 suggests that patients in the dostarlimab arm are living longer without subsequent progression events (Section 2.6.4.1). The efficacy of dostarlimab in combination with CP extends beyond the first-line, supporting the earlier integration of immunotherapies into the treatment pathway.

2.14. Strengths of the clinical evidence

RUBY-1 provides a direct, head-to-head comparison to the current SoC used within UK clinical practice and includes a population reflective of the real-world patients who would be eligible for treatment (107). The RUBY-1 trial included patients with endometrioid carcinoma as well as mixed and high-risk histologies, including carcinosarcomas, reflective of the diverse patient population treated in UK clinical practice, which was noted positively by UK clinicians (107).

RUBY-1 assessed OS, a gold standard in oncology trials, as a dual-primary endpoint in the ITT population and OS as a pre-specified subgroup analysis in the MMRp/MSS population. It is the only trial of immunotherapy use in the primary advanced or recurrent endometrial cancer population to show statistically significant OS benefit in the overall population with improved OS observed regardless of MMR status (15).

Additionally, RUBY-1 has an extensive global reach, with 164 participating centres, which enhances the generalisability of the results. The inclusion of five UK sites ensures the findings are relevant to UK clinical practice. The patient population in the trial is representative of those who would typically receive dostarlimab in combination with PCC in routine clinical settings, reinforcing the applicability of the trial outcomes. Additionally, confirmation from UK clinical experts that the RUBY population reflects the UK patient demographic supports the trial's credibility, indicating that its reported benefits are likely to be observed in real-world clinical practice in England and Wales (107). This alignment with clinical realities strengthens the robustness and reliability of the RUBY-1 results.

2.15. Limitations of the clinical evidence

The OS data from the RUBY-1 trial have not yet reached full maturity. At the time of IA2, the trial had reached only 54.8% maturity of the OS data in the MMRp/MSS population (15). However, it would be unethical to delay access to dostarlimab for this group of patients with high unmet need and poor prognosis, given the limited treatment options currently available to them, until the full OS data are mature.

While the RUBY-1 study encompasses a broad patient population with primary advanced or recurrent endometrial cancer, this submission focuses specifically on the subgroup of patients with MMRp/MSS tumour status. Although this subgroup represents the majority of patients included in the RUBY-1 trial (76.1% of the ITT population), it is important to acknowledge that this study was stratified by MMR status but not powered to demonstrate statistical significance within the MMRp/MSS subgroup. Therefore, the improvement in PFS and OS seen in MMRp/MSS subpopulation of this trial is considered only nominally statistically significant despite the consistent and meaningful improvements reported across the primary and secondary endpoints.

2.16. Innovation

Dostarlimab represents a significant advancement in the management of MMRp/MSS primary advanced or recurrent endometrial cancer for patients who are candidates for systemic therapy. Access to innovative therapies for these patients has lagged far behind other cancer types, where immunotherapies have been available in the first-line setting for several years, significantly improving patient outcomes (117-119). Conventional platinum-containing chemotherapy has remained the SoC in this treatment setting for over 40 years, with few notable advancements in first-line treatment options (6). This highlights the urgent need for innovative therapies to improve outcomes for patients with MMRp/MSS primary advanced or recurrent endometrial cancer.

Dostarlimab features an innovative mechanism of action that disrupts T cell-mediated PD-1/PD-L1 signalling, mobilising the adaptive immune system to drive anticancer activity through immune-mediated apoptosis rather than chemotoxicity, resulting in durable responses (56). Unlike anti-PD-L1 immunotherapies, dostarlimab blocks PD-1 interactions with both PD-L1 and PD-L2, offering a broader disruption of PD-1/ligand interactions (57). Furthermore, dostarlimab targets novel binding sites on the PD-1 protein and demonstrates a smaller maximum drop-in time-varying clearance compared with older anti-PD1

treatments. This suggests that dostarlimab offers a differentiated mechanism of action and a more stable pharmacokinetic profile (58).

2.17. Conclusion

The efficacy and safety of dostarlimab in combination with CP compared with CP alone in the MMRp/MSS primary advanced or recurrent endometrial cancer population was demonstrated in the RUBY-1 trial. This trial represents the most robust source of evidence due to it being a direct head-to-head RCT aligned with the decision problem. The introduction of dostarlimab in this setting would be a step change in the care of patients in this area of high unmet medical need where existing therapy confers modest and often short-lived benefits.

Bringing immunotherapy into earlier-line settings is expected to provide a significant proportion of patients with primary advanced or recurrent endometrial cancer access to this treatment, extending the time people live without a relapse and ultimately improving OS outcomes. The addition of dostarlimab to CP in the MMRp/MSS population represents a meaningful advancement in managing primary advanced or recurrent endometrial cancer, offering improved clinical outcomes and addressing an important treatment access disparity in this population.

3. Cost effectiveness

Summary of cost-effectiveness analysis

- A partitioned survival model (PSM) with three health states (progression-free survival [PFS], progressed disease [PD] and death) was developed, adapted from the cost-effectiveness model (CEM) that was utilised in the appraisal of a similar indication in NICE TA963: patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer (54).
- The CEM evaluated the cost-effectiveness of dostarlimab in combination with carboplatin and paclitaxel (CP) versus CP alone for the treatment of adult patients with mismatch repair proficient (MMRp)/microsatellite stable (MSS) endometrial cancer who are candidates for systemic therapy.
- 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 (94).
- Clinical outcomes (PFS, overall survival [OS] and time to treatment discontinuation [TTD]) were based on the MMRp/MSS population of part 1 of the RUBY trial (RUBY-1).
- Health-state utilities for PFS and PD were informed by European Quality of Life scale, 5-Dimensions (EQ-5D), 5-Levels data collected in the RUBY-1 study, cross-walked to EQ-5D, 3-Levels per the NICE Manual (94).
- Costs and healthcare resource use captured in the analysis included treatment acquisition and administration costs, monitoring costs, adverse event (AE) costs, subsequent treatment, and end-of-life care costs.

Summary of cost-effectiveness results

- In the deterministic base case economic analysis, inclusive of PAS discount, dostarlimab in combination with CP was associated with £[redacted] incremental costs and 0.755 incremental quality-adjusted life years (QALYs) compared with CP, which corresponds to an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY gained.
- The probabilistic results are centred around the deterministic results and show that at a willingness to pay (WTP) threshold of £30,000 and £20,000, dostarlimab in combination with CP has an 93% and 81% chance of being cost effective, respectively.
- The results from the deterministic sensitivity analysis show that the cost-effectiveness results are most sensitive to the subsequent treatments, however scenarios are robust to changes in model structure and inputs, with the ICERs remaining below £[redacted] per QALY gained for dostarlimab in combination with CP versus CP across almost all scenarios.

3.1. Published cost-effectiveness studies

An economic systematic literature review (SLR) was undertaken on 10 November 2021, with updates on 22 February 2023, 26 October 2023 and again on 16 May 2024, to identify all available evidence to inform the development of the cost-effectiveness model for dostarlimab in the treatment of patients with primary advanced or recurrent endometrial cancer. Full

details of the methodology used to identify all relevant studies, results and quality assessment of the identified studies are presented in Appendix E.

Table 18 provides a summary of the identified published cost-effectiveness studies. The models by Benjamin et al., 2024 and Kim et al., 2023 focused exclusively on patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced and recurrent endometrial cancer (120, 121). As this patient population falls outside the scope of the current appraisal, these studies are not directly relevant to the decision problem. Consequently, they are not included in the main submission. Nonetheless, full details of these cost-effectiveness analyses are provided in Appendix E.

Treatments evaluated in the models included: pembrolizumab/lenvatinib; trastuzumab/carboplatin/paclitaxel; dostarlimab/carboplatin/paclitaxel; pembrolizumab/carboplatin/paclitaxel, and atezolizumab/carboplatin/paclitaxel.

All published models used a Markov structure, with the exception of Francoeur et al., 2024 (122) (PSM), and all models included three health states.

The time horizon in the models by Ackroyd et al., 2021 (123) and Francoeur et al., 2024 (122) was three years. The time horizon was four years in the Batman et al., 2021 model (124), and 20 years in the You et al., 2023 model (125). While a lifetime time horizon was adopted by Huo et al., 2024a (126), it was set between the ages of 64 and 82 by Huo et al., 2024b (127).

Overall, there were various limitations associated with the identified models, including:

- The majority were Markov models, which do not typically capture time-to-event outcomes typical of oncology endpoints.
- Time horizons were mostly shorter than lifetime which may not capture the full scope of the disease and its progression. In the one study which had a lifetime horizon (126), this was a Markov model from a United States (US) public healthcare payers' perspective, making it less relevant.
- Use of medians or aggregate trial data rather than individual patient data.
- Use of naïve comparisons without proper feasibility assessment and examination of the potential heterogeneity, leading to high uncertainty and questionable robustness in the results.

- Missing key components like impact on subsequent therapies.
- Inappropriate assumptions e.g. equivalence in efficacy at different lines of treatment and assumptions around progression such as if patients do not progress within a short time, they are assumed to not progress any further.

Of the two models that specifically evaluated dostarlimab in primary advanced and recurrent endometrial cancer, each had significant limitations (122, 125). You et al., 2023, based in China, employed a Markov model with a 20-year time horizon but did not use individual patient data to inform survival predictions (125). Important factors such as time to treatment discontinuation and the use of additional treatments in later lines of therapy were absent from the model. Francoeur et al., 2024 used a three-year time horizon, relying on published aggregate trial data rather than individual-level data (122). The study also lacked a clear justification for the model selection, with an unclear rationale for stratifying patients by treatment toxicity and insufficient explanation of the model structure (122).

In addition to the published economic evaluations identified, the SLR identified four Health Technology Assessments (HTA) in relation to dostarlimab in primary advanced or recurrent dMMR/MSI-H endometrial cancer (Table 18).

Table 18: Summary list of published cost-effectiveness studies

Study	Summary of model	Patient population	Intervention	Comparator	QALYs intervention vs. comparator	Incremental costs intervention vs. comparator	ICER (per QALY gained)
Ackroyd, 2021 (123)	- Markov model - US Healthcare perspective - Three-year horizon - Costs and utilities were discounted annually at 3%	Advanced or recurrent endometrial cancer, specific stages: NR, subgroups: MSS or MSI-high	PEM + LEN	CB + PAC	-0.28	$212,670	NR [CB+PAC was considered the dominant treatment]
		Advanced or recurrent endometrial cancer, specific stages: NR, subgroup: MSI-high	PEM + LEN	CB + PAC	0.11	$313,487	$2,849,882/ QALY, USD inflated to 2020
Batman, 2021 (124)	- Markov model - US Societal perspective - Four-year time horizon - Costs and utilities were discounted annually at 3%	HER2/neu-positive advanced or recurrent UPSC in one year, specific stages: NR, subgroup: NA	CB + PAC + TRA	CB + PAC	2,065	$144,335,895	$69,903/ QALY, USD inflated to 2019
You, 2023 (125)	- Markov model - Chinese healthcare perspective - 20-year time horizon - Costs and utilities were discounted annually at 5% - Used price of pembrolizumab in China for dostarlimab	Advanced or recurrent endometrial cancer, subgroups: overall population	DOS + CB + PAC followed by DOS	CB + PAC followed by PBO	1.49	$146,182.58	$98,276.61/QALY
		Advanced or recurrent endometrial cancer, subgroups: MSI-H			4.16	$220,465.51	$53,063.61/QALY
		Advanced or recurrent endometrial cancer, subgroups: MSS			1.03	$128,081.44	$124,088.56/QALY
Huo, 2024a (126)	- Markov model - US public healthcare payers	Advanced or recurrent endometrial cancer, subgroups: dMMR	PEM + CB + PAC	CB + PAC	4.05	$167,224	$41,305.09/QALY

Study	Summary of model	Patient population	Intervention	Comparator	QALYs intervention vs. comparator	Incremental costs intervention vs. comparator	ICER (per QALY gained)
	- Lifetime horizon - Costs and utilities were discounted annually at 3%	Advanced or recurrent endometrial cancer, subgroups: MMRp			0.93	$83,661	$90,284.80/QALY
Huo, 2024b (127)	- Markov model - US public healthcare payers - Time horizon was set between the ages of 64 and 82 - Costs and utilities were discounted annually at 3%	Advanced or recurrent endometrial cancer, subgroups: overall population	Atezolizumab + CB + PAC	CB + PAC	0.82	$177,033	$216,459.34/QALY
		Advanced or recurrent endometrial cancer, subgroups: dMMR			3.31	$855,042	$258,391.07/QALY
		Advanced or recurrent endometrial cancer, subgroups: MMRp			0.50	$140,502	$279,239.72/QALY
Francoeur, 2024 (122)	- Partitioned survival model - Perspective: NR - Three-year horizon - Discount rate: NR	Advanced or recurrent endometrial cancer, subgroups: dMMR	DOS + Chemotherapy	Chemotherapy	0.543	$267,418	$492,905/QALY
		Advanced or recurrent endometrial cancer, subgroups: MMRp			0.150	$187,052	$1,245,504/QALY
		Advanced or recurrent endometrial cancer, subgroups: dMMR	PEM + Chemotherapy		0.526	$203,269	$380,046/QALY
		Advanced or recurrent endometrial cancer, subgroups: MMRp			0.325	$156,601	$481,845/QALY
CDA-AMC, 2024 (128)	- Partitioned survival model - Perspective: NR - Lifetime horizon (36.7 years) - Discount rate: NR	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	DOS + CB + PAC	CB + PAC	5.45	$285,186	$52,296/QALY

Study	Summary of model	Patient population	Intervention	Comparator	QALYs intervention vs. comparator	Incremental costs intervention vs. comparator	ICER (per QALY gained)
NICE, 2024 (54)	- Partitioned survival model - Perspective: NHS and PSS - Lifetime horizon - Discount rate: 3.5%	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	DOS + CB + PAC	CB + PAC	4.26	NR	NR
SMC, 2024 (129)	- Partitioned survival model - Perspective: NHS Scotland - Lifetime horizon - Discount rate: NR	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	DOS + CB + PAC	CB + PAC	4.18	NR	NR
PBAC, 2023 (130)	- Partitioned survival model - Perspective: NR - Lifetime horizon - Discount rate: NR	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	DOS + CB + PAC	CB + PAC	1.21	NR	NR

Abbreviations: CB, carboplatin; CDA-AMC, Canada's Drug Agency; DOS, dostarlimab; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; MSI microsatellite instability; MSS, microsatellite stable; NA, not applicable; NICE, National Institute for Health and Care Excellence; NR, not reported; PAC, paclitaxel; PBAC, Pharmaceutical Benefits Advisory Committee; PEM, pembrolizumab; PSS, Personal Social Services; QALYs, quality-adjusted life years; SMC, Scottish Medicines Consortium; TRA, trastuzumab; UPSC, uterine papillary serous carcinoma; USD, United States dollar.

3.2. Economic analysis

Two existing economic studies of dostarlimab in combination with CP in the primary advanced or recurrent endometrial cancer setting were identified in the economic SLR, as well as four HTA reports. These have been discussed in Section 3.1 and are also reported in Table 18.

3.2.1. Patient population

In line with the decision problem, the cost-effectiveness analysis conducted for this appraisal considers adult patients with MMRp/MSS endometrial cancer who are candidates for systemic therapy.

3.2.2. Model structure

A CEM was developed in Excel version 2410 (Microsoft 365) using a PSM approach.

The structure of a PSM accurately reflects the progressive nature of disease in oncology, as it does not permit transitions to an improved health state. PSMs are commonly used in oncology appraisals, including those for dostarlimab for previously treated advanced or recurrent dMMR/MSI-H endometrial cancer with (TA779), and for pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer (TA904) (82, 92, 131-134).

A PSM framework also best utilises the available RUBY-1 PFS and OS data (dual-primary efficacy endpoints). This framework doesn't require modelling an explicit relationship between PFS and OS which would be associated with significant uncertainty using a Markov approach due to the limited data available to quantify the relationship between PFS and post-progression endpoints (Section 2.6). In addition, a PSM approach allows for flexible scenario analysis across a range of various extrapolations.

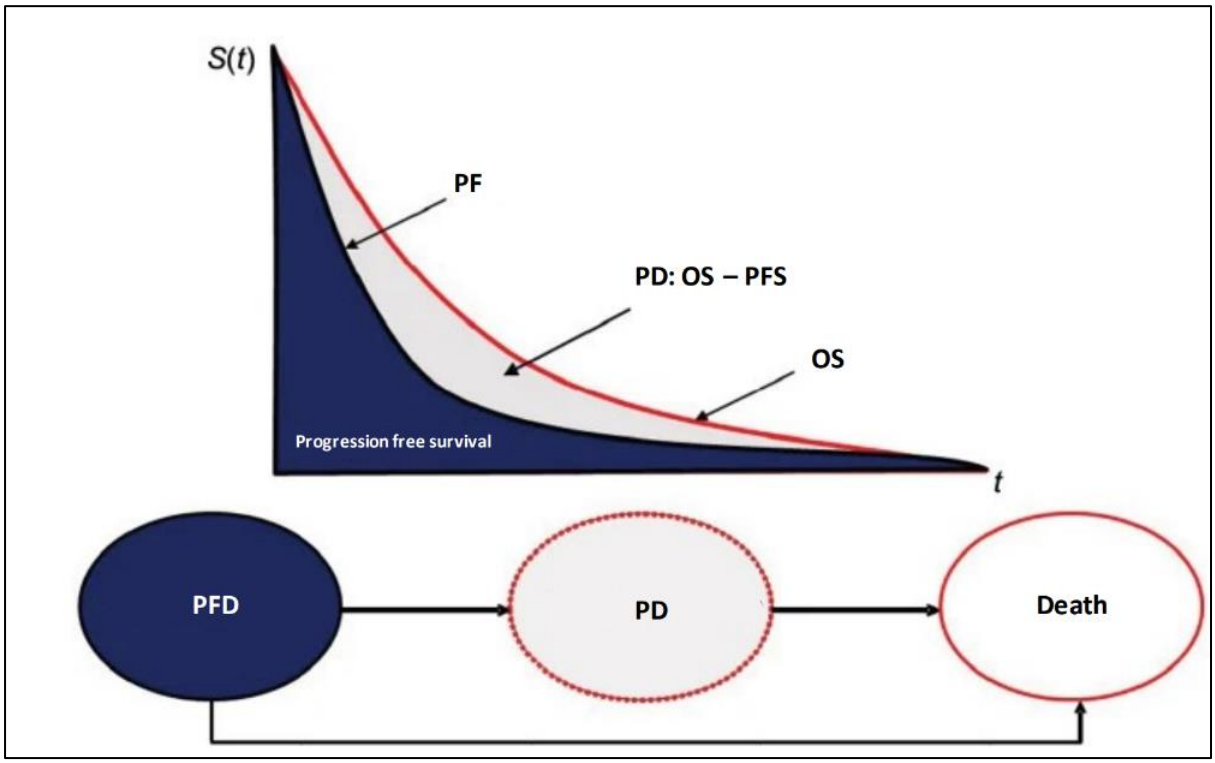
The CEM was adapted from the model deemed suitable for decision-making in NICE TA963 for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer (88). The model estimates the proportion of a cohort in each state based on parametric survival equations. In the PSM model, PFS and OS data from the RUBY-1 trial are directly used to model state occupancy using "progression-free disease", "progressed disease" and "death" health states, as shown in Table 19 and Figure 13.

Table 19: PSM model inputs

Model input	Description	Elements captured
PFS	The proportion of patients in the pre-progression state is estimated by extrapolating PFS KM curves	Costs and consequences of treatment, administration, monitoring, and adverse events
PD	The proportion of patients in the post-progression state was estimated as the difference between OS and PFS curves over time (i.e., post-progression = OS – PFS)	Costs and consequences of subsequent treatments, monitoring and end of life care
Death	Survival was estimated by extrapolating OS KM curves (i.e., death = 1 - OS)	

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PD, progressed disease; TTD, time to death.

Figure 13: PSM structure schematic



Abbreviations: OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival.

Costs, life years (LY) and QALYs were accrued according to the proportion of patients in the PFS and PD health states over time to calculate total costs, LYs, and QALYs for the two cohorts entering the model to receive dostarlimab in combination with CP and CP alone, respectively. The ICER of dostarlimab in combination with CP versus CP was evaluated in terms of the incremental cost per QALY and LY gained. The incremental net health benefit (NHB) of the intervention is also estimated.

3.2.3. Time Horizon

The cost-effectiveness model adopted a 'lifetime' time horizon in line with NICE guidance which states that the model time horizon should be "sufficiently long to reflect all differences in costs and outcomes between technologies over a patient's lifetime" (94). This aligns with previous HTAs in primary advanced or recurrent endometrial cancer (54, 84).

A lifetime horizon was selected, assuming that no patients survive past age 100 in the model, this equates to a time horizon of [redacted] years based on the mean age of patients ([redacted] years) with MMRp/MSS tumours in the RUBY-1 trial.

3.2.4. Cycle length

The model adopts a weekly cycle length to sufficiently capture all relevant costs and health outcomes, in alignment with the treatment schedules outlined in Section 2.3. Given the short cycle length, the application of a half-cycle correction to costs and outcomes was deemed unnecessary.

3.2.5. Discounting

A discount rate of 3.5% per annum was applied to costs and outcomes in the model in line with the NICE reference case (94). Other discount rates have been tested in scenario analyses (Section 3.10.3).

3.2.6. Perspective

The analyses are conducted from the perspective of the NHS and PSS in England and Wales, in line with the NICE reference case (94).

3.2.7. Intervention technology and comparators

Dostarlimab is administered through intravenous (IV) infusion. The dose of dostarlimab incorporated in the economic model aligns with the summary of product characteristics (SmPC) (Appendix A) and the RUBY-1 study. In the dostarlimab (intervention) arm of the RUBY-1 study, patients received 500 mg of dostarlimab in combination with carboplatin at an area under the curve (AUC) of 5 mg/ml/min and 175 mg/m^2 of paclitaxel every 3 weeks (Q3W) for six cycles (i.e. weeks 1, 4, 7, 10, 12, 16). This was followed by 1,000 mg of dostarlimab every 6 weeks (Q6W) from week 19 onwards until disease progression, unacceptable toxicity, or a maximum treatment duration of three years.

The comparator is CP, the standard of care (SoC) in the UK in the absence of dostarlimab, as outlined in the scope and Section 1.3.4. This reflects the comparator arm of the RUBY-1

trial, in which patients received placebo in combination with carboplatin at an AUC of 5 mg/ml/min and 175 mg/m^2 of paclitaxel Q3W for six cycles (i.e. Weeks 1, 4, 7, 10, 12, 16).

3.3. Clinical parameters and variables

The RUBY-1 trial was used to inform clinical parameters in the economic model. These parameters include baseline characteristics, PFS, OS, TTD, health-related quality of life (HRQoL) and AE.

3.3.1. Baseline characteristics

The patient baseline characteristics used as inputs in the CEM are provided in Table 20. Model baseline characteristics align with the MMRp/MSS population in the RUBY-1 trial. Real-world evidence (RWE) using NHS trust data reported a baseline mean age of 65.5 years for MMRp/MSS patients with primary advanced or recurrent endometrial cancer (106). This value has been explored in a scenario analysis.

Table 20: Patient baseline characteristics for the base-case economic analysis

Parameter	Value	Reference
Mean age (years)	[redacted]	RUBY-1 trial (135)
Mean weight (kg)	[redacted]	RUBY-1 trial (135)
Mean body surface area (m2)	[redacted]	
GFR (ml/min)	[redacted]	Calculation based on RUBY-1 trial (135)

*Calculation: 142 x min(Scr/κ, 1)α x max(Scr/κ, 1)-1.200 x 0.9938 Age x 1.012 x (BSA/1.73) (Scr = standardized serum creatinine in mg/dL, κ = 0.7 (females) or 0.9 (males), α = -0.241 (female) or -0.302 (male), min(Scr/κ, 1) is the minimum of Scr/κ or 1.0, max(Scr/κ, 1) is the maximum of Scr/κ or 1.0, Age (years)).
Abbreviations: GFR, glomerular filtration rate.

3.3.2. Survival analyses

For PFS and OS outcomes in the RUBY-1 trial, the follow-up period was shorter than the model lifetime horizon. Therefore, extrapolations were required. The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 was considered when selecting the survival models for the base case analysis (136). Survival analyses were conducted in weeks due to the model cycle length.

Several statistical tests were conducted for OS and PFS to understand if the proportional hazards (PH) assumption and constant accelerated failure time (AFT) assumptions would be violated. The most appropriate distribution was selected based on statistical and visual fit, as well as clinical validation of landmark survival estimates.

For PFS, where standard parametric curves were deemed inappropriate following an assessment of model fit, flexible modelling approaches were considered. Specifically,

flexible parametric models, using restricted cubic splines to enable hazard and survival functions with complex shapes to be more accurately modelled.

The more mature OS and TTD data from IA2 has been incorporated into the cost-effectiveness model, where OS reached statistical significance for the overall trial population (Section 2.6.3). Statistical significance was reached for PFS data as part of the first interim analysis (IA1), therefore PFS extrapolation uses IA1 data (Section 2.6.2). TTD KM data was relatively mature at IA2 data cut-off and available out to 3 years which aligned with the dostarlimab stopping rule for this indication, therefore KM data has been used for the full IA2 follow-up period.

To maintain clinical plausibility, for any pair of extrapolated PFS and OS curve permutations, the selected PFS curve is prevented from exceeding the selected OS curve.

3.3.2.1. Progression-free survival

Investigator-assessed PFS was the primary endpoint of the RUBY-1 trial and has been modelled accordingly.

As presented in Section 2.6.2, addition of dostarlimab to CP resulted in statistically significant PFS benefit in the overall RUBY-1 population. Within the MMRp/MSS population, dostarlimab in combination with CP reduced the risk of progression or death by 24% compared with CP alone (HR: 0.76, 95% CI: 0.59, 0.98), with a sustained separation in the KM data from approximately 6 months.

Inspection of the log-cumulative hazards (Figure 14), Schoenfeld residual plot (Figure 15), and the quantile-quantile plot (Figure 16) suggest that the relative hazards are likely to vary over time, and as such, it was not possible to conclude that the PH assumption holds. In Figure 14, the respective lines cross, indicating a violation of the PH assumption. The residual plot in Figure 15 does not suggest a non-random pattern against time, providing evidence that the PH assumption is violated, however, the PH assumption cannot be formally rejected in this plot as the p-value is >0.05. Figure 16 indicates that the quantiles do not lie in a straight line, suggesting that the constant acceleration factor (AF) assumption may also be violated. Therefore, dependent models which assumed a proportional treatment effect are not considered appropriate.

Figure 14: Log-cumulative hazards plot for IA1 PFS

Figure 15: Schoenfeld residuals plot for IA1 PFS

Figure 16: Quantile-quantile plot for IA1 PFS

Abbreviations: CP, carboplatin plus paclitaxel; PFS, progression-free survival

The hazard rate for both treatment arms is non-monotonic, exhibiting multiple turning points over time (as shown in Figure 17). This suggests that flexible modelling approaches may be more appropriate for extrapolating PFS, mirroring the modelling approach taken for CP PFS in TA963, also in primary advanced or recurrent endometrial cancer (54).

Figure 17: Hazard rate plot for IA1 PFS

Abbreviations: CP, carboplatin plus paclitaxel; IA1, first interim analysis; PFS, progression-free survival.

3.3.2.1.1 CP PFS

As discussed in section 3.3.2.1, flexible modelling approaches are considered more appropriate for the extrapolation of CP PFS from the RUBY-1 trial. Clinicians at an advisory

board were in agreement that the hazard plot for CP shows a complex hazard function with multiple turning points, and therefore flexible models would produce a better statistical and visual fit (137). This also aligns with the approach used to model the PFS placebo arm in TA963 (54). Standard parametric models provided a poor visual fit, but for completeness, are presented and discussed in Appendix L.

Among the methods for flexible modelling reviewed in NICE DSU TSD 21, the flexible spline model was identified as the most suitable for addressing the challenges associated with the standard parametric extrapolation of the RUBY-1 data (138).

Recent literature, specific to immunotherapy and advanced cancers, has shown that spline models tended to demonstrate a better fit to the observed hazard functions than standard parametric models (139, 140). The use of spline models in previous NICE HTA submissions for cancer therapies has also resulted in better fits compared with traditional models (82, 132). Furthermore, spline models have been shown to perform well when extrapolating beyond observed oncology data follow-up periods.

The 9 flexible spline models fit to the PFS data from RUBY-1 for the placebo arm were: Hazard, knots (k)=1,2,3; Odds, k=1,2,3; and Normal, k=1,2,3. The choice of the curve in the base case was selected by visual analysis and consideration of external data sources, alongside analysis of goodness-of-fit statistics such as Akaike information criterion (AIC).

Among flexible distributions, the Odds and Normal curves behave like the log-logistic and log-normal parametric models when k=0. This, coupled with the poor statistical and visual fit of the hazard's models resulted in them bring inappropriate for extrapolating dostarlimab arm PFS.

The AIC scores for Odds models with k=2 and k=3, and Normal models with k=2 and k=3, were within 3 points of each other, indicating that none of these models could be considered statistically superior to each other (Table 21). In addition, the Odds, k=2,3 and Normal distributions k=2,3 aligned well with the observed data for PFS, particularly at the tail of the KM curve (Figure 18).

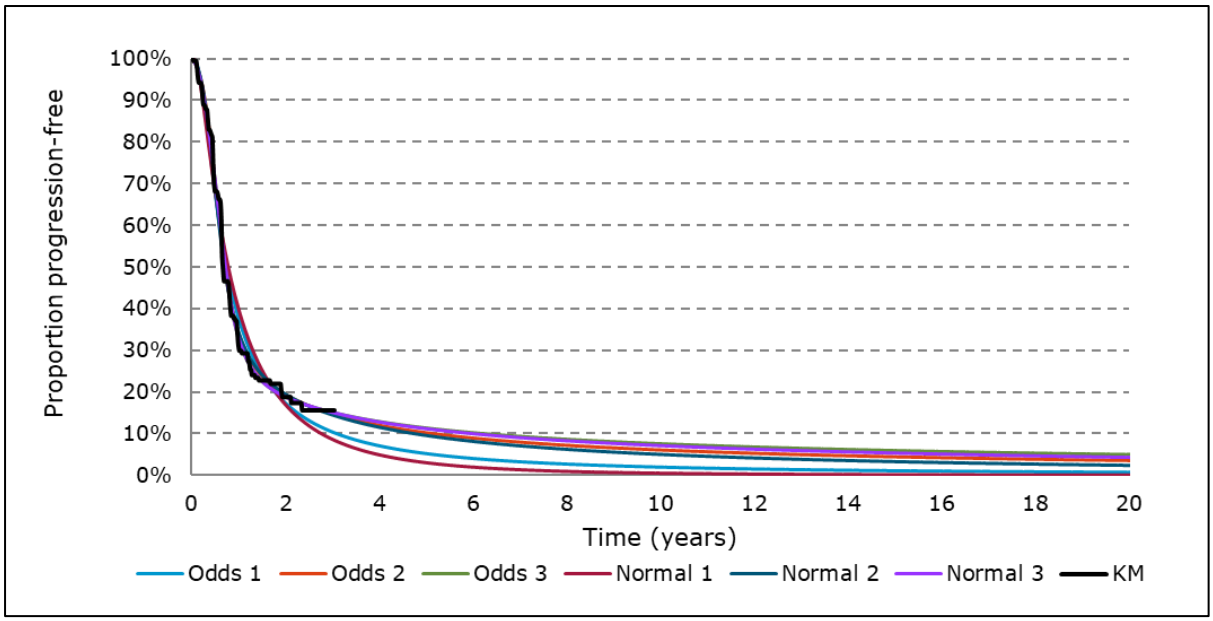
Table 21: Summary of goodness-of-fit data for the PFS of CP (flexible models)

PFS	CP	
Distribution	**AIC**	**Ranking**
Odds, k=1	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]
Odds, k=3	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]

Normal, k=2		[redacted]	
Normal, k=3		[redacted]	

Note: A small AIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; CP, carboplatin plus paclitaxel; PFS, progression-free survival.

Figure 18: Flexible models for PFS compared with KM data, CP



Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; PFS, progression-free survival.

The Normal, k=2 flexible spline model was selected for the base case due to its strong statistical and visual fit to the observed data. Landmark survival estimates (Table 22) using this model aligns closely with those from GSK and the external assessment group (EAG) preferred PFS curve in TA963 for CP in primary advanced or recurrent endometrial cancer (9%, 5% and 3% at 5, 10 and 20 years, respectively), and validated by UK clinical experts (54). The PFS efficacy of CP was consistent regardless of mismatch repair (MMR) status in the RUBY-1 trial PFS data, with a comparison of the CP PFS curves for both the MMRp/MSS and dMMR/MSI-H cohorts included in Appendix L (16).

A scenario analysis has also been tested using the Odds, k=2 flexible spline model, which also had a good statistical fit and results in more optimistic long-term PFS estimates. In addition, for completeness, an independent log-logistic extrapolation (the best fitting independent curve) as detailed in Appendix L, has been tested in scenario analyses.

Table 22: Flexible model estimates of the proportion of patients who would be progression-free at landmark time points treated with CP

Months (years)	CP					
	Odds, k=1	Odds, k=2	Odds, k=3	Normal, k=1	Normal, k=2	Normal, k=3
24 (2)	17%	19%	19%	17%	20%	19%

36 (3)	10%	15%	15%	9%	15%	15%
60 (5)	5%	10%	11%	3%	10%	11%
120 (10)	2%	6%	8%	1%	5%	7%
240 (20)	1%	4%	5%	0%	2%	4%

Abbreviations: CP, carboplatin plus paclitaxel.

3.3.2.1.2 Dostarlimab in combination with CP progression-free survival

In line with NICE DSU TSD 14, standard parametric distributions were initially fitted to PFS from RUBY-1 for the dostarlimab arm independently (136). Visual analysis, goodness-of-fit statistics and UK clinical expert opinion and external data sources were assessed and considered.

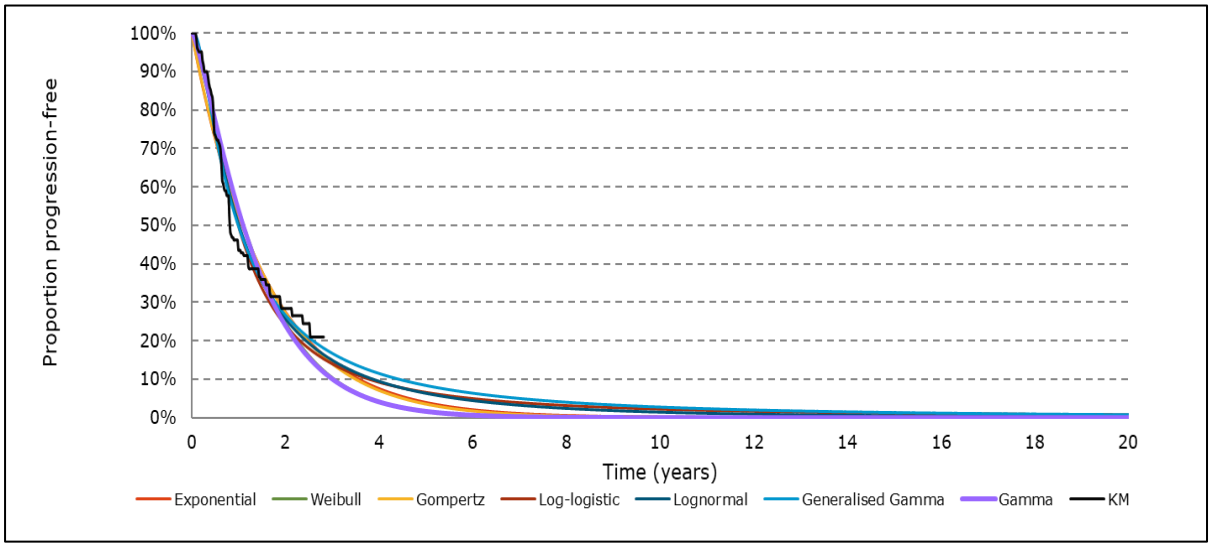
Table 23 summarises the AIC and BIC values for each extrapolation, and Figure 19 presents the standard parametric curves compared with the KM data. On visual inspection, all standard parametric curves provided a similar fit within the observed period. All standard parametric curves overpredict the observed data at around 1 year and underpredict at the tail of the KM data.

Table 23: Summary of goodness-of-fit data for dostarlimab in combination with CP for PFS (standard parametric independent models)

PFS	Dostarlimab in combination with CP			
Distribution	**AIC**	**Ranking**	**BIC**	**Ranking**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin plus paclitaxel; PFS, progression-free survival.

Figure 19: Parametric fits for PFS (independent models) compared with KM data, dostarlimab in combination with CP



Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; PFS, profession-free survival.

The standard parametric models for the dostarlimab arm estimate landmark PFS (Table 24) lower than that predicted for the placebo arm using the base-case flexible models in Section 3.3.2.1.1. This is not considered plausible given the observed benefit of dostarlimab in combination with CP vs CP alone in the RUBY-1 trial (Section 2.6.2) and advice received by clinical experts (137). Therefore, similarly to the placebo arm, flexible modelling approaches were considered more appropriate for the extrapolation of dostarlimab in combination with CP PFS.

Table 24: Parametric PFS landmark estimates, dostarlimab in combination with CP

Months (years)	Selected CP curve	Dostarlimab in combination with CP						
		Exp	Weibull	Gomp	Log-logistic	Log-normal	Gen gamma	Gamma
24 (2)	20%	28%	25%	27%	24%	26%	27%	24%
36 (3)	15%	15%	10%	14%	14%	15%	17%	10%
60 (5)	10%	4%	2%	4%	7%	6%	8%	2%
120 (10)	5%	0%	0%	0%	2%	1%	3%	0%
240 (20)	2%	0%	0%	0%	1%	0%	1%	0%

Abbreviations: CP, carboplatin plus paclitaxel; Exp, exponential; Gen gamma, generalised gamma; Gomp, Gompertz.

In line with the approach for the placebo arm, flexible spline models were fit to the PFS from RUBY-1 for the dostarlimab arm. The 9 flexible spline models were: Hazard, k=1,2,3; Odds, k=1,2,3; and Normal, k=1,2,3. The choice of curve in the base case was selected by visual analysis, UK clinical opinion and consideration of external data sources, alongside analysis of goodness-of-fit statistics such as AIC.

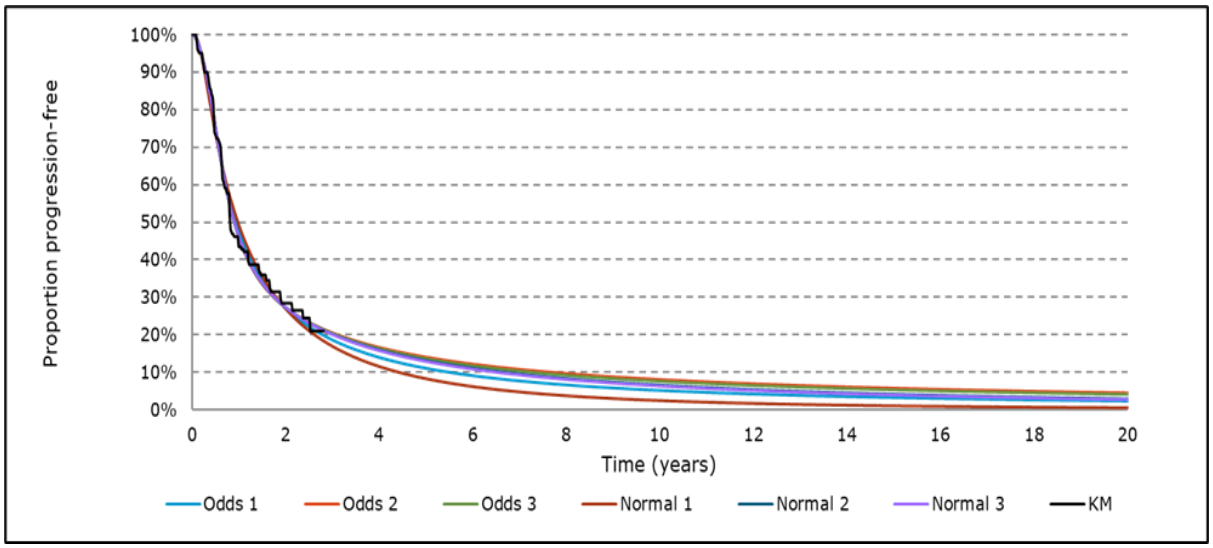
The dostarlimab arm hazard was observed to be non-monotonic (Figure 17), suggesting that AFT models, such as log-logistic, log-normal, or generalized gamma distributions, may be appropriate. Among flexible distributions, the Odds and Normal curves behave like the log-logistic and log-normal parametric models when k=0. This, coupled with the poor statistical and visual fit of the hazard models allowed hazard models to be excluded for extrapolating dostarlimab PFS.

Table 25: Summary of goodness-of-fit data for dostarlimab in combination with CP for PFS (flexible models)

PFS	Dostarlimab in combination with CP	
Distribution	**AIC**	**Ranking**
Odds, k=1	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]
Odds, k=3	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]
Normal, k=2	[redacted]	[redacted]
Normal, k=3	[redacted]	[redacted]

Note: A small AIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; CP, carboplatin plus paclitaxel; PFS, progression-free survival

Figure 20: Flexible models for PFS compared with KM data, dostarlimab in combination with CP



Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; PFS, progression-free survival.

Given that dostarlimab in combination with CP has been shown to improve PFS, the Odds, k=1 is not considered plausible given it produces an extrapolation which is equivalent to the most appropriate CP curve at 10 and 20-years (Table 26). Similarly, the Normal, k=1 appears to underpredict the expected PFS. The Normal, k=2 and k=3 curves produce plausible PFS extrapolations, however when examining the implied treatment effect over time (Appendix L) they appear to underpredict the PFS treatment effect. Each of the Normal,

k=2 and k=3 models result in the HR exceeding 1 at 1.72 years and 1.69 years, respectively, and remain greater than 1 for the remained of the model time horizon.

Both the Odds, k=2 and the Odds, k=3 provide reasonable estimates of PFS for dostarlimab, particularly at the tail of the KM curve (Figure 20). Furthermore, they show good statistical fits to the observed data. **The Odds, k=3 flexible spline model was selected for the base case** as it is considered to best reflect the observed benefit of dostarlimab in combination with CP and is more conservative than the alternative Odds, k=2.

A scenario analysis was also tested using the Normal, k=2 flexible spline model which should be considered a conservative estimate for PFS, given the HR implied by this combination of PFS curves (See Appendix L).

Table 26: Flexible model estimates of the proportion of patients who would be progression-free at landmark time points treated with dostarlimab in combination with CP

Months (years)	Selected CP curve	Dostarlimab in combination with CP					
		Odds, k=1	Odds, k=2	Odds, k=3	Normal, k=1	Normal, k=2	Normal, k=3
24 (2)	20%	27%	27%	27%	27%	27%	27%
36 (3)	15%	19%	21%	20%	17%	20%	20%
60 (5)	10%	11%	14%	14%	8%	13%	13%
120 (10)	5%	5%	8%	8%	2%	7%	6%
240 (20)	2%	2%	5%	4%	1%	3%	3%

Abbreviations: CP, carboplatin plus paclitaxel.

In addition, for completeness, an independent generalised gamma extrapolation, which aligns best of the independent curves with the landmark 5- and 10-year estimates produced by the base case curve, was tested in scenario analyses.

3.3.2.2. Overall survival

OS was a dual primary endpoint of the RUBY-1 trial and has been modelled according to the most recent available data cut (IA2, 22 September 2023).

As presented in Section 2.6.3, addition of dostarlimab to CP resulted in statistically significant OS benefit in the overall RUBY-1 population. Within the MMRp/MSS population, dostarlimab in combination with CP reduced the risk of death by 21% compared with CP alone (HR:0.79, 95% CI: 0.602, 1.044)

Inspection of the log-cumulative hazards (Figure 21), Schoenfeld residual plot (Figure 22), and the quantile-quantile plot (Figure 23) suggests that the relative hazards are likely to vary over time. As such, it is not possible to conclude that the PH assumption holds. In Figure 21 the respective log-cumulative hazards intersect, indicating a violation of the PH assumption. The residual plot in Figure 22 shows that the residuals do not lie around 0, also indicating a violation of the PH assumption, however the PH assumption cannot be formally rejected in this plot due to the >0.05 p-value. Figure 23 illustrates quantiles which do sit on a straight line indicating that the treatment does not exert a multiplicative effect over time. This observation provides evidence of a violation of the constant AF assumption.

Overall, the diagnostic plots indicate that the PH assumption is unlikely to hold, consistent with the delayed treatment effect observed in many immunotherapies (11, 54, 85). This pattern can also be observed in the PFS, OS, and progression-free survival 2 (PFS2) KM curves (Sections 2.6.2, 2.6.3 and 2.6.4.1), which show a pronounced and sustained benefit in the dostarlimab arm after an initial delay. Consequently, dependent models assuming a proportional treatment effect are not considered appropriate. Modelling OS independently was supported by insights from a UK advisory board in July 2024 and is consistent with the mechanism of action of immunotherapies (137).

Figure 21: Log-cumulative hazards plot for IA2 OS

Figure 22: Schoenfeld residuals plot for the IA2 OS

Figure 23: Quantile-quantile plot for IA2 OS

Abbreviations: CP, carboplatin plus paclitaxel; OS, overall survival.

The OS hazards are comparable between arms until approximately week 20, after which, the CP hazard is consistently higher than in the dostarlimab arm. A turning point in the placebo arm resulting in elevated hazard at approximately 150 weeks appears consistent with the spike in the CP PFS hazard at a slightly earlier time point (Figure 24). The dostarlimab hazard rate plot also exhibits a turning point, peaking at approximately week 100 and falling thereafter. The monotonic nature of the hazard rate for both treatment arms, as evidenced by the turning points in the hazard over time, suggests that distributions capable of capturing

such turning points, such as AFT models, would be most appropriate for extrapolating OS (Figure 24).

Figure 24: Hazard rate plot for IA2 OS

Abbreviations: CP, carboplatin plus paclitaxel; IA2, second interim analysis; OS, overall survival

3.3.2.2.1 CP overall survival

Standard parametric distributions were fitted independently to OS from the RUBY-1 placebo arm. The base case curve was selected through visual analysis, informed by UK clinical expert opinion, external data sources, goodness-of-fit statistics, and advice received during TA963, alongside committee preferences for OS extrapolation (88).

Table 27 summarises the AIC and BIC values for each extrapolation. The log-logistic, log-normal, generalised gamma and gamma curves were associated with the best statistical fit of the seven parametric curves. The log-logistic, log-normal and generalised gamma are considered the most appropriate of these distributions given that they allow for the non-monotonic shape observed for the CP hazard rate (Figure 24).

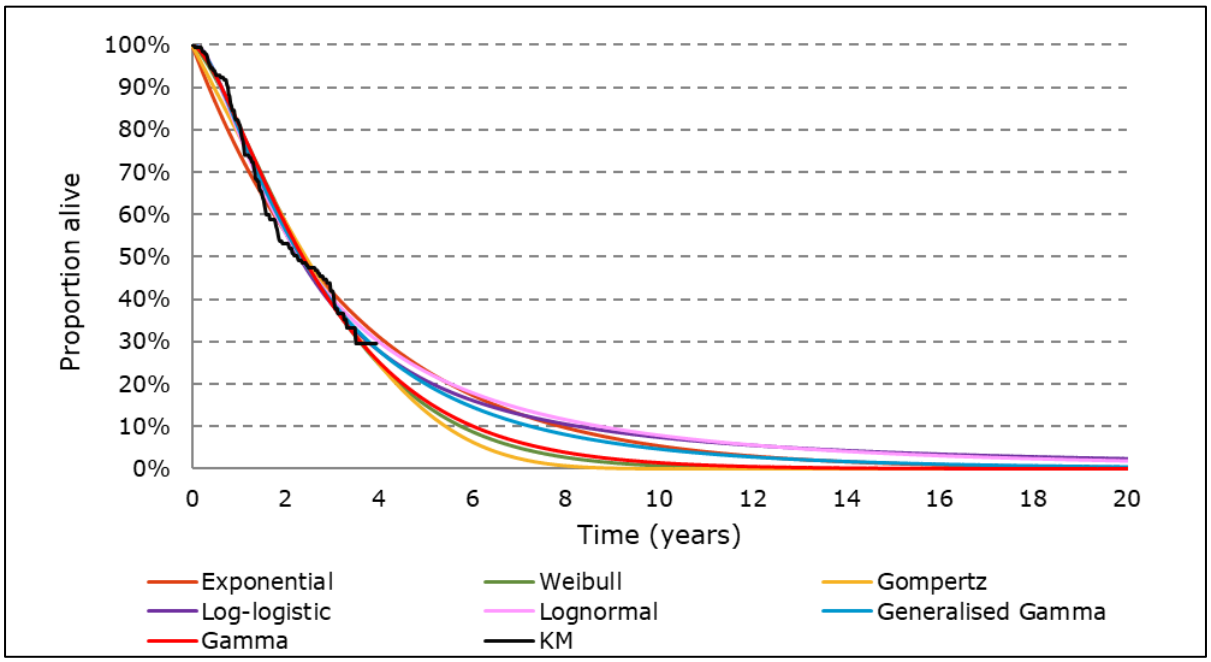
Upon visual inspection, all standard parametric curves appear to provide a good fit to the observed data except for the exponential distribution, which initially underpredicts the KM data (Figure 25).

Table 27: Summary of goodness-of-fit data for CP for OS (standard parametric independent models)

OS	CP			
Distribution	**AIC**	**Ranking**	**BIC**	**Ranking**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin plus paclitaxel; OS, overall survival.

Figure 25: Parametric fits for OS (independent models) compared with KM data, CP



Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; OS, overall survival.

Landmark survival estimates were calculated from values elicited from UK clinicians (Table 28) and aligned closest with proportions from the log-logistic, log-normal and generalised gamma curves (Table 29). **The log-logistic curve was selected for the base case** based on having a good statistical and visual fit to the KM data and providing the most appropriate proportion of patients in the OS state for CP to align with advisor estimates at 15 and 20-years.

Table 28: Advisor estimates of the proportion of patients who would be alive at landmark time points treated with CP

Months (years)	MMRp/MSS						
	Mean (A1-6)	A1	A2	A3	A4	A5	A6
60 (5)	18%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
180 (15)	3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	2%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: [Data on File]_OS_SubequentTreatment_Outputs (141).
Note: advisor 4 was from Scotland.
Abbreviations: A1–5, advisor 1–5; CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable.

Table 29: Advisor mean estimates and parametric model estimates of the proportion of patients who would be alive at landmark time points treated with CP

Months (years)	Advisor mean	CP						
		Exp	Weibull	Gomp	Log-log	Log-normal	Gen Gamma	Gamma
60 (5)	18%	23%	15%	14%	21%	23%	20%	16%
120 (10)	5%	5%	1%	0%	7%	8%	5%	1%
180 (15)	3%	1%	0%	0%	4%	4%	1%	0%
240 (20)	2%	0%	0%	0%	2%	2%	0%	0%

Abbreviations: CP, carboplatin plus paclitaxel; Exp, exponential; Gen gamma, generalised gamma; Gomp, Gompertz.

3.3.2.2.2 Dostarlimab in combination with CP overall survival

Standard parametric distributions were independently fitted to OS from RUBY-1 for the dostarlimab arm. The base case curve was selected by visual analysis, considering UK clinical expert opinion and external data sources, alongside an analysis of goodness-of-fit statistics.

Table 30 summarises the AIC and BIC values for each extrapolation. The log-logistic, gamma, log-normal, and Weibull curves were associated with the best statistical fit and were all within 3 AIC and BIC points of each other, suggesting similar statistical fit. Based on the non-monotonic shape of the dostarlimab arm hazard, the log-logistic or log-normal curves would be the most appropriate.

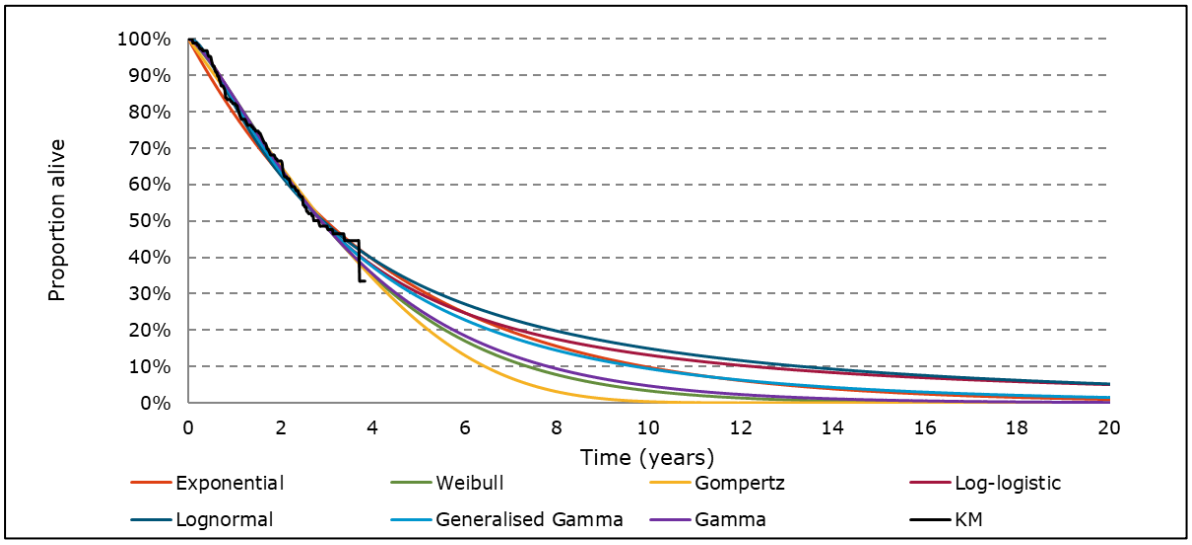
On visual inspection, all standard parametric curves appear to provide a good fit to the observed data, with the curves only appearing to separate after the observed period (Figure 26).

Table 30: Summary of goodness-of-fit data for dostarlimab in combination with CP for OS (standard parametric independent models)

OS	Dostarlimab in combination with CP			
Distribution	**AIC**	**Ranking**	**BIC**	**Ranking**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin plus paclitaxel; OS, overall survival.

Figure 26: Parametric fits for OS (independent models) compared with KM data, dostarlimab in combination with CP



Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; OS. Overall survival.

Landmark survival estimates were calculated from values elicited from UK clinicians (Table 31) which aligned closest with proportions from the log-normal and log-logistic curves (Table 32). **The log-normal curve was selected for the base case** based on having a good statistical fit and aligning closely with advisor estimates, which estimated that a small percentage of patients would remain alive at 20 years. The proportions also appear plausible when compared those presented in Table 29 for CP, given the observed OS benefit for dostarlimab. The log-logistic curve has been tested in scenario analysis, as the second-best fitting curve based on advisor estimates and being within three AIC/BIC points of the log-normal curve.

Table 31: Advisor landmark survival estimates, dostarlimab in combination with CP

Months (years)	MMRp/MSS						
	Mean (A1-6)	A1	A2	A3	A4	A5	A6
60 (5)	36%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	21%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
180 (15)	13%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: advisor 4 was from Scotland.
Abbreviations: A1-6, advisor 1-6; CP, carboplatin plus paclitaxel; MMRp, DNA mismatch repair proficiency; MSS, microsatellite stable; OS, overall survival.

Table 32: Advisor mean estimates and parametric model landmark survival estimates, dostarlimab in combination with CP

Months (years)	Advisor mean	Dostarlimab in combination with CP						
		Exp	Weibull	Gomp	Log-log	Log-normal	Gen Gamma	Gamma
60 (5)	36%	31%	25%	22%	30%	33%	29%	26%
120 (10)	21%	10%	3%	0%	13%	15%	9%	5%
180 (15)	13%	3%	0%	0%	8%	8%	4%	1%
240 (20)	7%	1%	0%	0%	5%	5%	2%	0%

Source: 20240509_OS_SubequentTreatment_Outputs
Abbreviations: CP, carboplatin plus paclitaxel; Exp, exponential; Gen gamma, generalised gamma; Gomp, Gompertz.

3.3.2.2.3 Treatment effect waning

As highlighted in Section 2.6.3, a sustained OS benefit over the placebo arm was observed for the dostarlimab arm. Treatment effect waning has not been included in the base case. Waning was considered at the July 2024 advisory board to be an “artificial way of producing plausible survival curves” compared with using the available data directly (137).

The selection of appropriate independent models should implicitly capture any waning of the treatment effect. This can be observed by the shape of the implied HR over time between the dostarlimab arm and placebo arm (Figure 27), which is maximised at approximately 3 years and gradually trends towards one (no treatment effect) beyond 3 years. Based on this rationale, no additional treatment effect waning is included in the base case for dostarlimab, as this is assumed to be implicitly captured.

Figure 27: Implied OS HR over time

Abbreviations: HR, hazard ratio; OS, overall survival.

Furthermore, a relative plateau or stabilisation of the OS KM curve (Section 2.6.3), can be observed from approximately month 30, mirroring a similar trend observed in the PFS2 (Section 2.6.4.1). This observed evidence suggests that the treatment effect on post-progression outcomes is sustained at least to the end of the trial follow-up.

For consistency with previous NICE technology appraisals in this disease area, scenario analyses are presented exploring the impact of applying an explicit waning of the treatment effect following treatment discontinuation, in addition to the waning implied by the base-case OS extrapolations. In the TA914 appraisal of pembrolizumab in the relapsed setting, waning

was applied at year 5 following discontinuation, i.e. at years 7-9 in the model (2-year stopping rule). A comparable waning scenario is applied to the dostarlimab OS extrapolation from 8–10 years, accounting for the additional year of treatment that patients on dostarlimab would receive compared with pembrolizumab (85). A further conservative scenario analysis is tested with waning applied from 5-7 years in line with the committee preferred assumption in TA904, also in endometrial cancer (92). This waning is also implemented for the PFS curve.

3.3.2.3. Time to treatment discontinuation

TTD was derived from the RUBY-1 trial data to capture the proportion of patients on treatment, and in turn the treatment acquisition drug costs of CP for the first six treatment cycles and of dostarlimab up to three years.

TTD data was based on the latest data cut (IA2, 22 September 2023), and is therefore available for the full duration of treatment, and as such the model relies on the observed KM data to capture treatment costs for both treatment arms. To reflect clinical practice and the SmPC (Appendix A), a stopping rule (impacting treatment associated costs only) was applied in the base case by which 100% of patients remaining on treatment, according to the TTD curve, discontinued treatment with:

- Dostarlimab at three years (156 weeks); corresponding with the RUBY-1 trial data, and the SmPC (35)
- CP at 18 weeks.

The adjusted KM curves are presented in Figure 28. TTD was capped by PFS in the model in line with the SmPC for each treatment.

Figure 28: Modelled time to treatment discontinuation

Abbreviations: CP, carboplatin plus paclitaxel; KM, Kaplan-Meier.

In the base case, the initial 18 weeks of treatment was adjusted using completion rates from the RUBY trial (Table 33) to account for treatment delays, missed doses and skipped doses. This adjustment accounts for the costs of patients who do not formally discontinued treatment but are not receiving therapy within a given cycle. Completion rates also provide a more precise representation of the individual components of CP. A consistent approach was applied to dostarlimab, to align with the placebo arm, assuming the same CP completion rates across treatment arms (Section 2.3.6 for patient disposition at IA2).

For completeness, a scenario has been run in which completion rates do not override the TTD estimation for dostarlimab and CP.

Table 33: Completion rates for carboplatin, paclitaxel and dostarlimab per treatment cycle

Completion rates per treatment cycle	Proportion receiving dose of carboplatin (%)	Proportion receiving dose of paclitaxel (%)	Weighted average across CP (%)	Proportion receiving dose of dostarlimab (%)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel.

3.4. Measurement and valuation of health effects

3.4.1. Health-related quality of life data from clinical trials

The EQ-5D-5L data collected within the RUBY-1 trial were analysed to estimate health state utility values. In the base-case and in line with the decision problem, PFS and PD utility values were derived from the MMRp/MSS population of RUBY-1. Utility values derived from the full ITT population of the trial were tested in scenario analyses.

Currently, there is no approved value set for the EQ-5D-5L in England. Therefore, aligned with NICE preference, the EQ-5D-5L were mapped to EQ-5D-3L (142). The EQ-5D-5L data from RUBY trial was mapped to the EQ-5D-3L data using the cross-walk approach by Hernández Alava M, Pudney S. (2017) as recommended in NICE guidelines (2022) (94, 143). The health state utility values from the RUBY trial analyses are [redacted] for PFS and [redacted] for PD for the MMRp/MSS population (Table 34).

Table 34: Health state utility values from RUBY trial

Health state	MMRp/MSS, mean (SE)	ITT, mean (SE)	Source:
PFS	[redacted]	[redacted]	RUBY-1 trial
PD	[redacted]	[redacted]	

Abbreviations: ITT, intention-to-treat; PD, progressed disease; PFS, progression-free survival; SE, standard error.

3.4.2. Health-related quality of life studies

A HRQoL SLR was undertaken on 10 November 2021 (with updates on 22 February, 26 October 2023 and 16 May 2024) to identify existing HRQoL evidence relevant to the decision problem. Full details of the methodology used to identify all relevant studies and results are presented in Appendix F.

The HRQoL SLR identified three studies evaluating health utilities in patients with advanced or recurrent endometrial cancer. All were questionnaire-based studies. The studies have been detailed below.

The identified study from Hildebrandt et al. 2014 (144) was a cross-sectional study of women with gynaecological cancers from Germany that evaluated health utilities using the EQ-5D questionnaire in a subgroup of 27 patients with endometrial cancer compared with 62 healthy controls. Of the 126 patients with endometrial cancer, EQ-5D-3L data was available for 12 women diagnosed with advanced disease. Baseline demographic and clinical characteristics of enrolled patients with advanced or recurrent endometrial cancer were not reported. The median health utility scores in patients with advanced endometrial cancer was

0.8870 (range: 0.676-1) which was lower than compared with the health utility scores in healthy controls (median: 0.9995; range: 0.262-1), with no health state specific utilities reported. Due to small patient numbers (n=12) in this literature study, and lack of information regarding patients' characteristics, the RUBY-1 trial was used for the health state utilities in the economic analysis.

Ackroyd et al, 2023 (145) was a US study which interviewed sixty women with advanced or recurrent endometrial cancer. The authors evaluated the time-related QoL as it related to time spent dealing with their cancer treatment. EQ-5D-5L scores were converted to utility scores for 16 groups of patients across seven different treatment types; data were presented for patients grouped by type of treatment, as well as by nine specific individual treatment regimens within those types. The median age of patients was 66 years. Utility values were reported for women across a variety of treatment types, from those who were not on treatment to those receiving cytotoxic chemotherapies, immunotherapies, hormone therapies, radiation therapy, bevacizumab, and clinical trial patients. Mean utility values ranged from 0.76 in the 16 patients treated with cytotoxic chemotherapy to 0.89 in the four patients treated with radiation therapy. Mean utility values for specific regimens under each treatment class were also reported, e.g. 0.76 (Range 0.27–1.00) in the 12 patients treated with CP.

In Ackroyd et al. 2024, 84 women with advanced or recurrent endometrial cancer were interviewed; the median age of participants was 67 years old. Study participants reported a median health utility score of 0.80 (IQR: 0.71- 0.85), which was positively correlated with better financial wellness (146).

Due to the small patient numbers in the two studies identified, and lack of information regarding patients' characteristics, the RUBY-1 trial was used for the health state utilities in the economic analysis.

3.4.3. Adverse reactions

Section 2.11 provides full details of AE data in the RUBY-1 trial. As per standard practice in CEMs, only Grade 3 and above AEs were included in the model (Section 2.11.3). AEs from the ITT population were used as the preferred source due to the availability of more patient data (Appendix D and Section 2.11). Minimal differences were observed between the AEs observed in the ITT and MMRp/MSS populations (Appendix D and Section 2.11).

Whilst the application of AE disutilities may be considered as double counting, this ensures the model includes an impact on healthcare resource use, costs, or an impact on HRQoL

due to AEs. A scenario analysis explored the impact of excluding AE disutilities. Utility decrements were applied on an absolute (rather than relative) basis and applied in the first model cycle per treatment arm, assuming that AEs were likely to occur rapidly after treatment and only require acute care. RUBY-1 events were also more likely to happen in the combination phase and not in the monotherapy phase (Appendix D).

Due to the paucity of data for patients with primary advanced or recurrent endometrial cancer in the literature, AE disutility estimates were informed by published evidence applied in gynaecological cancer (Table 35). A scenario was tested in which AE disutilities were excluded.

Table 35: Adverse event disutilities

Adverse event	Disutility	Source
Abdominal pain	-0.069	Swinburn et al. Elicitation of health state utilities in metastatic renal cell carcinoma (147) Assumed equal to mucositis.
Anaemia	-0.119	Swinburn et al. Elicitation of health state utilities in metastatic renal cell carcinoma (147)
Asthenia	−0.073	Nafees et al. Health state utilities for non-small cell lung cancer (148). Assumed equal to responding plus fatigue.
Hypertension	−0.020	NICE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (132)
Hypokalaemia	−0.074	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411) (149).
Lipase increased	−0.010	Assumption
Lymphocyte count decreased	0.000	Assumed to be the same as neutrophil count decreased
Nausea and hyponatremia	-0.0450	NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779) (82)
Neutropenia	−0.090	Nafees et al. Health state utilities for non-small cell lung cancer. (148). Assumed equal to responding plus neutropenia
Neutrophil count decreased	0.000	Assumed to have no utility impact
Pulmonary embolism	−0.320	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411) (149)
Rash	−0.116	Assumed equal to hand and foot syndrome, Lloyd (2006) (150)
Urinary tract infection	−0.010	Assumption
White blood cell decreased	0.000	Assumed to have no utility impact

3.4.4. Health-related quality of life data used in the cost-effectiveness model

Table 36 summarises the utility values used. Age-adjusted utilities were applied to reflect decreases in HRQoL seen in the general population and to ensure that utilities did not exceed general population values at a given age. Utility decrements associated with age were derived using the expected EQ-5D-3L values for females published by Hernández Alava, Pudney and Wailoo, 2022 (143). A scenario analysis is included where no age-adjustment is applied.

Table 36: Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% CI	Reference in submission (section and page number)	Justification
PFS	Base case (MMRp/MSS): [redacted]	[redacted]	Section 2.6.4.3 (Page 54) • HRQoL data from clinical trials Section 3.4.1 (Page 95) • HRQoL data used in the CEM	EQ-5D-5L data from the MMRp/MSS population of the RUBY-1 trial were mapped to EQ-5D-3L aligned with NICE guidelines (94)
PD	Base case (MMRp/MSS): [redacted]	[redacted]		
Age-adjusted utilities	Base case: included			Age adjusted utilities were applied to align with NICE guidelines (94)
AEs				
AEs	Base case: included	Section 2.11 (Page 61) • Adverse reactions		Applied to first cycle in the model under the assumption that AEs were likely to occur rapidly after treatment and only require acute care

Abbreviations: AE, adverse event; CEM, cost-effectiveness model; CI, confidence interval; HRQoL, health-related quality-of-life; MMRp, DNA mismatch repair proficient; MSS, microsatellite stable; PD, progressed disease; PFS, progression-free survival.

3.5. Cost and healthcare resource use identification, measurement

An economic SLR was undertaken on 10 November 2021 (with updates on 22 February 2023, 26 October 2023 and 16 May 2024) to identify existing healthcare resource use (HCRU) evidence on the first-line treatments of primary advanced or recurrent endometrial cancer. Full details of the methodology used to identify all relevant studies and results are presented in Appendix G.

The SLR identified seventeen publications reporting on HCRU that met the inclusion criteria. Kebede et al. 2022 (SLR update #4) was identified as an update to the Nwankwo et al. 2020 publication (identified update #1), and therefore there was a total of sixteen relevant HCRU publications included as part of the SLR (151) (152). All studies enrolled adult women diagnosed with endometrial cancer. Nine studies were conducted in the US, with four studies carried out in Denmark, Germany, Italy, and the UK, and one study conducted in Brazil.

Total costs, including direct medical and indirect costs, were not reported by any of the included publications. Direct costs associated with the management and treatment of endometrial cancer, medical visits, hospitalisations, diagnostic tests, and medication costs were reported in one study conducted in the UK and three studies covering the US. The UK costs were reported at an aggregate level for 2 years only (inclusive of diagnosis, surgery, adjuvant therapy, and further treatment).

Hospitalisation rates by the type of intervention received were reported in only one study based in the US (153). The mean length of inpatient hospitalisation among patients with endometrial cancer was reported in three studies(152, 154). Two were US studies; In Galaznik et al. 2019 this was in a predominantly Medicare fee-for-service population (154); and in Kebede et al. 2022, the mean length of stay increased gradually with increasing lines of therapy (152). Only Pennington et al. 2016 reported UK resource use data, detailing the number and proportion of patients who received medical procedures and prescription drugs (155).

None of the studies reporting resource use were used in the economic model, either because they were US based, or they contained limited UK-specific data that was not relevant to the model inputs. Therefore, UK clinical opinion was sought for HCRU inputs and costs were sourced from the electronic Market Information Tool (eMIT), British National Formulary (BNF) and NHS reference costs where applicable (156-158).

3.5.1. Costs included in the model

As the CEM was built from the perspective of the NHS and PSS, and in line with the NICE reference case (94), NHS reference costs were deemed an appropriate source for the HCRU cost inputs. Treatment costs were sourced from eMIT via the national database, and the BNF via the NICE website. A targeted literature review was conducted to identify acute care costs to treat AEs identified from RUBY-1.

The CEM included the following cost components:

- Treatment acquisition:
    - Active treatments in decision problem
    - Subsequent treatments.
- Treatment administration:
    - Active treatments in decision problem
    - Subsequent treatments.
- Monitoring
- AEs
- End-of-life care.

Where necessary, costs were inflated to the most recent cost year using inflation indices annual percentage increase for adult services published by Personal Social Services Research Unit (PSSRU) (159).

3.5.2. Intervention and comparators' costs and resource use

3.5.2.1. Treatment acquisition costs

Treatment acquisition costs were calculated using treatment prices and dosing schedules. The RUBY-1 trial and SmPC provided data for the dosing schedule for the dostarlimab and placebo arms. Treatment prices were sourced from eMIT where possible, and the BNF (156, 160).

Cost per unit was multiplied by dose per treatment cycle and again by the duration of the treatment cycle to calculate the treatment cost per cycle. Wastage was assumed in the base case with a scenario exploring the impact of no wastage. The duration of treatment was modelled as described in Section 3.3.2.3 using TTD data from the RUBY-1 trial with completion rates applied for the first six treatment cycles and a discontinuation rule at 3 years.

3.5.2.1.1 Dostarlimab in combination with CP

The cost of 50 mg per 1 ml vial of dostarlimab was £5,887.33. Dostarlimab is administered Q3W for six doses administered on Weeks 1, 4, 7, 10, 13, and 16, followed by a 1,000 mg dose Q6W from Week 19 onwards up to a maximum of 3 years (Section 2.3.3). The patient access scheme (PAS) discount is [redacted]% with a net price of £[redacted] per 50 mg per 1 ml vial.

There are four vial sizes available for carboplatin on the NHS cost collection database for 2024 (156). The cost of 50 mg, 150 mg, 450 mg and 600 mg were £6.71, £12.18, £23.18, and £38.93, respectively. Carboplatin is administered intravenously at a unit dose of area under the plasma or serum concentration-time curve 5 mg/ml/min Q3W.

The cost of 100 mg vial of paclitaxel was £12.89 (156). Paclitaxel is administered intravenously at a unit dose of 175 mg/m^2 Q3W (Table 37).

3.5.2.1.2 CP

Carboplatin and paclitaxel are administered intravenously for the first six cycles only. Table 37 and Table 38 summarise the treatment acquisition cost for dostarlimab in combination with CP and CP.

Table 37: Drug acquisition unit costs for dostarlimab and CP per treatment cycle

Intervention	Unit size (mg)	Cost per unit (£)	Dose per Cycle (mg)	Units (up to Cycle 18)	Total cost for units (up to Cycle 18, £)	Units (Cycle 19+)	Total cost for units (Cycle 19+, £)
Dostarlimab	500	5,887.33 (list price) [redacted] (PAS price)	500	1	5,887.33 (list price) [redacted] (PAS price)	2	11,774.66 (list price) [redacted] (PAS price)
Carboplatin	50	6.71	433.58	0.00	0.00	0	0
	150	12.18		0.00	0.00	0	0
	450	23.18		1.00	23.18	0	0
	600	38.93		0.00	0.00	0	0
Paclitaxel	100	12.89	333.20	4.00	51.54	0	0

Abbreviations: CP, carboplatin plus paclitaxel; PAS, patient access scheme.

Table 38: Total drug acquisition cost per treatment cycle with wastage

Cycle (week)	Acquisition cost per treatment cycle (£)	
	Dostarlimab	CP
Cycle ≤18	5,887.33 (list price) [redacted] (PAS price)	74.73
Cycle ≥19	11,774.66 (list price) [redacted] (PAS price)	0.00

Abbreviations: CP, carboplatin plus paclitaxel; PAS, patient access scheme

3.5.2.1.3 Treatment administration cost

Administration costs for both dostarlimab and CP were sourced from NHS national cost collection data publication 2023/24 (158) (Table 39). Treatment administration costs were applied in addition to treatment acquisition costs to derive the total cost per treatment cycle (Table 39). The outpatient code was used for administration costs as this was assumed to more accurately represent the opportunity-cost of administering dostarlimab in clinical practice.

Table 39: Administration costs and total costs per treatment cycle

	Administration cost		Total cost per treatment cycle (acquisition plus administration)		Reference
	Up to model Cycle 18	Model Cycle 19+	Up to model Cycle 18	Model Cycle 19+ (up to Year 3)	
Dostarlimab in combination with CP	£201.66 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Outpatient attendance]	£152.13 [SB12Z – Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient attendance]	£6,163.72 (list price) £[redacted] (PAS price)	£11,926.79 (list price) £[redacted] (PAS price)	NHS. National Cost Collection Data Publication 2023/2024. (158)
CP	£201.66 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Outpatient attendance]	£0.00	£276.39	£0.00	NHS. National Cost Collection Data Publication 2023/2024. (158)

Abbreviations: BNF, British National Formulary; CP, carboplatin plus paclitaxel; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme

3.5.3. Health-state unit costs and resource use

Costs associated with the ongoing management of patients were captured and included in the CEM over the time horizon and applied to the proportion of patients in the PFS health state (based on PFS modelled as described in Section 3.3.2.1) and PD health state (based on the difference between the PFS and OS modelled as described in Sections 3.3.2.1 and 3.3.2.2, respectively).

Resource use included within the model were derived based on rates provided by UK clinical experts (88). This resource use was initially collected to support TA963, which also evaluated dostarlimab in primary advanced or recurrent endometrial cancer and were agreed upon by the committee and clinicians (54). The rates provided by clinical experts were converted to weekly cycles by health state and treatment phase to include in the model. The cost for each unit resource use was sourced from NHS Reference Costs 2023/24 (158). HCRU per weekly cycle applied per health state for dostarlimab and CP are presented in Table 40.

Table 40: Cost and resource use per weekly model cycle for dostarlimab in combination with CP, and CP alone

Resource	Unit cost (£)	Health state	Dostarlimab + CP		CP		Dostarlimab + CP		CP	
			Resource use (up to Cycle 18)	Resource use (Cycle 19+)	Resource use (up to Cycle 18)	Resource use (Cycle 19+)	Total costs (up to Cycle 18) (£)	Total costs (Cycle 19+) (£)	Total costs (up to Cycle 18) (£)	Total costs (Cycle 19+) (£)
Outpatient visit	205.82	PFS	0.30	0.13	0.30	0.08	61.40	26.61	61.40	16.37
		PD	0.12	0.12	0.12	0.12	24.56	24.56	24.56	24.56
CT scan	118.58	PFS	0.13	0.06	0.13	0.05	18.40	8.49	18.40	7.08
		PD	0.07	0.07	0.07	0.07	9.91	9.91	9.91	9.91
Complete blood count	8.04	PFS	0.33	0.22	0.33	0.06	1.68	1.12	1.68	0.31
		PD	0.09	0.09	0.09	0.09	0.46	0.46	0.46	0.46
Specialist nurse visit	57.00	PFS	0.11	0.07	0.11	0.07	6.27	3.99	6.27	3.99
		PD	0.10	0.10	0.10	0.10	5.70	5.70	5.70	5.70
GP visit	47.00	PFS	0.00	0.01	0.00	0.01	0.00	0.47	0.00	0.47
		PD	0.01	0.01	0.01	0.01	0.47	0.47	0.47	0.47

Abbreviations: CT, computerised tomography; GP, general practitioner; NHS, National Health Service; CP, carboplatin plus paclitaxel; PD, progressed disease; PFS, progression-free survival.

3.5.3.1. End of life costs

Healthcare costs substantially increase at the end of life due to high resource use. Terminal care costs were sourced from a targeted literature search. In line with the previous appraisal (TA963), terminal care costs were applied to the proportion of patients who transition to the death state and applied as a one-off cost (54). Costs were taken from Guest et al, 2006 and inflated to the 2023 cost year (161). Guest et al, 2006 estimated the costs of palliative care associated with ovarian cancer to be £4,789 (2000/2001 UK setting) (161). Given a lack of direct evidence for palliative care costs for endometrial cancer, this estimate was considered to be the most relevant. This approach was used in TA963, where this estimate was inflated from the 2018/2019 to 2022/23 UK cost setting, resulting in an estimate of £8,716.94 (82).

3.5.3.2. Adverse reaction unit costs and resource use

Grade ≥3 AEs affecting at least 2% of patients in either arm of the RUBY-1 trial were included in the model, as this was preferred by the EAG in TA963 (54). AE data are based on IA2. Incidence of Grade ≥3 AEs from the ITT population was used as there was more data available, and rates of AEs were similar to those seen in the MMRp/MSS population (Section 2.11 and Appendix D). A scenario has been tested that also includes Grade ≥3 AEs affecting at least 5% of patients and occurring more frequently in the dostarlimab arm, as is standard practise.

Costs were multiplied by AE incidence rates to evaluate the total costs associated with AEs by treatment. These total AE costs were applied in the first model cycle per treatment arm, assuming that AEs were likely to occur rapidly after treatment and only require acute care. RUBY-1 events were also more likely to happen in the combination phase than in the monotherapy phase (Appendix D).

Table 41 summarises the costs for each Grade ≥3 AE and AE incidence for AEs occurring in at least 2% of patients in either the dostarlimab or placebo arm, included in the cost-effectiveness analysis.

Table 41: List of AE unit costs, AE incidence and summary of costs for dostarlimab in combination with CP, and CP

AE	Unit cost (£)	Incidence dostarlimab in combination with CP	Incidence CP	Total costs (£) dostarlimab in combination with CP	Total costs (£) CP	Reference for cost
Anaemia	612.92	14.9%	16.7%	91.56	102.15	NHS. National Cost Collection Data Publication 2023/24 (158)
Neutropenia	560.68	9.5%	9.3%	53.51	52.42	
Neutrophil count decreased	901.96	8.3%	13.8%	74.85	124.66	
Hypertension	360.74	7.1%	3.3%	25.45	11.73	
White blood cell count decreased	901.96	6.6%	5.3%	59.88	47.66	Assumed same as neutrophil count decreased
Hypokalaemia	1,789.88	5.0%	3.7%	89.12	65.48	NHS. National Cost Collection Data Publication 2023/24 (158)
Pulmonary embolism	2,048.26	5.8%	4.9%	118.99	99.91	NHS. National Cost Collection Data Publication 2023/24 (158)
Lymphocyte count decreased	901.96	5.4%	7.3%	48.65	66.00	Assumed same as neutrophil count decreased
Lipase increased	901.96	4.6%	1.2%	41.17	11.00	Assumed same as lymphocyte count decreased
Abdominal pain	437.01	3.7%	1.6%	16.32	7.11	NHS. National Cost Collection Data Publication 2023/24 (158)
Urinary tract infection	2,020.71	2.9%	1.6%	58.69	32.86	NHS. National Cost Collection Data Publication 2023/24 (158)
Rash	227.88	4.6%	1.2%	10.40	2.78	NHS. National Cost Collection Data Publication 2023/24 (158)
Nausea and hyponatremia	564.22	6.6%	4.9%	37.46	27.52	NHS. National Cost Collection Data Publication 2023/24 (158)
TOTAL				**726.05**	**651.29**	

Abbreviations: AE, adverse event; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; CP, carboplatin plus paclitaxel.

3.5.3.3. Subsequent treatment costs

The cost of subsequent treatments was included to account for the costs incurred by patients who relapse and require treatment in the second-line setting. Subsequent treatments were derived from those recorded as part of the RUBY-1 trial and adapted to reflect UK clinical practice. A complete list of treatments received in the trial are presented in Appendix K. To estimate the proportion of patients receiving each treatment, the number of patients recorded as receiving each treatment regimen in the RUBY-1 trial is expressed as a proportion of patients with progressed disease in each arm of the trial.

Table 42: Patients receiving a subsequent treatment in the RUBY-1 trial (IA1)

	Dostarlimab in combination with CP	CP
Progression events	[redacted]	[redacted]
Follow-up anti-cancer therapy recorded	[redacted]	[redacted]
Proportion of patients receiving a subsequent therapy	92%	100%

Abbreviations: CP, carboplatin plus paclitaxel.

Subsequent treatment costs are applied only to patients who progress to the PD state. Consistent with partition survival modelling, the exact number or proportion of patients entering this state within each cycle is not explicitly known. However, consistent with the natural history of the disease, it is observed that the majority of OS events occur from those with progressive disease and very few ([redacted]) occurring from those who are progression free. Therefore, for the purpose of deriving subsequent treatment costs, it is assumed that [redacted] of PFS events result in movement to the PD thereby accruing the cost of subsequent treatments. This proportion is applied to both dostarlimab and placebo arm.

3.5.3.3.1 Subsequent treatment included

The following therapeutic classes were recorded as follow-up anticancer therapies in the RUBY trial and were confirmed by UK clinicians as treatment options in clinical practice in the relapsed setting for patients with MMRp/MSS disease:

- Chemotherapy
- Immunotherapy
- Antiangiogenic (bevacizumab)
- Hormone therapy
- Radiation therapy
- No treatment

For modelling subsequent treatments, immunotherapy is assumed to be the pembrolizumab with lenvatinib combination as this is the only immunotherapy-based regimen routinely available in the NHS for patients with MMRp disease in the relapsed setting. Given the large number of chemotherapy regimens recorded in the trial, many of which are utilized by a single patient, only the 6 most common chemotherapy regimens which are also available in UK practice were included. Hormone therapy is assumed to be megestrol acetate.

3.5.3.3.2 Proportion receiving each treatment

Immunotherapy regimens are not available or recommended following previous treatment with dostarlimab. The proportion of patients receiving chemotherapies is reweighted to account for the proportion of patients who received immunotherapy in the RUBY-1 trial but would not receive these in clinical practice. There is no clinical rationale to re-treat with an immunotherapy upon progression following dostarlimab (an immunotherapy) treatment, however, as blinding was maintained beyond the first progression event, immunotherapy usage was observed in both arms of the RUBY-1 trial.

Approximately 8% of patients in the dostarlimab arm receive 'no treatment' as a subsequent therapy. This likely reflects the more limited treatment options for this group of patients in the relapsed setting where the cancer has relapsed following treatment with paclitaxel, a platinum containing agent, and an immunotherapy. Conversely, in the comparator arm, patients may still be treated subsequently with an immunotherapy.

A more conservative scenario analysis is provided where the proportion of patients receiving 'no treatment' is the same across treatment arms. Another scenario analysis is provided to reflect the increased expected uptake to 75% of the pembrolizumab with lenvatinib regime in 2025/26 per the associated NICE Resource Impact Report (162).

Table 43: Proportion of patients receiving each subsequent treatment

	RUBY-1 trial		RUBY-1 trial (adjusted)	
	Dostarlimab in combination with CP	CP	Dostarlimab in combination with CP	CP
Carboplatin and doxorubicin	2.8%	0.8%	4.4%	0.8%
Carboplatin and paclitaxel	8.3%	10.4%	13.2%	10.4%
Paclitaxel	3.7%	2.4%	5.9%	2.4%
Doxorubicin	20.2%	20.8%	32.3%	20.8%
Carboplatin	3.7%	1.6%	5.9%	1.6%
Cisplatin	1.8%	2.4%	2.9%	2.4%
Pembrolizumab with lenvatinib	27.5%	48.8%	0%	48.8%

	RUBY-1 trial		RUBY-1 trial (adjusted)	
	Dostarlimab in combination with CP	CP	Dostarlimab in combination with CP	CP
Bevacizumab	5.5%	5.6%	8.8%	5.6%
Hormone therapy	14.7%	13.6%	14.7%	13.6%
Radiotherapy	21.1%	14.4%	21.1%	14.4%
No treatment	8.3%	0.0%	8.3%	0.0%

Abbreviations: CP, carboplatin plus paclitaxel.

Table 44 presents the cost and percentage of patients treated with each subsequent treatment in the base case. The cost of administration of each subsequent therapy is also included in the total cost. The cost of management of AEs for subsequent treatments was calculated based on incidence and costs sourced from the literature, aligned with the methodology described in Section 2.3. The list price for all subsequent treatments were used and their time on treatment was informed by the literature or a fixed number of cycles. Monitoring costs have not been included since PD health state costs captures the costs and consequences of subsequent treatment monitoring.

The total subsequent treatment costs, inclusive of drugs at list prices and AE costs, of dostarlimab in combination with CP were £3,363.96. Total subsequent treatment costs of CP were £47,057.71, excluding any confidential PAS discount in place for pembrolizumab with lenvatinib (163).

Table 44: Subsequent treatments (RUBY-1 trial with no immunotherapy re-treatment)

Second-line treatment	Carboplatin and doxorubicin	Carboplatin and paclitaxel	Paclitaxel	Doxorubicin	Carboplatin	Pembrolizumab with lenvatinib	Cisplatin	Hormone therapy	Radiotherapy	Bevacizumab	No treatment
Total cost per class for average total treatment duration (£)	1,821.57	2,290.28	1,174.37	705.66	1,115.90	91,632.55	1,658.19	63.37	3,388.24	17,459.25	0.00
Total cost of AEs during subsequent treatment (£)	283.46	283.46	283.46	661.14	283.46	393.43	283.46	0.00	0.00	35.72	0.00
Percentage usage post dostarlimab	4.4%	13.2%	5.9%	32.3%	5.9%	0.0%	2.9%	14.7%	21.1%	8.8%	8.3%
Percentage usage post CP	0.8%	10.4%	2.4%	20.8%	1.6%	48.8%	2.4%	13.6%	14.4%	5.6%	0.0%

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel.

3.5.4. Miscellaneous units costs and resource use

No additional costs or resource use were used to inform this cost-effectiveness analysis.

3.6. Severity

The lifetime QALY gain of patients in the placebo arm of the CEM and corresponding age and sex from the RUBY-1 trial (Table 45) was used to understand the extent to which the disease impacts the remaining QALYs of patients. Utility data are outlined in Section 3.4 (Table 34).

Patients with primary advanced or recurrent endometrial cancer experience dire health outcomes, demonstrated by the absolute shortfall of almost [redacted] QALYs, which is a [redacted]% proportional shortfall compared with patients in the general population (Table 47). This analysis concluded that primary advanced or recurrent endometrial cancer still does not qualify for any severity modifier. Therefore, no adjustments to the QALYs in the CEM were made.

Table 45: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	100% female	All trial participants were female
Starting age	[redacted] years old	Section 3.3.1

Abbreviations: QALY, quality-adjusted life year.

Table 46: Base case summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)
PFS	[redacted]
PD	[redacted]

Abbreviations: PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year.

Table 47: Summary of QALY shortfall analysis

Utility source	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with CP	Absolute QALY shortfall	Proportional
RUBY trial	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; CP, carboplatin plus paclitaxel.

Despite not qualifying for a severity modifier under the above criteria, as highlighted in Section 1.4, GSK is concerned that the willingness to pay (WTP) thresholds for novel treatments for incurable endometrial cancer, which predominantly affects women, are being

set lower than those applied to comparable diseases that affect men. Specifically, recent appraisals for prostate cancer treatments, such as olaparib (TA887) and lutetium-177 vipivotide tetraxetan (TA930), have been appraised at a £50,000/QALY cost-effectiveness threshold under end-of-life criteria (99, 100). This equates to a QALY weighting of 1.7 for men with incurable prostate cancer. However, it is crucial to recognize that, under the revised NICE methods, these prostate cancer indications would no longer qualify for the 1.7 modifier (assuming 0.884 total QALYs for the comparator in each appraisal, cabazlitaxel, per TA908) just as primary advanced or recurrent endometrial cancer does not qualify (164). This disparity demonstrates that women with incurable endometrial cancer are being disadvantaged in comparison to men with prostate cancer through inconsistent application of both the severity modifier and end-of-life criteria across therapy areas where sex is a distinguishing factor.

3.7. Uncertainty

Consistent with results seen in the ITT population, a sustained improvement in OS is observed for patients with MMRp/MSS endometrial cancer in the RUBY-1 trial, with almost 4 years of data available at IA2 data cut-off (September 2023) (Section 2.6.3). Statistical tests indicate the PH assumption is violated therefore independent models were selected for the base case OS. Various scenario analyses were undertaken around the OS for dostarlimab, including testing alternative survival distributions and assuming more conservative estimates of the treatment effect by modelling waning of the treatment effect over time.

Statistical significance was reached in the ITT population for PFS data as part of IA1 (Section 2.6.2). Independent models did not fit the observed PFS data well, and flexible spline models were selected for the base case. Various scenario analyses were undertaken for PFS, testing alternative survival distributions. TTD KM data from the RUBY-1 trial was complete and has been used directly in the model.

3.8. Summary of base-case analysis inputs and assumptions

3.8.1. Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 48.

Table 48: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Settings			
Time horizon	[redacted]	-	3.2.3
Age at baseline (years)	[redacted]	-	3.3.1
Body surface area	[redacted]	[redacted] Gamma	
Weight	[redacted]	[redacted] Gamma	
GFR (ml/min/1.73m^2):	[redacted]	[redacted] Gamma	
Discount rate costs and outcomes	3.5%	-	3.2.5
Clinical inputs			
PFS (dostarlimab arm)	IA PFS, flexible Odds K=3	Each survival analysis sheet contains a calculation for probabilistic analysis	3.3.2.1.2
PFS (CP)	IA PFS, flexible Normal K=2		3.3.2.1.1
OS ((dostarlimab arm)	Log-normal		3.3.2.2.2
OS (CP)	Log-logistic		3.3.2.2.1
TTD (dostarlimab arm)	KM for full follow up period, three year stopping rule and completion rates applied	Completion rates varied using beta distribution. Each survival analysis sheet contains a calculation for probabilistic analysis	3.3.2.3
TTD (CP)	KM for full follow up period, stopping rule at 18 weeks and completion rates applied		3.3.2.3
Cost inputs			
Dostarlimab cost (up to cycle 18)	[redacted]	-	3.5.2
Dostarlimab cost (up to cycle 19+)	[redacted]	-	
Carboplatin and paclitaxel cost (up to cycle 18)	£74.73	-	
Admin cost up to cycle 18 dostarlimab+CP	£201.66	164.08, 243.06 Gamma	3.5.2
Admin cost cycle 19+ dostarlimab	£152.13	123.78, 183.36 Gamma	
Administration cost per cycle with CP (up to cycle 18)	£201.66	164.08, 243.06 Gamma	
Outpatient visit unit cost	£205.82	167.47, 248.08 Gamma	3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
CT scan unit cost	£118.58	96.48, 142.93 Gamma	
Complete blood count unit cost	£8.04	6.54, 9.69 Gamma	
Specialist nurse visit unit cost	£57.00	46.38, 68.7 Gamma	
GP visit unit cost	£47.00	38.24, 56.65 Gamma	
Resource use frequency			
Outpatient visit dostarlimab+CP in PF state up to cycle 18	0.30	0.24, 0.36 Gamma	3.5.3
Outpatient visit dostarlimab+CP in PD state up to cycle 18	0.12	0.1, 0.14 Gamma	
CT scan dostarlimab+CP in PF state up to cycle 18	0.13	0.11, 0.16 Gamma	
CT scan dostarlimab+CP in PD state up to cycle 18	0.07	0.06, 0.08 Gamma	
Complete blood count dostarlimab+CP in PF state up to cycle 18	0.33	0.27, 0.4 Gamma	
Complete blood count dostarlimab+CP in PD state up to cycle 18	0.09	0.07, 0.11 Gamma	
Blood pressure and heart rate dostarlimab+CP in PF state up to cycle 18	0.00	0.00, 0.00 Gamma	
Blood pressure and heart rate dostarlimab+CP in PD state up to cycle 18	0.00	0.00, 0.00 Gamma	
Specialist nurse visit dostarlimab+CP in PF state up to cycle 18	0.11	0.09, 0.13 Gamma	
Specialist nurse visit dostarlimab+CP in PD state up to cycle 18	0.10	0.08, 0.12 Gamma	
GP visit dostarlimab+CP in PF state up to cycle 18	0.00	0.00, 0.00 Gamma	
GP visit dostarlimab+CP in PD state up to cycle 18	0.01	0.01, 0.01 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Outpatient visit dostarlimab+CP in PF state from cycle 19+	0.13	0.11, 0.16 Gamma	
Outpatient visit dostarlimab+CP in PD state from cycle 19+	0.12	0.1, 0.14 Gamma	
CT scan dostarlimab+CP in PF state from cycle 19+	0.06	0.05, 0.07 Gamma	
CT scan dostarlimab+CP in PD state from cycle 19+	0.07	0.06, 0.08 Gamma	
Complete blood count dostarlimab+CP in PF state from cycle 19+	0.22	0.18, 0.27 Gamma	
Complete blood count dostarlimab+CP in PD state from cycle 19+	0.09	0.07, 0.11 Gamma	
Blood pressure and heart rate dostarlimab+CP in PF state from cycle 19+	0.00	0, 0 Gamma	
Blood pressure and heart rate dostarlimab+CP in PD state from cycle 19+	0.00	0, 0 Gamma	
Specialist nurse visit dostarlimab+CP in PF state from cycle 19+	0.07	0.06, 0.08 Gamma	
Specialist nurse visit dostarlimab+CP in PD state from cycle 19+	0.10	0.08, 0.12 Gamma	
GP visit dostarlimab+CP in PF state from cycle 19+	0.01	0.01, 0.01 Gamma	
GP visit dostarlimab+CP in PD state from cycle 19+	0.01	0.01, 0.01 Gamma	
Outpatient visit CP in PF state up to cycle 18	0.30	0.24, 0.36 Gamma	
Outpatient visit CP in PD state up to cycle 18	0.12	0.1, 0.14 Gamma	
CT scan CP in PF state up to cycle 18	0.13	0.11, 0.16 Gamma	
CT scan CP in PD state up to cycle 18	0.07	0.06, 0.08 Gamma	
Complete blood count CP in PF state up to cycle 18	0.33	0.27, 0.4 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Complete blood count CP in PD state up to cycle 18	0.09	0.07, 0.11 Gamma	
Blood pressure and heart rate CP in PF state up to cycle 18	0.00	0, 0 Gamma	
Blood pressure and heart rate CP in PD state up to cycle 18	0.00	0, 0 Gamma	
Specialist nurse visit CP in PF state up to cycle 18	0.11	0.09, 0.13 Gamma	
Specialist nurse visit CP in PD state up to cycle 18	0.10	0.08, 0.12 Gamma	
GP visit CP in PF state up to cycle 18	0.00	0, 0 Gamma	
GP visit CP in PD state up to cycle 18	0.01	0.01, 0.01 Gamma	
Outpatient visit CP in PF state from cycle 19+	0.08	0.07, 0.1 Gamma	
Outpatient visit CP in PD state from cycle 19+	0.12	0.1, 0.14 Gamma	
CT scan CP in PF state from cycle 19+	0.05	0.04, 0.06 Gamma	
CT scan CP in PD state from cycle 19+	0.07	0.06, 0.08 Gamma	
Complete blood count CP in PF state from cycle 19+	0.06	0.05, 0.07 Gamma	
Complete blood count CP in PD state from cycle 19+	0.09	0.07, 0.11 Gamma	
Blood pressure and heart rate CP in PF state from cycle 19+	0.00	0, 0 Gamma	
Blood pressure and heart rate CP in PD state from cycle 19+	0.00	0, 0 Gamma	
Specialist nurse visit CP in PF state from cycle 19+	0.07	0.06, 0.08 Gamma	
Specialist nurse visit CP in PD state from cycle 19+	0.10	0.08, 0.12 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
GP visit CP in PF state from cycle 19+	0.01	0.01, 0.01 Gamma	
GP visit CP in PD state from cycle 19+	0.01	0.01, 0.01 Gamma	
End of life costs			
End of life cost	8,716.94	7,092.45, 10,506.44 Gamma	3.5.3.1
Adverse event costs			
Anaemia unit cost	612.92	498.69, 738.74 Gamma	3.5.3.2
Neutropenia unit cost	560.68	456.19, 675.79 Gamma	
Neutrophil count decreased unit cost	901.96	733.87, 1,087.12 Gamma	
Hypertension unit cost	360.74	293.51, 434.79 Gamma	
White blood cell count decreased unit cost	901.96	733.87, 1,087.12 Gamma	
Hypokalaemia unit cost	1,789.88	1,456.32, 2,157.32 Gamma	
Pulmonary embolism unit cost	2,048.26	1,666.54, 2,468.74 Gamma	
Asthenia	0.00	0, 0 Gamma	
Lymphocyte count decreased unit cost	901.96	733.87, 1,087.12 Gamma	
Lipase increased unit cost	901.96		
Abdominal pain	437.01	355.57, 526.73 Gamma	
Urinary tract infection unit cost	2,020.71	1,644.13, 2,435.54 Gamma	
Nausea and hyponatremia unit cost	564.22	459.07, 680.05 Gamma	
Rash unit cost	227.88	185.41, 274.66 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
AE probabilities			
Anaemia dostarlimab+CP up to cycle 18	0.15	0.12, 0.18 Beta	3.5.3.2
Neutropenia dostarlimab+CP up to cycle 18	0.10	0.08, 0.11 Beta	
Neutrophil count decreased dostarlimab+CP up to cycle 18	0.08	0.07, 0.1 Beta	
Hypertension dostarlimab+CP up to cycle 18	0.07	0.06, 0.08 Beta	
White blood cell count decreased dostarlimab+CP up to cycle 18	0.07	0.05, 0.08 Beta	
Hypokalaemia dostarlimab+CP up to cycle 18	0.05	0.04, 0.06 Beta	
Pulmonary embolism dostarlimab+CP up to cycle 18	0.06	0.05, 0.07 Beta	
Asthenia dostarlimab+CP up to cycle 18	0.00	0, 0 Beta	
Lymphocyte count decreased dostarlimab+CP up to cycle 18	0.05	0.04, 0.06 Beta	
Lipase increased dostarlimab+CP up to cycle 18	0.05	0.04, 0.05 Beta	
Abdominal pain and amylase increased dostarlimab+CP up to cycle 18	0.04	0.03, 0.04 Beta	
Urinary tract infection dostarlimab+CP up to cycle 18	0.03	0.02, 0.04 Beta	
Nausea and hyponatremia dostarlimab+CP up to cycle 18	0.07	0.05, 0.08 Beta	
Rash dostarlimab+CP up to cycle 18	0.05	0.04, 0.05 Beta	
Anaemia CP up to cycle 18	0.17	0.14, 0.2 Beta	
Neutropenia CP up to cycle 18	0.09	0.08, 0.11 Beta	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Neutrophil count decreased CP up to cycle 18	0.14	0.11, 0.17 Beta	
Hypertension CP up to cycle 18	0.03	0.03, 0.04 Beta	
White blood cell count decreased CP up to cycle 18	0.05	0.04, 0.06 Beta	
Hypokalaemia CP up to cycle 18	0.04	0.03, 0.04 Beta	
Pulmonary embolism CP up to cycle 18	0.05	0.04, 0.06 Beta	
Asthenia CP up to cycle 18	0.00	0, 0 Beta	
Lymphocyte count decreased CP up to cycle 18	0.07	0.06, 0.09 Beta	
Lipase increased CP up to cycle 18	0.01	0.01, 0.01 Beta	
Abdominal pain and amylase increased CP up to cycle 18	0.02	0.01, 0.02 Beta	
Urinary tract infection CP up to cycle 18	0.02	0.01, 0.02 Beta	
Nausea and hyponatremia CP up to cycle 18	0.05	0.04, 0.06 Beta	
Rash CP up to cycle 18	0.01	0.01, 0.01 Beta	
Subsequent treatment			
Proportion receiving carboplatin and doxorubicin following discontinuation from dostarlimab	0.04	0.04, 0.05 Dirichlet	3.5.3.3
Proportion receiving carboplatin and paclitaxel following discontinuation from dostarlimab	0.13	0.11, 0.16 Dirichlet	
Proportion receiving paclitaxel following discontinuation from dostarlimab	0.06	0.05, 0.07 Dirichlet	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion receiving doxorubicin following discontinuation from dostarlimab	0.32	0.26, 0.39 Dirichlet	
Proportion receiving carboplatin and lenvatinib following discontinuation from dostarlimab	0.06	0.05, 0.07 Dirichlet	
Proportion receiving pembrolizumab with lenvatinib following discontinuation from dostarlimab	0.00	0, 0 Dirichlet	
Proportion receiving cisplatin following discontinuation from dostarlimab	0.03	0.02, 0.04 Dirichlet	
Proportion receiving hormone therapy following discontinuation from dostarlimab	0.15	0.12, 0.18 Dirichlet	
Proportion receiving radiotherapy following discontinuation from dostarlimab	0.21	0.17, 0.25 Dirichlet	
Proportion receiving bevacizumab following discontinuation from CP	0.09	0.07, 0.11 Dirichlet	
Proportion receiving no treatment following discontinuation from CP	0.08	0.07, 0.1 Dirichlet	
Proportion receiving carboplatin and doxorubicin following discontinuation from CP	0.01	0.01, 0.01 Dirichlet	
Proportion receiving carboplatin and paclitaxel following discontinuation from CP	0.10	0.08, 0.13 Dirichlet	
Proportion receiving paclitaxel following discontinuation from CP	0.02	0.02, 0.03 Dirichlet	
Proportion receiving doxorubicin following discontinuation from CP	0.21	0.17, 0.25 Dirichlet	
Proportion receiving carboplatin and lenvatinib following discontinuation from CP	0.02	0.01, 0.02 Dirichlet	
Proportion receiving pembrolizumab with lenvatinib following discontinuation from CP	0.49	0.39, 0.58 Dirichlet	
Proportion receiving cisplatin following discontinuation from CP	0.02	0.02, 0.03 Dirichlet	
Proportion receiving hormone therapy following discontinuation from CP	0.14	0.11, 0.16 Dirichlet	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion receiving radiotherapy following discontinuation from CP	0.14	0.12, 0.17 Dirichlet	
Proportion receiving bevacizumab following discontinuation from CP	0.06	0.05, 0.07 Dirichlet	
Proportion receiving no treatment following discontinuation from CP	0.00	0, 0 Dirichlet	
Subsequent treatment cost dostarlimab+CP	3,363.96	-	
Subsequent treatment cost CP	47,057.71	-	
Quality of life			
Utility: PF	[redacted]	[redacted] Beta	3.4.1
Utility: PD	[redacted]	[redacted] Beta	
Anaemia disutility	0.12	0.1, 0.14 Beta	3.4.3
Neutropenia disutility	0.09	0.07, 0.11 Beta	
Neutrophil count decreased disutility	0.00	0, 0 Beta	
Hypertension disutility	0.02	0.02, 0.02 Beta	
White blood cell count decreased disutility	0.00	0, 0 Beta	
Hypokalaemia disutility	0.07	0.06, 0.09 Beta	
Pulmonary embolism disutility	0.32	0.26, 0.38 Beta	
Asthenia	0.07	0.06, 0.09 Beta	
Lymphocyte count decreased disutility	0.00	0, 0 Beta	
Lipase increased disutility	0.01	0.01, 0.01 Beta	
Abdominal pain and amylase increased disutility	0.07	0.06, 0.08 Beta	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Urinary tract infection disutility	0.01	0.01, 0.01 Beta	
Nausea and hyponatremia disutility	0.05	0.04, 0.05 Beta	
Rash disutility	0.12	0.09, 0.14 Beta	

Abbreviations: CP, carboplatin plus paclitaxel; CT, computed tomography; GFR, glomerular filtration rate; GP, general practitioner; OS, overall survival; PD, progressed disease; PF profession-free; PFS, progression-free survival.

3.8.2. Assumptions

A summary of the assumptions made in the model is presented in Table 49.

Table 49: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Population and comparators	Adult patients with MMRp/MSS endometrial cancer who are candidates for systemic therapy	This is aligned with the decision problem for this appraisal
	CP is an appropriate comparator for dostarlimab in combination with CP	
Model structure and settings	Lifetime horizon	A lifetime horizon was chosen because patients accumulate costs and QALYs until death. A [redacted]-year time horizon was chosen as the mean age of MMRp/MSS patients in RUBY trial was [redacted] years – assuming no patients survive beyond a mean age of 100 years
	The important costs and outcomes associated with endometrial cancer can be captured by PFS and PD health states	The partitioned survival model (PSM) structure is an established model framework to assess cost-effectiveness of oncology treatments and has been used in many prior NICE submissions. They often reproduce the observed survival outcomes (i.e., high face validity). The health states are consistent with the natural disease progression in patients with advanced or recurrent MMRp/MSS endometrial cancer
Cost and resource use inputs	Wastage of doses	In line with the treatment of endometrial cancer in clinical practice
	Resource use estimated by UK clinical experts based on treatment phase, health state and treatment	Based on UK clinical expert opinion, aligns with NICE TA963 submission (88)
	Treatment discontinuation for dostarlimab plus CP and comparators aligned with RUBY trial discontinuation criteria and treatment SmPCs	RUBY trial and SmPC discontinuation criteria reflect anticipated clinical practice as validated by UK clinicians
	Subsequent treatment proportions from RUBY trial, with no immunotherapy retreatment as per clinical practice.	In line with the PFS data in the trial and reflective of therapies used in UK clinical practice.
	End-of life costs applied as a one-off cost in the year at which patients die	Patients will accrue end-of life care costs before they die and therefore, they are applied within the year of death
Quality of life inputs	Grade ≥ 3 AEs included that occur in more than 2% of people, and assumed occur in the first cycle of the model time horizon	AEs were likely to occur rapidly after treatment and only require acute care

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; CDF, cancer drugs fund; MMRp, mismatch repair proficient; MSS, microsatellite stable; NHS, National Health System; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressed disease; PFS, progression-free survival; SmPC, summary of product characteristics; UK, United Kingdom; QALYs, quality-adjusted life years.

3.9. Base-case results

3.9.1. Base-case incremental cost-effectiveness analysis results

The base-case results are presented using the list price for CP and a simple PAS discount of [redacted]% on the list price for dostarlimab.

Table 50 presents the base-case deterministic results for dostarlimab in combination with CP compared with CP, and Table 51 presents the corresponding NHB at the NICE WTP thresholds of £20,000 and £30,000 per QALY, respectively.

In the base-case, dostarlimab was associated with £[redacted] incremental costs and 0.755 incremental QALYs compared to CP, resulting in an ICER of £[redacted] per QALY gained. This is below the NICE £20,000 per QALY threshold. The incremental NHB of dostarlimab at the £20,000 per QALY and £30,000 per QALY WTP thresholds was [redacted] and [redacted], respectively. Disaggregated results are presented in Appendix H.

Table 50: Base-case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]				
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.755	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 51: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Dostarlimab in combination with CP	[redacted]	[redacted]				
CP	[redacted]	[redacted]	[redacted]	0.755	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

3.10. Exploring uncertainty

Probabilistic sensitivity analysis (PSA), deterministic one-way sensitivity analysis (OWSA) and scenario analysis have been conducted to explore the level of uncertainty in the base-case model results.

3.10.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA, where each variable associated with uncertainty in the model was varied jointly by drawing a value from its uncertainty distribution. The parameters varied, and the corresponding distribution have been outlined in Table 48.

Table 48 For the PSA, 1,000 simulations were run to allow for convergence in the incremental costs and QALYs.

Base-case results for the PSA are presented in Table 52. The ICER is consistent with that of the deterministic base-case (Table 50). At a £20,000 per QALY and £30,000 per QALY WTP threshold, [redacted]% and [redacted]% of dostarlimab simulations were cost-effective, respectively.

An incremental cost-effectiveness plane (ICEP) scatterplot (Figure 29) and cost-effectiveness acceptability curve (CEAC) (Figure 30) were produced to illustrate the level of uncertainty in the results.

Table 52: Base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.760	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 29: Incremental cost-effectiveness plane scatterplot

Abbreviations: CP, carboplatin plus paclitaxel; QALY, quality-adjusted life year.

Figure 30: Cost-effectiveness acceptability curve

Abbreviations: CP, carboplatin plus paclitaxel; QALY, quality-adjusted life year.

3.10.2. Deterministic sensitivity analysis

The OWSA varied one parameter at a time, assessing the impact on the incremental QALYs and incremental costs, and subsequently the ICER. A lower and upper bound was assigned to suitable parameters (presented in Table 53) based on the 95% CI around the mean. In the absence of CI data, a standard error of ±10% of the mean for each parameter was assumed and the lower and upper bounds were estimated depending on the assigned distribution. Survival parameters were not included in the OWSA as they are associated with multiple correlated parameters which are not appropriate to vary individually.

Results of the OWSA are presented in Table 53 and show the top 10 model drivers of the ICER for dostarlimab with CP versus CP. The ICER was most sensitive to the proportion receiving pembrolizumab with lenvatinib as a subsequent treatment in the placebo arm followed by the Dostarlimab with CP completion rates and medical resource use. The results are also presented in a tornado diagram (Figure 31).

Table 53: Tabulated OWSA results

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Base case		[redacted]	
Proportion receiving pembrolizumab with lenvatinib following discontinuation from CP	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 16)	[redacted]	[redacted]	[redacted]
Outpatient visit dostarlimab+CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit dostarlimab+CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 4)	[redacted]	[redacted]	[redacted]
Outpatient visit unit cost	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 7)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 10)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 13)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: dostarlimab completion rates per cycle (week) (cycle 1)	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; OS, overall survival; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free.

Figure 31: Tornado diagram

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression-free.

3.10.3. Scenario analysis

Scenario analyses were conducted to test specific alternative inputs for the assessment of structural and parametric uncertainty. Scenario analyses have been specified throughout this document and the results are summarised in Table 54.

Generally, the cost-effectiveness results remained robust across the scenario analyses, with the ICER remaining below £[redacted] per QALY in 17 out of the 18 tested scenarios. The scenario analyses that had the biggest impact on the ICER were those that tested the assumptions associated with subsequent therapy. Increasing the proportion of patients in the placebo arm being treated with pembrolizumab with lenvatinib upon progression to 75% to account for the projected market uptake of pembrolizumab with lenvatinib at second-line in 2025, resulted in CP being dominated by dostarlimab in combination with CP.

Table 54: Scenario analyses

No.	Category	Base-case value	Scenario value	Deterministic				Probabilistic
				Inc. costs (£)	Inc. Lys	Inc. QALYs	ICER (£/ QALY)	ICER (£/ QALY)
1	Base case	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Starting age	[redacted] (RUBY-1)	65.5 (UK RWE) (106)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs	3.50%	1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4			5.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	PFS Curve selection (CP)	Normal, k=2 flexible spline model	Odds, k=2 flexible spline model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	PFS curve selection (dostarlimab+CP)	Odds, k=3 flexible spline model	Normal, k=2 flexible spline model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	PFS curve selection	Flexible spline models	Independent models (CP, log-logistic; dostarlimab, generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	OS curve selection (dostarlimab+CP)	Independent, log-normal	Independent, log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Treatment effect waning: OS and PFS	No waning	Waning from 8-10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10			Waning from 5-7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	TTD Completion rates	Completion rates used	Completion rates not used	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	Vial wastage	Vial wastage assumed	No vial wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	Adverse event threshold	Grade 3+ AEs ≥2% in either arm of RUBY-1	Grade 3+ AEs ≥5% in either arm of RUBY-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	Subsequent treatment assumptions	RUBY-1 data used, with no IO retreatment	Proportion receiving 'no treatment' assumed to be the same for dostarlimab and CP (set to dostarlimab proportion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No.	Category	Base-case value	Scenario value	Deterministic				Probabilistic
				Inc. costs (£)	Inc. Lys	Inc. QALYs	ICER (£/ QALY)	ICER (£/ QALY)
15			75% market share assumed for PEM+LEN in CP proportions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	Utility values	MMRp RUBY-1 source	ITT RUBY-1 source	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18		AE disutilities included	AE disutilities excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19		Age-adjustment included	No age adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; LEN, lenvatinib; LY, life years; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; QALYs, quality-adjusted life years; RWE, real-world evidence; TTD, time to treatment discontinuation.

3.11. Subgroup analysis

Subgroup analysis was not performed as part of this submission because MMRp/MSS was already a pre-specified population in the RUBY-1 trial.

3.12. Benefits not captured in the QALY calculation

Bringing an immunotherapy into earlier line settings will result in patients being offered the treatment sooner, which can be expected to delay time to disease progression in a greater proportion of patients. This has the potential to significantly delay disease progression and prolong OS without negatively impacting QoL in these patients (80, 165, 166)).

Patients with primary advanced or recurrent endometrial cancer experience dire health outcomes, demonstrated by the absolute shortfall of almost [redacted] QALYs versus patients in the general population. There is an unmet need for the introduction of novel treatment options beyond chemotherapy for the treatment of primary advanced or recurrent MMRp/MSS endometrial cancer. Currently, innovative treatment options for patients with primary advanced or recurrent endometrial cancer are restricted to patients who have experienced disease relapse.

3.13. Validation

3.13.1. Validation of cost-effectiveness analysis

Internal validity checks were performed by the original model developers as part of the TA963 appraisal (54). Validation was also performed by health economists on the updates made to the model for this specific decision problem. This included cell-by-cell checks, logical tests and validation of model outputs.

3.13.2. Clinical expert validation

GSK ran two advisory boards to seek clinical and health economic expert insight on the current treatment pathway in the UK, advice on the latest clinical data from the RUBY-1 trial and to seek estimates of long-term survival outcomes (137, 167). An advisory board (July 2024) was specifically run to understand appropriate modelling methods and curve selection for the economic model (137).

Clinical feedback was that the OS benefit was extremely meaningful, however the health economist at an advisory board noted that limited long-term OS would need to be supported by other similarly mature outcomes to mitigate uncertainty in OS extrapolations.

PFS2 was noted as both clinically meaningful and supportive of the durable benefit of dostarlimab in this population. Figure 32 overlays the Dostarlimab PFS2 KM with the base-case PFS and OS curve to illustrate the consistency between outcomes. The selection in OS curve may be considered conservative given the apparent convergence of the PFS2 KM with the selected OS distribution. The PFS2 KM sits between the extrapolations of OS and PFS, which is consistent with the expected relationship between PFS, PFS2 and OS.

Figure 32: PFS2 KM compared with selected PFS and OS curves – Dostarlimab in combination with CP

Abbreviations: CP, carboplatin plus paclitaxel; Dost, dostarlimab; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2.

Landmark survival estimates and average clinical advisor PFS estimates were also elicited from clinicians at the two advisory boards for the MMRp/MSS population. These estimates have been used throughout this submission to validate the chosen survival curves in terms of providing clinically plausible long-term estimates. Experts at the July 2024 advisory board agreed with the use of flexible models for PFS given that the shape of the hazard rates was non-monotonic (137).

3.13.3. External validation versus RWE

The external validity of the modelled outcomes was also tested by comparing outcomes to RWE identified in the literature for patients with primary advanced or recurrent endometrial cancer. A summary of the UK RWE identified is provided in Section 2.2.1. The median OS reported for patients receiving chemotherapy in these studies is compared to the results of CP in the RUBY-1 trial and the median OS predicted by the model. The results of the model are highly congruent with the values reported in the RUBY-1 trial, and the RWE studies.

Table 55: Comparison of RUBY-1 with RWE studies (CP)

Source	Median OS (months)
NHS trust England RWE (MMRp) (106)	28.3 [95% CI: 25.2, 48.6]
Banerjee et al. 2024 (all-comers, CP treated) (8)	17.2 [95% CI: 15.5, 19.0]
Banerjee et al. 2024 (all-comers, all 1L) (8)	27.2 [95% CI 24.7, 30.2]
RUBY-1 MMRp observed data (15)	27.0 [95% CI: 21.5, 35.6]
Modelled MMRp OS curve	[redacted]

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; NHS, National Health Service; OS, overall survival; RWE, real-world evidence; 1L: first-line.

3.14. Interpretation and conclusions of economic evidence

3.14.1. Summary of cost-effectiveness analysis

Over a lifetime time horizon, at a PAS price, dostarlimab in combination with CP is associated with incremental costs of £[redacted] and incremental QALYs of 0.755 compared to CP in the base case analysis. The resulting ICER is £[redacted] per QALY which is significantly below the NICE £20,000 per QALY WTP threshold.

Deterministic and probabilistic sensitivity analysis was undertaken to test the impact of uncertainty in inputs and assumptions in the model. The mean PSA results were aligned with the base case in terms of the ICER (£[redacted] per QALY gained). At a £20,000 per QALY and £30,000 per QALY WTP threshold, [redacted]% and [redacted]% of dostarlimab simulations were cost-effective, respectively.

In the OWSA, the subsequent treatment proportion for pembrolizumab with lenvatinib for patients in the placebo arm was the parameter that had the greatest impact on the base case ICER when varied at its lower and upper confidence interval. Other parameters that impacted the ICER were the completion rates and the resource use for dostarlimab. The majority of scenario analyses undertaken had little impact on the base case ICER, with the ICER remaining below £[redacted] per QALY in 17 out of 18 of the tested scenarios. Scenarios around the subsequent therapy assumptions had the biggest impact on the ICER.

3.14.2. Generalisability of the cost-effectiveness analysis

The economic evaluation is based on the patient population from MMRp/MSS cohort of the RUBY-1 trial, which is considered representative of patients with primary advanced or recurrent MMRp/MSS endometrial cancer in the UK. In the UK, the current clinical management and most relevant comparator is CP, and thus CP is used as the comparator within the economic case. Real-world median OS data reported in the literature aligned

closely with the median OS from the RUBY-1 trial for patients receiving chemotherapy. The mean age reported for MMRp/MSS patients in the RUBY-1 trial was also aligned with real-world evidence.

3.14.3. Strengths of cost-effectiveness analysis

The economic evaluation is based on the MMRp/MSS patient population from the robust Phase III, RUBY-1 trial, which is representative of patients with primary advanced or recurrent endometrial cancer. The RUBY-1 trial is the only trial that evaluated the efficacy and safety of dostarlimab in combination with CP as a first-line treatment in female adult patients with primary advanced or recurrent endometrial cancer (see Section 2.2). The MMRp/MSS population was a predefined, stratified population in the RUBY-1 trial, avoiding post-hoc bias.

Median survival has been reached for both OS (IA2) and PFS (IA1) in the dostarlimab arm of RUBY-1, which both show a clear benefit in favour of dostarlimab. In addition, TTD from the latest data cut of IA2 was complete at data cut off and has been used within the modelling.

The survival outcomes from RUBY-1, along with model inputs, have been confirmed through clinical validation. In addition, a wide range of scenarios have been presented exploring the inputs and approaches used within the economic model. This includes exploring alternative approaches to the dostarlimab treatment effect.

The economic analysis met all aspects of the NICE reference case, including performance of a cost-utility analysis from an NHS and PSS perspective, assessment of HRQoL using the EQ-5D, discounting of costs and benefits at 3.5% and treatment efficacy sourced from the pivotal trial.

3.14.4. Limitations of cost-effectiveness analysis

A limitation of the economic analysis is that despite OS data being more mature from the more recent IA2 data cut, extrapolations are required to derive long-term estimates of time-to-event outcomes. To overcome this limitation, alternative survival distributions in both arms were explored in scenario analysis. Long-term OS estimates have also been validated by clinical experts and compared to estimates reported in RWE studies.

3.14.5. Conclusion

The cost-effectiveness analysis demonstrates the potential for dostarlimab to be a cost-effective addition to the existing SoC in the NHS, CP. There remains an exceptionally high

unmet need which has existed for decades for this patient population who have been diagnosed with an incurable malignancy. Currently, the only novel treatment which has demonstrated efficacy for patients with MMRp/MSS endometrial cancer is the pembrolizumab with lenvatinib regimen which is only available following relapse. This regimen has demonstrated improvements versus chemo-monotherapy in the relapsed setting but, notably, no improvement in health outcomes in a first-line, 'RUBY-like' trial compared with CP (168). It is therefore critically important to expand patient access to these innovative therapies to the first-line setting where they are most effective and can provide the greatest benefits to patients.

Dostarlimab is the first and only novel therapy to demonstrate a significant OS benefit in a first-line, all-comer clinical trial, with clinically meaningful improvements to PFS, DOR, PFS2 and OS regardless of MMR status. The analysis outlined in the above economic evaluation demonstrates that making dostarlimab available in the first-line setting will help slow disease progression whilst maintaining QoL and ultimately prolong survival for these patients. Furthermore, the results from the cost-effectiveness analysis demonstrate dostarlimab in combination with CP to be a cost-effective use of NHS resources. Unfortunately, in the absence of dostarlimab, many patients will still go on to receive expensive, novel, treatments in later treatment lines, a setting where they have only a modest impact.

References

1. Kalampokas E, Giannis G, Kalampokas T, Papathanasiou AA, Mitsopoulou D, Tsironi E, et al. Current Approaches to the Management of Patients with Endometrial Cancer. Cancers (Basel). 2022;14(18).

2. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. 2020;38(33):3841-50.

3. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer. 2008;18(4):803-8.

4. Bae-Jump VL, Sill M, Gehrig PA, Moxley K, Hagemann AR, Waggoner SE, et al. A randomized phase II/III study of paclitaxel/carboplatin/metformin versus paclitaxel/carboplatin/placebo as initial therapy for measurable stage III or IVA, stage IVB, or recurrent endometrial cancer: An NRG Oncology/GOG study. Gynecologic Oncology. 2020;159:7.

5. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu. J Clin Oncol. 2018;36(20):2044-51.

6. Miller DS, Randall ME, Filiaci V. Progress in endometrial cancer: Contributions of the former Gynecologic Oncology Group. Gynecol Oncol. 2020;157(2):312-22.

7. Seligson ND, Knepper TC, Ragg S, Walko CM. Developing Drugs for Tissue-Agnostic Indications: A Paradigm Shift in Leveraging Cancer Biology for Precision Medicine. Clin Pharmacol Ther. 2021;109(2):334-42.

8. Banerjee S, Ingles Russo Garces A, Garside J, Rahman T, Pearson C, Heffernan K. Real-world patient characteristics and survival outcomes in patients with advanced or recurrent endometrial cancer in England: a retrospective, population-based study. BMJ Open. 2024;14(11):e083540.

9. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2022;270:50-89.

10. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(9):860-77.

11. National institute for Health and Care Excellence. Single Technology Appraisal | Committee Papers | Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]. Available on: https://www.nice.org.uk/guidance/ta904/evidence/appraisal-consultation-committee-papers-pdf-13070962189 (last accessed: January 2025). 2023.

12. Oaknin A, Gilbert L, Tinker AV, Brown J, Mathews C, Press J, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study. Journal for ImmunoTherapy of Cancer. 2022;10(1):e003777.

13. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020;38(1):1-10.

14. Makker V, Colombo N, Herráez AC, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. New England Journal of Medicine. 2022;386(5):437-48.

15. Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of Oncology. 2024.

16. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388(23):2145-58.

17. National Health Service England. Cancer Registration Statistics, England, 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2022# (last accessed: January 2025). 2024.

18. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(3):520-9.

19. Ryan NAJ, McMahon R, Tobi S, Snowsill T, Esquibel S, Wallace AJ, et al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. PLoS Med. 2020;17(9):e1003263.

20. GSK. Data on file. EC Eligible patient numbers. 2024.

21. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 2023;73(1):17-48.

22. Henry Ford Health. Olivia's story: Uterine Cancer. Available at: https://www.henryford.com/services/uterine-cancer/stories/olivia (accessed on: January 2025).

23. Peaches Womb Cancer Trust. Patient Stories. Available at: https://www.peachestrust.org/category/patient-stories/ (accessed on: January 2025). 2022.

24. Chen J, Zou Q, Chen X, Liu X, Ding S, Mo Y, et al. Quality of life in patients with endometrial carcinoma: A Longitudinal Study. Nurs Open. 2022;9(3):1815-21.

25. Ferrandina G, Petrillo M, Mantegna G, Fuoco G, Terzano S, Venditti L, et al. Evaluation of quality of life and emotional distress in endometrial cancer patients: a 2-year prospective, longitudinal study. Gynecol Oncol. 2014;133(3):518-25.

26. Huijgens AN, Mertens HJ. Factors predicting recurrent endometrial cancer. Facts Views Vis Obgyn. 2013;5(3):179-86.

27. Odagiri T, Watari H, Hosaka M, Mitamura T, Konno Y, Kato T, et al. Multivariate survival analysis of the patients with recurrent endometrial cancer. J Gynecol Oncol. 2011;22(1):3-8.

28. Cancer Research UK. Survival for womb cancer. Available at: https://www.cancerresearchuk.org/about-cancer/womb-cancer/survival (accessed on: January 2025). 2024.

29. Macmillan Cancer Support. No one overlooked: Experiences of older people affected by cancer. Available at: https://www.macmillan.org.uk/_images/experiencesofolderpeople_tcm9-271121.pdf (accessed on: January 2024).

30. Passarello K, Kurian S, Villanueva V. Endometrial Cancer: An Overview of Pathophysiology, Management, and Care. Semin Oncol Nurs. 2019;35(2):157-65.

31. National Health Service. Womb (uterus) cancer - Symptoms.. Available at: https://www.nhs.uk/conditions/womb-cancer/symptoms/ (accessed on: January 2025). Updated: 2024.

32. Niedzwiedz CL, Knifton L, Robb KA, Katikireddi SV, Smith DJ. Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. BMC Cancer. 2019;19(1):943.

33. Heo J, Chun M, Oh YT, Noh OK. Psychiatric comorbidities among endometrial cancer survivors in South Korea: a nationwide population-based, longitudinal study. J Gynecol Oncol. 2019;30(2):e15.

34. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecologic Cancer. 2021;31(1):12-39.

35. Medicines & Healthcare products Regulatory Agency (MHRA). Jemperli (Dostarlimab) Summary of Product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963 (last accessed: January 2025). 2024.

36. National Institute for Health and Care Excellence. Diagnostics guidance [DG42]. Testing strategies for Lynch syndrome in people with endometrial cancer. Available at: https://www.nice.org.uk/guidance/dg42 (accessed on: January 2025). 2020.

37. National Institute for Health and Care Excellence. British National Formulary | Medicinal forms | Dostarlimab [Specialist drug]. Available on: https://bnf.nice.org.uk/drugs/dostarlimab-specialist-drug/medicinal-forms/ (accessed on: September 2024).

38. Cancer Research UK. Uterine cancer incidence statistics. 2017-19. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence. (accessed on: January 2025).

39. Njoku K, Barr CE, Crosbie EJ. Current and Emerging Prognostic Biomarkers in Endometrial Cancer. Front Oncol. 2022;12:890908.

40. Münstedt K, Grant P, Woenckhaus J, Roth G, Tinneberg HR. Cancer of the endometrium: current aspects of diagnostics and treatment. World J Surg Oncol. 2004;2:24.

41. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 2014;15(7):e268-78.

42. El-Nashar SA, Mariani A. Uterine carcinosarcoma. Clin Obstet Gynecol. 2011;54(2):292-304.

43. European Society for Medical Oncology. Endometrial Cancer: A Guide for Patients, Patient Information Based on ESMO Clinical Practice Guidelines. 2012. Available at: https://www.esmo.org/content/download/6604/115031/file/EN-Endometrial-Cancer-Guide-for-Patients.pdf (accessed on: January 2025).

44. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103-4.

45. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. International Journal of Gynecology & Obstetrics. 2023;162(2):383-94.

46. Trojano G, Olivieri C, Tinelli R, Damiani GR, Pellegrino A, Cicinelli E. Conservative treatment in early stage endometrial cancer: a review. Acta Biomed. 2019;90(4):405-10.

47. Cancer Research UK. Early Diagnosis Data Hub. Available at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ (accessed on: January 2025).

48. Elshaikh MA, Yashar CM, Wolfson AH, Cardenes HR, Erickson B, Jhingran A, et al. Advanced stage endometrial cancer. Available from: https://acsearch.acr.org/docs/3083084/narrative/ (last accessed: January 2025). 2014.

49. Jeppesen MM, Mogensen O, Hansen DG, Iachina M, Korsholm M, Jensen PT. Detection of recurrence in early stage endometrial cancer - the role of symptoms and routine follow-up. Acta Oncol. 2017;56(2):262-9.

50. British Gynaecological Cancer Society (BGCS). Uterine Cancer Guidelines: Recommendations for Practice. Available at: https://www.bgcs.org.uk/wp-content/uploads/2019/05/BGCS-Endometrial-Guidelines-2017.pdf (accessed on: December 2024).

51. Mulet-Margalef N, Linares J, Badia-Ramentol J, Jimeno M, Sanz Monte C, Manzano Mozo JL, et al. Challenges and Therapeutic Opportunities in the dMMR/MSI-H Colorectal Cancer Landscape. Cancers (Basel). 2023;15(4).

52. Li G-M. Mechanisms and functions of DNA mismatch repair. Cell Research. 2008;18(1):85-98.

53. Antill Y, Buchanan DD, Scott CL. Mismatch repair and clinical response to immune checkpoint inhibitors in endometrial cancer. Cancer. 2022;128(6):1157-61.

54. National institute for Health and Care Excellence. Committee Papers | Single Technology Appraisal | Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3986]. Available on: https://www.nice.org.uk/guidance/ta963/evidence/committee-papers-pdf-13366765117. 2024.

55. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

56. Heffernan K, Nikitas FS, Shukla U, Camejo HS, Knott C. Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis. Gynecol Oncol. 2022;166(2):317-25.

57. Park UB, Jeong TJ, Gu N, Lee HT, Heo YS. Molecular basis of PD-1 blockade by dostarlimab, the FDA-approved antibody for cancer immunotherapy. Biochem Biophys Res Commun. 2022;599:31-7.

58. Costa B, Vale N. Dostarlimab: A Review. Biomolecules. 2022;12(8).

59. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science. 2012;337(6102):1678-84.

60. Sevko A, Michels T, Vrohlings M, Umansky L, Beckhove P, Kato M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. J Immunol. 2013;190(5):2464-71.

61. Liechtenstein T, Perez-Janices N, Gato M, Caliendo F, Kochan G, Blanco-Luquin I, et al. A highly efficient tumor-infiltrating MDSC differentiation system for discovery of anti-neoplastic targets, which circumvents the need for tumor establishment in mice. Oncotarget. 2014;5(17):7843-57.

62. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res. 2014;20(11):2831-7.

63. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. Cell Immunol. 2010;263(1):79-87.

64. Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Caruso G, et al. Endometrial carcinosarcoma. Int J Gynecol Cancer. 2023;33(2):147-74.

65. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer Cell. 2015;28(6):690-714.

66. Siegenthaler F, Lindemann K, Epstein E, Rau TT, Nastic D, Ghaderi M, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecol Oncol. 2022;165(2):230-8.

67. Cancer Research UK. Uterine cancer statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Five (accessed on: January 2024). 2020.

68. Cancer Research UK. Uterine cancer risk. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/risk-factors. (accessed on: January 2025).

69. Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018;118(8):1130-41.

70. Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract. 2017;4:19.

71. National Health Service England. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021/cancer-survival-by-stage (accessed on: October 2024). 2023.

72. . !!! INVALID CITATION !!! (10-12).

73. Patient. Endometrial cancer. Available from: https://patient.info/doctor/endometrial-cancer (accessed on: January 2025). 2021.

74. Stefanacci RG. Changes in the Body With Aging MSD Manual Consumer Version: MSD Manual; 2024 [Available from: https://www.msdmanuals.com/home/older-people's-health-issues/the-aging-body/changes-in-the-body-with-aging.

75. World Health Organization. Ageing and health. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (accessed on: January 2025). 2024.

76. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, et al. Endometrial cancer. Nat Rev Dis Primers. 2021;7(1):88.

77. Gao H, Xiao M, Bai H, Zhang Z. Sexual Function and Quality of Life Among Patients With Endometrial Cancer After Surgery. Int J Gynecol Cancer. 2017;27(3):608-12.

78. GSK. Data on file. Global Advanced/Recurrent Endometrial Cancer Patient Expert Council run by GSK. Nov 2022.

79. Rubinstein M, Shen S, Monk BJ, Tan DSP, Nogueira-Rodrigues A, Aoki D, et al. Looking beyond carboplatin and paclitaxel for the treatment of advanced/recurrent endometrial cancer. Gynecol Oncol. 2022;167(3):540-6.

80. Hui R, Garon EB, Goldman JW, Leighl NB, Hellmann MD, Patnaik A, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Ann Oncol. 2017;28(4):874-81.

81. National institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. Available from: https://www.nice.org.uk/guidance/ta531 (last accessed: September 2024). 2018.

82. National Institute for Health and Care Excellence. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779]. Available at: https://www.nice.org.uk/guidance/ta779/documents/committee-papers (accessed on: December 2024). 2022.

83. National Institute for Health and Care Excellence. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer [IPG356]. Available at: https://www.nice.org.uk/guidance/ipg356 (accessed on: September 2024). 2010.

84. National institute for Health and Care Excellence. NICE guidance. TA904. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Published 21 June 2023. Available at: https://www.nice.org.uk/guidance/ta904 (last accessed: September 2024). 2023.

85. National institute for Health and Care Excellence. Technology appraisal guidance | TA914 | Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. Available on: https://www.nice.org.uk/guidance/ta914 (last accessed: January 2025). 2023.

86. GSK. Data on file. Endometrial cancer RUBY advisory board. July 2022.

87. National Institute for Health and Care Excellence. Managed Access Agreement | Dostarlimab with platinum-containing chemotherapy for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3968]. Available on: https://www.nice.org.uk/guidance/ta963/resources/managed-access-agreement-pdf-13366766413 (last accessed: September 2024). 2024.

88. National institute for Health and Care Excellence. Technology appraisal guidance | Dostarlimab with platinum-containing chemotherapy for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA963]. Available on: https://www.nice.org.uk/guidance/ta963 (accessed on: December 2024). 2024.

89. Oaknin A, Pothuri B, Gilbert L, Sabatier R, Brown J, Ghamande S, et al. Safety, Efficacy, and Biomarker Analyses of Dostarlimab in Patients with Endometrial Cancer: Interim Results of the Phase I GARNET Study. Clinical Cancer Research. 2023;29(22):4564-74.

90. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol. 2020;38(26):2981-92.

91. National Health Service England. National Cancer Drugs Fund List. Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ (last accessed: January 2025). 2025.

92. National institute for Health and Care Excellence. Technology appraisal guidance | TA904 | Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Available on: https://www.nice.org.uk/guidance/ta904 (last accessed: September 2024). 2023.

93. Wagner VM, Backes FJ. Do Not Forget about Hormonal Therapy for Recurrent Endometrial Cancer: A Review of Options, Updates, and New Combinations. Cancers (Basel). 2023;15(6).

94. National institute for Health and Care Excellence. NICE health technology evaluations: the manual. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (accessed on: January 2025). 2022.

95. European Medicines Agency. Imfinzi EPAR. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi (accessed on: October 2024). 2024.

96. Food and Drug Adminisration (FDA). Imfinzi product information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf (accessed on: January 2025). 2024.

97. National institute for Health and Care Excellence. Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating primary advanced or recurrent endometrial cancer [ID6381]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11461 (last accessed: January 2025). 2024.

98. Gov.UK. Equality Act 2010: guidance. Available from: https://www.gov.uk/guidance/equality-act-2010-guidance (last accessed: January 2025). 2015.

99. National Institute for Health and Care Excellence. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer [TA887]. Available from: https://www.nice.org.uk/guidance/ta887 (accessed on: January 2025). 2023.

100. National Institute for Health and Care Excellence. Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more treatments [TA930]. Available from: https://www.nice.org.uk/guidance/ta930 (last accessed: January 2025). 2023.

101. Moss EL, Teece L, Darko N. Uterine cancer mortality and Black women: time to act. The Lancet Oncology. 2023;24(6):586-8.

102. Njoku K, Barr CE, Hotchkies L, Quille N, Wan YL, Crosbie EJ. Impact of socio-economic deprivation on endometrial cancer survival in the North West of England: a prospective database analysis. Bjog. 2021;128(7):1215-24.

103. Zhu C, Ma X, Hu Y, Guo L, Chen B, Shen K, et al. Safety and efficacy profile of lenvatinib in cancer therapy: a systematic review and meta-analysis. Oncotarget. 2016;7(28).

104. Mohammed S, Polymeros K, Wickham-Joseph R, Luqman I, Charadva C, Morris T, et al. Comparing Characteristics of Endometrial Cancer in Women of South Asian and White Ethnicity in England. Cancers. 2021;13(23):6123.

105. GSK. Data on file. Ruby Clinical Study Protocol 4010-03-001 Version 4.0. Mar 2022.

106. Wesselbaum A, Wallis J, Luhar S, Tunaru F, Carpenter L, Schneider D, et al. A real-world study of patients with advanced/recurrent endometrial cancer across England and Scotland2024.

107. GSK. Data on file. UK advisory board: External insights into the RUBY data. April 2023.

108. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 07-March-2023 (data cut off: 28-SEP-2022).

109. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 19-Janurary-2024 (data cut off: 22-SEP-2023).

110. Mirza MR, Sharma S, Herrstedt J, Shahin MS, Cibula D, Fleming E, et al. 740MO Dostarlimab + chemotherapy for the treatment of primary advanced or recurrent endometrial cancer (pA/rEC): Analysis of progression free survival (PFS) and overall survival (OS) outcomes by molecular classification in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. Annals of Oncology. 2023;34:S507.

111. Powell MA, Auranen A, Willmott LJ, Gilbert L, Black D, Cibula D, et al. 37MO Dostarlimab plus chemotherapy in primary advanced or recurrent endometrial cancer (pA/rEC) in the RUBY trial: Overall survival (OS) by MMR status and molecular subgroups. ESMO Open. 2024;9.

112. Auranen A, Powell MA, Sukhin V, Landrum LM, Ronzino G, Buscema J, et al. Safety of dostarlimab in combination with chemotherapy in patients with primary advanced or recurrent endometrial cancer in a phase III, randomized, placebo-controlled trial (ENGOT-EN6-NSGO/GOG-3031/RUBY). Ther Adv Med Oncol. 2024;16:17588359241277656.

113. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med. 2020;18(1):87.

114. Sung M, Zer A, Walia P, Khoja L, Maganti M, Labbe C, et al. Correlation of immune-related adverse events and response from immune checkpoint inhibitors in patients with advanced non-small cell lung cancer. J Thorac Dis. 2020;12(5):2706-12.

115. GSK. Data on file. UK advisory boad: UK RUBY Part 1 IA2 ('Post-SGO'). April 2024.

116. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes. Journal of Clinical Oncology. 2014;32(12):1277-80.

117. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.

118. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.

119. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021;385(8):683-94.

120. Kim J, Lim J, Lee SW, Park JY, Suh DS, Kim JH, et al. Immune checkpoint inhibitors with chemotherapy for primary advanced mismatch repair-deficient endometrial cancer: A cost-effectiveness analysis. Gynecol Oncol. 2023;179:106-14.

121. Benjamin DJ, Padula WV, Hsu RC. Cost effectiveness of immunotherapy combination therapies for endometrial cancer. Gynecol Oncol Rep. 2024;52:101351.

122. Francoeur AA, Richardson, M. T., Johnson, C. R., Liang, S-Y., Tewari, K. S., Chan, J. K. Cost-effectiveness analysis of immunotherapy regimens in advanced or recurrent endometrial cancer: an analysis of the NRG-GY 018 and RUBY trials. SGO 2024.

123. Ackroyd SA, Huang ES, Kurnit KC, Lee NK. Pembrolizumab and lenvatinib versus carboplatin and paclitaxel as first-line therapy for advanced or recurrent endometrial cancer: A Markov analysis. Gynecol Oncol. 2021;162(2):249-55.

124. Batman S, Bohn J, Weisenberger MW, Hersh A, Bruegl A, Caughey A, et al. Trastuzumab with carboplatin/paclitaxel for treatment of advanced stage and recurrent uterine papillary serous carcinoma: A cost-effectiveness analysis. Gynecol Oncol. 2021;160(1):214-8.

125. You M, Zeng X, Zhang J, Huang Y, Zhang Y, Cai Z, et al. Cost-effectiveness analysis of dostarlimab plus carboplatin-paclitaxel as first-line treatment for advanced endometrial cancer. Front Immunol. 2023;14:1267322.

126. Huo G, Song Y, Chen P. Cost-effectiveness of pembrolizumab plus chemotherapy for advanced endometrial cancer. J Gynecol Oncol. 2024.

127. Huo G, Song Y, Chen P. Cost-effectiveness of atezolizumab plus chemotherapy for advanced/recurrent endometrial cancer. J Gynecol Oncol. 2024;35.

128. Canada's Drug Agency. Reimbursement Recommendation: Dostarlimab (Jemperli). Available from: https://www.cda-amc.ca/sites/default/files/DRR/2024/PC0325%20Jemperli_Rec.pdf (last accessed: January 2025). 2024.

129. Scottish Medicines Consortium. Dostarlimab concentrate for solution for infusion (Jemperli®). Available from: https://scottishmedicines.org.uk/media/8231/dostarlimab-jemperli-final-march-2024-for-website.pdf (last accessed: January 2025). 2024.

130. Pharmaceutical Benefits Advisory Committee. Dostarlimab, Solution concentrate for I.V. infusion 500 mg in 10 mL, Jemperli®. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-11/files/dostarlimab-psd-nov-2023.pdf (last accessed: January 2025). 2023.

131. GSK. Data on file. UK advisory board: Advanced endometrial cancer survival outcomes. March 2023.

132. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based

chemotherapy [TA673]. Available from: https://www.nice.org.uk/guidance/ta673/history (accessed on: January 2025). 2021.

133. Woods BS, Sideris E, Palmer S, Latimer N, Soares M. Partitioned Survival and State Transition Models for Healthcare Decision Making in Oncology: Where Are We Now? Value in Health. 2020;23(12):1613-21.

134. Woods BS SE, Palmer SJ, Latimer N, Soares MFO. NICE Decision Support Unit. technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review. Available at: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD19-Partitioned-Survival-Analysis-final-report.pdf (accessed on: 02 May 2024). 2023.

135. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY) [Internet]. 2019. Available from: https://clinicaltrials.gov/study/NCT03981796.

136. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Report by the Decision Support Unit. 2011.

137. GSK. Data on file. UK Advisory Board advanced endometrial cancer survival outcomes in RUBY-1. July 2024.

138. Rutherford M, Lamber, P., Sweeting, MJ., Pennington, B., Crowther, MJ., Abrams, KR., Latimer, NR. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD21-Flex-Surv-TSD-21_Final_alt_text.pdf (last accessed: August 2024). 2020.

139. Palmer S, Borget I, Friede T, Husereau D, Karnon J, Kearns B, et al. A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies. Value in Health. 2023;26(2):185-92.

140. Gray J, Sullivan T, Latimer NR, Salter A, Sorich MJ, Ward RL, et al. Extrapolation of Survival Curves Using Standard Parametric Models and Flexible Parametric Spline Models: Comparisons in Large Registry Cohorts with Advanced Cancer. Medical Decision Making. 2021;41(2):179-93.

141. GSK. [Data on File] OS SubequentTreatment Outputs 2024.

142. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England (updated October 2019). Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (last accessed: November 2024). 2019.

143. M Hernández Alava SP, A Wailoo,. Estimating EQ-5D by age and sex for the UK. Available on: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d (accessed on: September 2024). 2022.

144. Hildebrandt T, Thiel FC, Fasching PA, Graf C, Bani MR, Loehberg CR, et al. Health utilities in gynecological oncology and mastology in Germany. Anticancer Res. 2014;34(2):829-35.

145. Ackroyd S, Kurnit K, Koripelly A, Zoleta C, Yamada D, Lee N. Time is of the essence; defining time toxicity in patients on treatment for advanced/recurrent endometrial cancer. Gynecologic Oncology. 2023;176:S14-S5.

146. Ackroyd SA, Fleming G, Attia N, Zoleta C, Lee NK. Abstract A005: The cause behind the COST – exploring qualitative and quantitative aspects of financial toxicity in women diagnosed with advanced/recurrent endometrial cancer. Clinical Cancer Research. 2024;30(5_Supplement):A005-A.

147. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010;26(5):1091-6.

148. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.

149. National institute for Health and Care Excellence. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer [TA411]. Available from: https://www.nice.org.uk/guidance/ta411 (accessed on: August 2024). 2016.

150. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British Journal of Cancer. 2006;95(6):683-90.

151. Nwankwo C, Shah R, Kebede N, Shah A, Corman S. 292 Real-world treatment patterns, healthcare resource use, and costs by line of therapy among endometrial cancer patients newly initiating systemic therapies2020. A34.1-A p.

152. Kebede N, Shah R, Shah A, Corman S, Nwankwo C. Treatment patterns and economic burden among cervical and endometrial cancer patients newly initiating systemic therapy. Future Oncol. 2022;18(8):953-64.

153. Chen LC, Huang Y, Hou JY, Khoury-Collado F, Melamed A, St Clair CM, et al. Toxicity after adjuvant therapy for stage III uterine cancer. Gynecol Oncol. 2020;159(3):737-43.

154. Galaznik A, Shilnikova A, Rusli E, Ransom J, Lempernesse B, Berger M. PCN93: Health resource utilization in advanced ovarian and endometrial cancer in a United States insurance claims database. Value in Health. 2019;22:S454.

155. Pennington M, Gentry-Maharaj A, Karpinskyj C, Miners A, Taylor J, Manchanda R, et al. Long-Term Secondary Care Costs of Endometrial Cancer: A Prospective Cohort Study Nested within the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). PLoS One. 2016;11(11):e0165539.

156. Gov.UK. Drugs and pharmaceutical electronic market information tool. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (accessed on: January 2025). 2024.

157. National Institute for Health and Care Excellence. British National Formulary. Available from https://bnf.nice.org.uk/ (last accessed: January 2025).

158. NHS England. National Schedule of NHS Costs 2023/24, available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed on: January 2025). 2023.

159. Personal Social Services Research Unit. Units costs of health and social care. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/. Last accessed: August 2024. 2022.

160. National institute for Health and Care Excellence. British National Formulary (BNF). Available from: https://bnf.nice.org.uk/ (last accessed: August 2024). 2024.

161. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. Eur J Cancer Care (Engl). 2006;15(1):65-73.

162. National institute for Health and Care Excellence. Resource impact report: Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer (TA904). Available from: https://www.nice.org.uk/guidance/ta904/resources/resource-impact-report-pdf-13074419917 (last accessed: January 2025). 2023.

163. Woodford R, Zhou D, Kok P-S, Lord S, Marschner I, Friedlander M, et al. The validity of progression-free survival (PFS) 2 as a surrogate endpoint for overall survival (OS) in randomized controlled trials (RCTs) of advanced solid tumors. Journal of Clinical Oncology. 2021;39(15_suppl):1516-.

164. National institute for Health and Care Excellence. Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemotherapy. Available from: https://www.nice.org.uk/guidance/ta908 (last accessed: January 2025). 2023.

165. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239-51.

166. Banerjee S, Gonzalez-Martin A, Harter P, Lorusso D, Moore KN, Oaknin A, et al. First-line PARP inhibitors in ovarian cancer: summary of an ESMO Open - Cancer Horizons round-table discussion. ESMO Open. 2020;5(6):e001110.

167. GSK. Data on file. UK advisory board: UK RUBY Part 1 IA2 ('Post-SGO'). April 2024.

168. Marth C, Moore RG, Bidziński M, Pignata S, Ayhan A, Rubio MJ, et al. First-Line Lenvatinib Plus Pembrolizumab Versus Chemotherapy for Advanced Endometrial Cancer: A Randomized, Open-Label, Phase III Trial. Journal of Clinical Oncology. 2024;0(0):JCO-24-01326.

Appendices

The following appendices are provided in a standalone document:

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analyses

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

Appendix F: Health-related quality of life studies

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Clinical outcomes and disaggregated results from the model

Appendix I: Price details of treatments included in the submission

Appendix J: Supplementary efficacy data

Appendix K: Subsequent treatment information

Appendix L: Additional detail to Section 3

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

Summary of Information for Patients (SIP)

[February 2025]

File name	Version	Contains confidential information	Date
ID6145_MMRp_Dostarlimab+PC_EC_SIP_FINAL	FINAL	No	3rd February 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic: Dostarlimab Brand name: Jemperli®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The main population being appraised is adult patients **diagnosed with** endometrial cancer. Specifically, this includes patients with '**primary advanced**' cancer at the time of diagnosis, where the disease has spread outside of the womb to areas like the ovaries, lymph nodes, or lungs (1), and those with '**recurrent**' cancer, which has returned after being undetectable following treatment such as surgery, chemotherapy, or radiotherapy (2). Patients must **also** have endometrial cancer that is **mismatch repair proficient (MMRp)** or **microsatellite stable (MSS) and** be considered appropriate to receive systemic chemotherapy. MMRp/MSS means the cancer has stable genetic material, with no changes that could cause important proteins to work incorrectly or make the cancer behave in an unpredictable way.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 13th December 2024 the Medicines and Healthcare products Regulatory Agency (MHRA) authorised a new use for dostarlimab (JEMPERLI). This decision means it can now be used in combination with platinum-containing chemotherapy for the treatment of all adult patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. Previously, it was only available for patients with specific tumour characteristics, called mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) tumours, but this approval expands its use to patients with MMRp/MSS tumours, providing more patients with access to dostarlimab.

Because dostarlimab is already available to patients with dMMR/MSI-H endometrial cancer as part of this indication, this NICE appraisal will only focus on patients with MMRp/MSS endometrial cancer.

The full details on this authorisation can be found in this link to the summary of product characteristics (SmPC) for dostarlimab:
https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Peaches Womb Cancer Trust have reviewed previous versions of the patient information leaflet for dostarlimab, to ensure it is written and designed in a patient friendly format and language. Peaches Womb Cancer Trust were paid a fee for their time providing this review service.

Peaches Womb Cancer Trust co-created a disease awareness campaign (Spot Check) with GSK and another patient organisation, The Eve Appeal, which was launched in September 2023. Spot Check was designed to alert members of the public to recognize abnormal vaginal bleeding as a potential early sign of womb cancer and encourage them to seek advice from a healthcare professional if this occurs. Peaches Womb Cancer Trust were paid a fee for their time spent co-creating and sharing this campaign.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Endometrial cancer starts in the lining of the womb, called the endometrium, and is the most common type of womb cancer (3). In England, around 8,200 people are diagnosed with endometrial cancer each year (4).

Most cases of endometrial cancer are caught early, before the cancer has spread beyond the womb. Early-stage cancer is usually treated with surgery, and many patients are cured at this point. However, about 1 in 5 people are diagnosed with advanced cancer, which is more difficult to treat and unlikely to be fully cured

(5). Additionally, about 13% of patients who are treated for early-stage cancer may see their cancer return later (6). Advanced and recurrent cancers are very hard to treat, and people with these types of endometrial cancer typically live an average of 2 to 3 years (7-11).

Endometrial cancer can have specific genetic features that help doctors to better understand how the tumour will likely develop. Some tumours have a genetic change called 'mismatch repair deficient' (dMMR) or 'microsatellite instability-high' (MSI-H), while others do not and are called 'mismatch repair proficient'(MMRp) or 'microsatellite stable' (MSS) (12-14). Dostarlimab is being reviewed by NICE as a treatment for MMRp/MSS endometrial cancer. Around 75% of advanced or recurrent endometrial cancers are MMRp/MSS, making it the most common type (15).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Symptoms (16)

The most common symptom of endometrial cancer is abnormal bleeding from the vagina. This is often in women who have stopped having periods (post-menopausal women). It can also occur in pre-menopausal women although this is less common.

Abnormal vaginal bleeding can be:

- bleeding after the menopause
- bleeding that is unusually heavy, occurs between periods, or happens after sex
- a vaginal discharge that may be pink and watery.

About 9 out of 10 womb cancers, including endometrial cancer, are found early when women experience post-menopausal or irregular vaginal bleeding. The main treatment for early-stage womb cancer is an operation to remove the womb, cervix, fallopian tubes, and ovaries. However, some women are diagnosed with more advanced endometrial cancer, which is harder to treat and has a worse outcome. In these cases, additional treatments like chemotherapy, radiotherapy or immunotherapy may be needed after surgery.

Other symptoms of womb cancer may include:

- tummy (abdominal) pain
- a swollen tummy
- feeling bloated
- changes in bowel or bladder habits
- a new or persistent cough.

Diagnosis (17)

It is important to get checked by your doctor (GP) if you notice any of these symptoms. The GP will ask about the symptoms experienced, when they happen and whether there is anything that makes them better or worse. The doctor might do a physical examination. The doctor may be able to feel that the womb is larger than normal or may feel a lump (mass) in the tummy (abdomen) or pelvis. The doctor will then decide whether to refer for tests or to a specialist.

The specialist will ask questions, complete a physical examination, and arrange one or more tests. These tests can include(18):

- ultrasound (procedure that uses high frequency sound waves to create a picture of the womb)

- biopsy of the womb lining (taking a sample of the tissue that lines the womb, known as the endometrium)
- blood tests (for example blood cell levels and how well the liver and kidneys are working)
- Magnetic resonance imaging (MRI) scan (pictures using magnetism and radio waves to help find out where in the womb the cancer is, how big it is, and whether it has spread)
- Computerised tomography (CT) scan (x-rays and a computer to create detailed pictures, to find out more about where the cancer is and whether it has spread).

Genetic testing

Not all endometrial cancers are the same. To understand the specific type of cancer you have, your doctor will look for certain markers, like genes, proteins, or other molecules, in the sample taken of the tumour or in your blood. One important marker is called mismatch repair (MMR) status, which shows whether the tumour is MMRp/MSS. This is checked using a standard test in the NHS in England. The test examines a small sample of cancer cells, taken during a biopsy, to identify specific features that help determine the type of tumour (19).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment for endometrial cancer (20)

The treatment of endometrial cancer depends on how large it is and whether it has spread. It also depends on the patient's general health.

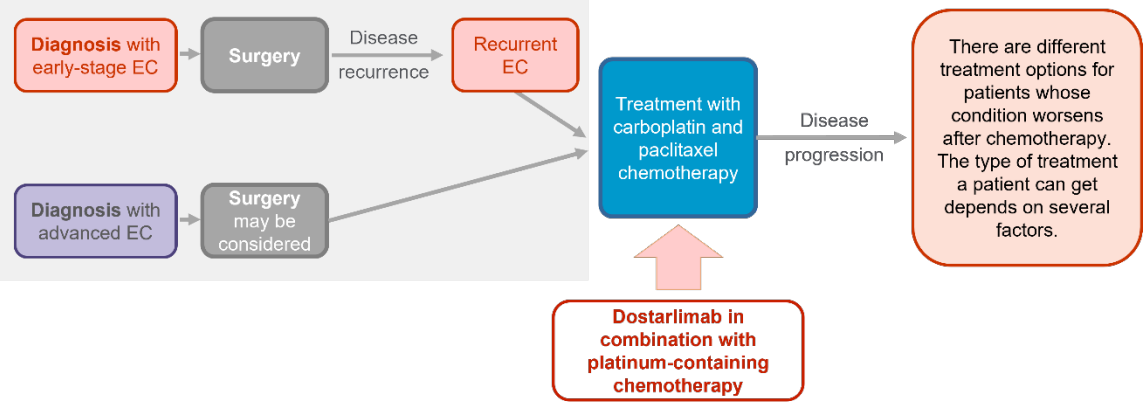
The primary treatment is surgery.

After surgery, or if surgery isn't possible, the patient might have chemotherapy, radiotherapy, or a combination of treatments.

Treatment for primary advanced or recurrent MMRp/MSS endometrial cancer (20)

While surgery can often cure endometrial cancer in its early stages, it is less likely to be effective if the cancer has spread and is at a more advanced stage (21, 22). For patients with MMRp/MSS tumours who can have chemotherapy, the most common treatment after surgery is a combination of two chemotherapy drugs – carboplatin and paclitaxel (23). These drugs target and destroy rapidly growing cells, like cancer cells (24). Dostarlimab would be used along with this carboplatin and paclitaxel regimen (Figure 1).

Figure 1: Current pathway for primary advanced or recurrent MMRp/MSS endometrial cancer with dostarlimab



Note: This is not a full list of all the treatment options available, and some patients may be offered other treatments like radiotherapy or chemotherapy before or after surgery.
Abbreviations: EC, endometrial cancer.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A systematic search of published literature, focussing on articles related to patient quality of life was completed to support this NICE submission (please see Section 3.4.1 and Appendix B of the company submission for the full results of this literature search). In addition, patient quotes from a GSK expert patient council and Peaches Womb Cancer Trust outline the PBE about living with the condition.

The main symptom of endometrial cancer is periodic, continuous or abnormal vaginal bleeding. The amount of bleeding experienced by patients prior to an endometrial cancer diagnosis can be incredibly heavy, patients report going through up to 44 sanitary pads every 10 days for months on end. One patient described that her body "felt like a ton of bricks" (8). Patient testimonials describe the debilitating nature of the disease symptoms - limiting a patient's ability to carry out everyday activities and impacting confidence and self-esteem (9).

After surgery for endometrial cancer, patients can experience pain during sex, have impaired physical functioning, impaired mobility and experience a reduction in usual daily activities. Radiotherapy is associated with side effects that can have substantial impact on quality of life and social functioning, and which may persist for years following treatment (25).

The use of chemotherapy in this setting is long-standing. There are well established management guidelines and protocols to manage side effects during treatment. Once treatment has been completed patients report concerns about the survivorship issues that still linger. Patients speak about a lack of health system

support for psychological and physical concerns following the initial 'flurry' of treatment that they experience, including what symptoms one should pay attention to, and sexual health issues (26).

Patients can experience increased anxiety, depression, and psychological problems due to the disease. Ahead of even beginning treatment, patients speak about feeling psychologically unprepared for the rigorous treatment that they are about to start. It is important to note the demographic of patients diagnosed with primary advanced or recurrent endometrial cancer is largely women in their 60s or older. These patients may be active in the workforce in addition to having caring responsibilities in the home, including caring for grandchildren and aging partners with independent health concerns. Patients worry about their inability to work and the impact on finances, inability to engage in everyday activities, alongside the emotional burden that the disease and treatment has on family and friends (9).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

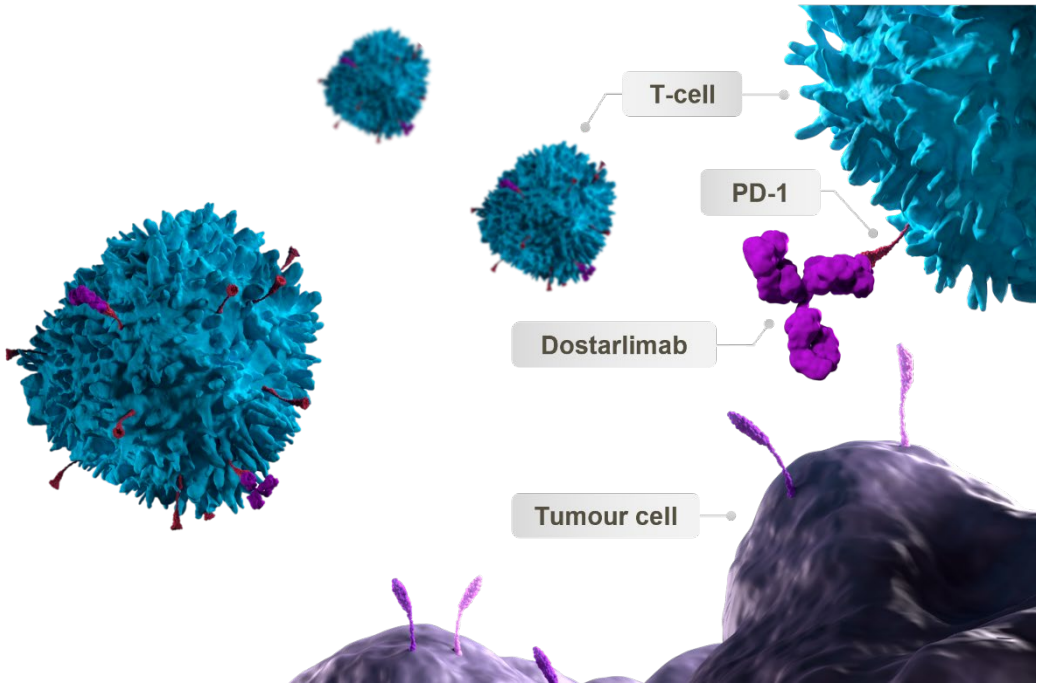
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Dostarlimab is a type of anti-cancer treatment called an *immunotherapy*, which works by helping the body's immune system better target and attack the tumour (cancer) cells (27). It works by binding to a protein called programmed death protein 1 (PD-1) on certain white blood cells of the immune system, known as T-cells (27). This boosts the immune system, making it more effective at recognising and destroying cancer cells. By blocking this protein, dostarlimab enhances the body's response to the tumour, helping to kill more cancer cells and prevent further tumour growth (28-30) (Figure 2).

Figure 2: Mechanism of action for dostarlimab (31)



Abbreviations: PD-1, programmed death receptor-1.

Dostarlimab is different from other treatments available for patients in this setting, such as chemotherapy, because it is an immuno-oncology treatment. Dostarlimab is the only treatment in this setting that specifically targets processes in the immune system to boost the body's own response against the tumour. Dostarlimab is given as an intravenous (IV) infusion, meaning it's delivered directly into the bloodstream.

The full details can be found in this link to the SmPC for dostarlimab:
https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Dostarlimab is intended to be used in combination with platinum-containing chemotherapy which is the recommended treatment for people with primary advanced or recurrent endometrial cancer (32).

As explained in section 2c, for patients with MMRp/MSS tumours who are fit and well enough to receive chemotherapy, the most common treatment following surgery is a combination of two chemotherapy drugs, carboplatin and paclitaxel, which are widely available (20).

Carboplatin is a platinum-containing chemotherapy drug. It works by entering the cancer cells and damaging their DNA, which prevents them from dividing and growing. This helps to slow down or stop the growth of cancer cells (33).

Paclitaxel belongs to a group of chemotherapy drugs called taxanes. It works by interfering with the ability of cancer cells to divide and multiply. Paclitaxel binds to structures inside the cells called microtubules, which are responsible for cell division. By binding to these structures, paclitaxel prevents them from functioning properly, leading to the death of cancer cells (34).

When carboplatin and paclitaxel are used together, they can have a more powerful effect on cancer cells than when used individually (23). They target different aspects of cell division and growth, making treatment with both agents combined more effective in killing cancer cells and reducing tumour size (24).

Dostarlimab works with chemotherapy and helps the body's natural immune defences to also target and destroy cancer cells, as explained in section 3a. By continuing treatment with dostarlimab after chemotherapy, it is thought to help create a long-lasting response. Combining chemotherapy with immunotherapy treatments like dostarlimab may be more effective, as chemotherapy may change the cancer cells in a way that makes them more responsive to treatments like dostarlimab (35-41).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Patients will receive their dostarlimab infusion in a hospital setting just as they would chemotherapy. Dostarlimab is given as a drip into a vein (intravenous infusion) over 30 minutes (32, 42).

Cycles (doses) 1 – 6: Dostarlimab is given as a dose of 500mg every 3 weeks in combination with chemotherapy for the first six cycles (doses).

Cycles (doses) 6+: After the initial doses, dostarlimab is given every 6 weeks at a dose of 1,000mg. Your doctor will decide how many doses of dostarlimab you need. Treatment can continue for up to 3 years, as long as there are no side effects which are difficult to manage, or signs of the cancer growing again, which would mean the cancer hasn't responded to treatment or has stopped responding.

As dostarlimab is administered on the same day as a patient's chemotherapy for the first 6 cycles (doses), the standard infusion time for platinum containing chemotherapy will have an additional 30 minutes added to account for the administration of dostarlimab.

After chemotherapy has finished, patients will need to return to the clinic for a dose of dostarlimab every 6 weeks. This is a change from current recommended treatment and will require additional appointments. This will increase the time a patient and caregiver may be expected to spend in the clinic as well as the potential increase in travel to and from appointments, providing patients with continued touchpoints with their healthcare professionals.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Evidence for the clinical efficacy (how well a drug works) of dostarlimab plus chemotherapy (CP) is supported by the RUBY trial (NCT03981796): a Phase 3, randomised, double-blind, multicentre study (43).

The RUBY trial compares the efficacy and safety of dostarlimab plus CP with CP alone for the treatment of primary advanced or recurrent endometrial cancer.

The trial included 494 adult patients, 376 of whom had cancer which was recorded as being MMRp/MSS. Patients were included in the trial if:

- They were a female patient at least 18 years of age
- Had confirmed diagnosis of primary advanced (Stage III or IV), or first recurrence of, endometrial cancer that was not considered to be curative by radiation therapy or surgery or both
- They had a procedure to take a sample of the tumour to identify its biomarkers, specifically its mismatch repair and microsatellite stability status
- They had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, which is a scale used to measure how much a patient's condition affects their ability to carry out everyday activities.

Patients were excluded from the trial if:

- They had received cancer treatment before or around the time of surgery for Stage III or IV cancer, and one of the following conditions applies:
    - They had not had a relapse of their cancer.

  OR
    - They had a rapid relapse within 6 months of their previous anticancer therapy
- They had more than 1 relapse of endometrial cancer
- They had previously received treatment with an agent that works in a similar way to dostarlimab
- They had another type of cancer at the same time or had received treatment for another cancer within the last 3 years
- They had uncontrolled cancer that had spread to brain and spinal cord.

The RUBY trial was set out to assess the impact of adding dostarlimab to chemotherapy on two main outcomes: progression-free survival (PFS) and overall survival (OS) for the overall population enrolled into the trial. PFS measures how long a patient lives without their cancer getting worse during or after treatment. OS refers to how long a patient lives after starting treatment, regardless of the cause of death. Both PFS and OS are commonly used in cancer trials to evaluate how well treatments help patients live longer and manage their disease.

People were recruited across 164 centres including five UK sites.

The RUBY trial is still ongoing but is no longer recruiting new patients.

The RUBY trial is registered on ClinicalTrials.gov under NCT03981796.

For further information on the RUBY trial, **please see the following publications**:
Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023; 388(23):2145-2158. Published online March 27, 2023. doi:10.1056/NEJMoa2216334.

Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of Oncology. 2024.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The two key objectives of the RUBY study were to investigate if adding dostarlimab to standard chemotherapy

I. Improves the length of time patients live for without their cancer getting worse, compared to those who receive chemotherapy only

II. Improves overall survival compared to those who receive chemotherapy only.

Overall, the RUBY trial, which included both dMMR/MSI-H and MMRp/MSS patients, showed that adding dostarlimab to chemotherapy not only increased the time patients lived without their disease getting worse but also improved their overall survival. The results also suggest that the benefit of this treatment is likely to be more durable than current standard of care, providing lasting effects for some patients.

Progression-free survival (Section 2.6.2 of the company submission)

PFS is defined as the length of time during or after the cancer treatment that a patient lives with the disease, but it does not get worse. PFS is used to measure how long a patient's condition remains stable or improves without the disease progressing.

In the RUBY trial, adding dostarlimab, an immunotherapy medicine, to standard chemotherapy improved outcomes for people that have MMRp/MSS endometrial cancer.

The RUBY trial reported that the addition of dostarlimab to chemotherapy reduced the chance of the cancer getting worse by 24%. At 12 months, patients treated with dostarlimab and chemotherapy had a 43.5% chance of being alive without their cancer progressing, compared to a 30.6% chance for those treated with chemotherapy alone. After 24 months, the chance of being alive and progression-free was 28.4% for patients treated with dostarlimab and chemotherapy, compared to 18.8% for those on chemotherapy alone.

Although the trial was not specifically designed to focus only on patients with MMRp/MSS cancer, the results show that adding dostarlimab to chemotherapy helps people live longer without their cancer worsening.

Overall survival (Section B.2.6.3 of the company submission)

OS represents the duration a patient lives from the start of treatment until death, regardless of whether the cause of death is related to the disease being treated or not. OS is an important outcome measure used in clinical trials and medical research to assess how effective treatments are at helping people with cancer live longer.

In the RUBY trial, adding dostarlimab to chemotherapy helped improve how long patients lived. Patients who received dostarlimab were 21% less likely to die than those who received chemotherapy alone.

At 12 months, the chance of survival was similar for both groups. However, beyond 12 months after starting treatment, patients being treated with dostarlimab were more likely to be alive. By 24 months, 66.5% of

patients treated with dostarlimab were likely to still be alive, compared to 53.2% of those treated with chemotherapy alone.

Limitations of the data

The RUBY study was not specifically designed to confirm the benefits of treatment for patients with MMRp/MSS tumours alone. However, these patients made up the majority of the study participants (75%), and the results showed clear and meaningful improvements in survival for patients with MMRp/MSS tumours. The study found that adding dostarlimab to treatment helped patients live longer and reduced the chance of their cancer getting worse. These benefits were seen across the whole group of patients in the study, with similar improvements observed in the MMRp/MSS subgroup. This suggests that adding dostarlimab to treatment could help this group of patients live longer without their cancer worsening.

For further information on the RUBY trial, **please see the following publications**:
Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023; 388(23):2145-2158. Published online March 27, 2023. doi:10.1056/NEJMoa2216334

Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of Oncology. 2024.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Clinical trial data

Patient reported outcomes (PROs) were included within the RUBY trial and measured using the EORTC QLQ-C30 global quality of life tool, which is a questionnaire developed specifically to assess the quality of life of people with cancer (44). The EQ-5D-5L Visual Analogue Scale (VAS) was also captured during this trial which records the patient's self-rated-health on a visual scale, where either end of the scale is labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS allows patients to provide their own judgment or assessment of their health status. The VAS can capture and quantify the patient's perspective on their own health, providing valuable insights into their well-being or any changes in their condition over time (45).

There were no significant differences observed between the patients receiving dostarlimab and chemotherapy compared to patients receiving only chemotherapy. This means the PFS and OS improvement associated with dostarlimab did not come at the cost of lower quality of life to those being treated.

Broader quality of life benefits

As discussed in Section 2d), it is common for patients to feel more anxious, depressed, or face psychological challenges when diagnosed with endometrial cancer. Maintaining access to more treatment options that may help delay the progression of the disease could help to reduce this anxiety. It would also give patients more time to spend with their loved ones and continue to be active in their communities.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety profile of combining dostarlimab with chemotherapy was consistent with the known safety profiles of the individual drugs. The regimen was tolerable, and toxicities were generally manageable. Both the overall study population and the specific subgroup of patients with MMRp/MSS tumours experienced low rates of treatment discontinuations and interruptions.

The safety of dostarlimab has been evaluated in the whole population of the RUBY trial (all 241 patients who received a least one dose of dostarlimab, regardless of whether or not they were MMRp/MSS). In these patients, the most common adverse reactions that happened in 10% or more of patients were:

- Rash, consisting of flat discoloured areas of skin (23.2%),
- Maculopapular rash, a mix of flat discoloured areas of skin and small raised bumps (14.5%)
- Hypothyroidism, when the thyroid gland does not make enough thyroid hormones to meet the body's demand (14.5%)
- Pyrexia, or fever (12.9%)
- Alanine aminotransferase (ALT) increased, indicating damage or injury to the cells in the liver (12.9%)

- Aspartate aminotransferase (AST) increased, indicating damage or injury to the cells in the liver (12.0%)
- Dry skin (10.0%) (32).

As dostarlimab works by activating the immune system, immune related side effects are of special interest in the RUBY trial and were evaluated as well. Immune related side effects are known to be more common with the class of drugs (PD-1 inhibitors) that dostarlimab is a part of. Immune related side effects are different to the side effects of chemotherapy. They include inflammatory and immune system complications, which can affect any part of the body. They most frequently affect the skin, colon, endocrine organs, liver, and lungs.

During the RUBY trial, 12 patients (5.0%) permanently discontinued due to side effects, most of which were immune related events (32). Side effects were serious in 5.8% of patients; most of which were immune-related (32).

For a full list of all side effects please refer to the JEMPERLI SmPC and patient information leaflet (PIL) which can be found here.

JEMPERLI SmPC: https://www.medicines.org.uk/emc/product/12669/smpc#gref

JEMPERLI PIL: https://www.medicines.org.uk/emc/product/12669/pil

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefit observed for patients with MMRp/MSS primary advanced or recurrent endometrial cancer, is that dostarlimab in addition to chemotherapy improves how long people live for without their cancer getting worse, and how long they live for overall. This is notable as this group of patients have few treatment options available and have had no new treatments that meaningfully improve survival expectations in over 20 years (46, 47). The RUBY trial demonstrated that adding dostarlimab to chemotherapy can reduce the rate of progression of the disease, enabling patients to live longer without the cancer worsening or the need for additional treatment. After two years, patients treated with dostarlimab and chemotherapy were more likely to remain free of disease progression compared to those receiving chemotherapy alone (48).

Importantly, dostarlimab improves survival for this group of patients. In the MMRp/MSS group, representing 75% of the total patients in the study, adding dostarlimab reduced the risk of death by 21%, resulting in an average OS benefit of 7 months compared to chemotherapy alone (49). This is more than double the survival benefit that originally established chemotherapy as the standard of care, underscoring dostarlimab's potential to transform outcomes for this patient population (50, 51).

Additionally, evidence from the RUBY trial supports the use of immunotherapy, like dostarlimab, earlier in the treatment pathway (49). Even though some patients who received chemotherapy only in the trial subsequently received immunotherapy when the cancer went on to progress, the results showed that dostarlimab was more effective when given in combination with chemotherapy upfront. Patients in the dostarlimab group lived longer without the cancer progressing, even after subsequent lines of therapy (49).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments.

The introduction of dostarlimab into standard of care would mean that patients spend more time attending hospital appointments due to:

- The additional time it takes to administer the 30 minute dostarlimab infusion on top of the standard infusion time for platinum containing chemotherapy (32, 42).

AND

- After chemotherapy has finished, patients will need to return to the clinic for a dose of dostarlimab every 6 weeks for up to 3 years. This is a change from current standard of care and will require extra appointments. This will increase the time a patient and caregiver may be expected to spend in the clinic as well as the time spent in travel to and from appointments (32, 42).

Like all medications, dostarlimab may cause side effects. A Patient Card will be given to patients to inform them of signs and symptoms of the most common immune-related events associated with dostarlimab therapy. The full list of side effects can be found in the patient information leaflet (PIL).

JEMPERLI PIL: https://www.medicines.org.uk/emc/product/12669/pil

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

When evaluating the cost effectiveness of dostarlimab, it is important to look beyond the duration of the RUBY clinical trial and consider its long-term impact. In this NICE submission, an economic model (more

specifically, a partition survival model) was used to estimate the long-term costs and benefits of making dostarlimab available within the NHS for this group of patients. These economic models help researchers estimate how long patients are likely to survive with the treatment, their quality of life, and associated costs over an extended period of time.

This model considers different factors like how the disease progresses, how patients respond to treatment, how patients' quality of life may change as the disease progresses, and how likely patients are to pass away. By taking all these factors into account, the model simulates how the disease will likely progress and how it will affect patients' outcomes.

Value proposition

As outlined in Section 3e), dostarlimab has been shown to improve the length of time that primary advanced or recurrent MMRp/MSS patients spend in the progression free health state when compared to those receiving current standard of care treatment.

This improvement in progression free survival comes at no cost to patients' quality of life when compared to the current standard of care treatment.

The results of the cost-effectiveness modelling indicate that making dostarlimab available in the NHS would result in additional costs to the NHS, however there would be some savings in other areas. For example, currently in the NHS, patients tend to be treated with chemotherapy initially and then when the cancer progresses many go on to receive an immunotherapy at that point. By making dostarlimab available upfront, it reduces the use of these therapies later in the pathway where they can be expensive and less effective overall.

The cost-effectiveness modelling also shows that making dostarlimab available would improve survival outcomes overall compared to existing NHS practice and also enable patients to maintain their quality of life, without disease progression, for longer.

Although dostarlimab is associated with higher costs, these have been shown using the company's economic model to be cost-effective given the improvement in health outcomes expected from the use of dostarlimab. However, the final decision on whether it is cost-effective will be made by the NICE appraisal committee, who will take into account several factors, including any discounts on other treatments that might not be publicly available. This means the cost-effectiveness could vary based on these details.

Uncertainty

As mentioned in Section 3e), there is limited long term data available for dostarlimab in this primary advanced or recurrent MMRp/MSS population. There are a maximum of 47.4 months of data available from the RUBY trial, so any longer-term survival outcomes have been estimated out into the future creating some uncertainty. However, the efficacy and safety data, already assessed at two separate time points, continue to demonstrate that the addition of dostarlimab to standard of care improves patient outcomes compared with standard of care alone.

Economic analysis

All these considerations impact the decision on whether dostarlimab represents good value for money and a good use of NHS resources. Based on the evidence available and the company's economic analysis, dostarlimab in combination with chemotherapy would be considered as offering a good use of NHS resources, as a new treatment for patients with MMRp/MSS primary advanced or recurrent endometrial cancer. However, the final decision will depend on the NICE appraisal committee's review, which will take into account all available evidence, including any confidential discounts for other treatments, and could influence the overall conclusion.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Dostarlimab represents a notable advancement in the management of MMRp/MSS primary advanced and recurrent endometrial cancer patients who are candidates for systemic therapy. For over 40 years, conventional chemotherapy has remained the standard in this setting, with few major advancements (52). In contrast, other cancers such as melanoma, kidney cancer, and lung cancer have benefited from immunotherapies in earlier lines of treatment, significantly improving patient outcomes (53-55). Access to innovative therapies like dostarlimab could help close this gap and offer new hope to patients.

The combination of dostarlimab with chemotherapy has the following innovative characteristics, which are meaningful to both patients & the NHS:

- Dostarlimab is an immunotherapy with an innovative way of working compared to the current standard of care, which involves platinum-containing chemotherapy (56). By blocking the PD-1 protein, dostarlimab helps the immune system target and destroy cancer cells through an immune-mediated process, rather than relying solely on traditional chemotherapy (57). This unique mechanism of action offers a different side effect profile and more stable, durable responses compared to older treatments (58).
- Dostarlimab is used in combination with platinum-containing chemotherapy during initial treatment and then continued on its own for up to three years in total. This extended use can suppress any remaining disease and increase the length of time patients remain progression-free, providing new hope for those with MMRp/MSS endometrial cancer.

While immunotherapies have long been available in earlier treatment lines for other cancers, access for MMRp/MSS endometrial cancer has lagged behind (54-56). Ensuring first-line access to dostarlimab will address this disparity and provide underserved patients with a considerable opportunity for better outcomes.

Dostarlimab is currently established within the clinical care pathway for dMMR/MSI-H primary advanced or recurrent endometrial cancer patients, as an add-on to chemotherapy treatment. This submission aims to extend the same access to MMRp/MSS patients, ensuring they too can benefit from this treatment as part of routine care on the NHS.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

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

Find more general information about the Equality Act and equalities issues here

Endometrial cancer primarily affects older women, making age and sex key considerations under the Equality Act 2010 (59).

As mentioned previously, there has been very little innovation or new treatments for women diagnosed with this type of endometrial cancer for decades. Despite the notable benefits dostarlimab can provide to patients with primary advanced or recurrent endometrial cancer, and being the first in decades to do so,

GSK are concerned that NICE will consider this under the same criteria as other diseases and conditions which are less severe, have better prognosis, and have lower unmet need.

In contrast, therapies which have been developed for advanced types of prostate cancer, which, affects only men, have previously been afforded special 'end-of-life' criteria which allows NICE to value those interventions more than is typical (60, 61). Due to the timing of this particular NICE assessment, relative to those for prostate cancer, women with primary advanced or recurrent endometrial cancer may be disadvantaged. GSK believe that this endometrial cancer appraisal should be afforded similar flexibilities as afforded to cancers primarily affecting men.

In addition, it is worth noting that significant disparities exist in survival rates and diagnosis timing among ethnic and socio-economic groups, with South Asian, Black Caribbean, and Black African patients, as well as those from deprived backgrounds, facing worse outcomes (62-64).

Expanding treatment options to an earlier point in the treatment pathway would not only improve outcomes for patients but also allow more patients to benefit from innovative treatments, reducing the inequality in accessing advanced or recurrent endometrial cancer treatments (65).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

The following websites may provide useful information on endometrial cancer, and dostarlimab:

- Cancer Research UK: Womb Cancer: https://www.cancerresearchuk.org/about-cancer/womb-cancer
- Macmillan Cancer Support: Womb Cancer: https://www.macmillan.org.uk/cancer-information-and-support/womb-cancer
- The RUBY study is registered on clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT03981796
- Home - Peaches Trust
- Womb cancer | Uterine Cancer Symptoms | The Eve Appeal

4b) Glossary of terms

Alanine aminotransferase (ALT): ALT is an enzyme that, when increased, is often associated with signs of liver disease or acute liver injury. A blood test is used to detect an increase in ALT levels.

Anaemia: Anaemia is when you have a lower-than-normal number of red blood cells. Red blood cells contain a protein called haemoglobin, which carries oxygen from your lungs to the rest of your body. When your red blood cells are too low you may feel tired, weak or short of breath.

Aspartate aminotransferase (AST): AST is an enzyme that, when increased, is often associate with signs of liver damage.

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Biopsy: The removal of cells or tissues for examination by a pathologist. The pathologist may study the tissue under a microscope or perform other tests on the cells or tissue.

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start.

Chemotherapy: Treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated. It may be given alone or with other treatments, such as surgery, radiation therapy, or biologic therapy.

Computed tomography (CT) scan: A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body.

dMMR/MSI-H: Mismatch repair deficient (dMMR) and microsatellite instability high (MSI-H) is a specific defect in the genetic code (DNA) of the cancer.

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.

Hypothyroidism: When the thyroid gland doesn't make enough thyroid hormones to meet the body's need

Immunotherapy: A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.

Intravenous (IV): An injection through a needle or tube inserted directly into a vein.

Maculopapular rash: A mix of macules (flat discoloured areas of skin) and papules (small, raised bumps) that usually covers a large area of skin.

MMRp/MSS: Mismatch repair proficient (MMRp) and microsatellite stable (MSS) describe cancer where the genetic code (DNA) repair system is working normally and does not show specific defects.

Magnetic resonance imaging (MRI): A procedure that uses radio waves, a powerful magnet, and a computer to make a series of detailed pictures of areas inside the body.

Overall survival (OS): How long people live.

PD-1: A protein found on T cells (a type of immune cell) that helps keep the body's immune responses in check.

PD-L1 and PD-L2: Proteins found on the surface of cells, including cancer cells, that help them escape the body's immune system. They work by "turning off" immune cells, preventing them from attacking the cancer or other cells. PD-L1 and PD-L2 interact with a protein called PD-1 on immune cells to reduce the immune system's response.

Progression-free survival (PFS): The time a patient lives without the cancer growing or spreading during or after treatment.

Pyrexia: Also known as fever, when body temperature increases in a person beyond the normal range.

Quality of life: How healthy and comfortable a person feels, and how able they are to take part in everyday activities. In clinical trials, it's used to measure how symptoms and disease affect these aspects of life.

Radiotherapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumours.

T-Cell: A type of white blood cell that is part of the body's natural immune system.

Ultrasound: A procedure that uses high-energy sound waves to look at tissues and organs inside the body.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Cancer Research UK. Stages of cancer. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/what-is-cancer/stages-of-cancer (last accessed: January 2025).
2. Cancer Research UK. Why some cancers come back. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/what-is-cancer/why-some-cancers-come-back (last accessed: January 2025).
3. Cancer Research UK. What is womb cancer. 2024. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/womb-cancer/about (last accessed: January 2025).
4. National Health Service England. Cancer Registration Statistics, England, 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2022# (last accessed: January 2025). 2024.
5. Siegenthaler F, Lindemann K, Epstein E, Rau TT, Nastic D, Ghaderi M, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecol Oncol. 2022;165(2):230-8.
6. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(3):520-9.
7. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: A Cancer Journal for Clinicians. 2023;73(1):17-48.
8. Henry Ford Health. Olivia's story: Uterine Cancer. Available at: https://www.henryford.com/services/uterine-cancer/stories/olivia (accessed on: January 2025).
9. Peaches Womb Cancer Trust. Patient Stories. Available at: https://www.peachestrust.org/category/patient-stories/ (accessed on: January 2025). 2022.
10. Chen J, Zou Q, Chen X, Liu X, Ding S, Mo Y, et al. Quality of life in patients with endometrial carcinoma: A Longitudinal Study. Nurs Open. 2022;9(3):1815-21.
11. Ferrandina G, Petrillo M, Mantegna G, Fuoco G, Terzano S, Venditti L, et al. Evaluation of quality of life and emotional distress in endometrial cancer patients: a 2-year prospective, longitudinal study. Gynecol Oncol. 2014;133(3):518-25.
12. Mulet-Margalef N, Linares J, Badia-Ramentol J, Jimeno M, Sanz Monte C, Manzano Mozo JL, et al. Challenges and Therapeutic Opportunities in the dMMR/MSI-H Colorectal Cancer Landscape. Cancers (Basel). 2023;15(4).
13. Li G-M. Mechanisms and functions of DNA mismatch repair. Cell Research. 2008;18(1):85-98.
14. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecologic Cancer. 2021;31(1):12-39.
15. Ryan NAJ, McMahon R, Tobi S, Snowsill T, Esquibel S, Wallace AJ, et al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. PLoS Med. 2020;17(9):e1003263.
16. Cancer Research UK. Symptoms of womb cancer. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/symptoms (last accessed: January 2025).
17. Cancer Research UK. Diagnosing womb cancer. 2024. https://www.cancerresearchuk.org/about-cancer/womb-cancer/getting-diagnosed (accessed on: January 2025).
18. Cancer Research UK. Tests for womb cancer. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/getting-diagnosed/tests-diagnose (last accessed: January 2025).
19. National Institute for Health and Care Excellence. Information for the public | Testing strategies for Lynch syndrome in people with endometrial cancer | Guidance | NICE. 2020. Available from: https://www.nice.org.uk/guidance/dg42/informationforpublic (last accessed: January 2025).

20. Cancer Research UK. Treatment for womb cancer. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/womb-cancer/advanced-cancer/treatment (last accessed: January 2025).
21. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2022;270:50-89.
22. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(9):860-77.
23. European Society for Medical Oncology. Endometrial Cancer: A Guide for Patients, Patient Information Based on ESMO Clinical Practice Guidelines. 2012. Available at: https://www.esmo.org/content/download/6604/115031/file/EN-Endometrial-Cancer-Guide-for-Patients.pdf (accessed on: January 2025).
24. Cancer Research UK. Paclitaxel and carboplatin (PC, CarboTaxol). 2025. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/pc-paclitaxel-carboplatin (last accessed: January 2025).
25. Stephanie M de Boer RAN, Ina M Jürgenliemk-Schulz, Jan J Jobsen, Ludy C H W Lutgens, Elzbieta M van der Steen-Banasik, Jan Willem M Mens, Annerie Slot, Marika C Stenfert Kroese, Simone Oerlemans, Hein Putter, Karen W Verhoeven-Adema, Hans W Nijman, Carien L Creutzberg. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. Int J Radiat Oncol Biol Phys 2015;93(4):797-809.
26. Data on File. Global Advanced/Recurrent Endometrial Cancer Patient Expert Council run by GSK. 2022.
27. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11(11):3887-95.
28. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. The Journal of clinical investigation. 2015;125(9):3384-91.
29. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nature reviews Immunology. 2008;8(6):467-77.
30. Juneja VR, McGuire KA, Manguso RT, LaFleur MW, Collins N, Haining WN, et al. PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8 T cell cytotoxicity. J Exp Med. 2017;214(4):895-904.
31. Data on File. Dostarlimab MOA for Jemperli. 2023.
32. Medicines & Healthcare products Regulatory Agency (MHRA). Jemperli (Dostarlimab) Summary of Product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963 (last accessed: January 2025). 2024.
33. Cancer Research UK. Carboplatin. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/carboplatin (last accessed: January 2025).
34. Cancer Research UK. Paclitaxel. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/paclitaxel (last accessed: January 2025).
35. Senovilla L, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, et al. An immunosurveillance mechanism controls cancer cell ploidy. Science. 2012;337(6102):1678-84.
36. Sevko A, Michels T, Vrohlings M, Umansky L, Beckhove P, Kato M, et al. Antitumor effect of paclitaxel is mediated by inhibition of myeloid-derived suppressor cells and chronic inflammation in the spontaneous melanoma model. J Immunol. 2013;190(5):2464-71.
37. Liechtenstein T, Perez-Janices N, Gato M, Caliendo F, Kochan G, Blanco-Luquin I, et al. A highly efficient tumor-infiltrating MDSC differentiation system for discovery of anti-neoplastic targets, which circumvents the need for tumor establishment in mice. Oncotarget. 2014;5(17):7843-57.
38. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res. 2014;20(11):2831-7.
39. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. Cell Immunol. 2010;263(1):79-87.

40. Bogani G, Ray-Coquard I, Concin N, Ngoi NYL, Morice P, Caruso G, et al. Endometrial carcinosarcoma. Int J Gynecol Cancer. 2023;33(2):147-74.
41. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. Cancer Cell. 2015;28(6):690-714.
42. Medicines & Healthcare products Regulatory Agency (MHRA). JEMPERLI 500 mg concentrate for solution for infusion - Patient Information Leaflet (PIL). 2024. Available from: https://www.medicines.org.uk/emc/files/pil.12669.pdf (last accessed: January 2025).
43. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY) [Internet]. 2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03981796.
44. European Organisation for Research and Treatment of Cancer. EORTC Quality of Life Website - EORTC - Quality of Life. Available from: https://qol.eortc.org/ (last accessed: January 2025).
45. EuroQol. EQ-5D | About. Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ (last accessed: January 2025).
46. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med. 2020;18(1):87.
47. Sung M, Zer A, Walia P, Khoja L, Maganti M, Labbe C, et al. Correlation of immune-related adverse events and response from immune checkpoint inhibitors in patients with advanced non-small cell lung cancer. J Thorac Dis. 2020;12(5):2706-12.
48. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388(23):2145-58.
49. Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of Oncology. 2024.
50. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. 2020;38(33):3841-50.
51. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes. Journal of Clinical Oncology. 2014;32(12):1277-80.
52. Miller DS, Randall ME, Filiaci V. Progress in endometrial cancer: Contributions of the former Gynecologic Oncology Group. Gynecol Oncol. 2020;157(2):312-22.
53. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
54. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.
55. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021;385(8):683-94.
56. Heffernan K, Nikitas FS, Shukla U, Camejo HS, Knott C. Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis. Gynecol Oncol. 2022;166(2):317-25.
57. Park UB, Jeong TJ, Gu N, Lee HT, Heo YS. Molecular basis of PD-1 blockade by dostarlimab, the FDA-approved antibody for cancer immunotherapy. Biochem Biophys Res Commun. 2022;599:31-7.
58. Costa B, Vale N. Dostarlimab: A Review. Biomolecules. 2022;12(8).
59. Gov.UK. Equality Act 2010: guidance. Available from: https://www.gov.uk/guidance/equality-act-2010-guidance (last accessed: January 2025). 2015.
60. National Institute for Health and Care Excellence. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer [TA887]. Available from: https://www.nice.org.uk/guidance/ta887 (accessed on: January 2025). 2023.
61. National Institute for Health and Care Excellence. Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more treatments [TA930]. Available from: https://www.nice.org.uk/guidance/ta930 (last accessed: January 2025). 2023.

62. Mohammed S, Polymeros K, Wickham-Joseph R, Luqman I, Charadva C, Morris T, et al. Comparing Characteristics of Endometrial Cancer in Women of South Asian and White Ethnicity in England. Cancers. 2021;13(23):6123.
63. Moss EL, Teece L, Darko N. Uterine cancer mortality and Black women: time to act. The Lancet Oncology. 2023;24(6):586-8.
64. Njoku K, Barr CE, Hotchkies L, Quille N, Wan YL, Crosbie EJ. Impact of socio-economic deprivation on endometrial cancer survival in the North West of England: a prospective database analysis. Bjog. 2021;128(7):1215-24.
65. Data on File. Advisory Board: Insights on treatment pathway and treatments used in first-line advanced/recurrent EC 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6415_Dostarlimab +PC_EC_GSK response to EAG clarification questions_v1.0	1.0	Redacted	17th March 2025

Abbreviations

AE	Adverse event
BICR	Blinded independent central review
CA-125	Cancer antigen 125 tests
CDF	Cancer Drugs Fund
CI	Confidence interval
CP	Carboplatin plus paclitaxel
CR	Complete response
CSR	Clinical study report
dMMR	Mismatch repair deficient
DOR	Duration of response
DSU	Decision Support Unit
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESGO/ESTRO/ESP	European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology
ESMO	European Society for Medical Oncology
EQ-5D-5L	European Quality of Life scale, 5-Dimensions, 5-Levels
FDA	Food and Drugs Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	First interim analysis
IA2	Second interim analysis
ICER	Incremental cost-effectiveness ratio
IO	Immunotherapy
INV	Investigator assessment
irAE	Immune-related adverse event
ITT	Intention-to-treat
KM	Kaplan-Meier
LSM	Least Squares Mean
MMR	Mismatch repair
MMRp	Mismatch repair proficient
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NA	North America
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMB	Net monetary benefit
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis

PAS	Patient access scheme
PCC	Platinum-containing chemotherapy
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PF	Progression free
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QLQ-EN24	Quality of Life Questionnaire Endometrial Cancer 24-item module
SAF	Safety analysis set
SE	Standard error
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse events
TTD	Time to treatment discontinuation
WE	Western Europe

Section A: Clarification on effectiveness data

RUBY-1 clinical effectiveness results

A1. Priority question. Company submission (CS), Document B, section B.2.6. The company submission presents results from RUBY-1 for each trial arm, dostarlimab plus carboplatin and paclitaxel (CP; from now, dostarlimab) and placebo plus CP (from now, placebo) for some outcomes without any formal comparison between the trial arms. Please provide results tables with comparative data between trial arms for the MMRp/MSS (mismatch repair proficient/microsatellite stable) patient population of RUBY-1, including 95% confidence intervals, for the following outcomes:

objective response rate (ORR)

Per the statistical analysis plan for the RUBY-1 trial, ORR was to be defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1). This analysis was to be undertaken for patients with target lesions or non-target lesion at baseline and reported by treatment group with 95% confidence intervals (CIs). Comparative analysis was not planned for this endpoint in either the ITT or the MMRp/MSS population.

As described in Section 2.6.4.2 of Document B and in Appendix J.2.2.2 of the Company Submission, ORR was similar between arms for the mismatch repair proficient (MMRp)/ microsatellite stable (MSS) population. This is consistent with what has been observed in the intention-to-treat (ITT) population and the mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) subgroup where ORR has been comparable in both arms but improved PFS primary driven by the increased duration of response with the addition of dostarlimab (1).

In response to Question A1a), a comparative analysis is provided in Table 1 below. Notably, consistent with other comparative analysis the response rate below is based on the number of patients randomised and not limited to those only with target or non-target disease at baseline. Nevertheless, ORR is comparable between arms with nominally higher response in the dostarlimab arm (57.8%) compared with the placebo arm (55.4%) corresponding to an absolute risk difference of [redacted]

Table 1: Summary of tumour response (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Best Overall Response by RECIST v1.1 [n (%)] [a]		
CR	38 (19.8%)	31 (16.8%)
PR	73 (38.0%)	71 (38.6%)
SD	36 (18.8%)	39 (21.2%)
Non-CR/Non-PD	0	0
No disease	27 (14.1%)	22 (12.0%)
PD	7 (3.6%)	12 (6.5%)
Not Evaluable	11 (5.7%)	9 (4.9%)
ORR[a]		
N (%)	111 (57.8%)	102 (55.4%)
95% CI	[redacted]	[redacted]
Absolute Risk Difference of ORR		
Estimate	[redacted]	
95% CI	[redacted]	
p-value	[redacted]	

[a]Denominator is number of patients randomised regardless of presence of target or non-target lesions at baseline.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; CR, complete response; MMRp, mismatch repair proficient; MSS, microsatellite stable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SD, stable disease.

duration of response (DOR)

Consistent with the primary endpoint of progression-free survival (PFS), patients experiencing a response to dostarlimab had longer duration of response compared to those treated with carboplatin plus paclitaxel (CP) alone (Table 2). Despite duration of response not being a powered endpoint, the rate of losing an initial response was [redacted] lower in the dostarlimab arm compared with the placebo arm with a hazard ratio (HR) of [redacted].

Table 2: KM analysis of DOR (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Number of Responders		
n	111	102
DOR		
Status [n (%)]		
Events observed	68 (61.3%)	82 (80.4%)
Disease progression	66 (59.5%)	79 (77.5%)
Death	2 (1.8%)	3 (2.9%)
Censored	43 (38.7%)	20 (19.6%)
Estimates for DOR (months)		

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Quartile (95% CI)[a]		
25%	4.5 (3.3, 6.0)	3.4 (2.7, 4.2)
50%	8.6 (6.9, 13.1)	6.3 (4.4, 6.9)
75%	26.9 (17.6, NE)	10.5 (8.4, 20.3)
Duration ≥6 months [n (%)]	66 (59.5%)	51 (50.0%)
Duration ≥12 months [n (%)]	38 (34.2%)	22 (21.6%)
Hazard ratio[b] (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	

[a]95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b]Stratified Cox Regression.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; DOR, duration or response; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable.

health-related quality of life (HRQoL), that is, EORTC QLQ-C30 global score, EQ-5D-5L and QLQ-EN24.

Table 3 includes a comparative analysis of each of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) global score, including the Least Squares Mean (LSM; reported as LSM ± standard error [SE]), 95% CIs, and associated p-value. These data are estimated using a mixed model for repeated measures (MMRM), adjusting for within-patient correlations across time points within a patient and controlling for baseline values. An increase in global score indicates an improvement from baseline with a reduction indicating a deterioration.

The least-squared mean (LSM) change from baseline for the dostarlimab arm was -1.1 (95% CI: -3.2 to +0.9) compared with +0.7 (95% CI: -1.5 to +3) in the placebo arm, corresponding to a non-significant LSM difference of -1.8 (95% CI: -4.9 to +1.2) compared to placebo. In addition, estimates for a Meaningful Change Thresholds for global EORTC QLQ-C30 have ranged from 5-11 points suggesting that these LSM differences are neither statistically nor clinically significant (2).

Table 3: EORTC QLQ-C30- Comparative data between trial arms for the MMRp/MSS patient population of RUBY-1

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EORTC Global QoL Score				
Overall	Change from Baseline	n	182	176
		LSM (SE)	-1.1 (1.05)	0.7 (1.14)
		95% CI	-3.2, 0.9	-1.5, 3.0
		Difference from placebo		
		LSM (SE)	-1.8 (1.56)	-
		95% CI	-4.9, 1.2	-
		p-value	0.2420	-

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error; QoL, quality of life.

Table 4 includes a comparative analysis on the European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) domains, including the LSM (SE), 95% CIs, and associated p-value. The LSM change from baseline for the dostarlimab arm was +0.3 (95% CI: -1.6 to +2.1) compared with +3.9 (95% CI: +1.9 to +6) in the placebo arm, corresponding to a non-significant LSM difference of -3.7 (95% CI: -6.4 to -0.9) compared to placebo. Similar that observed with QLQ-C30 quality of life scores, a -3.7 point difference in EQ-5D between arms is not considered clinically relevant differences within oncology indicating comparable global quality of life between treatment arms (3).

Table 4: EQ-5D-5L VAS- Comparative data between trial arms for the MMRp/MSS patient population of RUBY-1

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EQ-5D-5L VAS Score				
Overall	Change from Baseline	n	180	174
		LSM (SE)	0.3 (0.93)	3.9 (1.02)
		95% CI	-1.6, 2.1	1.9, 6.0
		Difference from placebo		
		LSM (SE)	-3.7 (1.39)	
		95% CI	-6.4, -0.9	
		p-value	0.0086	

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; EQ-5D-5L, European Quality of Life scale, 5-Dimensions, 5-Levels; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error; VAS, Visual Analogue Scale.

Table 5 includes a comparative analysis on the Quality of Life Questionnaire Endometrial Cancer 24-item module (QLQ-EN24) domains, including the LSM (SE), 95% CIs, and associated p-value.

Similar changes from baseline were observed in both arm across all domains with two exceptions. EN24 Sexual Interest score was relatively stable over the course of the trial in the dostarlimab arm (-0.5; 95% CI: -.2.7 to +1.7) while the placebo arm increased (+3.6; 95% CI: +1.3 to +5.9), indicating improvement, resulting in a -4.1 point lower score in the dostarlimab arm compared to placebo. EN24 Tingling/Numbness Score increased markedly in both the dostarlimab (+31.5; 95% CI: +27.4 to 35.7) and placebo (+23.8; 95% CI: +19.4 to +28.2) arm, indicating increased levels of tingling and numbness. The LSM difference versus placebo was +7.7 (95% CI: +1.5 to 13.9) indicating higher impact of tingling/numbness in the dostarlimab arm.

Table 5: QLQ-EN24- Comparative data between trial arms for the MMRp/MSS patient population of RUBY-1

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EN24 Sexual Interest Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Sexual Activity Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Sexual Enjoyment Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EN24 Lymphoedema Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Urological Symptoms Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Gastrointestinal Symptoms Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Poor Body Image Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Sexual/Vaginal Problems Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EN24 Pain in Back and Pelvis Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Tingling/Numbness Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Muscular Pain Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Hair Loss Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-
Scale/Item: EN24 Taste Change Score				
Overall	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	-
		95% CI	[redacted]	-
		p-value	[redacted]	-

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; QLQ-EN24, Quality of Life Questionnaire Endometrial Cancer 24-item module; SE, standard error.

A2. Priority question. CS, Document B, section 2. Throughout the company submission, nominal stratified log-rank p-values have been reported for progression-free survival (PFS) and overall survival (OS) outcomes in the MMRp/MSS patient population of RUBY-1. Please address the following points regarding the use of nominal p-values:

a) Clarify why the company has reported nominal p-values over actual p-values and provide a justification for their use.

A p-value reflects the likelihood of the result occurring under the null hypothesis. Nominal p-values have been used within the company submission to indicate that p-values are derived from pre-specified analyses of the MMRp/MSS population that has not been subject to formal statistical hypothesis testing. This reflects the RUBY-1 trial not being powered to specifically test the null hypothesis for PFS and overall survival (OS) within the MMRp/MSS population (see Section 2.15 of the company submission).

b) Provide an overview, including an example from the company submission of how the interpretation of nominal p-values differs from the interpretation of actual p-values.

The nominal p-values have been estimated using the same methods as the corresponding statistically significant p-value but have been reported for outcomes which were not powered within the statistical analysis plan of the RUBY-1 trial. For example, as illustrated in Table 6, within the MMRp/MSS population the PFS HR was 0.76 with a corresponding nominal p-value of [redacted]. Despite the nominal p-value being <0.05 statistical significance is not met due to the absence of a pre-specified null hypothesis for which the trial is powered. Alternatively, as OS in the ITT was a powered endpoint, the HR of 0.64 is statistically significant with a significant p-value of <0.0001 (Table 6).

Table 6: KM analysis of PFS (MMRp/MSS and ITT patient populations)

MMRp/MSS population			ITT		
Category subcategory	**Dostarlimab in combination with CP (N=192)**	**Placebo in combination with CP (N=184)**	**Category subcategory**	**Dostarlimab in combination with CP (N=245)**	**Placebo in combination with CP (N=249)**
PFS probability (95% CI)					
Month 12	43.5% (35.7%, 51.0%)	30.6% (23.6%, 37.8%)	**Month 12**	48.2% (41.3%, 54.8%)	29.0% (23.0%, 35.2%)
Month 24	28.4% (21.2%, 36.0%)	18.8% (12.8%, 25.7%)	**Month 24**	36.1% (29.3%, 42.9%)	18.1% (13.0%, 23.9%)
Hazard ratio (95% CI)	0.76 (0.59, 0.98)		**Hazard ratio (95% CI)**	0.64 (0.507, 0.800)	
Nominal p-value	[redacted]		**p-value**	<0.0001	

Source: IA1 CSR Table 14.2.1.1 (4).
Data cutoff: 28 September 2022.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; ITT, intention-to-treat; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

c) Provide an explanation as to how a nominal p-value can be considered statistically significant (that is, <0.05) yet the 95% confidence intervals for the corresponding hazard ratio (HR) may overlap 1 indicating a statistically non-significant result. For example, in CS, Document B, Table 12, the upper bound of the 95% confidence interval for the HR for OS in MMRp/MSS population overlaps 1 (1.044) while the corresponding nominal p-value indicates statistical significance (nominal p-value = 0.0493).

Typically, if the 95% CI includes 1, it suggests that the effect is not statistically significant at the 0.05 level, however, it is worth noting that although the p-value and the CI are related, they are not identical measures. The p-value is influenced by the sample size and the effect size, while the CI is influenced by the variability in the data and the confidence level.

For OS in the MMRp/MSS population, the HR and Cis were derived from a Cox model, which assumes proportional hazards. In contrast, the p-value came from a stratified log-rank test, which was a non-parametric test, thus not requiring a proportional hazards assumption. Furthermore, the p-value is nominal, and therefore not for formal statistical hypothesis testing. Therefore, this can result in differences from the CIs with regards to significance.

Despite the small discrepancy, the upper limit of 95% CI for the OS HR is very close to 1. It can frequently be observed that analysis within subpopulations have wide CIs, often due to having a smaller sample size, and potentially differing magnitudes of observed benefit

relative to a ‘true powered analysis’. Therefore, the upper CI crossing one is expected, given the design of the trial and the insufficient power to formally test OS in the MMRp/MSS population.

A3. CS, Document B, Figure 6. For OS, the Kaplan-Meier curves in Figure 6 suggest improved OS for the placebo arm compared with the dostarlimab arm between months 7 and 12. Please provide an explanation for this observation.

The KM curves in Figure 6 of the company submission show an early crossing of the KM curves before the 12-month mark. Common reasons from a statistical standpoint for curves crossing, include random variation, differential early censoring, population heterogeneity and early vs late effects. In this case, the fluctuating crossing of the KM curves early on is most likely due to random fluctuations that may occur with the lower number of events through this period. Notably, similar phenomena are not observed in the corresponding PFS and PFS2 outcomes (Figures 5 and 7 of the company submission, respectively) which demonstrates comparable outcomes in the initial period following randomisation after which a sustained separation of curves is observed.

Health-related quality of life

A4. Priority question. CS, Document B, section B.3.4.1. There is a lack of detail in the CS around the EQ-5D-5L index data collected in RUBY-1 and used in the economic model.

a) Please provide details on how EQ-5D-5L was measured in the trial (for example, timepoints of measurement, number of responses at each time point, length of follow up, etc.) along with the mean EQ-5D values (crosswalked to the 3L using UK value set) at each timepoint

Patient reported outcomes (PROs), including EQ-5D-5L, were captured at each administration day while receiving treatment, at the end of treatment visit, at the safety follow-up visit which should occur 90±7 days after the last dose of drug, and at Survival Follow-ups which should occur every 90±14 days after the Safety Follow-up Visit (Figure 1).

Figure 1: Schedule of events in RUBY-1

	Screening Period	Treatment Period									Posttreatment Period		
		Q3W Dose Schedule (1 cycle=3 weeks)						Q6W Dose Schedule (1 cycle=6 weeks)					
Cycle Day/Visit	**Screening[a]**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**CxD1**	**EOT[b]**	**Safety Follow-up[c]**	**Survival Follow-up[d]**
Week	**-4 to 0**	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**25**	**-**	**-**	**-**	**-**
Window (days)	**-**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±14**
Procedure													
Informed consent[a]	X												
Inclusion/exclusion criteria	X	X											
Demographics	X												
Medical, surgical, cancer, and medication history	X												
Tumor tissue (MMR/MSI status)[e]	X												
Tumor tissue (exploratory biomarkers)	X												
Blood sample for PK/ADA[f]		X	X				X	X		X	X	X	
Blood sample for exploratory biomarkers[g]		X	X				X				X		
Tumor assessment (RECIST v.1.1)	X[h]	On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by Investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later,or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.[i]											
PRO assessments[j]		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[k]													
CBC with differential	X	X[l]	X	X	X	X	X	X	X	X	X	X[m]	

Source: RUBY clinical study protocol (5)

[a]It is recommended that patients receive first dose on day of randomisation; otherwise, the site has a maximum of 7 days to dose the patient. This allows a window of 35 days from the signing of the informed consent to administration of the first dose (28-day Screening Period plus 7 days from day of randomisation). If the day of randomisation was more than 7 days before the first dose, laboratory tests performed on the day of randomisation must be repeated.

[b]The EOT Visit should occur 30±7 days after the last dose of study drug during Cycles 1 through 6 (Q3W dosing) or 42±7 days after the last dose of study drug for Cycle 7 and up (Q6W dosing). For patients who decide to discontinue treatment after a treatment interruption of > 4 weeks, the EOT Visit should take place within 2 weeks of making the decision to discontinue treatment or before initiation of alternate anticancer therapy, whichever occurs first.

[c]The Safety Follow-up Visit should occur 90±7 days after the last dose of study drug.

[d]The Survival Follow-up Period begins 90 days after the Safety Follow-up Visit and continues until death or the end of study data collection (i.e., up to 4 years after the enrolment of the last patient, provided that this allows for the collection of sufficient OS events). Telephone calls should occur every 90±14 days.

[e]Tumor tissue sample to be sent for centralized MSI testing if local testing result is not available.

[f]Blood samples to be collected predose (within 1 hour prior to infusion) and at the end of the infusion (0.5h+15 min) in Day 1 of Cycles 1, 2, 6, 7, 10, 15, and 20. Samples will also be collected at EOT and the Safety Follow-up Visit.

[g]Blood samples to be collected predose.

[h]Scans performed prior to the signing of the informed consent form as part of routine clinical management are acceptable for use as initial tumour imaging if they are of diagnostic quality and are performed within 28 days prior to the first dose date.

[i]All radiographic images/scans at the specified timepoints as well as any unscheduled images/scans will be collected and stored centrally for potential future evaluation.

[j]All PRO assessments should be collected prior to any procedures or interventions being conducted that day.

[k]Clinical laboratory tests may be performed within 72 hours prior to each visit. Haematology and serum chemistry assessments need to be performed and results evaluated prior to dosing.

[l]If screening assessment was performed within 72 hours of Cycle 1 Day 1, assessment does not need to be repeated.

[m]Only if clinically indicated.

Abbreviations: ADA, anti-drug antibodies; C, Cycle; CBC, complete blood count; D, Dose; EOT, end of treatment; MMRp, mismatch repair proficient; MSS, microsatellite stable; OS, overall survival; PD, progressed disease; PK, pharmacokinetic; PRO, patient reported outcome; Q3W, every three weeks; Q6W, every six weeks; Q9W, every 9 weeks; RECIST v1.1; Response Evaluation Criteria in Solid Tumours version 1.1.

The number of responses at each time point are outlined under the x-axis of Figure 2 below and within the company submission, Figure 10.

Figure 2: Changes from baseline and CIs in EQ-5D-5L VAS, interim analysis (MMRp/MSS patient population)

Source: IA1 CSR Figure 15.4.2 (4).
Data cutoff: 28 September 2022.
Abbreviations: BSLN, baseline; CI, confidence interval; Cx, cycle X; EOT, end of treatment; MMRp, mismatch repair proficient; MSS, microsatellite stable; QOL, quality of life; SFU, safety follow-up visit; SVFU, survival follow-up visit; VAS, Visual Analogue Score; WPB, worst post-baseline.

Details on the length of follow-up are found below in Table 7. For the MMRp/MSS population, the median length of follow up was [redacted] and [redacted] months for the dostarlimab arm and placebo arm, respectively.

Table 7: Median, minimum, and maximum for duration of follow-up time (months) of EQ-5D-5L measures by treatment arm (MMRp/MSS population)

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; EQ-5D-5L, European Quality of Life scale, 5-Dimensions, 5-Levels; Max, maximum; Min, minimum; MMRp, mismatch repair proficient; MSS, microsatellite stable

The number of EQ-5D-5L responses at each time point and the mean utility, cross-walked to the EQ-5D-3L using the UK value set in the MMRp/MMS population, are shown in Table 8 (6). EQ-5D was recorded at baseline, each treatment cycle (Q3W in induction phase and Q6W in the maintenance phase), end of treatment, safety follow up (occurring 90 days after

the last dose of the study drug) and during the survival follow up period (beginning 90 days after the safety follow up)

Where EQ-5D-5L was analysed for the purpose of deriving utility weights, this was undertaken according to the treatment assigned at randomisation even if no study treatment was received. Patients who were incorrectly stratified at randomisation were analysed and presented according to the stratum assigned at randomisation. Patients in the analysis were required to have a baseline and post-baseline EQ-5D assessment.

Table 8: EQ-5D-5L - Comparative data cross-walked to EQ-5D-3L between trial arms (MMRp/MSS patient population)

Visit	Statistic	Dostarlimab in combination with CP (N=181)	Placebo in combination with CP (N=174)
Scale/Item: EQ-5D-5L Score cross-walked to EQ-5D-3L			
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 2	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 3	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 4	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 5	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 6	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 7	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 8	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 9	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 10	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 11	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 12	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 13	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 14	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 15	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

Visit	Statistic	Dostarlimab in combination with CP (N=181)	Placebo in combination with CP (N=174)
Cycle 16	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 17	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 18	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 19	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 20	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 21	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 22	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 23	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 24	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 25	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 26	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 27	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Cycle 28	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
EOT	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Safety Follow-up[a]	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 1[b]	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 2	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 3	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 4	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 5	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 6	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Survival Follow-up Assessment 7	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

Visit	Statistic	Dostarlimab in combination with CP (N=181)	Placebo in combination with CP (N=174)
Survival Follow-up Assessment 8	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

[a]The Safety Follow-up Visit should occur 90±7 days after the last dose of study drug.
[b]The Survival Follow-up Period begins 90 days after the Safety Follow-up Visit and continues until death or the end of study data collection (i.e., up to 4 years after the enrolment of the last patient, provided that this allows for the collection of sufficient OS events).
Source: Data on file. ru_uk_t_stat_p3 (6).
Data cut off: 28 September 2022.
Note: Utility analysis for modelling is based off MMR status at randomisation and only included patients with a baseline and post-baseline EQ-5D score, while descriptive analyses are based on source-verified ITT population.
Abbreviations: CP, carboplatin plus paclitaxel; EOT, end of treatment; EQ-5D-3L, European Quality of Life scale, 5-Dimensions, 3 Levels; EQ-5D-5L, European Quality of Life scale, 5-Dimensions, 5 Levels; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; SD, standard deviation; VAS, Visual Analogue Scale.

b) Please provide the number of responses that inform the PFS and progressed disease (PD) health state utilities used in the economic model.

Table 9 below reports the number of utility responses according to progression status at each visit and follow-up measure of EQ-5D.

Table 9: Utility responses by progression status and EQ-5D follow-up (MMRp/MSS population)

Visit	State	Dostarlimab in combination with CP, n (%)	Placebo in combination with CP, n (%)	Total, n (%)
Baseline	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	Progression-free	[redacted]	[redacted]	[redacted]

Visit	State	Dostarlimab in combination with CP, n (%)	Placebo in combination with CP, n (%)	Total, n (%)
	Progression	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	Progression-free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 26 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]

Visit	State	Dostarlimab in combination with CP, n (%)	Placebo in combination with CP, n (%)	Total, n (%)
	Progression	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
End Of Treatment	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Safety Follow-Up	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 1	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 2	Progression-Free	[redacted]	[redacted]	[redacted]
	Progression	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; EQ-5D, European Quality of Life scale, 5-Dimensions; MMRp, mismatch repair proficient; MSS, microsatellite stable.

A5. CS, Document B, section B.2. Please provide results tables for QLQ-EN24 in the MMRp/MSS population of RUBY-1 including baseline values and change from baseline.

Please see answer to Clarification Question A10.

Baseline characteristics

A6. Priority question. CS, Document B, section B.2.4.5. Please provide the baseline characteristics for each trial arm in the MMRp/MSS population of RUBY-1 for the following regional subgroups:

a) North America

Table 10 shows the baseline characteristics for both the dostarlimab arm and the placebo arm from the RUBY-1 MMRp/MSS population for the North America (NA) subgroup. There were [redacted] patients in the dostarlimab arm and [redacted] patients in the placebo arm. Most patients were White with a median age of [redacted] years.

The baseline characteristics of patients were generally well balanced between treatment arms in the NA subgroup.

Table 10:Summary of baseline characteristics for NA population (MMRp/MSS population)

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Number of patients in the Subgroup	[redacted]	[redacted]	[redacted]
Race [n (%)]			
n	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Mixed Race	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Age (years)			
n	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI (kg/m^2) [a]			
n	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Histology [n (%)]			
n	[redacted]	[redacted]	[redacted]
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]	[redacted]
Serous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Clear Cell Adenocarcinoma	[redacted]	[redacted]	[redacted]
Mucinous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Undifferentiated Carcinoma	[redacted]	[redacted]	[redacted]
Neuroendocrine tumors	[redacted]	[redacted]	[redacted]
Carcinosarcoma	[redacted]	[redacted]	[redacted]

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]	[redacted]
Mixed Carcinoma, Other	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
ECOG Performance Status [n (%)]			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Prior EPR [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Endometrial cancer disease status [n (%)]			
n	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Primary Stage III	[redacted]	[redacted]	[redacted]
Primary Stage IV	[redacted]	[redacted]	[redacted]
Evaluable Disease at Baseline [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Measurable Disease at Baseline [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
PD-L1 Status [n (%)]			
n	[redacted]	[redacted]	[redacted]
PD-L1+	[redacted]	[redacted]	[redacted]
PD-L1-	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; EPR, oestrogen and progesterone receptor; Max, maximum; Min, minimum; MMRp, mismatch repair proficient; MSS, microsatellite stable; NA, North American; PD-L1, programmed death-ligand 1.

b) Western Europe.

The baseline characteristics of patients enrolled in the trial from Western Europe (WE) is described in Table 11 below. Some imbalances are observed between arms, notably with regards to ECOG Performance Status, Histology, disease status and presence of evaluable

and of measurable disease at baseline. These imbalances reflect the small sample size of the subgroup and the absence of stratification by region in the RUBY-1 trial.

Table 11: Summary of baseline characteristics for WE subgroup (MMRp/MSS population)

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Number of patients in the subgroup	[redacted]	[redacted]	[redacted]
Race [n (%)]			
n	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Mixed Race	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Age (years)			
n	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI (kg/m^2) [a]			
n	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Histology [n (%)]			
n	[redacted]	[redacted]	[redacted]
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]	[redacted]
Serous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Clear Cell Adenocarcinoma	[redacted]	[redacted]	[redacted]
Mucinous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Undifferentiated Carcinoma	[redacted]	[redacted]	[redacted]

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Neuroendocrine tumors	[redacted]	[redacted]	[redacted]
Carcinosarcoma	[redacted]	[redacted]	[redacted]
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]	[redacted]
Mixed Carcinoma, Other	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
ECOG Performance Status [n (%)]			
n	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Prior EPR [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Endometrial cancer disease status [n (%)]			
n	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Primary Stage III	[redacted]	[redacted]	[redacted]
Primary Stage IV	[redacted]	[redacted]	[redacted]
Evaluable Disease at Baseline [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Measurable Disease at Baseline [n (%)]			
n	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
PD-L1 Status [n (%)]			
n	[redacted]	[redacted]	[redacted]
PD-L1+	[redacted]	[redacted]	[redacted]
PD-L1-	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; EPR, oestrogen and progesterone receptor; Max, maximum; Min, minimum; MMRp, mismatch repair proficient; MSS, microsatellite stable; PD-L1, programmed death-ligand 1.

A7. CS, Document B, section B.2.4.5. Please provide the median age of patients for each trial arm of the MMRp/MSS population in RUBY-1 and the proportions of patients aged <60 years and ≥60 years at baseline.

Table 12 shows a summary of age characteristics in the MMRp/MSS population. The median age of patients was [redacted] versus [redacted] for the dostarlimab arm and placebo arm, respectively. The proportion of patients <60 years and ≥60 years at baseline was comparable between arms.

Table 12: Summary of age characteristics (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Age (years)		
Mean (std)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
<60 (n, %)	[redacted]	[redacted]
>60 (n, %)	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; Max, maximum; Min, minimum; MMRp, mismatch repair proficient; MSS, microsatellite stable.

A8. CS, Document B, section B.2.4.5. Please provide the number of patients from UK centres in each trial arm of the MMRp/MSS population of RUBY-1.

In the RUBY-1 study, the number of patients from UK centres in the MMRp/MSS population [redacted], with [redacted] in the dostarlimab arm and [redacted] in the placebo arm (IA1 CSR, Table 14.1.1.2) (4).

Subgroups

A9. Priority question. CS, Document B, sections B.2.9.1 and B.2.9.2. Please provide a clinical rationale for the differences in PFS and OS with dostarlimab in the North American subgroup compared with the Western European subgroup in the MMRp/MSS population of RUBY-1 (Figures 11 and 12).

There is no biological reason why patients in Europe would respond different to treatment with dostarlimab compared with patients in NA. It is not expected for patients in Europe to respond to treatment differently than those in NA, and this cannot be attributed to variances in treatment practice outlined by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) and European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology (ESGO/ESTRO/ESP) guidelines (7-9).

The differences in PFS and OS with dostarlimab in the NA subgroup compared with the WE subgroup in the MMRp/MSS population of the RUBY-1 study can be attributed to the following factors:

1. **Geographical stratification**: The lack of trial stratification by geographical region and the small sample size in the WE subgroup further complicate the interpretation of the results. The absence of stratification and resulting break of randomisation can result in imbalances in baseline characteristics that affect the outcomes both within and between subgroups. This appears to have resulted in an introduction of bias both between the arms in the WE group and also between the dostarlimab arms of the NA and WE subgroups. For example, the proportion of patients in the dostarlimab arm of the WE subgroup with no measurable disease at baseline (a positive prognostic factor) was lower ([redacted]) than the placebo arm of this subgroup ([redacted]), and also lower than the corresponding dostarlimab arm in the NA subgroup ([redacted]). Similar imbalances were observed in tumour histology and ECOG scores, likely due to this breaking of randomisation.
2. **Sample size**: Owing to the limitations of remote clinical trial monitoring during the COVID-19 pandemic impacting sites in Europe, trial recruitment in this region was low during this period, resulting in the smaller sample size observed in WE (n=88) versus NA (n=272). Furthermore, the trial was not powered to show a difference between geographical locations within the MMRp/MSS and therefore, results should be interpreted with caution.

A10. Priority question. CS, Document B, section B.2.8. Please provide a table with the subsequent treatments received by patients in each trial arm of the Western European subgroup in the MMRp/MSS population of RUBY-1.

Table 13 shows a summary of follow-up anti-cancer treatments within the WE subgroup.

In the WE subgroup, a higher proportion of patients in the placebo arm received subsequent anticancer therapy than patients in the dostarlimab arm ([redacted]% vs [redacted]%). In total, [redacted]% of randomised patients received a subsequent therapy. The most common class of therapy received across both arms was chemotherapy ([redacted]%), followed by hormone therapy ([redacted]%), radiation therapy ([redacted]%) and immunotherapy ([redacted]%).

Notably, there was [redacted] in the WE subgroup compared with the ITT population or the NA subgroup (Table 14). This is likely a feature of the timing of the RUBY-1 trial which initiated in July 2019 (10). Within WE, IO-based

regimens were not yet routinely available, with the European Medicines Agency (EMA) approval for pembrolizumab plus lenvatinib occurring in November 2022 (11). In England, pembrolizumab plus lenvatinib became available for use within the National Health Service (NHS) following a recommendation by National Institute of Health and Care Excellence (NICE) in June 2023 (12). However, in the United States (US) pembrolizumab plus lenvatinib was approved for use by the Food and Drugs Administration (FDA) much earlier in 2019, under an accelerated approval process (13). The higher use of pembrolizumab plus lenvatinib and other innovative subsequent treatments in the NA subgroup likely reflects the generally earlier availability of such therapies in the US compared with other regions.

Table 13: Summary of follow-up anti-cancer treatments- WE subgroup (MMRp/MSS population).

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Number of patients in the subgroup, n (%)	[redacted]	[redacted]	[redacted]
Any follow-up anti-cancer therapy, n (%)	[redacted]	[redacted]	[redacted]
Any FUACT received post-progression (Inv Assessed), n (%)	[redacted]	[redacted]	[redacted]
Type of FUACT received post-progression (Inv Assessed), n (%)			
Chemotherapy	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Epirubicin	[redacted]	[redacted]	[redacted]
Paclitaxel/Carboplatin	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin/Carboplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Carboplatin/Gemcitabine	[redacted]	[redacted]	[redacted]
Carboplatin/Paclitaxel/Bevacizumab	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]
Paclitaxel/Bevacizumab	[redacted]	[redacted]	[redacted]
Paclitaxel/Carboplatin/Trastuzumab	[redacted]	[redacted]	[redacted]
Hormonal Therapy	[redacted]	[redacted]	[redacted]
Megestrol Acetate	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]
Medroxyprogesterone Acetate	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]
Radiation Therapy	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Palliative Radiation	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]
Investigational Product	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Investigational Product	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; FUACT, follow-up anti-cancer treatments; Inv, investigator; MMRp, mismatch repair proficient; MSS, microsatellite stable; WE, Western European.

A11. CS, Document B, section B.2.8. Please provide a table with the subsequent treatments received by patients in each trial arm of the North American subgroup in the MMRp/MSS population of RUBY-1.

Table 14 shows a summary of follow-up anti-cancer treatments within the NA subgroup.

In the NA subgroup, a higher proportion of patients in the placebo arm received subsequent anticancer therapy than patients in the dostarlimab arm ([redacted]). In total, [redacted]% of patients received a subsequent therapy. The most common class of therapy received across both arms was immunotherapy ([redacted]%), followed by chemotherapy ([redacted]%), radiation therapy ([redacted]%) and hormone therapy ([redacted]%).

Table 14: Summary of follow-up anti-cancer treatments- NA subgroup

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Number of patients in the subgroup, n (%)	[redacted]	[redacted]	[redacted]
Any follow-up anti-cancer therapy, n (%)	[redacted]	[redacted]	[redacted]
Any FUACT received post-progression (Inv Assessed), n (%)	[redacted]	[redacted]	[redacted]
Type of FUACT received post-progression (Inv Assessed), n (%)			
Immunotherapy	[redacted]	[redacted]	[redacted]
Pembrolizumab/Lenvatinib	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Atezolizumab/Ipatasertib	[redacted]	[redacted]	[redacted]
Avelumab/Axitinib	[redacted]	[redacted]	[redacted]
Bevacizumab /Atezolizumab	[redacted]	[redacted]	[redacted]
Durvalumab/Olaparib	[redacted]	[redacted]	[redacted]
Investigational Product	[redacted]	[redacted]	[redacted]
Nivolumab/Bms-986207/Com701	[redacted]	[redacted]	[redacted]
Nivolumab/Lucitanib	[redacted]	[redacted]	[redacted]
Retifanlimab/Epacadostat	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin	[redacted]	[redacted]	[redacted]
Paclitaxel/Carboplatin	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Carboplatin/Doxorubicin	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin/Gemcitabine	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin/Bevacizumab	[redacted]	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]	[redacted]
Carboplatin/Doxorubicin/Bevacizumab	[redacted]	[redacted]	[redacted]
Carboplatin/Paclitaxel/Bevacizumab	[redacted]	[redacted]	[redacted]
Cisplatin/Doxorubicin	[redacted]	[redacted]	[redacted]
Cisplatin/Infosfamide/Mesna	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]
Doxorubicin/Bevacizumab	[redacted]	[redacted]	[redacted]

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Gemcitabine/Docetaxel	[redacted]	[redacted]	[redacted]
Ifosfamide	[redacted]	[redacted]	[redacted]
Paclitaxel/Bevacizumab	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin/Carboplatin	[redacted]	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin/Carboplatin/Lenvatinib	[redacted]	[redacted]	[redacted]
Radiation Therapy	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
External Beam Radiotherapy	[redacted]	[redacted]	[redacted]
Brachytherapy	[redacted]	[redacted]	[redacted]
Stereotactic Radiotherapy	[redacted]	[redacted]	[redacted]
Palliative Radiation	[redacted]	[redacted]	[redacted]
Hormonal Therapy	[redacted]	[redacted]	[redacted]
Everolimus/Letrozole	[redacted]	[redacted]	[redacted]
Megestrol Acetate	[redacted]	[redacted]	[redacted]
Megestrol Acetate/Tamoxifen	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]
Abemaciclib/Letrozole	[redacted]	[redacted]	[redacted]
Ly3484356	[redacted]	[redacted]	[redacted]
Onapristone/ Anastrozole	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]
Tamoxifen/Trastuzumab	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]
Cediranib	[redacted]	[redacted]	[redacted]
Cpi-0209	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]
Sacutuzimab Govitecan	[redacted]	[redacted]	[redacted]
Trastuzumab	[redacted]	[redacted]	[redacted]
Trastuzumab/Tucatinib	[redacted]	[redacted]	[redacted]
Zn-C3	[redacted]	[redacted]	[redacted]
Zolendronic Acid	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; FUACT, follow-up anti-cancer treatments; Inv, investigator; MMRp, mismatch repair proficient; MSS, microsatellite stable; NA, North American.

Additional questions

A12. Priority question. The EAG notes that from the [redacted] that PFS data were available from interim analysis 2 (IA2) of RUBY-1. Please provide the results for the MMRp/MSS subgroup of RUBY-1 for PFS and any other outcomes with data available from the IA2 data cut that has not already been provided in the company submission.

GSK would like to clarify that PFS was not initially analysed as part of the second interim analysis (IA2) and therefore not reported within the corresponding clinical study report (CSR). A re-analysis of the PFS from RUBY-1 was undertaken as part of a reactive request from a regulatory body. The PFS from this more mature data cut is consistent with the IA1 PFS analysis presented in Figure 5 of the Company submission (Figure 3). [redacted] (Table 15).

Figure 3: KM curves of IA2 PFS (MMRp/MSS population).

[redacted]

Data cut off: 22 September 2023.
Abbreviations: IA2, second interim analysis KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

Table 15: KM analysis of IA2 PFS (MMRp/MSS population)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS, months (95% CI)	[redacted]	[redacted]
PFS		
Status [n (%)]		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for PFS (months)		
Quartile (95% CI)[a]		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
PFS probability (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Month 30	[redacted]	[redacted]
Month 36	[redacted]	[redacted]
Hazard ratio[b] (95% CI)	[redacted]	

[a]95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b]Stratified Cox Regression.
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; IA2, second interim analysis; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

A13. Priority question. The EAG notes that from the [redacted] that the EAG highlighted inconsistencies between PFS and time-to-treatment discontinuation (TTD) for the dMMR/MSI-H (DNA mismatch repair deficient/microsatellite instability-high) subgroup of RUBY-1. Specifically, different censoring rules are applied for PFS and TTD, resulting in patients withdrawing from treatment, but still being considered progression free.

Whereas, in RUBY-1, it was observed that most patients who were still progression free were also still on dostarlimab treatment. Please:

a) provide the definition of TTD used in the analysis for the MMRp/MSS subgroup from RUBY-1 (including censoring rules)

Censoring flags for time to treatment discontinuation (TTD) estimates were derived on the basis of end-of-treatment status such that only patients with an ongoing treatment status at data cut-off were considered censored. Those coded as 'discontinued' (due either to death or cessation of treatment) were considered a discontinuation event.

Per the study protocol, all outcomes relating to study drug exposure were analysed using the Safety Analysis Set (SAF). The SAF includes all subjects who received at least one dose of study drug and subjects were analysed according to the treatment received. By comparison, efficacy outcomes including PFS are analysed using the ITT analysis set. The ITT analysis set includes all subjects randomised and subjects were analysed according to the treatment assigned at randomization even if no study treatment was received. Whilst 192 subjects with MMRp/MSS tumours were randomised to the dostarlimab arm, 189 patients received at least 1 dose of study drug.

b) provide the results for TTD in the MMRp/MSS subgroup of RUBY-1 from IA2, including Kaplan-Meier plots and numbers at risk

Time-to-event analysis of the TTD data from the most recent data cut is reported in Table 16. Median TTD was [redacted] months and [redacted] months for the dostarlimab in combination with CP and the placebo plus CP arms respectively.

Table 16: IA2 TTD (MMRp/MSS population)

Variable	Dostarlimab (N=189)	Placebo (N=181)
Status [n (%)]		
Events observed	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for TTD (months)		
Quartile (95% CI)a		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
TTD probability (95% CI)		
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

Variable	Dostarlimab (N=189)	Placebo (N=181)
Month 30	[redacted]	[redacted]
Month 36	[redacted]	[redacted]
Month 42	[redacted]	[redacted]
Hazard ratio[b] (95% CI)	[redacted]	
p-value of 1-sided stratified log-rank test	[redacted]	

Note: TTD data is derived from the Safety Analysis Set, which includes only those patients who received the study drug.
[a]95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b]Stratified Cox Regression.
Data cutoff: 22 September 2023.
Abbreviations: CP, carboplatin plus paclitaxel; CI, confidence interval; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; TTD, time to treatment discontinuation.

Figure 4: KM curves of IA2 TTD (MMRp/MSS population)

Note: TTD data is derived from the Safety Analysis Set, which includes only those patients who received the study drug.
Abbreviations: CI, confidence interval; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; TTD, time to treatment discontinuation.

The proportion of patients in each arm discontinuing treatment is similar in both arms. At the most recent data cut, [redacted] dostarlimab patients who initiated treatment had discontinued with [redacted] patients still receiving treatment, and therefore recorded as being censored in the KM analysis outlined in Table 16. In the placebo arm [redacted] patients had discontinued treatment and [redacted] remaining on placebo. Fewer patients in the dostarlimab arm [redacted] discontinued due to disease progression than in the placebo arm [redacted]. Conversely, more patients in the dostarlimab arm discontinued study drug due to adverse events [redacted] compared with the placebo arm ([redacted]).

Table 17: Reason for discontinuing dostarlimab/placebo, IA2 (MMRp/MSS population)

	Dostarlimab in combination with CP	Placebo in combination with CP	Total
Discontinued dostarlimab/placebo	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Clinical Progression	[redacted]	[redacted]	[redacted]
PD according to RECIST v1.1 Criteria per Investigator Assessment	[redacted]	[redacted]	[redacted]
Risk to Subject, as Judged by the Investigator, Sponsor, or Both	[redacted]	[redacted]	[redacted]
Severe Noncompliance with the Protocol, as Judged by the Investigator, Sponsor, or Both	[redacted]	[redacted]	[redacted]
Subject Becomes Pregnant	[redacted]	[redacted]	[redacted]
Withdrawal by Subject	[redacted]	[redacted]	[redacted]
Lost to Follow-Up	[redacted]	[redacted]	[redacted]
Death from Any Cause	[redacted]	[redacted]	[redacted]
Sponsor decision to terminate study	[redacted]	[redacted]	[redacted]
Confirmed CR, Treated for at least 3 Years with study treatment	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Abbreviations: CR, complete response; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; PD, progressed disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.

c) explain why the different censoring rules for PFS and TTD do not introduce bias into the model.

The censoring rules used in the time-to-event analysis of both TTD and PFS are aligned with convention, accepted methodology and guidance from regulators on oncology trial design and assessment of endpoints.

PFS as the primary endpoint of the RUBY-1 trial was analysed according to FDA Guidance to Industry at the time of the RUBY-1 trial with the PFS censoring rules consistent with other oncology clinical trials (14). Notably, this FDA guidance and associated censoring rules are mirrored across other pivotal trials for immune-oncology treatments including in endometrial cancer (15, 16). PFS as a primary endpoint in the trial was determined by investigator assessment (INV) with PFS based on blinded independent central review (BICR) being a secondary endpoint. This PFS by INV was used for modelling purposes, being reflective of real-world practice and aligning with how physicians typically monitor and manage patients in a clinical setting. Nevertheless, PFS by BICR was generally consistent with PFS by INV (17).

As described in the response to Question A13, discontinuation data from the RUBY trial was complete with no missing data. As expected with TTD data, only patients still receiving study

drug at the time of study cut off were censored (<10% in both arms). For modelling purposes, the TTD was re-analysed using the ITT analysis set and incorporated into the model. This was to minimise bias and ensure the TTD, PFS and OS endpoints used in the model are derived from the same population. Given the ITT population is slightly larger than the safety analysis set (SAF), this results in the ITT TTD curve sitting very slightly higher than the corresponding SAF TTD curve, however as illustrated in Figure 5 this difference is negligible.

Figure 5 Comparison of dostarlimab TTD using safety and intention-to-treat analysis sets

Abbreviations: ITT, intentention to treat; SAF, safety analysis set; TTD, time to treatment discontinuation

A14. Priority question. CS, Document B, section 2.6. For the ITT analyses of PFS in the MMRp/MSS subgroup of RUBY-1, please provide:

a) the number of patients on dostarlimab treatment observed in the trial every 2 months from time of randomisation up to 3 years and the corresponding number of patients predicted to be on treatment from the model

The number of patients remaining on study drug in the dostarlimab arm at the start of each 2-monthly interval is reported in the second column in Table 18 below. This aligns very closely with the numbers predicted by the model, as expected given the high degree of completeness and relatively little censoring of the TTD data. The most notable difference is

the absence of patients on treatment beyond 3-years as a result of the stopping rule for dostarlimab as required per the summary of product characteristics (SmPC).

Table 18: Proportion of patients on dostarlimab treatment in the trial and corresponding number of patients (MMRp/MSS population)

Month	Dostarlimab in combination with CP	Predicted -KM applied in model	Difference predicted versus observed
0	[redacted]	[redacted]	0.00
2	[redacted]	[redacted]	0.09
4	[redacted]	[redacted]	1.08
6	[redacted]	[redacted]	0.06
8	[redacted]	[redacted]	1.05
10	[redacted]	[redacted]	0.04
12	[redacted]	[redacted]	0.03
14	[redacted]	[redacted]	1.03
16	[redacted]	[redacted]	0.02
18	[redacted]	[redacted]	2.02
20	[redacted]	[redacted]	0.02
22	[redacted]	[redacted]	0.02
24	[redacted]	[redacted]	0.02
26	[redacted]	[redacted]	0.01
28	[redacted]	[redacted]	0.01
30	[redacted]	[redacted]	0.01
32	[redacted]	[redacted]	0.01
34	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]

Note: TTD data is derived from the Safety Analysis Set, which includes only those patients who received the study drug.
Abbreviations: CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable; KM, Kaplan-Maier

b) the number of people in each trial arm who were progression free at their last observation

A higher proportion of patients in the dostarlimab arm ([redacted]) were confirmed as being progression free at their last available assessment compared with the placebo arm ([redacted]) (Table 19). This includes patients who had died or withdrew from the trial without a progression event and also patients who were still being followed up at the time of the most recent data cut. Similarly, a lower proportion of patients in the dostarlimab arm had a confirmed progression event ([redacted]) compared with the placebo arm ([redacted]), and a similar proportion of patients in each arm were censored for other reasons within the PFS analysis.

Table 19: Number of patients progression free at their last available assessment (MMRp/MSS population)

n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Documented disease progression	[redacted]	[redacted]
Confirmed progression free at last assessment	[redacted]	[redacted]
Censored [other]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel.

c) the number of people in each trial arm who were progression free at their last observation and still receiving randomised study treatment.

Due to time constraint in addressing the additional questions by the EAG it was not possible to analyse the data to quantify the number of patients who were progression-free and still receiving study drug at their recorded assessment date while alive during the RUBY-1 trial. However, as clarified in the response to Questions A13 TTD data is relatively complete and reasons for discontinuation well-captured as reported in Table 17.

Table 20 shows the number of people in each trial arm who were progression free and still receiving study treatment at the time of the most recent data cut-off. In the dostarlimab arm 15 (7.9%) of patients were still on treatment and progression free at the time of data cut-off, whilst in the placebo arm 17 (9.4%) patients were still on treatment and progression-free.

Table 20: Proportion of patients PF at last observation and still receiving randomised study treatment (MMRp/MSS population)

Variable	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
N (%) PF at last observation and still receiving randomised study treatment	15 (7.9)	17 (9.4)

Abbreviations: CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable; PF, progression free.

A15. The EAG notes that from the [redacted] that there was an analysis of PFS2 in people who received a subsequent therapy in the dMMR/MSI-H subgroup of RUBY-1. Please provide the results including Kaplan-Meier curves for PFS2 in each arm of RUBY-1 for only the people who received subsequent therapies in the MMRp/MSS subgroup.

The analysis cited as part of ID6426 was a post-hoc analysis requested by the corresponding EAG and was not part of the RUBY-1 analysis plan. GSK do not believe this

is an informative analysis due to its post-hoc nature and patient selection based on a post-randomisation event.

The PFS2 analysis presented in Section 2.6.4.1 of the Company Submission reports the PFS2 analysis per the trial Statistical Analysis Plan. The analysis requested by the EAG is presented in Figure 6 below. This analysis is broadly supportive of the primary PFS2 analysis. Fewer patients in the dostarlimab arm ([redacted]) went on to receive a subsequent anticancer therapy in the RUBY-1 trial compared with the placebo arm ([redacted]) (Table 21). Amongst patients who received a subsequent anti-cancer therapy, the median time to progression after receipt of the subsequent therapy was [redacted] months in the dostarlimab arm compared to [redacted] months in the placebo arm.

Figure 6: KM analysis of PFS2 in people who received FUACT (MMRp/MSS population)

Abbreviations: CI, confidence interval; FUACT, follow-up anti-cancer therapy; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression-free survival 2.

Table 21: KM analysis of PFS2 in people who received FUACT (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Number of Subjects who have FUACT		
N (%)	[redacted]	[redacted]
PFS2		
Status [n (%)]		
Events observed	[redacted]	[redacted]

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for PFS2 (months)		
Quartile (95% CI)[a]		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
PFS2 Probability (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Duration >=6 months [n (%)]	[redacted]	[redacted]
Duration >=12 months [n (%)]	[redacted]	[redacted]
Hazard ratio[b] (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	

[a]95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b]Stratified Cox Regression.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; FUACT, follow-up anti-cancer therapy; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression-free survival 2.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("Settings" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

All requested scenarios have been implemented as user selectable options within the 'settings' sheet in the model, for ease of external assessment group (EAG) view.

Based on some of the EAG requested scenarios, an updated base case has been provided. Please see Appendix 1 for:

- A summary of the updated settings, their impact and the updated company base case (Table 50).
- Updated model base case results (Table 51)
- Updated model sensitivity analyses (Table 52, Table 53, and Table 54)
- And the impact of the EAG scenarios on the updated base case (Table 55)

NHSCII inflation index

B1. Priority question. CS, Document B, section B.3.5 and Excel model. The company's economic model uses an outdated version of the NHSCII inflation index from the Unit Costs of Health and Social Care 2022 Manual (tab "Data store", cells E246:252). However, the company submission states that prices are inflated to 2022/23 prices, so the NHSCII inflation index from the Unit Costs of Health and Social Care 2023 Manual should be used. Please correct the model to use the latest inflation index as per the approach suggested in the company submission.

An option has been included in cell 'G50' of the Settings tab of the Excel model to use the inflation index from the Unit Costs of Health and Social Care 2023 Manual (when 'Yes' is selected, cells E245:252 in the 'Data store' tab are updated). The updated company base case has been adjusted to reflect the updated costs, with results presented in Table 22. Using the updated inflation indices has minimal impact on the incremental cost-effectiveness ratio (ICER).

Table 22: Results using updated PSSRU inflation indices from 2022/23

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + updated PSSRU indices	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

Survival extrapolations

B2. Priority question. The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 states that "*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 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*".

Based on observed data from RUBY-1, please provide an explanation for why it was considered appropriate to use different types of survival curves to model an outcome for each treatment (normal [CP] and odds [dostarlimab+CP] splines for PFS, log-logistic [CP] and lognormal [dostarlimab+CP] for OS).

Selection of parametric survival curves was undertaken based on statistical and visual goodness-of-fit and with input from external experts, as described in Section 3.3.2 of the company submission.

In this instance, different parametric distributions may be suitable for fitting curves to the observed data due to several factors. These include the differentiated mechanism of action of dostarlimab compared to chemotherapy alone, the atypical exposure-response relationship observed with dostarlimab and other immunotherapies, and the significantly longer mean duration of treatment. Consequently, the underlying hazard in time-to-event efficacy outcomes appears to differ between dostarlimab, an IO treatment, and the placebo plus chemotherapy arms of the trial.

As illustrated in Figure 7, the PFS and OS empirical hazard plots indicate different trends in the underlying hazard between both arms for each outcome, thereby supporting the use of different parametric distributions. This differentiation can be attributed to three primary reasons:

- differentiated mechanism of action of dostarlimab versus chemotherapy alone
- delayed exposure-response relationship with immunotherapies
- longer duration of treatment

Figure 7: Empirical hazard plot for PFS (Left) and OS (Right)

Abbreviations: CP, carboplatin plus paclitaxel; OS, overall survival; PFS, progression-free survival.

IO agents such as dostarlimab have a recognised differentiated mechanism of action compared with more conventional chemotherapy agents. Dostarlimab does not exhibit direct anti-cancer activity but functions by removing the blockade that prevents the immune system from identifying and destroying cancer cells (18). There is typically a lag between IO exposure and clinical outcomes, as can be seen in the overlapping PFS curves between dostarlimab and placebo arms within the RUBY-1 trial (Figure 5 of the company submission) during the chemotherapy phase of the trial followed by sustained separation from approximately 6 months. Furthermore, emerging evidence suggests that cancer cell exposure to chemotherapy can enhance the immunogenicity of cancer cells, thereby increasing susceptibility to IOs (19, 20). The anticancer activity of immunotherapies is expected to be durable for many patients due to the sustained activation of the immune system even after treatment discontinuation. As noted within the company submission, dostarlimab can be continued for up to three years while platinum-containing chemotherapy is typically administered over six 3-weekly cycles.

In summary, the differentiated mechanism of action of dostarlimab, the atypical exposure-response relationship and much longer duration of treatment mean that the underlying hazard in time-to-event efficacy outcomes is likely to differ between the dostarlimab and placebo arms of the trial. Consequently, it is appropriate to employ different model types to fit parametric survival curves to the relevant outcomes.

B3. CS, Document B, sections B.3.3.2 and B.3.3.2.1 and Excel model. Please describe how the location of the knots was determined for the spline models explored for the extrapolation of PFS for both CP and dostarlimab+CP.

a) The location of the knots for each spline is provided in the economic model (tab “RUBY Survival Coefficients”). However, please clarify what measurement of time is used (that is, months or years). For example, the location of the knots for the normal k=2 spline for CP is 0.45 (lower boundary knot), 3.18, 3.58 and 4.81 (upper boundary knot), but it is unclear how the location relates to the PFS KM curve for CP.

The specific points in time of the knots are located within the submitted economic model (‘Flexible Survival Analysis’ sheet- cells K10:K51 for dostarlimab in combination with CP and cells AB10:AB51 for CP alone).

The location of the knots was determined using RStudio, with knots placed uniformly along the distribution of uncensored log event times (defined in weeks) with boundary knots placed at the minimum and maximum uncensored log event times, in line with NICE Decision Support Unit (DSU) 21 (21, 22). Therefore, with the normal, k=2, for example, the knots are set at the minimum and maximum bounds (0%, 100% for boundary knots) and then set uniformly along the distribution, therefore at the 33% and 67% of log time with two knots.

When looking at the PFS KM curve for CP, to determine the location of the knots, the knots are exponentiated to yield the corresponding values (provided in Table 23 below).

Table 23: CP- location of knots and corresponding time

Knots	Time (weeks)
0.45	1.57
3.18	24.14
3.58	35.86
4.81	123.00

Abbreviations: CP, carboplatin plus paclitaxel.

b) Please use the hazard rate plot provided in Figure 17 of the company submission and demonstrate the location of the knots in the company’s base case PFS curves align with observed change in the PFS.

Figure 8 contains the hazard rate plot for PFS with the location of the knots for both the dostarlimab and CP arm. The location of the knots and corresponding time in weeks can be found in Table 23 and Table 24 for CP and dostarlimab respectively.

Figure 8: Location of knots and corresponding time points

Note: that the maximum bound for dostarlimab is outside of the scope of the image, however, the location can be found in the table below.
Abbreviations: CP, carboplatin plus paclitaxel.

Table 24: Dostarlimab- location of knots and corresponding time

Knots	Time (weeks)
1.49	4.44
3.13	22.87
3.51	33.45
3.8	44.70
4.99	146.94

c) B4. CS, Document B, section B.3.3.2.1.1. Please provide a visual comparison of the log-logistic, lognormal and normal k=2 spline PFS extrapolations for CP and discuss the findings.

Figure 9 shows the visual comparison of the log-logistic, lognormal and normal, k=2 flexible spline PFS extrapolations for CP. Overall, there is minimal difference between the independent parametric extrapolations, lognormal and log-logistic curves, with nearly identical proportions throughout the observed period. Initially, the normal, k=2 model estimates lower PFS compared to the lognormal and log-logistic models. However, at approximately 1.7 years, a divergence occurs, with the normal, k=2 model indicating a higher proportion of individuals in the progression-free (PF) state compared to the log-logistic and lognormal models. Table 25 shows point estimates at various time points for the

three distributions. The log-normal and log-logistic distributions show similar proportions across the 20-year duration. As outlined in the clinical advisory board conducted in July 2024, the hazard plot for CP shows a complex hazard function therefore simple models will underestimate the CP PFS (23). Clinicians also felt that none of the standard parametric curves fit well, and flexible models would produce a better statistical and visual fit for CP.

Figure 9: Visual comparison of log-logistic, log-normal and normal, k=2 spline PFS extrapolations for CP

Abbreviations: CP, carboplatin plus paclitaxel; PFS, progression-free survival.

Table 25: Proportion of patients in PFS state using log-logistic, log-normal and normal, k=2 spline PFS extrapolations for PFS

	Normal, k=2	Lognormal	Log-logistic
1 year	34.52%	40.34%	38.15%
3 years	14.55%	8.07%	7.32%
5 years	9.58%	2.61%	2.93%
10 years	5.02%	0.38%	0.82%
15 years	3.30%	0.10%	0.39%
20 years	2.39%	0.03%	0.23%

Non-fatal progression events

a) B5. Priority question. CS, Document B, section B.3.5.3.3. The proportion of newly progressed patients per cycle in the model is a key driver of costs as a one-off cost of subsequent treatments is applied to these patients.

b) In TA963 (dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency), it appears that the estimation of non-fatal progression events was not included in the economic model, which is a key difference from the current submission that the company states uses the same economic model.

    i) Please explain what approach was taken in TA963 for applying subsequent treatment costs and why it was not considered appropriate for this submission.

In TA963, similar to the method used within this appraisal, subsequent treatment costs were applied to the proportion of patients who progressed within each cycle (24). As partition survival models do not explicitly model the transition between the PF and PD heath states, assumptions are required to approximate the transition probability between PF and PD health states, for the purpose of assigning subsequent treatment costs.

In TA963 the proportion of patients progressing was assumed to be equal to the incremental proportion of patients in the PD state between cycles (24). This was a simplifying assumption which underestimated the number of progression events as these events could only be estimated when the PD state was increasing in size. As a result, no progression events were assumed when the PD state was stable or decreasing in size (i.e. similar or higher rate of deaths from PD as the rate of those entering PD). It should also be noted that subsequent therapies in endometrial cancer at the time of TA963 for dMMR/MSI-H tumours was limited to mainly chemotherapies and relatively inexpensive treatments, given that dostarlimab monotherapy was available only via the Cancer Drugs Fund (CDF) and pembrolizumab monotherapy was not yet commercially available, and therefore, a simplified approach was deemed appropriate (24). In addition, for patients with dMMR/MSI-H tumours it is expected that a notable proportion of patients will experience a long-term remission with dostarlimab therapy resulting in few progression events or use of subsequent treatments (25).

Within this submission, in respect of the MMRp/MSS population, the existing standard-of-care at second line for those previously treated with platinum-containing chemotherapy (PCC) in first-line includes pembrolizumab in combination with lenvatinib, a relatively expensive treatment regimen (26). Therefore, the simplifying assumptions utilised in TA963 are unsuitable for this appraisal and would fail to capture the benefits of administering an IO in first line, thus reducing second line treatment costs (24). The updated approach used in the submitted model uses direct evidence from the RUBY trial to more accurately approximate the proportion of non-fatal PFS events. This approach more accurately estimates the cost of subsequent treatments upon progression which is more relevant for MMRp/MSS population where the sustained long-term remission and resulting PFS plateau is less likely than for the corresponding dMMR/MSI-H population.

ii) Please provide a scenario that uses the approach taken in TA963 for estimating the proportion of PD events to apply subsequent treatment costs.

As described in question B5 a) i) above, the method used in TA963 is inappropriate for estimating subsequent treatment costs for this appraisal given the limitations described (24). GSK therefore do not believe adapting the model to present this scenario would be helpful for the NICE committee.

c) Using data from RUBY-1,

i) Please provide time-to-event data for PFS with disease progression as the only event of interest for CP and dostarlimab+CP for the pMMR population.

The Kaplan-Meier graph and corresponding table are presented below in Figure 10 and Table 26. These align very closely with the corresponding PFS curves and treatment effect estimate presented in the company submission, demonstrating high level of concordance between time-to-progression and PFS.

Figure 10: KM curves of time-to-progression, MMRp/MSS subpopulation

Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable.

Table 26: KM analysis of time-to-progression (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Status [n (%)]		
Events observed	109 (56.8%)	125 (67.9%)
Censored	83 (43.2%)	59 (32.1%)
Estimates for PFS (months)		
Quartile (95% CI) [a]		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
PF probability (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Hazard ratio[b] **(95% CI)**	[redacted]	
p-value of 1-sided stratified log-rank test	[redacted]	

a.95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b.Stratified Cox Regression;
Abbreviations: CP, carboplatin plus paclitaxel; PF, progression free; PFS, progression-free survival; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable.

ii) Please demonstrate that the proportion of non-fatal progression events ([redacted]) is stable over time.

A description of the PFS events is presented in Table 27, categorising each event as either a disease progression or a death event. The total number of fatal PFS events appears to decrease over time, with all death events bar one occurring within the first year of follow-up, and all events from month 16 being non-fatal progression events. This is a trend that is consistent across both arms and suggests that the base case modelling approach whereby [redacted] of all events across the model time horizon are assumed to be non-fatal, over the entire model horizon is appropriate and if anything may result in a negligibly small underestimate of the true incremental cost differences between the treatment arms.

Table 27: Progression events categorised by progression and death events (MMRp/MSS population)

	Dostarlimab in combination with CP (N=192)			Placebo in combination with CP (N=184)		
Month	PFS events	Number of progressions	Number of deaths	PFS events	Number of progressions	Number of deaths
0	0	[redacted]	[redacted]	0	[redacted]	[redacted]
2	9	[redacted]	[redacted]	10	[redacted]	[redacted]
4	10	[redacted]	[redacted]	12	[redacted]	[redacted]
6	26	[redacted]	[redacted]	31	[redacted]	[redacted]
8	20	[redacted]	[redacted]	30	[redacted]	[redacted]
10	21	[redacted]	[redacted]	17	[redacted]	[redacted]
12	6	[redacted]	[redacted]	12	[redacted]	[redacted]
14	2	[redacted]	[redacted]	2	[redacted]	[redacted]
16	5	[redacted]	[redacted]	8	[redacted]	[redacted]
18	4	[redacted]	[redacted]	2	[redacted]	[redacted]
20	5	[redacted]	[redacted]	0	[redacted]	[redacted]
22	1	[redacted]	[redacted]	1	[redacted]	[redacted]
24	3	[redacted]	[redacted]	3	[redacted]	[redacted]
26	1	[redacted]	[redacted]	1	[redacted]	[redacted]
28	0	[redacted]	[redacted]	0	[redacted]	[redacted]
30	1	[redacted]	[redacted]	1	[redacted]	[redacted]
32	1	[redacted]	[redacted]	0	[redacted]	[redacted]
34	1	[redacted]	[redacted]	0	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; PFS, progression-free survival.

i) If the proportion of non-fatal progression events is not found to be stable over time, please use the data requested in B5bi in a scenario to estimate newly progressed patients per cycle.

As highlighted in the response to Question B5ii), given that the proportion of PFS events which are fatalities appears to decrease over time, the suggested approach taken in the submission base case may underestimate the true ICER. This is especially true given the impact of subsequent treatments as a driver of cost-effectiveness.

Furthermore, given the small absolute number and variable frequency of death events occurring, it is difficult to estimate a time-varying rate of non-fatal progression events for incorporation into the model. Therefore, GSK do not believe it would be of value for decision making to adapt the model for such a scenario given the expected impact on the ICER and feasibility challenges.

Treatment duration

B6. Priority question. CS, Document B, section B.1.2, Table 2 and section B.3.3.2.3. The company submission states that "Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years". Please explain the reasons why patients remained on dostarlimab treatment beyond three years.

The protocol for RUBY-1 specified that patients should be treated until disease progression, unacceptable toxicity, or up to 3 years, in line with the SmPC (27). During the RUBY-1 trial, where patients were stable, and the investigator believed they were still deriving benefit, the investigator could request to continue treatment for over three years. Such a request required approval from the study sponsor (Tesaro, GSK). Individual patient-level information on reasons for continuation past 3 years for each patient is not available.

a) If the reasons are because of missed or delayed doses, please discuss what impact patients treated beyond three years would have on relative dose intensity (RDI). Would RDI be 100%?

In the RUBY-1 trial patients were able to continue treatment beyond three years at the request of the investigator if they were still deriving benefit, as long as this was agreed by the sponsor. Continuation of treatment beyond three years was not due to missed or delayed doses, as the duration of treatment was specified as 'until disease progression, unacceptable toxicity, or up to 3 years' and was not dependent on a fixed number of doses. Therefore, and consistent with the SmPC for dostarlimab, regardless of any skipped or delayed doses (for example, to manage adverse events), treatment is not expected to continue beyond three years.

An RDI of 100% would correspond to all patients receiving the scheduled dose consistently without any delays or missed doses. As observed in the RUBY-1 trial and specified in the SmPC, dose delays and interruptions (see company submission Table 17) are required to manage adverse events, and this then results in the RDI being <100%.

b) Please provide a scenario where the truncation of the dostarlimab time-to-treatment discontinuation (TTD) curve at three years is removed.

It is not considered appropriate to fully extrapolate the TTD curve for the duration of the model time horizon due to the existence of a stopping rule within the license. In addition, there is a paucity of TTD data following the 3-year mark, which would be required to derive for a post-stopping rule extrapolation. This scarcity of data diminishes the reliability of extrapolations.

For completeness, an option has been added to the model (Cell 'G51' of the 'Settings' sheet) whereby the TTD KM curve is used for the full follow-up period (up to cycle 187), including a small portion after the 3-year stopping rule.

Results of this scenario compared with the submitted base case are presented in Table 28.

Table 28: Results using TTD KM for the full follow-up period

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + TTD KM for full follow-up period	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; QALY, quality-adjusted life year; TTD; time to treatment discontinuation.

Treatment waning

B7. CS, Document B, section B.3.3.2.2.3. Please describe the methods of the treatment waning scenario included in the economic model.

The submitted economic model contains the functionality to apply treatment waning to both PFS and OS, with treatment waning being applied either immediately or gradually, based on user selection. An immediate waning to the dostarlimab arm is applied at the end of the observed period, whilst a gradual linear waning to the dostarlimab arm is initiated and ends at user defined timepoints.

By selecting the dostarlimab treatment waning approach in cells D12 and D50 of the 'Clinical inputs' sheet, the user can specify the waning effect for PFS and OS respectively.

Two scenarios have been included within document B of the company submission:

- Waning from years 5 to 7; with waning beginning in Cycle 260 for 2 years.
- Waning from years 8 to 10, with waning beginning in Cycle 416 for 2 years.

Waning is applied by adjusting the hazard in the dostarlimab arm to gradually equal that of the placebo arm over the defined duration. These calculations can be seen in the 'extrapolations' sheet.

Health-related quality of life

B8. CS, Document B, section B.3.4.1. Please clarify if a mixed model for repeated measures (MMRM) regression was considered when analysing utility data from RUBY-1.

a) If a MMRM was explored, please provide a description of the analysis along with results and accompanying scenarios.

Utility index values were estimated using population-specific reference value sets. Subsequently, utility values by progression states and time to death were derived using Generalized Estimating Equations (GEE). This method estimated the population-level average utilities necessary for economic modelling. The GEE approach models a known function of the marginal expectation of the dependent variable as a linear function of the explanatory variables, resulting in parameter estimates that reflect population averages. Additionally, GEE models accommodate correlated repeated measures, such as EQ-5D assessments obtained from the same patient across different visits. This methodology is further described by Liang and Zeger (1986) (28). Moreover, an MMRM was used to analyse the repeated measures across different visits. The results, including the Least Squares Mean (LSM) change from baseline for the utility scores, were provided by treatment and visit (Table 29). This approach ensures a robust handling of repeated measures data, offering insights into the treatment effects over time.

Table 29: EQ-5D utility score - Analysis of change from Baseline, mixed effects model for repeated measures (MMRp/MSS patient population)

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
Cycle 2 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 3 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 4 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 5 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		p-value	[redacted]	
Cycle 6 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 7 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 8 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 9 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
Cycle 10 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 11 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 12 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 13 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 14 Day 1	Change from Baseline	n	[redacted]	[redacted]

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 15 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 16 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 17 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 18 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 19 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 20 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 21 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 22 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 23 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Cycle 24 Day 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
End of treatment	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Safety Follow-Up	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 1	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 2	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 3	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 4	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=179)	Placebo in combination with CP (N=172)
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 5	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	
Survival Follow-Up Assessment 6	Change from Baseline	n	[redacted]	[redacted]
		LSM (SE)	[redacted]	[redacted]
		95% CI	[redacted]	[redacted]
		Difference from placebo		
		LSM (SE)	[redacted]	
		95% CI	[redacted]	
		p-value	[redacted]	

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error.

b) Please describe why a descriptive analysis of utility data from RUBY-1 is more appropriate that a MMRM regression analysis.

Utility weights were analysed using GEE rather than relying solely on a simple descriptive analysis. In the GEE model, the utility score served as the dependent variable, with treatment as the primary exposure variable. Several baseline covariates were assessed as potential effect modifiers, including age group (<65, ≥65), ECOG status (1, 0), prior external pelvic radiotherapy (Y/N), prior surgery (Y/N), and disease status (primary III, IV, recurrent). Interaction terms (treatment × candidate for effect modification) were included for each of these covariates. As none of these interaction terms were found to be statistically significant, the final model included treatment, progression (the key covariate of interest), and the treatment × progression interaction.

Adverse events

B9. Priority question. CS, Document B, section B.2.11.6. The EAG's clinical experts advised that immune-related adverse events (irAEs) are important to consider for immunotherapy treatment. Section 2.11.6 of the company submission states that "irAEs were identified as any Grade ≥2 AEs that met the pre-specified criteria based on a pre-defined list of preferred terms and MedDRA Version 26.0". Please provide data on irAEs and explore a scenario where the costs and disutility of these irAEs are included in the model.

GSK acknowledges the scenario requested by the EAG and has updated the company base case as a result, including Grade 3+ irAEs occurring in at least 2% of patients.

In line with the threshold for treatment-related adverse events (AEs) in the model, the inclusion of Grade 3+ immune-related adverse events (irAEs) occurring in at least 2% of patients when more frequent in the dostarlimab arm, has been added as an option (Cell 'G52' of the 'Settings' tab). The additional events included for dostarlimab in combination with CP, and the respective costs and disutilities sourced for these additional events are provided in Table 30. No additional events were included for CP based on the trial data

Table 30: irAEs included in model scenario

Adverse event	Dostarlimab in combination with (N=241) Frequency- n(%)	Unit Cost	Disutility	Source(s)
Rash	16 (6.6)	£227.88	0.116	Cost: NHS CC: JD07K; Skin disorders. National Cost Collection Data Publication 2023/24 (29) Disutility: Assumed equal to hand and foot syndrome, Lloyd (2006) (30)
ALT increased	5 (2.1)	£193.89	0.05	Cost: NHS CC: 370 – Medical Oncology consultant-led follow-up visit. National Cost Collection Data Publication 2023/24 (29) Disutility: NICE TA813 (31)
AST increased	5 (2.1)	£193.89	0.05	Cost: NHS CC: 370 – Medical Oncology consultant-led follow-up visit. National Cost Collection Data Publication 2023/24 (29) Disutility: Assumed same as ALT increased

Abbreviations: ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; CP, carboplatin plus paclitaxel; irAE, immune-related adverse events.

The results associated with this scenario are presented in Table 31, and demonstrates that this scenario has minimal impact on the ICER.

Table 31: Results including irAEs in model

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + Grade 3+ irAE in at least 2% of patients included	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; irAE, immune-related adverse events; QALY, quality-adjusted life year.

B10. CS, Document B, sections B.3.4.3 and B.3.5.3.2. Please clarify why duration of adverse events (AEs) was not included in the estimation of disutility and costs associated with first- and second-line treatment.

a) Please provide a scenario that includes the duration of AEs to estimate the disutility and costs associated with AEs.

Data on the duration of AEs was not collected as part of the RUBY-1 trial. Disutility data for AEs was collected from the published literature as outlined in Document B, Table 35. In the economic model, a simplifying assumption was used, whereby each AE has an implied duration of one cycle (one week). This simplifying assumption was justified by the low incidence of serious AEs reported in the RUBY-1 trial and the comparable rates between the dostarlimab and CP arms. Thus, a one-week duration was considered appropriate. This is consistent with the approach taken in the model for TA963 (24).

The one-way sensitivity analysis submitted within the company submission indicated that serious AE disutilities and costs for both first- and second-line treatments were not key drivers of the model. This suggests that the duration of AEs is unlikely to significantly impact the cost-effectiveness results.

Although AE duration data is unavailable from the RUBY-1 trial, a scenario has been provided in Table 32 which doubles the frequency of AEs in both the dostarlimab, and CP arms for first- and second-line. This effectively doubles the costs and disutilities, reflecting an average duration of two weeks for each AE instead of one week. This adjustment has a negligible impact on the ICER.

Table 32: Results after doubling AE frequency in the model

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + doubled AE frequency	£[redacted]	0.755	£[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B11. The company has included disutility associated with subsequent treatment adverse events in its model but has not provided a description in its submission. Please justify the inclusion of adverse events disutilities for subsequent treatments, taking into consideration whether the impact may be captured in the PD utilities from the RUBY-1.

a) Please provide a scenario where the disutility of subsequent treatment adverse events is excluded from the economic model.

GSK does not believe it is appropriate to exclude disutilities associated with subsequent treatment, as this would result in an inconsistency in approach, with AE costs and disutilities only being captured for a subset of treatment options despite evidence demonstrating the occurrence of adverse events for the available subsequent treatment options.

In the model, disutility associated with subsequent treatment AEs was included in the base case, consistent with the inclusion of disutilities in respect of first line interventions. This is considered appropriate as utility estimates derived from EQ-5D responses at fixed timepoints within the RUBY-1 trial may not be sufficiently sensitive to capture the quality-of-life impact from AEs which occur episodically. As highlighted in the response to Question B10, subsequent treatment AE disutilities are were not identified as a key model driver.

For completeness, a scenario analysis has been provided in Table 33 where subsequent treatment AE disutilities are excluded. This has a negligible impact on the ICER.

Table 33: Results after excluding subsequent treatment AE disutilities in the model

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + exclude AE disutilities at 2L	£[redacted]	0.755	£[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B12. Please provide a scenario where costs of subsequent treatment adverse event costs are excluded from the model. The requested scenario may be combined with the scenario requested in B11a for consistency.

GSK do not believe it is appropriate to exclude AE costs associated with subsequent treatments as this approach is inconsistent with the inclusion of AEs related to first-line interventions.

A scenario has been provided where the costs of subsequent treatment AEs are excluded from the model. A scenario has also been provided where both the costs and the disutilities associated with subsequent treatment AEs is excluded in the model. The results are presented in Table 34 and the impact of both scenarios on the ICER is negligible.

Table 34: Results after excluding subsequent treatment AE costs and disutilities in the model

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + exclude AE costs at 2L	£[redacted]	0.755	£[redacted]
Submitted company base case + exclude AE disutilities and costs at 2L	£[redacted]	0.755	£[redacted]

Abbreviations: 2L, second-line; AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

Drug acquisition costs

B13. Company Excel model. In the Excel model, a RDI of [redacted]% for dostarlimab has been included for use after week 19 to adjust drug acquisition costs, but this has not been described in the company submission. Please clarify if these data are from RUBY-1 and how RDI has been estimated (for example, based on data from week 19 onwards until the end of follow-up for IA2).

The value of [redacted] RDI was calculated as per the SAP and is outlined in Table 35. The RDI calculation is based on the number of patients receiving a dose by cycle, by population. It has been sourced from RUBY at every 3 weeks (Q3W) and every 6 weeks (Q6W) intervals and has been calculated using the completion rates.

Table 35: Explanation of RDI calculation for dostarlimab

Parameter	Dostarlimab
Actual cumulative dose (unit)	(mg)
	Sum of the doses administered to a patient during the treatment period. It is calculated separately for the first 6 cycles and cycles after Cycle 7 (week 19+) and also overall.
ADI (unit)	(mg/day)

Parameter	Dostarlimab
	Actual cumulative dose / duration of treatment for calculation of actual dose intensity. For dostarlimab, ADI will be calculated separately for the first 6 cycles and cycles at or after Cycle 7 (week 19+) and also overall.
RDI (%)	For dostarlimab, RDI=ADI / [500/21 (mg/day)] *100% For dostarlimab, RDI will be calculated separately for the first 6 cycles and cycles at or after Cycle 7 (week 19+) and also overall.

Source: RUBY-1 statistical analysis plan
Abbreviations: RDI, relative dose intensity; ADI, actual dose intensity.

B14. CS, Document B, section B.3.3.2.3. Please clarify why the completion rate for treatment cycle 1 (Table 33) is not 100% for carboplatin, paclitaxel and dostarlimab.

The completion rates for treatment Cycle 1 of carboplatin, paclitaxel, and dostarlimab are derived from the intention-to-treat population, which includes all patients initially assigned to the treatment groups, irrespective of whether they ultimately received the treatment. As a result, the completion rate is not 100% because not all patients in the intention-to-treat population received the treatment in the first cycle. The exact reasons for patients not receiving the full treatment in Cycle 1 are not available, however reasons may include, but are not limited to, patients discontinuing on the trial between enrolment and Cycle 1 due for example to patient choice or a clinical decision, or an adverse reaction occurring during the infusion of one of the study drugs at this cycle that then prevented the administration of the remaining regimen.

B15. CS, Document B, section B.3.3.2.3. In Section 3.3.2.3, the company assumes that the completion rates for CP are the same across treatment arms.

a) Please clarify if the completion rates are based on the CP arm of RUBY-1 for the MMRp population or are based on the pooled data for CP across the whole trial.

The completion rates used within the economic model are based on total CP use across both the dostarlimab arm and the placebo arm, specific to the MMRp/MSS population.

b) Please provide the completion rates of CP for the dostarlimab+CP arm of the model and provide a scenario using these data.

The completion rate data for carboplatin and paclitaxel within the dostarlimab arm is provided in Table 36.

Table 36: Completion rates of CP for the dostarlimab arm (MMRp/MSS population)

Cycle (Q3W)	Carboplatin n (%)	Paclitaxel n (%)
Cycle 1	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; Q3W, every 3 weeks.

A scenario analysis with results is provided in Table 37 which uses the completion rates for CP from the dostarlimab arm for carboplatin and paclitaxel in the model for both arms. This scenario has a negligible impact on the ICER.

Table 37: Results after completion rates taken from the dostarlimab arm of RUBY-1

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + dostarlimab with CP completion rates	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

B16. CS, Document B, section B.3.5.2.1.1 and Excel model. In the Excel model, 0.72 units for carboplatin 600 (tab “Cost inputs”, cell C38) has been used but in the company submission, it states it should be 1 unit for carboplatin 450 (Table 37). The EAG considers the figure in the company submission would be correct given the dose per cycle. Please check and correct the model as needed.

Within the submitted economic model, the functionality to include and exclude treatment wastage is included. In the base case scenario, treatment wastage is included, resulting in the use of one unit of the 450mg pack size of carboplatin, as indicated in the company's submission (Table 37). When treatment wastage is excluded from the model, the dosage is adjusted to 0.72 units of the 600mg pack size of carboplatin, as reflected in the Excel model (tab "Cost inputs," cell C38). Therefore, the discrepancy between the two dosages arises from the inclusion or exclusion of treatment wastage. The base case correctly applies one unit of the 450mg pack size, consistent with the company's submission.

Subsequent treatment costs

B17. Priority question. CS, Document B, section B.3.5.3.3.1. The EAG's clinical experts advised that bevacizumab is not used in UK clinical practice to treat endometrial cancer. Additionally, bevacizumab does not have a marketing authorisation for treating endometrial cancer at any line. Please provide a scenario where subsequent bevacizumab is excluded from subsequent treatment costs.

The scenario presented in Table 38 shows the impact on the submitted base case of removing bevacizumab from available subsequent treatments. In this scenario, the proportions estimated to receive bevacizumab within the submitted base case being redistributed proportionally to other interventions. The proportion of patients receiving each subsequent treatment in this scenario, compared with the company submitted base case is presented in Table 38.

The inclusion of bevacizumab as a subsequent treatment was based on several studies that showed in pre-treated advanced endometrial cancer, bevacizumab was associated with modest clinical efficacy (32). Additional desk research has not identified bevacizumab as being routinely used in the setting in the NHS, nor has it been identified within English real-world evidence as a commonly used treatment (33). In light of this, GSK would propose to incorporate this scenario into an updated company base case to reflect the absence of bevacizumab in routine use in second line clinical practice in England.

Table 38: Subsequent treatments scenario removing bevacizumab

Second-line treatment	Carboplatin and doxorubicin	Carboplatin and paclitaxel	Paclitaxel	Doxorubicin (and PLD)	Carboplatin	Pembrolizumab and lenvatinib	Cisplatin	Hormone therapy	Radiotherapy	Bevacizumab	No treatment
Submitted company base case											
Percentage usage post dostarlimab in combination with CP	4.4%	13.2%	5.9%	32.3%	5.9%	0.0%	2.9%	14.7%	21.1%	8.8%	8.3%
Percentage usage post CP	0.8%	10.4%	2.4%	20.8%	1.6%	48.8%	2.4%	13.6%	14.4%	5.6%	0.0%
Scenario removing subsequent bevacizumab											
Percentage usage post dostarlimab in combination with CP	4.8%	14.4%	6.4%	35.1%	6.4%	0.0%	3.2%	16.0%	23.0%	0.0%	8.3%
Percentage usage post CP	0.8%	10.9%	2.5%	21.8%	1.7%	51.2%	2.5%	14.3%	15.1%	0.0%	0.0%

Abbreviations: CP, carboplatin plus paclitaxel; PLD, pegylated liposomal doxorubicin.

The results from the above scenario are presented in Table 39.

Table 39: Results after excluding bevacizumab as a subsequent treatment

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + exclude bevacizumab	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

B18. Priority question. CS, Document B, sections B.2.7 and B.3.5.3.3.2. The proportions of patients on subsequent treatments presented in Table 15 do not align with the proportions presented in Table 43 (columns 2 and 3 for unadjusted RUBY-1 results of Table 43). Additionally, Table 15 is marked as confidential whereas the data in Table 43 is not.

a) Please clarify if the RUBY-1 data in Table 43 are for the MMRp population.

Yes, Table 43 is specific to the MMRp/MSS population.

b) Please explain the differences between Table 15 and Table 43 and why the data in Table 43 are more appropriate for use in the economic model.

Table 15 of the company Submission reports the number of each subsequent treatment received in the MMRp/MSS subgroup of the RUBY-1 trial at the time of the most recent data cut (IA2). These proportions reported in Table 15 are based on the number of patients randomised to each arm.

Table 43 of the company submission reports the subsequent treatment received as a proportion of patients who had progressed as explained in Section 3.5.3.3, and further in Appendix K. Section K.2 in Appendix K details how the proportions in Table 43 were derived.

Within the model, subsequent therapies' costs are accrued only by those entering the PD state. Subsequent therapy usage as a proportion of those who have progressed, as reported in Table 15, are therefore most appropriate for modelling the subsequent treatment cost upon progression.

c) Based on the response in part b, if it is appropriate, please explore the data in Table 15 in a scenario (adjusted to remove immunotherapy usage for the dostarlimab arm and bevacizumab for both arms [as per question B17]).

GSK do not believe it is appropriate to explore a scenario using Table 15 for modelling as this is reports subsequent treatments as a proportion of those randomised to reach arm and not as a proportion of those who progress which is required for modelling purposes, per Table 43 of the company submission.

B19. Priority question. Company Excel model. In the Excel model, the duration of pembrolizumab and lenvatinib was taken from KEYNOTE-775 (Makker *et al.* 2022). Based on KEYNOTE-775, median PFS was 6.6 months (0.55 yrs), median duration of treatment was 231 days (0.63 yrs) and median number of cycles of pembrolizumab was 10. In the Excel model (tab "Data store", cells P418:P419), the number of pembrolizumab cycles is 12 and the number of days is 252.

a) Additionally, median dose intensity of lenvatinib from KEYNOTE-775 was 13.8mg per day. The EAG's clinical experts advised that for patients who are on second-line pembrolizumab+lenvatinib, most would have dose reductions for lenvatinib.

Therefore, the EAG considers that the costs of pembrolizumab and lenvatinib may be overestimated.

Please clarify how the duration of pembrolizumab with lenvatinib (0.69 years) was calculated.

The duration of pembrolizumab and lenvatinib used within the economic model and submission is taken from Makker et al 2022 (15). Makker et al 2022 supplemental material includes the mean time on treatment of 252 days for each of pembrolizumab and lenvatinib, equating to 0.69 years (252/365.25=0.69) (15).

Using data from KEYNOTE-775, please provide a scenario that uses the median duration of treatment and cycles, as well as the median dose intensity of 13.8mg for lenvatinib to estimate the costs of pembrolizumab and lenvatinib in the economic model.

Given that the mean duration of treatment is available for both pembrolizumab and lenvatinib, utilising the median duration would be inappropriate for modelling purposes within a cohort modelling framework, such as a partitioned survival model.

GSK acknowledges that dose adjustments are commonly required to manage the treatment-emergent adverse events (TEAEs) associated with lenvatinib (34, 35). Nevertheless, since lenvatinib is uniformly priced across the commercially available 4 mg and 10 mg strengths, these dose adjustments do not lead to a corresponding reduction in the per-person treatment costs (36). Specifically, dose reductions to daily regimens requiring 3 (18 mg, 12 mg) or 4 (16 mg) tablets would result in a higher daily cost compared to the modelled 20 mg dose. Only dose reductions to precisely 4 mg or 10 mg daily would lead to a decrease in treatment costs. Notably, dose reductions to 14 mg (13.8 mg, rounded) would incur the same daily cost as a 20 mg dose, thereby having no impact on the cost-effectiveness outcomes.

B20. Priority question. CS, Document B, section B.3.5.3.3.2 and Excel model. Lenvatinib is an oral treatment and typically in cost-effectiveness analysis, oral treatments do not incur administration costs. In the company's Excel model, hormone therapy, which is also an oral treatment, does not incur an administration cost.

a) Please justify the inclusion of a monthly administration cost for lenvatinib and explain why the cost code 'SB13Z - deliver more complex parenteral chemotherapy at first attendance, outpatient attendance', was considered appropriate.

Lenvatinib is an oral high-cost drug oncology treatment requiring specialist oversight in its procurement, prescribing, dispensing and administration (35).

The inclusion of a drug administration cost for lenvatinib is consistent with the approach taken in the appraisal of lenvatinib with everolimus for previously treated advanced renal cell carcinoma (TA498), clinical opinion to the EAG in the appraisal of lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858), and inclusion in the budget impact template for the appraisal of cabozantinib, a similar tyrosine-kinase inhibitor, with nivolumab for untreated advanced renal cell carcinoma (TA964; for which pembrolizumab with lenvatinib was a comparator) (37-39).

GSK would like to clarify that the administration cost used in the model for lenvatinib is from the cost code 'SB11Z – Deliver Exclusively Oral Chemotherapy' and uses the outpatient

procedures unit cost. This is considered to be the most appropriate cost code to reflect the oral administration of lenvatinib.

Megestrol acetate (Megace) is a pregestin with hormonal activity rather than direct cytotoxic activity and is not a high cost-drug. GSK are not aware of addition resource utilisation costs associated with its use in practice nor suggestion from NICE that additional costs should be associated with hormone therapy administration either during technology appraisals or in development of Resource Impact Templates, and therefore no administration cost is attached.

b) Please provide a scenario where the administration cost of lenvatinib is excluded.

GSK considers it inappropriate to exclude an oral administration cost for lenvatinib due to its high-cost nature as an oncology drug, which necessitates specialist oversight in its procurement, prescribing, dispensing, and administration (35).

GSK acknowledges that in the 2022/23 NHS cost collection data, the unit cost for oral administration is higher than the outpatient cost code for 'SB13Z - Deliver More Complex Parenteral Chemotherapy at First Attendance'. Consequently, a scenario analysis has been conducted using the administration costs reported in TA498, without adjusting for inflation. This scenario aligns with the administration costs used in previous technology appraisals involving lenvatinib. In addition, a scenario is also provided where the administration cost of lenvatinib is excluded entirely. The results of these scenarios are presented in Table 40.

Table 40: Results after adjusting the administration cost assumed for lenvatinib

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + TA498 administration cost for LEN	£[redacted]	0.755	£[redacted]
Submitted company base case + No administration cost for LEN	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LEN, lenvatinib; QALY, quality-adjusted life year.

B21. CS, Document B, section B.3.5.2.1. In TA963, the costs of subsequent treatments for dostarlimab+CP was £5,152.19 and for CP was £14,035.19. For the current appraisal, the costs estimated for dostarlimab+CP is £3,363.96 and for CP is £47,057.71. Please explain why the costs for CP have been estimated to be substantially greater in the current appraisal than in TA963, given that pembrolizumab+lenvatinib was also included in TA963.

At the time of submission of TA963 in July 2023 the standard of care in second-line dMMR/MSI-H advanced or recurrent endometrial cancer was anti-programmed cell death protein 1 (PD-1) monotherapy with dostarlimab monotherapy (40). Pembrolizumab monotherapy was not yet commercially available and the pembrolizumab-lenvatinib was recommended by NICE only around the time of the TA963 dossier submission in June 2023, resulting in limited uptake while TA963 appraisal was ongoing. As CDF-funding therapies are not considered a standard-of-care dostarlimab monotherapy could not be considered within the cost-effectiveness modelling. This resulted in relatively inexpensive chemotherapy regimens accounting for the majority of the subsequent treatment costs during TA963.

Currently, the pembrolizumab-lenvatinib combination is the only regimen recommended by NICE in the secondly line setting for patients with MMRp/MSS tumours and is the current standard-of-care following the use of CP in first line. This results in relatively high subsequent treatment costs for the CP arm within the cost-effectiveness model.

Health state resource use and costs

B22. CS, Document B, section B.3.5.3. Please provide a scenario where the health state resource use for dostarlimab+CP patients who are progression-free after 3 years (off treatment) reflects PFS CP resource use (cycle 19+).

Results of a scenario analysis where the health state resource use for dostarlimab in combination with CP patients who are PF after 3 years (off treatment) is set equal to PFS CP resource use (Cycle 19+) is provided in Table 41.

Table 41: Results after setting resource use for dostarlimab equal to CP after 3 years

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + Dostarlimab resource use equal to CP after 3 years	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

B23. CS, Document B, section B.3.5.3. The EAG's clinical experts validated the company's health-state resource use assumptions and considered that they did not reflect UK clinical practice. Instead, the EAG's clinical experts advised on alternative health state resource use assumptions presented in the below tables. For ease of interpretation, the data are represented as 3-monthly usage. Please conduct a scenario using the EAG's health state resource use assumptions, providing unit cost data and sources for the additional tests considered relevant by the EAG's clinical experts.

Resource use per 3 months - CP arm

Resource	Chemotherapy phase - up to week 18	Assumption	Progression-free - week 19+	Assumption	Progressed disease	Assumption
Outpatient visit	4	Once every 3 weeks (aligned with treatment cycle	1	Once every 3 months	3	Once per month (patients on 2L treatment
CT scan	1	Once every 3 months	0.5	Once every 6 months	1	Once every 3 months (patients on 2L treatment)
Complete blood count	4	Once every 3 weeks (aligned with treatment cycle	1	Once every 3 months	3	Once per month (patients on 2L treatment
Specialist nurse visit	1.44	Company assumption	0.9	Company assumption	1.44	Company assumption
GP visit	0	Company assumption	0.12	Company assumption	0	Patients back in secondary care
Cancer antigen (CA)-125	0	-	0	-	2	For the 49% of patients on 2L immunotherapy, tests might occur once every 3 weeks according to treatment cycle)
Thyroid function tests (TSH, T3 and T4)	0	-	0	-	2	
Liver function tests	0	-	0	-	2	
Kidney function tests	0	-	0	-	2	
Cortisol level tests	0	-	0	-	2	

Resource use per 3 months - dostarlimab+CP arm

Resource	Chemotherapy phase - up to week 18	Assumption	Progression-free - week 19 to end of treatment (3 years)	Assumption	End of treatment (3 years) to progression	Assumption	Progressed disease	Assumption
Outpatient visit	4	Once every 3 weeks (aligned with treatment cycle	2	Once every 6 weeks (aligned with treatment cycle	1	Once every 3 months	3	Once per month (patients on 2L treatment)
CT scan	1	Once every 3 months	1	Once every 3 months	0.5	Once every 6 months	1	Once every 3 months (patients on 2L treatment)
Complete blood count	4	Once every 3 weeks (aligned with treatment cycle	2	Once every 6 weeks (aligned with treatment cycle	1	Once every 3 months	3	Once per month (patients on 2L treatment
Specialist nurse visit	1.44	Company assumption	0.9	Company assumption	0.9	Company assumption	1.44	Company assumption
GP visit	0	Company assumption	0	Company assumption	0.12	Company assumption	0	Patients back in secondary care
Cancer antigen (CA)-125*	4	Once every 3 weeks (aligned with treatment cycle)	2	Once every 6 weeks (aligned with treatment cycle	0	-	0	-
Thyroid function tests (TSH, T3 and T4)	4		2		0.5	Once every 6 months	0	-
Liver function tests	4		2		0	-	0	-
Kidney function tests	4		2		0	-	0	-
Cortisol level tests	4		2		0	-	0	-

A scenario analysis is provided which uses the EAG clinical expert resource use estimates in the model. To incorporate these values into the model, some adjustments have been made to the scenario. These are described below and outlined in Table 42.

- Resource use in the 'chemotherapy phase' is assumed to apply regardless of progression status.

- Progression-free week 19+ resource use described by the EAG clinical experts is applied to the entirety of the PFS state (not just for the duration on dostarlimab treatment) as the model does not enable differing resource utilisation by on/off treatment within the PFS health state. This results in the application of higher resource use in the dostarlimab arm than suggested by the EAG's expert, therefore overestimating the costs, and is therefore a very conservative method of addressing the limitation of the model.

- Progressed disease resource use, described by the EAG clinical expert as being associated with second line therapies, are applied only for the duration of these therapies (functionality exists within the model in 'Data Store'!C430:E33 to apply costs associated with second line therapies). To avoid double-counting, no resource use associated with second line therapies is applied to the PD state. Any additional resource use following discontinuation of the second line therapies is assumed to be captured within the end-of-life care cost.

- The relevant tests are applied only to patients receiving immunotherapy-based regimens at first and second line.

Overall, EAG clinical expert estimates of resource use in the model, have been applied where feasible within the structural constraints of the model, as accurately and conservatively as possible. This results in a very small decrease in the ICER from £[redacted] to £[redacted].

Table 42: EAG resource use estimates adjusted for the model

Resource	Progression free								Progressed disease (Applied to subsequent treatment costs)	
	Chemo phase - up to week 18 (applied to PFS and PD states)				Progression-free - week 19+					
	CP		Dostarlimab		CP		Dostarlimab			
	N	Assumption	N	Assumption	N	Assumption	N	Assumption	N	Assumption
Outpatient visit	4	Once every 3 weeks	4	Once every 3 weeks	1	Once every 3 months	2	Once every 6 weeks	3	Once per month
CT scan	1	Once every 3 months	1	Once every 3 months	0.5	Once every 6 months	1	Once every 3 months	1	Once every 3 months
Complete blood count	4	Once every 3 weeks	4	Once every 3 weeks	1	Once every 3 months	2	Once every 6 weeks	3	Once per month
Specialist nurse visit	1.44	Company assumption	1.44	Company assumption	0.9	Company assumption	0.9	Company assumption	1.44	Company assumption
GP visit	0	Company assumption	0	Company assumption	0.12	Company assumption	0	Company assumption	0	Patients back in secondary care
Cancer antigen (CA)-125	0	-	4	Once every 3 weeks	0	-	2	Once every 6 weeks†	2	For the 49% of patients on 2L pembrolizumab, once every 3 weeks
Thyroid function tests (TSH, T3 and T4)	0	-	4	Once every 3 weeks	0	-	2	Once every 6 weeks†	2	
Liver function tests	0	-	4	Once every 3 weeks	0	-	2	Once every 3 months†	2	
Kidney function tests	0	-	4	Once every 3 weeks	0	-	2	Once every 6 weeks†	2	
Cortisol level tests	0	-	4	Once every 3 weeks	0	-	0.9	Company assumption†	2	

†Tests have been added into the model as a single input, with a weighted average calculated to estimate frequency. This is equivalent to separating the tests.
Abbreviations: 2L, second line; CP, carboplatin plus paclitaxel; CT, computerised tomography; DOST, dostarlimab; GP, general practitioner; PD, progressed disease; PFS, progression-free survival; TSD, thyroid stimulating hormone.

The results of the scenario analysis are presented in Table 43.

Table 43: Results after using resource use estimates informed by clinical expert opinion to the EAG

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + EAG resource use estimates	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; vs, versus.

The resource use estimates assumed within the company submission were considered appropriate and accepted by the committee in the appraisal of dostarlimab for dMMR/MSI-H primary advanced or recurrent endometrial cancer (TA963) (24). It is not expected that resource utilisation would differ by MMR status.

GSK acknowledges certain tests are now in clinical guidelines and would agree these should be captured within the model, and the base case has been updated to reflect this. GSK accepts that thyroid function tests, liver function tests and kidney function tests are likely a part of routine monitoring in endometrial cancer with cortisol testing being recommended symptomatically(41). However, cancer antigen 125 tests (CA-125) were not considered appropriate for inclusion in the base case, given that they are not used routinely for patients with endometrial cancer. The additional tests have been incorporated into the base case in the following ways:

- In order to reflect the administration of these tests aligning with the treatment cycle, the model has been updated to include these tests as an addition to administration costs in the model for dostarlimab. The frequency of tests is aligned with the EAG clinical expert opinion presented above.
- These additional tests have also been included in the subsequent therapy cost calculations for patients in the CP arm receiving the pembrolizumab-based regimen, in line with EAG clinical expert opinion.

The costs for the additional tests are taken from the NHS reference costs [DAPS03; clinical biochemistry (370 – Medical Oncology service)] and are assumed to all be equal (29).

B24. CS, Document B, section B.3.5.3 and Excel model. The Total costs in Table 40 do not match what is estimated in the Excel model (tab “Cost inputs”, cells I161:I176, K161:K176, I183:I198, K186:K198). Please clarify which figures are correct, those provided in Table 40 of the company submission or in the Excel model. Please amend as needed.

The total costs estimated in the Excel model are the correct values. Please see Table 44 for the corrected values for Document B.

Table 44: Cost and resource use per weekly model cycle for dostarlimab in combination with CP, and CP alone (Corrected)

Resource	Unit cost (£)	Health state	Dostarlimab in combination with CP		CP		Dostarlimab in combination with CP		CP	
			Resource use (up to Cycle 18)	Resource use (Cycle 19+)	Resource use (up to Cycle 18)	Resource use (Cycle 19+)	Total costs (up to Cycle 18) (£)	Total costs (Cycle 19+) (£)	Total costs (up to Cycle 18) (£)	Total costs (Cycle 19+) (£)
Outpatient visit	205.82	PFS	0.30	0.13	0.30	0.08	61.75	26.76	61.75	16.47
		PD	0.12	0.12	0.12	0.12	24.70	24.70	24.70	24.70
CT scan	118.58	PFS	0.13	0.06	0.13	0.05	15.42	7.11	15.42	5.93
		PD	0.07	0.07	0.07	0.07	8.30	8.30	8.30	8.30
Complete blood count	8.04	PFS	0.33	0.22	0.33	0.06	2.65	1.77	2.65	0.48
		PD	0.09	0.09	0.09	0.09	0.72	0.72	0.72	0.72
Specialist nurse visit	57.00	PFS	0.11	0.07	0.11	0.07	6.27	3.99	6.27	3.99
		PD	0.10	0.10	0.10	0.10	5.70	5.70	5.70	5.70
GP visit	47.00	PFS	0.00	0.01	0.00	0.01	0.00	0.47	0.00	0.47
		PD	0.01	0.01	0.01	0.01	0.47	0.47	0.47	0.47

Abbreviations: CP, carboplatin plus paclitaxel; CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PD, progressed disease; PFS, progression-free survival.

End of life cost

B25. CS, Document B, section B.3.5.3.1. The Unit Costs of Health and Social Care 2023 Manual (PSSRU), Section 7.2 (Table 7.2.2) provides the cost of hospital care in the final year of life for cancer (£11,508). Please conduct a scenario analysis that uses the PSSRU's end of life cost.

A scenario analysis has been provided in the economic model, including the cost of hospital care in the final year of life for cancer (£11,508) from the PSSRU 2023 manual (42). The results of this scenario analysis are presented in Table 45 and the scenario has a negligible impact on the ICER.

Table 45: Results after using PSSRU end of life costs

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + PSSRU end of life costs	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

B26. CS, Document B, section B.3.5.3.1. End of life costs are applied to all patients who die irrespective of whether they were progression free or had progressed disease. However, the EAG considers that it may be more appropriate to apply end of life costs only to patients who die from the progressed disease health state. Please provide a scenario where end of life costs are only accrued by those patients dying from the progressed disease health state.

The model does not differentiate the costs of death based on which state the death occurred (PFS or PD), therefore this would require a programming change to the engines that would take additional time. The proportion of deaths that are PFS deaths is based on data from the RUBY-1 trial (cell F344 on the 'cost inputs' sheet), and is a very small proportion ([redacted]%), with the majority of deaths coming from the PD state.

Given this, a scenario has been provided which adjusts the EAG end of life cost to reflect the estimate of deaths from the progressed state in the model. This results in an end-of-life cost of £[redacted]. The result of this scenario analysis is presented in Table 46 and shows a minimal impact on the ICER.

Table 46: Results after using PSSRU end of life costs for those dying from the progressed disease state

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + PSSRU end of life costs for those in the progressed disease state	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

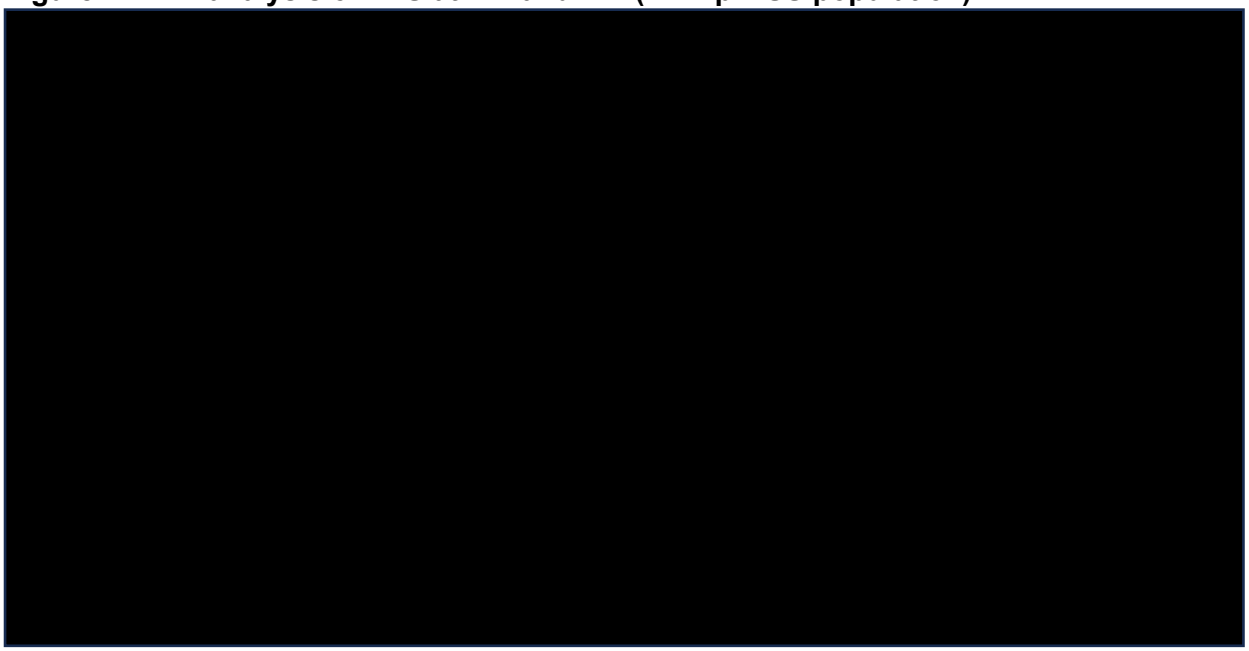
Progression-free survival

B27. Priority question. Based on the response to A12, please update the survival analysis of progression-free survival to be based on the IA2 data cut. Please include analysis of curve selection and final selection, ensuring all curves are included in the updated economic model as user selectable options.

Due to time constraints, GSK is unable to update the survival analysis of PFS based on the IA2 data cut. The parametric and flexible survival analyses of the PFS from IA1 were conducted by a third party, and the codes for re-running the analysis are protected by intellectual property rights. Transferring the IA2 PFS patient-level data, re-running the analysis, and incorporating it into the model to provide updated analyses is not feasible within this timeframe. However, it can be observed that the PFS from IA2 is consistent with both the IA1 PFS and the PFS predicted by the existing survival analysis.

Figure 11 below illustrates the PFS from the initial IA1 data cut which is used for modelling purposes overlayed onto the more mature IA2 PFS. The IA2 PFS mirrors that of the IA1 for the majority of the follow-up with only minor divergences towards the end of the IA1 follow-up.

Figure 11: KM analysis of PFS at IA1 and IA2 (MMRp/MSS population)



IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

Table 47 presents a summary of IA1 PFS and IA2 PFS. As described in response to Question A12, the PFS from this more mature data cut is consistent with the IA1 PFS analysis presented in Figure 5 of the company submission. [redacted] at IA2, reflecting the relatively stable PFS within each arm with the extended follow-up.

Table 47: KM analysis of PFS (MMRp/MSS population)

Category subcategory	IA1		IA2	
	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS, months (95% CI)	9.9 (9.0, 13.3)	7.9 (7.6, 9.8)	[redacted]	[redacted]
PFS probability (95% CI)				
Month 12	43.5% (35.7%, 51.0%)	30.6% (23.6%, 37.8%)	[redacted]	[redacted]
Month 24	28.4% (21.2%, 36.0%)	18.8% (12.8%, 25.7%)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.76 (0.592, 0.981)		[redacted]	
Nominal p-value of 1-sided stratified log-rank test	0.0177		NR	

Source: IA1 CSR Table 14.2.1.1 (4).
IA1 Data cutoff: 28 September 2022, IA2 Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; NR, Not reported; PFS, progression-fee survival.

Table 48 below presents the probability of being PF and alive at 6-month intervals, as derived from the PFS KM analysis in the IA1 and IA2 data cuts, and as predicted in the submitted base-case. The modelled PFS closely aligns with the results reported in the RUBY-1 trial, with the predicted PFS being slightly lower in both arms at months 30 and 36 compared to the Kaplan-Meier analysis. Given the relatively small impact the selected PFS extrapolation makes on the ICER as demonstrated in the submitted scenario analysis, updating the model with PFS extrapolations based on the IA2 data is not expected to make any material impact to the overall cost-effectiveness of dostarlimab.

Table 48: KM analysis of PFS and probability of being PF and alive (MMRp/MSS population)

	Dostarlimab in combination with CP			Placebo in combination with CP		
	IA1 KM	IA2 KM	PFS - predicted	IA1 KM	IA2 KM	PFS - predicted
Month 6	73.40%	[redacted]	75.6%	68.10%	[redacted]	69.4%
Month 12	43.50%	[redacted]	46.2%	30.60%	[redacted]	34.5%
Month 18	35.90%	[redacted]	33.9%	22.80%	[redacted]	24.2%
Month 24	28.40%	[redacted]	27.4%	18.80%	[redacted]	19.5%
Month 30	-	[redacted]	23.4%	-	[redacted]	16.7%
Month 36	-	[redacted]	20.4%	-	[redacted]	14.5%

Source: IA1 CSR Table 14.2.1.1 (4).
IA1 Data cutoff: 28 September 2022, IA2 Data cutoff: 22 September 2023.
Abbreviations: CP, carboplatin plus paclitaxel; IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PF, progression free; PFS, progression-fee survival.

B28. Priority question. Please provide a scenario analysis where TTD is equal to PFS.

A scenario where TTD is equal to PFS is presented in Table 49. However, GSK asserts that this scenario is not appropriate for estimating the overall cost of dostarlimab treatment or for assessing its cost-effectiveness. This is because mature and complete trial-level TTD data is available for modelling purposes, as described in the response to question A13b. Additionally, as outlined in the response to question A14a, there is a high level of concordance between the modelled TTD and the observed number of patients on treatment due to the high level of data completeness.

In oncology treatments such as dostarlimab, patients discontinue treatment for reasons other than disease progression, reflecting real-world use. This results in the separation of TTD and PFS curves, as observed in the cost-effectiveness model. For example, in the RUBY-1 trial, out of 174 patients who discontinued dostarlimab, only 103 (59.2%) discontinued due to disease progression, while adverse events were the second most common reason (n=41).

Therefore, aligning TTD with PFS for the purpose of costing dostarlimab treatment is inappropriate, contradicts observed data, and is not aligned with real-world expectations.

Table 49: Results after equalling TTD to PFS

Parameter	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)
Submitted company base case	£[redacted]	0.755	£[redacted]
Submitted company base case + TTD equal to PFS	£[redacted]	0.755	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; TTD, time to treatment discontinuation.

Aligning TTD with PFS would not provide an accurate estimation of the treatment costs or cost-effectiveness of dostarlimab. The observed data from the RUBY-1 trial and real-world expectations indicate that patients discontinue treatment for a variety of reasons, leading to differences between TTD and PFS. Therefore, using the mature and complete TTD data for economic modelling remains the most appropriate approach.

Section C: Textual clarification and additional points

C1. Priority question. CS, Document B, section B.3.10.1 and Excel model. Please provide a convergence plot for the probabilistic sensitivity analysis (PSA) and ensure this is included in the economic model.

A convergence plot has been added to the economic model ‘PSA’ sheet for the ICER (Figure 12). The plot demonstrates relative stabilisation from around 1200 iterations.

Figure 12: Convergence plot- ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis.

C2. Please provide reference 127 (Huo G, Song Y, Chen P. Cost-effectiveness of atezolizumab plus chemotherapy for advanced/recurrent endometrial cancer. J Gynecol Oncol. 2024;35), as this seems to be missing from the reference pack.

The reference has now been provided under the title ‘Huo 2024’.

Appendix 1

1. Scenarios explored as part of EAG requests

Table 50: Scenarios explored as part of EAG requests

	Include in updated company base case	Incremental costs (dostarlimab+ CP vs CP)	Incremental QALYs (dostarlimab+C P vs CP)	ICER (dostarlimab +CP vs CP)	Impact on ICER
Submitted company base case	-	£[redacted]	0.755	£[redacted]	-
B1. Use 2023 inflation indices	Yes	£[redacted]	0.755	£[redacted]	Decrease
B6. TTD KM used for full follow-up period (Up to cycle 187)	No	£[redacted]	0.755	£[redacted]	Increase
B9. Include the cost and disutility of Grade≥3 treatment related irAEs	Yes	£[redacted]	0.755	£[redacted]	Increase
B10. Doubled AE rates in both arms (1L and 2L)	No	£[redacted]	0.755	£[redacted]	Increase
B11. Exclude AE disutilities for subsequent treatments	No	£[redacted]	0.755	£[redacted]	Increase
B12. Exclude AE costs for subsequent treatments	No	£[redacted]	0.755	£[redacted]	Increase
B15. Use dostarlimab+CP arm completion rates for CP	No	£[redacted]	0.755	£[redacted]	Increase
B17. Remove bevacizumab from subsequent treatment costs and disutilities (and redistribute)	Yes	£[redacted]	0.755	£[redacted]	Decrease
B20. a) Exclude Admin cost for Lenvatinib	No	£[redacted]	0.755	£[redacted]	Increase
B22. Set resource use equal after 3 years in the PF state	No	£[redacted]	0.755	£[redacted]	Decrease
B23. (i) Use EAG clinical expert resource use	No	£[redacted]	0.755	£[redacted]	Decrease
B23. (ii) Include thyroid/kidney/liver/cortisol tests for dostarlimab and for second line IO's.	Yes	£[redacted]	0.755	£[redacted]	Increase
B25. Use PSSRU end of life cost	Yes	£[redacted]	0.755	£[redacted]	Decrease
B26. Apply PSSRU end of life cost to those dying from PD only	No	£[redacted]	0.755	£[redacted]	Decrease

	Include in updated company base case	Incremental costs (dostarlimab+ CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab +CP vs CP)	Impact on ICER
B28. Equal TTD to PFS	No	£[redacted]	0.755	£[redacted]	Increase
Updated company base case	-	£[redacted]	0.755	£[redacted]	Decrease

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; EAG, External assessment group; IO, immunotherapy; irAEs, immune-related adverse events; PD, progressed disease; PF, progression free; PSSRU, Personal Social Services Research Unit; TTD, time to treatment discontinuation.

2. Updated company base case incremental cost-effectiveness analysis results

Table 51: Updated company base case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.755	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

3. Probabilistic sensitivity analysis

Table 52: Updated company base case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.760	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 13: Incremental cost-effectiveness plane scatterplot

Abbreviations: CP, carboplatin plus paclitaxel; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 14: Cost-effectiveness acceptability curve

Abbreviations: CP, carboplatin plus paclitaxel.

4. Deterministic sensitivity analysis

The OWSA varied one parameter at a time, assessing the impact on the incremental QALYs and incremental costs, and subsequently the ICER. A lower and upper bound was assigned to suitable parameters.

Results of the OWSA are presented in Table 53 and show the top 10 model drivers of the ICER for dostarlimab with CP versus CP. The ICER was most sensitive to the proportion receiving pembrolizumab with lenvatinib as a subsequent treatment in the placebo arm followed by the Dostarlimab with CP completion rates and medical resource use. It is worth noting that at the upper bound, the total cost and proportion receiving pembrolizumab and lenvatinib was dominating and therefore does not appear in the tornado diagram. The results are also presented in a tornado diagram (Figure 15).

Table 53: Tabulated OWSA results (deterministic)

Parameter	Lower bound ICER (£/QALY)	Upper bound ICER (£/QALY)	Difference (£/QALY)
Updated company base case	£[redacted]		
Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib	£17,815	Dominating	
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP	£18,430	Dominating	
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 16)	£[redacted]	£[redacted]	£[redacted]
Outpatient visit Dostarlimab+CP in PF state from cycle 19+	£[redacted]	£[redacted]	£[redacted]
Outpatient visit Dostarlimab+CP in PD state from cycle 19+	£[redacted]	£[redacted]	£[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 4)	£[redacted]	£[redacted]	£[redacted]
Outpatient visit unit cost	£[redacted]	£[redacted]	£[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 7)	£[redacted]	£[redacted]	£[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 10)	£[redacted]	£[redacted]	£[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 13)	£[redacted]	£[redacted]	£[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 1)	£[redacted]	£[redacted]	£[redacted]
Outpatient visit CP in PD state from cycle 19+	£[redacted]	£[redacted]	£[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, Incremental cost-effectiveness ratio; OS, overall survival; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity.

Figure 15: Tornado diagram

Abbreviations: CP, carboplatin plus paclitaxel; NMB, net monetary benefit.

5. Scenario analysis

Note that only deterministic scenario analyses have been undertaken due to time constraints.

Also please note that scenarios 14 and 15 have required changes to the submitted proportions, to incorporate that the updated base case includes the redistribution of the proportion that was originally allocated to bevacizumab. Scenario 13 includes a ≥5% threshold for irAEs as well as the AEs originally included in the model.

Table 54: Scenario analyses (deterministic)

No	Category	Base-case value	Scenario value	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
1	Updated company base case	-	-	[redacted]	[redacted]	0.755	[redacted]
2	Starting age	[redacted] (RUBY-1)	65.5 (UK RWE) (43)	[redacted]	[redacted]	0.748	[redacted]
3	Annual discount rate for costs and QALYs	3.50%	1.5%	[redacted]	[redacted]	0.905	[redacted]
4			5.0%	[redacted]	[redacted]	0.666	[redacted]
5	PFS Curve selection (CP)	Normal, k=2 flexible spline model	Odds, k=2 flexible spline model	[redacted]	[redacted]	0.750	[redacted]
6	PFS curve selection (dostarlimab +CP)	Odds, k=3 flexible spline model	Normal, k=2 flexible spline model	[redacted]	[redacted]	0.747	[redacted]
7	PFS curve selection	Flexible spline models	Independent models (CP, log-logistic; dostarlimab, generalised gamma)	[redacted]	[redacted]	0.745	[redacted]
8	OS curve selection (dostarlimab +CP)	Independent, log-normal	Independent, log-logistic	[redacted]	[redacted]	0.650	[redacted]
9	Treatment effect waning: OS and PFS	No waning	Waning from 8-10 years	[redacted]	[redacted]	0.711	[redacted]
10			Waning from 5-7 years	[redacted]	[redacted]	0.615	[redacted]
11	TTD Completion rates	Completion rates used	Completion rates not used	[redacted]	[redacted]	0.755	[redacted]
12	Vial wastage	Vial wastage assumed	No vial wastage	[redacted]	[redacted]	0.755	[redacted]
13	Adverse event threshold	Grade 3+ AEs ≥2% in either arm of RUBY-1	Grade 3+ AEs ≥5% in either arm of RUBY-1	[redacted]	[redacted]	0.755	[redacted]
14		RUBY-1 data used, with no IO retreatment	Equal proportion receiving no treatment (set to dostarlimab proportion for both)	[redacted]	[redacted]	0.755	[redacted]

No	Category	Base-case value	Scenario value	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
15	Subsequent treatment assumptions		75% market share assumed for PEM+LEN in CP proportions	[redacted]	[redacted]	0.755	[redacted]
16	Utility values	MMRp RUBY-1 source	ITT RUBY-1 source	[redacted]	[redacted]	0.752	[redacted]
17		AE disutilities included	AE disutilities excluded	[redacted]	[redacted]	0.755	[redacted]
18		Age-adjustment included	No age adjustment	[redacted]	[redacted]	0.797	[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; LEN, lenvatinib; LY, life years; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; QALYs, quality-adjusted life years; RWE, real-world evidence; TTD, time to treatment discontinuation.

6. *Impact of EAG scenario analyses on updated company base case*

Table 55: Impact of EAG scenarios on updated company base case

Question number	Description	Impact on updated company base case ICER
	Updated company base case	£[redacted]
B6	TTD KM used for full follow-up period (Up to cycle 187)	£[redacted]
B10	Doubled AE rates in both arms (1L and 2L)	£[redacted]
B11	Exclude AE disutilities for subsequent treatments	£[redacted]
B12	Exclude AE costs for subsequent treatments	£[redacted]
B15	Use dostarlimab+CP arm completion rates for CP	£[redacted]
B20	a) Exclude Admin cost for Lenvatinib	£[redacted]
B22	Set resource use equal after 3 years in the PF state	£[redacted]
B23	i) Use EAG clinical expert resource use	£[redacted]
B26	Apply PSSRU end of life cost to those dying from PD only	£[redacted]
B28	Equal TTD to PFS	£[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; EAG, External assessment group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PD, progressed disease; PF, progression free; TTD, time to treatment discontinuation.

References:

1. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388(23):2145-58.
2. Clarke NA, Braverman J, Worthy G, Shaw JW, Bennett B, Dhanda D, et al. A Review of Meaningful Change Thresholds for EORTC QLQ-C30 and FACT-G Within Oncology. Value in Health. 2024;27(4):458-68.
3. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
4. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 07-March-2023 (data cut off: 28-SEP-2022).
5. GSK. Data on file. Ruby Clinical Study Protocol 4010-03-001 Version 4.0. Mar 2022.
6. GSK. Data on file. ru_uk_t_stat_p3.
7. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(9):860-77.
8. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecologic Cancer. 2021;31(1):12-39.
9. National Comprehensive Cancer Network. Clinical Practice Guidelines: Uterine Neoplasms, Version 1.2024. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2024. .
10. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY) [Internet]. 2019. Available from: https://clinicaltrials.gov/study/NCT03981796.
11. European Medicines Agency. Keytruda pembrolizumab. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda (accessed on: March 2025). 2024.
12. National institute for Health and Care Excellence. NICE guidance. TA904. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Published 21 June 2023. Available at: https://www.nice.org.uk/guidance/ta904 (last accessed: March 2025). 2023.
13. Arora S, Balasubramaniam S, Zhang W, Zhang L, Sridhara R, Spillman D, et al. FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis. Clin Cancer Res. 2020;26(19):5062-7.
14. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39(21):2339-49.
15. Makker V, Colombo N, Herráez AC, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. New England Journal of Medicine. 2022;386(5):437-48.
16. Food and Drug Adminisration (FDA). Clinical Trial Endpoints for the Approval of NonSmall Cell Lung Cancer Drugs and Biologics Guidance for Industry. Available from: https://www.fda.gov/media/116860/download (accessed on: March 2025). 2015.
17. Powell MA, Hietanen S, Coleman RL, Monk BJ, Zub O, O'Malley DM, et al. Dostarlimab for primary advanced or recurrent (A/R) endometrial cancer (EC): Outcomes by blinded independent central review (BICR) of the RUBY trial (ENGOT-EN6-NSGO/GOG-3031/RUBY). Journal of Clinical Oncology. 2023;41(16_suppl):5503-.
18. Alkholifi FK, Alsaffar RM. Dostarlimab an Inhibitor of PD-1/PD-L1: A New Paradigm for the Treatment of Cancer. Medicina (Kaunas). 2022;58(11).
19. Hato SV, Khong A, de Vries IJ, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res. 2014;20(11):2831-7.
20. Pfannenstiel LW, Lam SS, Emens LA, Jaffee EM, Armstrong TD. Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice. Cell Immunol. 2010;263(1):79-87.
21. Rdocumentation. flexsurvspline: Flexible survival regression using the Royston/Parmar spline model. Available from:

https://www.rdocumentation.org/packages/flexsurv/versions/2.0/topics/flexsurvspline (accessed on: March 2025).
22. Rutherford M, Lamber, P., Sweeting, MJ., Pennington, B., Crowther, MJ., Abrams, KR., Latimer, NR. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD21-Flex-Surv-TSD-21_Final_alt_text.pdf (last accessed: March 2025). 2020.
23. GSK. Data on file. UK Advisory Board advanced endometrial cancer survival outcomes in RUBY-1. July 2024.
24. National institute for Health and Care Excellence. Committee Papers | Single Technology Appraisal | Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3986]. Available on: https://www.nice.org.uk/guidance/ta963/evidence/committee-papers-pdf-13366765117. 2024.
25. Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of Oncology. 2024.
26. National institute for Health and Care Excellence. Technology appraisal guidance | TA904 | Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Available on: https://www.nice.org.uk/guidance/ta904 (last accessed: March 2025). 2023.
27. Medicines & Healthcare products Regulatory Agency (MHRA). Jemperli (Dostarlimab) Summary of Product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963 (last accessed: January 2025). 2024.
28. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986;42(1):121-30.
29. NHS England. National Schedule of NHS Costs 2023/24, available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed on: January 2025). 2023.
30. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British Journal of Cancer. 2006;95(6):683-90.
31. Scottish Medicines Consortium. Pembrolizumab (Keytruda) advice (SMC2474). Available from: https://scottishmedicines.org.uk/medicines-advice/pembrolizumab-keytruda-ec-full-smc2474/ (last accessed: March 2025). 2022.
32. Rubinstein MM, Dickinson S, Narayan P, Zhou Q, Iasonos A, Ma W, et al. Bevacizumab in advanced endometrial cancer. Gynecol Oncol. 2021;161(3):720-6.
33. Heffernan K, Nikitas FS, Shukla U, Camejo HS, Knott C. Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis. Gynecol Oncol. 2022;166(2):317-25.
34. Medicines & Healthcare products Regulatory Agency (MHRA). KEYTRUDA (pembrolizumab) Summary of Product Charachteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/6bd17c91768b3cfae9c1d8ff8664023fb03ee369 (last accessed: January 2025). 2025.
35. Medicines & Healthcare products Regulatory Agency (MHRA). LENVIMA summary of product characteristics. Available from: https://mhraproducts4853.blob.core.windows.net/docs/18f91401b0f16142cdbfe5b50698003009947fb6 (accessed on: March 2025). 2024.
36. National Institute for Health and Care Excellence. British National Formulary. Available from https://bnf.nice.org.uk/ (last accessed: January 2025).
37. National institute for Health and Care Excellence. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [TA498]. Available from: https://www.nice.org.uk/guidance/ta498 (last accessed: March 2025). 2018.
38. National Institute for Health and Care Excellence. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [TA858]. Available from: https://www.nice.org.uk/guidance/ta858 (accessed on: March 2025). 2023.
39. National institute for Health and Care Excellence. Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (TA964). Available from: https://www.nice.org.uk/guidance/ta964 (last accessed: March 2025). 2024.
40. National Institute for Health and Care Excellence. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair

deficiency [TA779]. Available at: https://www.nice.org.uk/guidance/ta779/documents/committee-papers (accessed on: December 2024). 2022.
41. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(12):1217-38.
42. Jones KC WH, Birch S, Castelli A, Chalkley M, Dargan A, Forder JE, Gao M, Hinde S, Markham S, Premji S, Findlay D, Teo H. . Unit Costs of Health and Social Care 2023 Manual. Technical report. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York), Kent, UK. 2024.
43. Wesselbaum A, Wallis J, Luhar S, Tunaru F, Carpenter L, Schneider D, et al. A real-world study of patients with advanced/recurrent endometrial cancer across England and Scotland2024.

Clarification Question B17. Addendum: Clarification of the approach to redistribute the bevacizumab proportions across the other subsequent treatments

Table 1 shows a summary of the subsequent treatment proportions submitted as part of the original company submission.

Table 1: Subsequent treatments proportions submitted as part of the original submission

Subsequent treatment	Carboplatin and doxorubicin	Carboplatin and paclitaxel	Paclitaxel	Doxorubicin (and PLD)	Carboplatin	Pembrolizumab and lenvatinib	Cisplatin	Hormone therapy	Radiotherapy	Bevacizumab	No treatment
% use post Dosta + CP	4.4%	13.2%	5.9%	32.3%	5.9%	0.0%	2.9%	14.7%	21.1%	8.8%	8.3%
% use post CP	0.8%	10.4%	2.4%	20.8%	1.6%	48.8%	2.4%	13.6%	14.4%	5.6%	0.0%

Abbreviations: CP, carboplatin plus paclitaxel; Dosta + CP, Dostarlimab in combination with CP; PLD, pegylated liposomal doxorubicin.

Updated base case: Removal of bevacizumab

To remove the cost of bevacizumab, the proportion of patients receiving bevacizumab in the original company submission is redistributed proportionally across other subsequent treatments. For example, in the CP arm, doxorubicin accounts for 18.1% (20.8% /1.115%) of all non-bevacizumab treatments. The proportion of patients not receiving bevacizumab in the requested scenario, but receiving doxorubicin instead, is therefore 1.01% (5.6% x 18.1%). The total proportion of patients receiving doxorubicin as a subsequent treatment is therefore adjusted from 20.8% to 21.81%, as outlined in Table 2 below.

In the case of pembrolizumab and lenvatinib, this regimen accounts for 42.36% of non-bevacizumab subsequent therapies in the CP arm. Of the 5.6% of patients initially costed as receiving bevacizumab as a subsequent treatment, 42.36% of these (i.e. 2.37%) are assumed to receive the pembrolizumab and lenvatinib regimen instead in the revised scenario.

The exact formula used to implement amendment is:

$$Updated\ proportion = \ Original\ proportion\ x\ (1 + \frac{Bevacizumab\ proportion}{Sum\ of\ non - bevacizumab\ treatments})$$

Please see Table 2 below for a full breakdown of the impact of redistributing bevacizumab across each of the other subsequent treatments.

Table 2: Subsequent treatments scenario removing bevacizumab

	Carboplatin and doxorubicin	Carboplatin and paclitaxel	Paclitaxel	Doxorubicin (and PLD)	Carboplatin	Pembrolizumab and lenvatinib	Cisplatin	Hormone therapy	Radiotherapy	Bevacizumab	No treatment
% use post Dosta + CP											
Original company submission	4.4%	13.2%	5.9%	32.3%	5.9%	0.0%	2.9%	14.7%	21.1%	8.8%	8.3%
Bevacizumab redistribution	+0.4%	+1.2%	+0.5%	+2.8%	+0.5%	0.0%	+0.3%	+1.3%	+1.9%	-8.8%	0.0%
Updated base-case	4.8%	14.4%	6.4%	35.1%	6.4%	0.0%	3.2%	16.0%	23.0%	0.0%	8.3%
% use post CP											
Original company submission	0.8%	10.4%	2.4%	20.8%	1.6%	48.8%	2.4%	13.6%	14.4%	5.6%	0.0%
Bevacizumab redistribution	+0.0%	+0.6%	+0.1%	+1.2%	+0.1%	+2.7%	+0.1%	+0.8%	+0.8%	-5.6%	0.0%
Updated base-case	0.8%	10.9%	2.5%	21.8%	1.7%	51.2%	2.5%	14.3%	15.1%	0.0%	0.0%

Abbreviations: CP, carboplatin plus paclitaxel; Dosta + CP, Dostarlimab in combination with CP; PLD, pegylated liposomal doxorubicin.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

Addendum

May 2025

File name	Version	Contains confidential information	Date
ID6145_Dostarlimab+PC_EC_ Addendum -[CON]	v1.0	No	20th May

[redacted]

1. Updated company base case incremental cost-effectiveness analysis results

Table 1 includes the deterministic results of GSK's base case as updated as part of the EAG clarification questions, [redacted]

Table 1: Updated company base case results, [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]				
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.755	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 2: Updated company base case results[redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.755	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.1. Probabilistic sensitivity analysis

Table 3 includes the deterministic results based on the updated base case [redacted]. Figure 1 and Figure 2 show the incremental cost-effectiveness plane scatterplot and CEAC associated with the probabilistic analysis of the companies updated base case.

Table 3: Updated company base case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]				
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.751	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 1: Incremental cost-effectiveness plane scatterplot

Abbreviations: CP, carboplatin plus paclitaxel; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 2: Cost-effectiveness acceptability curve

Abbreviations: CP, carboplatin plus paclitaxel.

1.2. Deterministic sensitivity analysis

[redacted] The OWSA varied one parameter at a time, assessing the impact on the incremental QALYs and incremental costs, and subsequently the ICER. A lower and upper bound was assigned to suitable parameters.

Results of the OWSA are presented in Table 4 and show the top 10 model drivers of the ICER for dostarlimab with CP versus CP. As shown in Table 4, there are seven parameters that result in a dominating ICER, and as such, these parameters are not included within the tornado diagram.

- Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 1, cycle 4, cycle 7 and cycle 16)
- Outpatient visit Dostarlimab+CP in PF state from cycle 19+
- Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib
- Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP

The results of the OWSA are also presented in a tornado diagram in Figure 3.

Table 4: Tabulated OWSA results (deterministic)

Parameter	Lower bound ICER (£/QALY)	Upper bound ICER (£/QALY)	Difference (£/QALY)
Updated company base case		[redacted]	
Outpatient visit Dostarlimab+CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit unit cost	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 10)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 13)	[redacted]	[redacted]	[redacted]
Outpatient visit CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Admin cost up to cycle 18 (£) Dostarlimab+CP	[redacted]	[redacted]	[redacted]
Admin cost (£) CP	[redacted]	[redacted]	[redacted]
Outpatient visit Dostarlimab+CP in PF state up to cycle 18	[redacted]	[redacted]	[redacted]
Outpatient visit CP in PF state up to cycle 18	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 1)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 4)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 7)	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 16)	[redacted]	[redacted]	[redacted]
Outpatient visit Dostarlimab+CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib	[redacted]	[redacted]	[redacted]
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; ICER, Incremental cost-effectiveness ratio; OS, overall survival; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity.

Figure 3: Tornado diagram

Abbreviations: CP, carboplatin plus paclitaxel; NMB, net monetary benefit.

1.3. Scenario analysis

[redacted] to test specific alternative inputs for the assessment of structural and parametric uncertainty. These scenarios remain consistent with those presented as part of the original company submission. Table 5 includes the results of scenario analyses.

Generally, the cost-effectiveness results remained robust across the scenario analyses, with the ICER remaining below [redacted] per QALY in all tested scenarios. The scenario analyses that had the biggest impact on the ICER were those that tested the assumptions associated with subsequent therapy. Increasing the proportion of patients in the placebo arm being treated with pembrolizumab with lenvatinib upon progression to 75% to account for the projected market uptake of pembrolizumab with lenvatinib at second line in 2025 [redacted]

Table 5: Scenario analyses (deterministic)

No	Category	Base-case value	Scenario value	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
1	Updated company base case	-	-	[redacted]	[redacted]	0.755	[redacted]
2	Starting age	[redacted] (RUBY-1)	65.5 (UK RWE) (1)	[redacted]	[redacted]	0.748	[redacted]
3	Annual discount rate for costs and QALYs	3.50%	1.5%	[redacted]	[redacted]	0.905	[redacted]
4			5.0%	[redacted]	[redacted]	0.666	[redacted]
5	PFS Curve selection (CP)	Normal, k=2 flexible spline model	Odds, k=2 flexible spline model	[redacted]	[redacted]	0.750	[redacted]
6	PFS curve selection (dostarlimab+CP)	Odds, k=3 flexible spline model	Normal, k=2 flexible spline model	[redacted]	[redacted]	0.747	[redacted]
7	PFS curve selection	Flexible spline models	Independent models (CP, log-logistic; dostarlimab, generalised gamma)	[redacted]	[redacted]	0.755	[redacted]
8	OS curve selection (dostarlimab+CP)	Independent, log-normal	Independent, log-logistic	[redacted]	[redacted]	0.650	[redacted]
9	Treatment effect waning: OS and PFS	No waning	Waning from 8-10 years	[redacted]	[redacted]	0.713	[redacted]
10			Waning from 5-7 years	[redacted]	[redacted]	0.617	[redacted]
11	TTD Completion rates	Completion rates used	Completion rates not used	[redacted]	[redacted]	0.755	[redacted]
12	Vial wastage	Vial wastage assumed	No vial wastage	[redacted]	[redacted]	0.755	[redacted]
13	Adverse event threshold	Grade 3+ AEs ≥2% in either arm of RUBY-1	Grade 3+ AEs ≥5% in either arm of RUBY-1	[redacted]	[redacted]	0.755	[redacted]
14	Subsequent treatment assumptions	RUBY-1 data used, with no IO retreatment	Equal proportion receiving no treatment (set to	[redacted]	[redacted]	0.755	[redacted]

No	Category	Base-case value	Scenario value	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
			dostarlimab proportion for both)				
15			75% market share assumed for PEM+LEN in CP proportions	[redacted]	[redacted]	0.755	[redacted]
16	Utility values	MMRp RUBY-1 source	ITT RUBY-1 source	[redacted]	[redacted]	0.752	[redacted]
17		AE disutilities included	AE disutilities excluded	[redacted]	[redacted]	0.755	[redacted]
18		Age-adjustment included	No age adjustment	[redacted]	[redacted]	0.797	[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; LEN, lenvatinib; LY, life years; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; QALYs, quality-adjusted life years; RWE, real-world evidence; TTD, time to treatment discontinuation.

2. Scenarios explored as part of EAG requests

Table 1 summarises the results of scenarios requested by the EAG as part of the clarification questions, and their impact on the submitted base-case [redacted]

Table 6: Scenarios explored as part of EAG requests

	Include in updated company base case	Incremental costs (dostarlimab+CP vs CP)	Incremental QALYs (dostarlimab+CP vs CP)	ICER (dostarlimab+CP vs CP)	Impact on ICER
Submitted company base case*	-	[redacted]	0.755	[redacted]	-
B1. Use 2023 inflation indices	Yes	[redacted]	0.755	[redacted]	Decrease
B6. TTD KM used for full follow-up period (Up to cycle 187)	No	[redacted]	0.755	[redacted]	Increase
B9. Include the cost and disutility of Grade≥3 treatment related irAEs	Yes	[redacted]	0.755	[redacted]	Increase
B10. Doubled AE rates in both arms (1L and 2L)	No	[redacted]	0.755	[redacted]	Increase
B11. Exclude AE disutilities for subsequent treatments	No	[redacted]	0.755	[redacted]	Increase
B12. Exclude AE costs for subsequent treatments	No	[redacted]	0.755	[redacted]	Increase
B15. Use dostarlimab+CP arm completion rates for CP	No	[redacted]	0.755	[redacted]	Increase
B17. Remove bevacizumab from subsequent treatment costs and disutilities (and redistribute)	Yes	[redacted]	0.755	[redacted]	Decrease
B20. a) Exclude Admin cost for Lenvatinib	No	[redacted]	0.755	[redacted]	Increase
B22. Set resource use equal after 3 years in the PF state	No	[redacted]	0.755	[redacted]	Decrease
B23. (i) Use EAG clinical expert resource use	No	[redacted]	0.755	[redacted]	Decrease
B23. (ii) Include thyroid/kidney/liver/cortisol tests for dostarlimab and for second line IO's.	Yes	[redacted]	0.755	[redacted]	Increase
B25. Use PSSRU end of life cost	Yes	[redacted]	0.755	[redacted]	Decrease
B26. Apply PSSRU end of life cost to those dying from PD only	No	[redacted]	0.755	[redacted]	Decrease
B28. Equal TTD to PFS	No	[redacted]	0.755	[redacted]	Increase
Updated company base case	-	[redacted]	0.755	[redacted]	Decrease

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; EAG, External assessment group; IO, immunotherapy; irAEs, immune-related adverse events; PD, progressed disease; PF, progression free; PSSRU, Personal Social Services Research Unit; TTD, time to treatment discontinuation.
*Base-case at time of initial company submission, which was subsequently amended as part of the EAG clarification questions.

3. Impact of EAG scenario analyses on updated company base case

Table 6 summarises the impact of the EAG's requested scenarios [redacted]

Table 7: Impact of EAG scenarios on updated company base case

Question number	Description	Impact on updated company base case ICER
	Updated company base case	[redacted]
B6	TTD KM used for full follow-up period (Up to cycle 187)	[redacted]
B10	Doubled AE rates in both arms (1L and 2L)	[redacted]
B11	Exclude AE disutilities for subsequent treatments	[redacted]
B12	Exclude AE costs for subsequent treatments	[redacted]
B15	Use dostarlimab+CP arm completion rates for CP	[redacted]
B20	a) Exclude Admin cost for Lenvatinib	[redacted]
B22	Set resource use equal after 3 years in the PF state	[redacted]
B23	i) Use EAG clinical expert resource use	[redacted]
B26	Apply PSSRU end of life cost to those dying from PD only	[redacted]
B28	Equal TTD to PFS	[redacted]

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; EAG, External assessment group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PD, progressed disease; PF, progression free; TTD, time to treatment discontinuation.

References

1. Wesselbaum A, Wallis J, Luhar S, Tunaru F, Carpenter L, Schneider D, et al. A real-world study of patients with advanced/recurrent endometrial cancer across England and Scotland2024.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Patient Organisation Submission

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 conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Peaches Womb Cancer Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Peaches Womb Cancer Trust is a charitable organisation with the mission to improve the lives of those affected by womb cancer by funding vital womb cancer research, increasing public awareness and providing support during and after diagnosis and treatment. The charity is funded through fundraising and donations. Peaches Womb Cancer Trust also hosts 'Peaches Patient Voices', a patient and public involvement group for people affected by womb cancer. We work with, and advocate for, people affected by womb cancer – diagnosed at all stages – and their loved ones.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	None

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Peaches Womb Cancer Trust has contributed the views, insights, and expertise of our Peaches Patient Voices network and used our evidence to highlight the difficult situation many patients face when diagnosed with primary advanced or recurrent endometrial cancer. As an organisation, we have presented our evidence on the impact of advanced and recurrent endometrial cancer, and available treatments, on our Patient Voices community. Peaches Womb Cancer Trust has valued the opportunity to use evidence obtained from members of Peaches Patient Voices to demonstrate both the potential positive outcomes and possible negative impacts of the proposed technology for many people facing primary advanced or recurrent mismatch repair proficient (pMMR) endometrial cancer. The following submission includes evidence obtained from extensive patient engagement, including: • focus groups and questionnaires that informed our previous submissions (ID3811 and ID3968), and involved women with lived experience of advanced or recurrent endometrial cancer • these focus groups included women with stage 3 and 4 endometrial cancer and, in the focus group that informed ID3968, two carers of women with stage 4 endometrial cancer who had undergone primary treatment with surgery and/or chemotherapy and radiotherapy. • previously used statement from a patient expert with lived experience of being on a PD-1 inhibitor immunotherapy (Hannah) – along with updated statement from the same patient to reflect her experiences following the completion of immunotherapy, in line with the 2-year stopping rule. Note that some quotes or experiences may reflect a PD-1 inhibitor immunotherapy that is not the same as the one under appraisal here and may reflect the experiences of individuals with mismatch repair deficient (dMMR) endometrial cancer. The rationale for including these is that side effects are likely to be similar.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of advanced or recurrent endometrial cancer has a significant impact on every aspect of women's lives. Many found their physical symptoms debilitating. At the time of diagnosis, these included vaginal bleeding, pain and discomfort, watery vaginal discharge, urinary urgency/ incontinence, reduced appetite, nausea, fatigue, and abdominal swelling. These symptoms impacted their quality of life, due to the practical implications of bleeding and urge incontinence, and some women found it challenging to leave the house to socialise and work. Many women experienced diagnosis-induced feelings of terror and fear at having to face their own mortality, and many of those diagnosed with stage 3 cancer felt in 'limbo' following treatment due to the uncertainty of recurrence. Some felt unable to cope with small things following treatment, affecting their previously positive outlook and causing them to cry more easily. Many felt like a different person following their diagnosis and treatment, in part due to feeling physically different, but mostly due to the psychological impact. Many felt that their relationships with family and friends altered following their diagnosis, and that people treated them differently. There was also ongoing worry and anxiety about how their diagnosis would impact family members and children, and how they would cope. One woman described how her teenage son's anxiety had become significantly worse following her diagnosis, resulting in him needing additional mental health support. Other patients reported: *"I panicked about dying. Nobody definitively told me I wouldn't. I cried about not seeing my children get married; maybe never holding my grandchildren."* *"I worry about dying if the treatment stops working. We try to make the most of my good days, but always worry what is round the corner, will I see my youngest grandchild start school? How far ahead can we make plans? Can I think about skiing next year, or will I be dead by Christmas?"* *"I am constantly anxious and hypervigilant for any signs of recurrence. I have symptoms that could be recurrence and have my 3-monthly check-up in 2 weeks. So, even though I finished treatment [last year], cancer is still part of my daily life."* *"Current treatments do not negate the possibility of recurrence, so the fear of recurrence is real and present. I have asked, but no one will make assurances or predictions for me. They generalise and make hopeful comments, whilst acknowledging they have no crystal ball. They know, and I know, that everyone did their best for me, but that sometimes the best still fails."*

	Women with stage 4 cancer are likely to report debilitating symptoms caused by the cancer. One of the women with stage 4 disease had ascites (fluid build-up in the abdomen) at the time of diagnosis. This caused significant pain and a reduction in her mobility, as well as impacting her ability to perform activities of daily living, leaving her increasingly reliant on friends and family for help. The ascites required recurrent drains resulting in frequent trips to the hospital with associated costs and impact on quality of life. As her cancer progressed, she also required bilateral nephrostomies due to ureteric obstruction, which impacted her physically, reducing her mobility. Another woman had ongoing bowel problems, including pain and constipation at the time of diagnosis due to a recurrence resulting in a tumour in her upper rectum. People caring for those with advanced or recurrent endometrial cancer face significant challenges. Many described the emotional challenges of being a carer, the constant feeling of helplessness, and the psychological impact on them. Caring for someone at home who is end of life causes significant challenges, both physically and psychologically. Many will require care around the clock, resulting in carers having to take time off work, impacting them financially, but also resulting in fatigue, burnout, guilt, frustration and grief. *"The carer takes over the huge burden of looking after the patient, the family, continuing work and providing emotional as well as physical support to the patient. They might be taking the patient to the hospital appointments, encounter long waiting times, arrange for GP appointments, etc. All these commitments for a carer are on top of all the other family commitments the carer has to take on."* *"[It's] terrible to watch your loved one failing and relying on you for support. My health and wellbeing [were] impacted trying to be strong and keep things together. The emotional support of loved ones is*

	seriously lacking as they have to be strong, but it is deeply emotional and resulted in me suffering from panic attacks and prescribed antidepressants." *"You feel guilt that you cannot fix it or do it for them."* One carer described the pain of anticipatory grief of caring for someone who is at the end of their life: *"You are constantly wondering when they will stop replying to your messages, or when the ticks on WhatsApp will stop turning blue."* Following the death of someone from advanced or recurrent endometrial cancer, there is a long-term impact of grief, including uncertainty about how you acted; whether you could have done more; whether you could have spent more time with them; or whether you should have done something differently.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**1. Women were dissatisfied and frustrated by current treatments for primary advanced and recurrent endometrial cancer, which include surgery, chemotherapy and radiotherapy.** Women found chemotherapy challenging due to a multitude of short- and long-term side effects, which have affected their quality of life. Short term effects included fatigue, nausea and vomiting, mouth pain, hair loss, changes in bladder and bowel habits, and neutropenia. Many had to take additional medication to reduce side effects, but they also experienced other side effects from these medications. Several women mentioned the effect of chemotherapy on the immune system and felt it left them vulnerable. This significantly impacted their quality of life, with many unable to work face-to-face, requiring time off, or unable to go out and spend time with family and friends. Some were also unable to undertake activities such as swimming, due to the risk of infection. *"I worry about the side effects of treatment, ending up in hospital […] with a fever."* It is important to note that individuals with advanced or recurrent pMMR endometrial cancer do not want to wait for disease progression or relapse before accessing treatment. Delaying access until the second-line setting risks patients becoming too unwell to benefit. They consistently express a desire for access to more effective treatment options as early as possible in their care pathway. **2. Many patients reported long term, often debilitating side effects from treatment that prevent them from living a fulfilling life.** Long term side effects of current treatments for primary advanced or recurrent endometrial cancer included pain, bowel and bladder issues, lymphoedema and fatigue, which have left women anxious. For some, it has affected their confidence going out to social events or gatherings due to tiredness, concerns about toilet access, and fear of 'accidents' such as urinary leakage. For others, limited mobility and pain means they are unable to leave the house. This also takes a significant toll on their mental health. Chemotherapy-induced peripheral neuropathy can cause pain in hands and feet. One patient reported: *"I still have neuropathy in my feet, sharp enough to make me yelp in surprise sometimes, painful enough to be annoying, but not life changing."* *"I experienced fatigue like never before. At times I would be doing ok and then it would feel as if something had been 'switched off' – no run down, gradual descent, just instantaneous."*

3. Many patients have been left unable to work, due to the after-effects of treatment, or have to work less than full-time, affecting them financially.

This leads to additional concerns and anxiety around how they might afford the cost of living. Even if they have felt well enough to go back to work, women report anxiety around controlling their treatment-related symptoms at work and access to a private toilet. Patients reported:

> *"I was left virtually incontinent of both bladder and bowel […] and although I have had physio for this, there has not been a huge amount of improvement. It is affecting my ability to return to a job I love."*

> *"I couldn't work for about 18 months so I ran out of sick pay, and I'm currently on a phased return to work, so reduced pay as I can only manage about 18 hours a week at the moment."*

> *"It has had a huge impact on my work, family and social life. I have lost a lot of confidence due to the effects I still struggle with and rarely go out on an evening. At the weekend I can't manage to do something sociable during the day and then go out on an evening too".*

> *"I had to stop work for 11 months because of my treatment. I was told unequivocally by my oncologist at the start that I wouldn't be returning to [work] that year. At the time, this seemed incredible to me, but the roller-coaster of all the treatment cycles (fatigue/ nausea/ low neutrophil counts/ frequent hospital visits which were a two hour round trip) meant that it would have been impossible for me to continue going to work."*

4. Womb cancer treatment has a substantial financial impact on patients.

Patients reported significant financial impact both through the time it takes to receive treatment and the long-term side effects. This included:

- cost of travel to treatment and parking at the hospital
- long term sick leave with implications to pay
- cost of living at home (e.g. heating)
- cost of complementary therapies to support wellbeing or manage side effects

5. Some women are unable to live fully independently due to physical symptoms and limited mobility

	Due to the impacts of treatment, some women have had to access help from family members for a number of activities of daily living, including; cooking, cleaning, help with bathing and medications. This leaves them feeling frustrated and a burden on family members. As a carer, this impacts financially due to time off work, psychologically, due to constant worry and anxiety about their loved one and less time for themselves, and physically, due to the additional activities on top of their own day-to-day living. *"I don't have the energy to do normal daily tasks which means that […] my husband took on more work/chores, my 76-year-old mother had to come over to do washing for me."* One of the carers we spoke to cared for her friend who sadly passed away from endometrial cancer in her mid to late thirties. She told us of the additional challenges of undergoing treatment when one is pre-menopausal with no children. Her friend struggled with menopausal symptoms following surgical treatment, including hot flushes, fatigue and difficulty sleeping. The psychological impact of treatment for endometrial cancer on fertility is huge, and delays in diagnosis leading to advanced stage disease may mean that fertility options are not available, leaving women angry, frustrated and distressed. **6. Treatments including hysterectomy and radiotherapy also significantly impacted on sexual intimacy** These impacts are due to multiple factors, including vaginal discomfort, bleeding and the vulnerability and trauma that comes with repeated intimate examinations. *"I was very traumatised by the diagnosis process regarding intimate examinations, which included painful examinations in an emergency situation and other multiple different examinations. This meant brachytherapy was particularly difficult for me, and my oncologist kindly performed the procedures, rather than the nursing team, because I trusted her. This has also greatly impacted my sexual function – both due to the trauma of invasive and difficult examinations and the long-term side effects of a shortened vagina from surgery, stenosis (narrowing) caused by radiotherapy, and menopause."*

8. Is there an unmet need for patients with this condition?	**Yes, there is a clear and urgent unmet need for women with primary advanced or recurrent pMMR endometrial cancer to access more effective treatment options** A growing disparity is emerging between the treatment pathways available to patients with dMMR disease and those with pMMR disease. Preliminary decisions from the NICE technical committees on both ID6317 (durvalumab) and ID6426 (dostarlimab) indicate that patients with dMMR disease are likely to benefit from increased access to novel and more effective first-line treatments. In contrast, the absence of similar options for those with pMMR disease risks creating a two-tiered system of care, where access to life-extending immunotherapies is determined solely by molecular subtype. This would be a deeply concerning and inequitable outcome for a large group of patients with significant clinical need. Additionally, this unmet need is also likely to make it more difficult from certain ethnic groups to access any innovative technology. Whilst the clinical trial data does not delineate into different molecular subtypes beyond pMMR (POLE-mut, NSMP and p53abn), there is evidence that there are racial disparities within the molecular profile of endometrial cancer[1,2]. As outlined in the Equalities section, there are particularly equalities issues regarding the unmet need for first line treatments which disproportionately impact Black women who are more likely to be diagnosed late, with pMMR subtype. Black women are also twice as likely to die from endometrial cancer as White women[3]. A review by Illah et al. (2024) has highlighted that Black women are twice as likely to die from endometrial cancer compared with white women, representing one of the worst global inequalities among ethnic groups in cancer[4]. *Please note that the above has been written from a patient advocacy perspective and not a clinical one.* **The unmet need for equal access to effective treatment options leaves women feeling frustrated, hopeless, and abandoned** Across all patients affected by late-stage endometrial cancer, women expressed frustration, disappointment, anger, and feelings of abandonment due to the limited effective first-line treatment options for advanced endometrial cancer. They felt left behind or not prioritised for effective treatment options, believing that women affected by endometrial cancer have fewer effective treatment options compared to other cancers. Several patients referred to the availability of multiple lines of treatment for breast cancer and expressed a desire for access to similar multiple lines of treatment for womb cancer. One patient expressed that:

	"The UK has some of the poorest cancer survival rates compared to Europe. However, where improvements in cancer survival rates are seen, it is in those cancers where a combined treatment approach is clinically available on the NHS, involving traditional chemotherapy plus newer targeted treatments. In many cancers, these are available in both first-line and second-line treatments. All patients, regardless of their cancer type, should have equal access to the potential survival benefits that these newer cancer treatments may offer." Currently, there are limited effective treatments available for patients with primary advanced or recurrent pMMR endometrial cancer, with the standard of care being so-called "bog standard" chemotherapy, which has limited effectiveness and causes significant side effects. Receiving effective and innovative treatments earlier in the treatment pathway would reduce the overall treatment burden and offer people with primary advanced or recurrent pMMR endometrial cancer hope of living with no—or well-managed disease—for longer. **Unmet need due to limited access to immunotherapy (pembrolizumab with lenvatinib) on the NHS in the second-line setting** People with advanced or recurrent pMMR endometrial cancer have clearly articulated the need for earlier access to innovative and effective treatment options. Currently, access to immunotherapy is delayed until the second-line setting, with pembrolizumab combined with lenvatinib being the only available option. As a result, people with pMMR endometrial cancer may only access more costly immunotherapies later in the treatment pathway, rather than in the first-line setting when they may be more effective. A proportion of patients may also become too unwell to receive treatment by the time it is available to them. Women we spoke to who had experienced stage 3 endometrial cancer commented: *"The current approach is geared towards expecting a recurrence and then adding a more effective second-line treatment. It is paramount to offer endometrial cancer patients a first-line treatment that will further reduce the chance of the cancer recurring."* *"I have […] twice been subject to clinical investigation for suspected recurrent disease. Being aware that survival rates for advanced disease are considered poor and knowing that my only treatment option offered by the NHS would be 'bog-standard chemotherapy' as first-line [option] filled me with dread and fear."* **Unmet need for patients with stage 4 or recurrent endometrial cancer** For patients with stage 4 or recurrent disease, the standard of care means that they must endure chemotherapy first, despite receiving this devastating diagnosis, before being able to access immunotherapy as a second-line

	treatment. By this time, their cancer may have progressed, and/or their health may have worsened, leading to further devastating impacts on their well-being and reducing their ability to tolerate subsequent treatments. Access to earlier, more effective treatment would provide better symptom control, extend the time before cancer progresses, and improve the possibility of a more meaningful and longer life. **Unmet need for patients with stage 3 endometrial cancer** For patients with newly diagnosed stage 3 disease, the current pathway requires them to wait for a recurrence before they can access immunotherapy. Living with the knowledge of a relatively high risk of recurrence—and the possibility of facing aggressive treatment, with the cancer potentially becoming incurable—creates ongoing fear and uncertainty about the future. The unmet need in this situation is for a treatment that prevents recurrence or progression to incurable stage 4 cancer. Such a treatment would offer hope for living free of cancer for longer, or even a potential cure. 1. Javadian P., Washington, C., Mukasa, S., Benbrook DM. (2023) Histopathologic, Genetic and Molecular Characterisation of Endometrial Racial Disparities. Cancers (Basel)13 (8) DOI:10.3390/cancers13081900 2. Guttery, S., Blighe, K., Polymeros, K., Symonds, R., Macip, S., Moss, E. (2018) Racial differences in the endometrial cancer molecular portraits in The Cancer Genome Atlas. Oncotarget 30 (9) DOI: https://doi.org/10.18632/oncotarget.24907 3. Delon, C., Brown, K.F., Payne, N.W.S., Kotrotsios, Y., Vernon, S. and Shelton, J. (2022). Differences in Cancer Incidence by Broad Ethnic Group in England, 2013–2017. *British Journal of Cancer*, [online] 126(12). doi:https://doi.org/10.1038/s41416-022-01718-5. 4. Office for National Statistics (2023). *Age-standardised mortality rates for uterine and cervical cancer by ethnic group, females aged 10 and above, deaths registered in England and Wales: 2012 and 2019 - Office for National Statistics*. [online] www.ons.gov.uk.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Potential role of new treatment:** • **Earlier access to more effective treatments for patients with pMMR disease:** Patients with pMMR endometrial cancer would benefit from receiving effective treatments earlier in their treatment pathway similar to dMMR patients. Patients with stage 3 pMMR disease would benefit from a first-line treatment that may reduce the risk of recurrence and offers the potential for longer survival—and even the possibility of cure. One patient shared: *"[I want] the cancer to be gone and the risk of recurrence to be hugely (ideally completely), eliminated."* For individuals with stage 4 or recurrent pMMR endometrial cancer, access to dostarlimab on the NHS would mean: • **Extended progression-free survival:** Patients can achieve longer periods without cancer progression. • **Improved overall quality of life:** Allowing more time with family and friends and fostering hope of living a meaningful life. *"I want a treatment that will stop the spread, reduce the size of, or get rid of the cancer. Preferably the latter. I want my life prolonged, the worry to stop, and to get back to normal."* • **Bridging to future treatments:** Staying well for longer improves the likelihood of accessing further innovative treatments in the future. • **Impact on treatment pathway and independence:** Gaining access to more effective treatments earlier in the treatment pathway could lead to: ○ **Better symptom control:** Fewer debilitating symptoms in the long term. ○ **Longer remission or stable disease:** Patients desire treatments that keep them in remission or maintain stable disease for extended periods, allowing them to retain independence longer and live life as fully as possible. • **Potential to avoid additional surgeries**: Earlier access to effective treatments may prevent the need for further surgeries to manage tumour growth after initial treatment. For instance, recurrence following stage 3 or progression of stage 4 cancer often necessitates additional surgical interventions. For example, in the

	case of Hannah (whose story is shared below), a recurrence in her rectum required a Hartmann's procedure to create a colostomy. Earlier intervention with immunotherapy and ongoing maintenance treatment might have prevented this additional surgery. • **Hope through immunotherapy**: Access to immunotherapies offers hope for patients facing a primary advanced or recurrent endometrial cancer diagnosis. One patient with stage 4 disease expressed the impact of being granted access to dostarlimab. *"HOPE… Optimism for a future. A treatment without the brutal side effects, a treatment that doesn't take over your life. A treatment that enables you to travel and plan for a future, giving me a belief that I might see my granddaughter start school. [...] Hope is the most important—an option when other doors are closing."* **Patient story:** *Although the patient quoted below was diagnosed with dMMR endometrial cancer, their story demonstrates the potential quality-of-life benefits of dostarlimab for those diagnosed with advanced or recurrent pMMR endometrial cancer and has been included here.* Hannah* was diagnosed with stage 4, grade 3 endometrial cancer in November 2019, age 30, and underwent hysterectomy, platinum-based chemotherapy, radiotherapy and brachytherapy. Hannah has the dMMR subtype, having been diagnosed with Lynch syndrome. She relapsed 6 months after finishing treatment for her primary cancer – with tumours in her bowel, scar tissue and one near her liver. After undergoing surgery which removed 3 of 4 tumours, she started a PD-1 inhibitor immunotherapy (not dostarlimab) as a monotherapy which shrunk the final tumour so that there is nothing visible on her scans. She has now finished treatment and has been in remission for over a year. Hannah has also been able to live a "healthier and more fulfilling life" despite an incurable cancer diagnosis and has been 'living well with cancer' for over 3 years both on and off immunotherapy. Although there have been a couple of setbacks (mainly underactive thyroid due to the treatment) and fatigue, the benefits much outweigh these – and are much easier to manage than those she experienced on chemotherapy.

	Hannah reported: *"I have found the treatment to be much kinder and more manageable than any others that I have had and I have experienced fewer side effects. With [immunotherapy], I feel much more relaxed and able to live a normal life and am able to go to the office, meet friends, occasionally go out dancing and attend social and family events. I am grateful every day that I am able to live my life fully and without many of the side effects of previous treatments. Sometimes, I even forget that I have stage 4 cancer!"* Hannah has since finished treatment and has been off treatment for over a year with no evidence of disease on scans. During this time, she has been able to have an active social and work life, travel to Greece, New Zealand, Australia and Costa Rica and attend festivals. *Pseudonym used

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As we have been unable to identify anyone who has undergone treatment with the technology, we have based the below on similar immunotherapies (i.e., PD-1 inhibitor immunotherapies). Key disadvantages of the technology that patients identified include: **1. Fatigue** Some patients receiving either chemotherapy combined with an immunotherapy or immunotherapy as a monotherapy report fatigue. One patient with recurrent endometrial cancer describes experiencing more severe fatigue than during treatment for her primary tumour with chemotherapy: *"I have one complete day when I can do nothing, I get exhausted walking up stairs."* Patient on an immunotherapy with chemotherapy) One patient, who received an immunotherapy as a monotherapy, reported: *"Whilst I was on treatment, I was able to live a nearly normal life, although I needed to rest more and avoid overdoing it. However, [the immunotherapy] had a cumulative impact on my energy levels and I have been living with fatigue for the past couple of years even after treatment. I have some periods of more intense fatigue where I struggle to do as much. However, without [the immunotherapy], I would not be alive so it's worth it."* **2. Impact on biochemical markers** Immunotherapies may have additional impact on biochemical markers. *"I'm taking magnesium supplements for low levels which hasn't happened before, and I know my haemoglobin levels are low."* (Patient on dostarlimab with chemotherapy) "*I have had some challenges with very low ferritin levels following immunotherapy. Although I am not sure if they are linked, I had to get an iron infusion to top them up and stop feeling so tired."* (Patient on an immunotherapy as a monotherapy) **3. Immune-related adverse impacts**

	One patient reported that they were diagnosed with an underactive thyroid caused by immunotherapy. Initially this led to feelings of profound fatigue. Following levothyroxine treatment, the patient does not have any ongoing side effects although treatment is lifelong. *"Due to the initial impact on my thyroid, I became incredibly fatigued (the worst of the entire treatment) and struggled to even get off the sofa and do basic things like cook or shower. It took a little while for my thyroid to completely stop functioning and I couldn't have treatment until then. This meant I had to live with debilitating fatigue for 4-6 weeks until I could start the treatment. It took another month or two to feel the benefit of the levothyroxine. This was one of the most difficult times on treatment."*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There is limited data on the efficacy of dostarlimab across the distinct molecular subtypes within the pMMR endometrial cancer group (POLEmut, p53abn, NSMP), which may obscure differences in treatment responsiveness between patient subgroups.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The lack of effective and innovative first-line treatments for people with advanced or recurrent pMMR endometrial cancer is likely to disproportionately impact some racial groups. Approving dostarlimab for pMMR endometrial cancer is likely to make it easier for certain racial groups to access a first line effective and innovative treatments. Whilst the clinical trial data is unlikely to delineate into different molecular subtypes beyond pMMR (POLE-mut, NSMP and p53abn), there is evidence that there are racial disparities within the molecular profile of endometrial cancer[1,2]. For example, the p53abn subtype of endometrial cancer is over-represented in Black women. Incidence rates of uterine cancer are higher among individuals of Black ethnicity compared to those of White ethnicity[3]. ONS data shows significant disparities in deaths from endometrial cancer – with Black ethnic groups in the UK being much more likely to die of the disease than other ethnic groups[4]. A review by Illah et al. (2024) has highlighted that Black women are twice as likely to die from endometrial cancer compared with white women, representing one of the worst global inequalities among ethnic groups in cancer[5]. There are multiple drivers of increased mortality in Black women including late diagnosis being more common in those from Black Caribbean and Black African women compared with other groups. Recent data in the UK has shown that African and Caribbean women are twice as likely to be diagnosed at an advanced stage compared with White British women[6]. As Illah et al. (2024) highlight, this “association is so strong that Cancer Research UK labelled ethnicity as a ‘significant factor’ in the stage at diagnosis of EC[7]. Additionally, Black women are more likely to be diagnosed with higher risk endometrial cancer and the most aggressive p53abn subtype, which has the poorest outcomes[8]. Around 15% of all endometrial cancers are p53abn subtype, which is mismatch repair proficient and responsible for 50-70% of deaths from endometrial cancer[9].

	Racial inequalities are further compounded by an under-reporting and low quality of reporting of racial characteristics of people diagnosed with endometrial cancer which could mean the full unmet need is not known[10]. Making dostarlimab available for people with advanced or recurrent endometrial cancer across for pMMR patients would help address this disparity and improve outcomes for people of all ethnicities. *Please note that the above has been written from a patient advocacy perspective and not a clinical one*

References for Equalities considerations:

1. Javadian P., Washington, C., Mukasa, S., Benbrook DM. (2023) Histopathologic, Genetic and Molecular Characterisation of Endometrial Racial Disparities. Cancers (Basel)13 (8) DOI:10.3390/cancers13081900

2. Guttery, S., Blighe, K., Polymeros, K., Symonds, R., Macip, S., Moss, E. (2018) Racial differences in the endometrial cancer molecular portraits in The Cancer Genome Atlas. Oncotarget 30 (9) DOI: https://doi.org/10.18632/oncotarget.24907

3. Whelan, K., Dillon, M., Strickland, K.C., Bhavana Pothuri, Bae-Jump, V., Borden, L.E., Thaker, P.H., Haight, P., Arend, R.C., Ko, E., Jackson, A.L., Corr, B.R., Martins Ayoola-Adeola, Wright, J.D., Podwika, S., Smitherman, C., Thomas, S., Lightfoot, M., Newton, M. and Washington, C. (2023). TP53 mutation and abnormal p53 expression in endometrial cancer: Associations with race and outcomes. *Gynecologic oncology*, 178, pp.44–53. doi:https://doi.org/10.1016/j.ygyno.2023.09.009.

4. Delon, C., Brown, K.F., Payne, N.W.S., Kotrotsios, Y., Vernon, S. and Shelton, J. (2022). Differences in Cancer Incidence by Broad Ethnic Group in England, 2013–2017. *British Journal of Cancer*, [online] 126(12). doi:https://doi.org/10.1038/s41416-022-01718-5.

5. Office for National Statistics (2023). *Age-standardised mortality rates for uterine and cervical cancer by ethnic group, females aged 10 and above, deaths registered in England and Wales: 2012 and 2019 - Office for National Statistics*. [online] www.ons.gov.uk. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/15495agestandardisedmortalityratesforuterineandcervicalcancerbyethnicgroupfemalesaged10andabovedeathsregisteredinenglandandwales2012and2019 [Accessed 15 Apr. 2025].

6. Ojone Illah, Adeeko, D., Adeola Olaitan and Aleksandra Gentry-Maharaj (2024). Racioethnic Disparities in Endometrial Cancer Outcomes. *Diagnostics*, 14(4), pp.417–417. doi:https://doi.org/10.3390/diagnostics14040417.

7. Limb, M. (2023). Black women in England are at greater risk of late cancer diagnosis than white women. *BMJ*, [online] 380, p.p211. doi:https://doi.org/10.1136/bmj.p211.

8. Raimondo, D., Raffone, A., Pezzullo, A.M., Doglioli, M., De Benedetti, P., Celerino, P., De Meis, L., Maletta, M., Raspollini, A., Travaglino, A., Guida, M., Casadio, P. and Seracchioli, R. (2023). Race and ethnicity reporting in endometrial cancer literature. *International Journal of Gynecological Cancer*, 33(9), pp.1402–1407. doi:https://doi.org/10.1136/ijgc-2023-004552.

9. Weigelt, B., Marra, A., Pier Selenica, Rios-Doria, E., Amir Momeni Boroujeni, Berger, M.F., Arora, K., Nemirovsky, D., Iasonos, A., Chakravarty, D., Abu-Rustum, N.R., Paula, C., Dessources, K., Ellenson, L.H., Liu, Y.L., Aghajanian, C. and Brown, C.L. (2023). Molecular Characterization of Endometrial Carcinomas in Black and White Patients Reveals Disparate Drivers with Therapeutic Implications. *Cancer Discovery*, 13(11), pp.2356–2369. doi:https://doi.org/10.1158/2159-8290.cd-23-0546.

10. Yang, Y., Su Fang Wu and Bao, W. (2023). Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies. *International journal of gynaecology and obstetrics*, 164(2), pp.436–459. doi:https://doi.org/10.1002/ijgo.14969.

Other issues

13. Are there any other issues that you would like the committee to consider?	None identified
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	1. There is a significant unmet need for earlier, timely and guaranteed access to effective, innovative treatments for people with primary advanced or recurrent pMMR endometrial cancer. 2. There is a risk of exacerbating existing health inequalities in endometrial cancer outcomes for Black women, who are more likely to be diagnosed with the aggressive pMMR molecular subtype (p53abn), often at a later stage, and are twice as likely to die from endometrial cancer than White women. 2. Patients must wait until their disease relapses or progresses before accessing an effective and innovative treatment (pembrolizumab with lenvatinib) in the second-line setting. For some, this delay means they may become too unwell to receive further treatment. 3. Individuals with stage 3 disease need access to first-line treatments that prevent or delay recurrence, stop progression to incurable stage 4 cancer, and help reduce fear of their cancer returning. Those with stage 4 or recurrent disease want immediate access to effective first-line treatments to prevent their condition from worsening and enable them to live a meaningful life for longer. 5. People with primary advanced or recurrent pMMR endometrial cancer feel frustrated and abandoned due to the lack of effective first-line treatment options, especially when compared to other cancers that have multiple lines of treatment available.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

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. 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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 5 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew Clamp
2. Name of organisation	The Christie NHS Foundation Trust, Manchester
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 microsatellite stability or mismatch repair proficiency ? ☒ A specialist in the clinical evidence base for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency 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 submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
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.
8. What is the main aim of treatment for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency ? (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 reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	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. Survival outcomes, both overall and progression-free are often more important markers of treatment benefit.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency?	Yes, outcomes with current treatment approaches are unsatisfactory and there is an urgent need to improve survival in this patient group. For those patients requiring systemic treatment for advanced/ recurrent endometrial cancer, carboplatin-paclitaxel is the established standard-of-care with response rates of 40-50% reported in clinical trials. However, median survival is disappointingly low with most trials reporting overall survival figures of less than 2 years. Indeed, in GOG0209, the seminal phase III trial which confirmed carboplatin-paclitaxel as the treatment standard, median overall survival was 20.9 months in patients who had measurable disease at trial entry (Miller et al J Clin Oncol 2020). Endometrial cancers are now routinely classified into 4 molecular subgroups (PoleE mutated, MMR-deficient, TP53 mutated and No Specific Mutational Profile) based on the presence/absence of PolE exonuclease domain mutations, DNA Mismatch Repair pathway protein loss and TP53 gene mutations. These subgroups have important prognostic/ predictive value and are used to guide patient management.

	About 25% of endometrial cancers are MMR-deficient. As a consequence of this, these cancers express high levels of neoantigens on the cell surface rendering them highly immunogenic and likely to respond to immunotherapy. The other 75% of endometrial cancers are considered MMR-proficient, although this is a molecularly heterogenous grouping. Although considered less responsive to immunotherapy, a 15% response rate to single-agent dostarlimab was seen in the 161 participants with MMR-proficient recurrent endometrial cancer previously treated with platinum-based chemotherapy in the GARNET trial (Oaknin et al Clin Cancer Res 2023) with a median response duration of 19.4 months providing one rationale for inclusion of participants with MMR-proficient endometrial cancer in the RUBY trial.
11. How is advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	The most commonly used guidelines are; BGCS (2022), ESGO-ESTRO-ESP (December 2020) and ESMO (June 2022). All of these recommend the use of carboplatin-paclitaxel doublet chemotherapy for patients with advanced/recurrent endometrial cancer, irrespective of molecular subtype, that is not amenable to locoregional treatment approaches. In a small minority of women with low grade hormone receptor positive recurrent disease of low volume, endocrine therapy, generally with a progestagen can be effective alternative treatment approach to chemotherapy. At present in these guidelines, immune checkpoint inhibitors are used in the second-line setting after failure of platinum-based chemotherapy in those patients who are fit enough for further treament. In MMR-proficient disease, the recommended regimen is pembrolizumab + lenvatinib based of the KEYNOTE-775 trial which reported a 6.8 month improvement in overall survival with this combination compared to second-line single agent chemotherapy (18.7mo vs 11.9 mo HR 0.65 Makker et al J Clin Oncol 2023). All these guidelines are being updated actively to take into account the results of RUBY1 and other trials detailed in section 21. The updated guidelines will likely

	recommend the use of immune checkpoint inhibitors with carboplatin-paclitaxel in the first-line setting for the patient group included in this TA. It should be noted that immunotherapy+carboplatin-paclitaxel has already been adopted as the de facto standard for the control arms of current international first-line phase III clinical trials in advanced/recurrent MMR-proficient endometrial cancer.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This treatment would be administered in secondary care overseen by medical/ clinical oncologists experienced in the management of advanced/recurrent endometrial cancer. There would be limited impact on SACT delivery capacity due to the requirement for additional dostarlimab treatment cycles (median 15 cycles delivered in experimental arm of RUBY trial). The 6-weekly schedule and 30 minute infusion length means that any impact would be small. These patients would also need monitoring for immunotherapy-related adverse events and treatment benefit which would require a small increase in oncology clinic capacity and staff resource. As immunotherapy is an established treatment modality for many other cancer types as well as for recurrent endometrial cancer after failure of platinum-based chemotherapy, 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? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The Phase III RUBY trial (Mirza et al NEJM 2023) randomised 494 patients with primary advanced or recurrent endometrial cancer to 6 cycles carboplatin-paclitaxel chemotherapy administered with either concurrent + maintenance dostarlimab or placebo continued for up to 3 years. The trial had a hierarchical design with 3 primary endpoints where the initial efficacy evaluation for PFS was planned to occur in the MMR-deficient subgroup. If the null hypothesis was rejected in this analysis, PFS was subsequently evaluated in the overall study

	population (MMR-deficient + MMR-proficient). If both PFS null hypotheses were rejected OS was assessed in the overall population. Evaluation of PFS and OS in the subgroup with MMR-proficient disease were preplanned exploratory analyses. 76% of trial participants has MMR-proficient disease. In this 376 patient subgroup, PFS was significantly improved. The 24 month PFS rate was 28.4% in the dostarlimab-containing arm compared to 18.8% in the placebo arm (HR 0.76 in favour of dostarlimab arm 95% CI 0.59-0.98). There was also a trend to improved OS at a simultaneous interim analysis (24 month OS 68% vs 55% HR 0.73 95% CIs 0.52-1.02 in favour of dostarlimab). In June 2024, the survival results from the second interim analysis were published (Powell et al Ann Oncol 2024). At this analysis with a median follow-up of 37.2 months, the dual primary endpoint of OS in the overall trial population was met. In the MMR-proficient subgroup, data maturity was 55%. 59% of patients who received placebo had died compared to 51% of those who received dostarlimab. Median OS was 7 months longer for patients receiving dostarlimab (34.0 vs 27.0 months) with a clear trend in favour of this arm (HR 0.79; 95% CIs 0.60-1.04; p=0.049). Analysis of PFS2 (time to progression after first subsequent therapy after study treatment or death), a preplanned secondary endpoint also demonstrated a clinically meaningful 8.4 month increase with dostarlimab compared to placebo (24.6 vs 15.9 months; HR 0.74 95% CIs 0.57-0.97) further supporting the increase seen in OS. These benefits were seen despite 37% of patients in the placebo arm receiving an immunotherapy-based treatment at cancer progression, most commonly lenvatinib-pembrolizumab, compared to 18% in the dostarlimab arm. Patient-reported outcomes were evaluated longitudinally as a secondary endpoint using the European Organisation for Research and Treatment of

	Cancer Quality of Life Questionnaire Core 30 and Endometrial Cancer Module. In the overall trial population (combined MMR-d and MMR-p), no significant difference was seen between treatment arms although a trend towards improved global QoL was seen after completion of chemotherapy treatment in the dostarlimab arm compared to placebo (Fig S6 Mirza et al New Engl J Med 2023)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This HTA is evaluating the addition of dostarlimab to carboplatin-paclitaxel chemotherapy in patients with MMR-proficient advanced/recurrent endometrial cancer. Dostarlimab is already approved by NICE in this setting in MMR-deficient disease which is the molecularly-defined subgroup that is most likely to benefit from immune checkpoint inhibitors (TA 1064). Exploratory evaluation of survival stratified by histological and molecular subtype in the RUBY trial was presented at the ESMO 2023 Congress (Mirza et al). Benefit from dostarlimab was consistent across histological subtypes and a trend in favour of dostarlimab was seen in both the 22% of participants with TP53 mutated cancer (HR 0.55) and the 54% with NSMP cancer (HR 0.77) indicating that utilising these routinely performed tests cannot be used to select patients with MMR-proficient cancers more likely to benefit from dostarlimab.
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)	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. Testing MMR status by immunohistochemistry is already performed routinely as part of the diagnostic histopathology workup for endometrial cancer.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The RUBY protocol included 3 years dostarlimab treatment. I think that centres will continue to deliver this duration of maintenance for those patients whose disease remains controlled and who do not have significant treatment-related side-effects.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No.
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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The improvements in both PFS and OS seen in the RUBY trial with first line dostarlimab are clinically relevant and provide patients with MMR-proficient advanced/recurrent endometrial cancer with significant additional time free from disease progression and the side-effects of further chemotherapy. The movement of immunotherapy into the first-line setting will also open this treatment option up to larger numbers of potentially eligible patients who may not be fit enough after progression of their cancer to receive subsequent second-line combination immunotherapy regimens.
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?	Some women receiving dostarlimab will experience additional immune-related adverse effects not seen with chemotherapy alone. The updated safety profile conducted at the time of the 2nd interim analysis (Powell et al Ann Oncol 2024) reported that the incidence of ≥G3 adverse events considered related to dostarlimab/placebo was higher in the dostarlimab arm (33.2% vs 19.5% with placebo). Treatment discontinuation due to an adverse event was low in both arms(19% dostarlimab vs 8% placebo). All specialist oncology centres have guidelines for the recognition and management of toxicities associated with

	immune checkpoint inhibitors that will enable rapid identification and treatment of these side-effects.
20. Do the clinical trials on the technology reflect current UK clinical practice? • 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? • 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?	Yes.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	It should be noted that in the last 2 years, 3 further phase III placebo-controlled trials have been reported evaluating the addition of immune checkpoint inhibitors to carboplatin-paclitaxel chemotherapy in the first-line treatment of advanced/ recurrent endometrial cancer. These studies recruited a similar patient population to the RUBY trial. Two of these trials also showed clinically significant improvements in PFS associated with immunotherapy in the subgroup of patients with MMR-proficient disease; Pembrolizumab- NRG GY018 trial (Eskander et al NEJM 2023)- 591 MMRp participants. HR 0.54 (95% CIs 0.41-0.71). Median PFS 13.1months pembrolizumab vs 8.7 months placebo. Durvalumab- DUO-E (Westin et al J Clin Oncol 2024). 392 MMRp participants- HR 0.77 (95% CIs 0.60-0.97) median PFS durvalumab- 9.9 months placebo 9.7 months. Atezolizumab-AtTEnd trial (Colombo et al Lancet Oncol 2024). 409 MMRp participants. HR 0.92 (95% CIs 0.73-1.16).

	These results indicate the robustness of the clinical benefit associated with the incorporation of immunotherapy into the first-line treatment setting of advanced/ recurrent MMR-deficient endometrial cancer.
22. How do data on real-world experience compare with the trial data?	I am not aware of any publications of RWE in this indication.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	Nil specific.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Until recently, carboplatin + paclitaxel chemotherapy was the standard-of-care first line treatment for advanced/recurrent endometrial cancer but despite this, median overall survival is less than 2 years.

MMR-proficient endometrial cancer is a molecularly heterogeneous grouping that includes around 75% of cases with advanced/ recurrent disease

In the RUBY trial, the addition of dostarlimab to first-line carboplatin-paclitaxel in the treatment of MMR-proficient advanced/recurrent endometrial cancer increased median overall survival by 7 months compared to placebo.

Dostarlimab treatment has manageable adverse effects and does not have a negative impact on quality-of-life compared to placebo.

Routinely available molecular testing cannot further identify a subgroup within MMR-proficient endometrial cancer that is more likely to benefit from dostarlimab

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

NICE National Institute for Health and Care Excellence

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

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. 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.

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 5 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

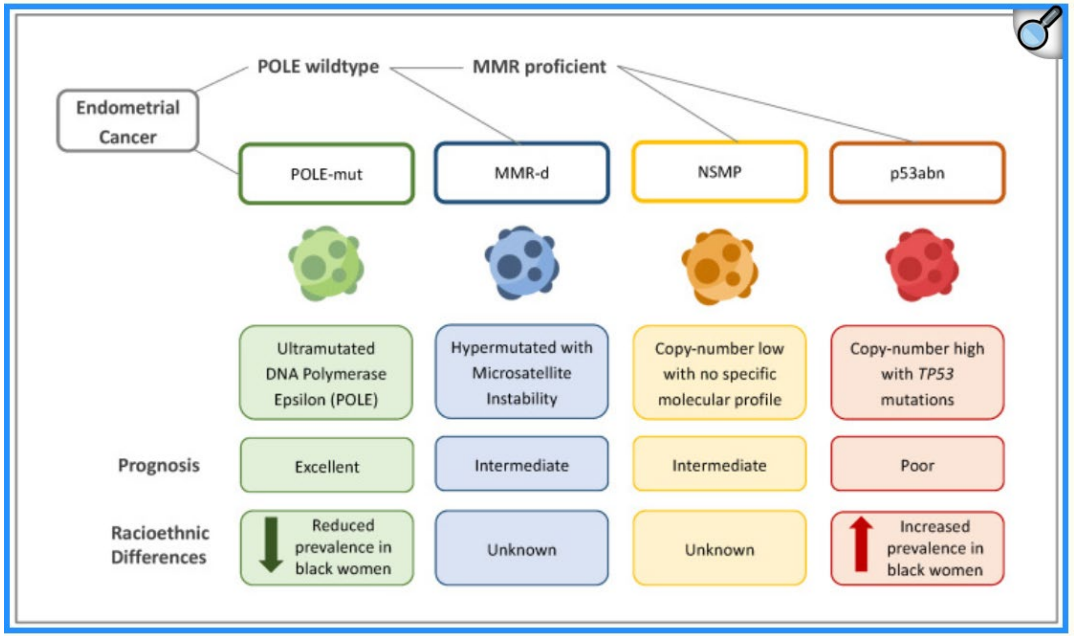
1. Your name	Dr John McGrane
2. Name of organisation	Royal Cornwall Hospital
3. Job title or position	Consultant Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency ? ☐ A specialist in the clinical evidence base for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency 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 submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
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.	N/A
8. What is the main aim of treatment for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim is to have access to immunotherapy for metastatic endometrial cancer patients in the first line setting. We know that many patients will be lost between first and second line therapy (approx. 30-40%).
9. 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)	A reduction in tumour size by 30%. Also the time of disease control is important.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency?	I think the RUBY data shows that the MMR proficient group also benefits from the addition of dostarlimab in the first line setting. The MMR proficient goup is approximately three quarters of the metastatic endometrial cancer group and many patients will not be fit for SACT in the second line.
11. How is advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Current pathway 1st line – If chemo fit - Chemotherapy – carboplatin & paclitaxel 2nd line – Lenvatinib and Pembrolizumab (as long as no contra-indications) or second line chemotherapy monotherapy 3rd line - Reverse above 4th – best supportive care or trials At all points select patients with ER positive disease and not fit for chemotherapy may be offered hormone therapy. Having access would change out the second or beyond line use of Lenvatinib and pembrolizumab.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It would be used as per the MMR deficient metastatic endometrial cancer group. First line carboplatin and paclitaxel + dostarlimab for all comers. That would then lead to second line chemotherapy monotherapy as second line and then trials or best supportive care as third line. At all points select patients with ER positive disease and not fit for chemotherapy may be offered hormone therapy.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The MMR proficient group saw a trend towards overall survival benefit with a 7% increase as 3 years **MMRp - HR 0.79 CI (0.6-1.04) p=0.0493.** The results from a second interim analysis of RUBY Part 1 data, presented at the SGO Annual Meeting on Women's Cancer 2024,confirmed that the PFS benefit translated to an OS benefit in RUBY Part 1.The results showed that dostarlimab plus chemotherapy was associated with a statistically significant and clinically meaningful improvement in OS compared with placebo plus chemotherapy in the overall patient population. (HR: 0.69; 95% CI: 0.54–0.89; p=0.0020) – 16 m improvement in OS. True much of this benefit was driven by the MMR deficient group but there was ¾ of the group were MMR proficient which had a 7month improvement in OS (although not significant)
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The p53 subset has been shown to have significant OS and PFS benefit. This was in a post hoc analysis presented at ESMO 2023. There was a trend of benefit seen in NSMP molecular profile and POLE was such a small number it was not significant – Albeit it would be expected to be a very positive group to receive immunotherapy.

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)	The one aspect of this technology that would be easier is that all patients could be given IO upfront in the metastatic setting and so standardising care. There are some centres struggling with full molecular sub classification of endometrial cancer.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing should be needed.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• Quality of life deterioration was delayed in the QoL assessment for the RUBY trial • Florian Heitz et al. Time to quality of life (QoL) improvement or deterioration in patients (pts) with primary advanced or recurrent endometrial cancer (pA/R EC) treated with dostarlimab plus chemotherapy in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial.. *JCO* **43**, 5600-5600(2025). DOI:10.1200/JCO.2025.43.16_suppl.5600
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? • Is the technology a 'step-change' in the management of the condition?	It would improve access to immunotherapy for metastatic endometrial cancer patients

• Does the use of the technology address any particular unmet need of the patient population?	
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?	Toxicity management for immunotherapy is well established and toxicity for dostarlimab is low and recognised in the trial.
20. Do the clinical trials on the technology reflect current UK clinical practice? • 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? • 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 current active trials
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	At SGO 2025 data from 27 patient was presented showing good tolerabitily and disease control. 30% of this group were MMRd so quite similar to the RUBY trial ratio. Lantsman T, Jia L, Edmiston C, Shea M, Widick P. Real-world RUBY: safety and efficacy of combination chemotherapy plus dostarlimab in advanced endometrial cancer. Presented at: 2025 SGO Annual Meeting on Women's Cancer; March 14-17, 2025; Seattle, WA. Abstract 1280.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	There is a higher ratio of p53 Abnormal endometrial cancer in black women which would fit into the MMR proficient group. See below  Illah O, Adeeko D, Olaitan A, Gentry-Maharaj A. Racioethnic Disparities in Endometrial Cancer Outcomes. Diagnostics (Basel). 2024 Feb 14;14(4):417. doi: 10.3390/diagnostics14040417. PMID: 38396458; PMCID: PMC10887632.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

BMJ TAG

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 172882.

Title:	Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London, Tracey Jhita, Health Economist Manager, BMJ-TAG, London Ben Burgess, Senior Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	08/04/2025
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 172882.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Santhanam Sundar (Consultant Oncologist, Nottingham University Hospitals NHS Trust), Dr Ahmed El-Modir (Consultant Oncologist, University Hospital Birmingham), Dr Melanie Powell (Consultant Clinical Oncologist, Barts Health NHS Trust London), and Dr Axel Walther (Consultant Medical Oncologist, Bristol Cancer Institute) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
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.
Report reference:	Edwards SJ, Wakefield V, Jhita T and Burgess B. Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency: A Single Technology Appraisal. BMJ Technology Assessment Group, 2025.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Ben Burgess	Critical appraisal of the company's submission; and critical appraisal of the clinical evidence.
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
AUC	Area under the curve
BIA	Budget impact analysis
BIC	Bayesian information criterion
BICR	Blinded independent central review
BGCS	British Gynaecological Cancer Society
BMI	Body mass index
BNF	British National Formulary
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CP	Carboplatin plus paclitaxel
DCR	Disease control rate
DOR	Duration of response
DSU	Decision Support Unit
EAG	External assessment group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life scale, 5-Dimensions, 5-Levels
ESGO/ESTRO/ESP	European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology
ESMO	European Society for Medical Oncology
FDA	Food and Drugs Administration
FIGO	International Federation of Gynaecology and Obstetrics
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IA1	First interim analysis
IA2	Second interim analysis
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor

IgG4	Immunoglobulin G4
irAE	Immune-related adverse event
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LY	Life year
MAA	Managed access agreement
MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Mismatch repair
dMMR	Mismatch repair deficient
MMRp	Mismatch repair proficient
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NCRAS	National Cancer Registration and Analysis Service
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMB	Net monetary benefit
NSMP	Non-specific molecular profile
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PCC	Platinum-containing chemotherapy
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival 2
PH	Proportional hazards
POLεmut	DNA polymerase epsilon-mutated
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit

PT	Preferred term
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaires
QLQ-EN24	Endometrial Cancer Module
QoL	Quality of life
RCT	Randomised controlled trial
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
STA	Single technology appraisal
TA	Technology appraisal
TAP	Cisplatin–doxorubicin–paclitaxel
TEAE	Treatment emergent adverse events
TP53mut	TP53-mutated
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
UK	United Kingdom
US	United States
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

A patient access scheme (PAS) discount is available for dostarlimab of [redacted] and all results are reported in this document include this discount. Confidential PAS discounts are available for the subsequent treatments, lenvatinib and pembrolizumab. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

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 1.4 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 EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of dostarlimab in addition to platinum-based chemotherapy (carboplatin and paclitaxel, hereafter known as CP) for the treatment of patients with newly diagnosed advanced or recurrent EC that is mismatch repair proficient (MMRp) or microsatellite stable (MSS).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Modelling of time on treatment from cycle one onwards for both arms of the model	4.2.5.2, 4.2.5.3
2	Health-state resource use for dostarlimab + CP patients who are progression-free after the maximum three years of treatment	4.2.5.4, 4.2.5.5
3	Redistribution of bevacizumab usage amongst other subsequent treatments	4.2.6, 4.2.6.1
4	Inclusion of oral administration cost for lenvatinib	4.2.6.2, 4.2.6.3

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Use of time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data from RUBY-1 from cycle one onwards for both arms of the model.

- Health-state resource use for dostarlimab + CP patients who are progression-free after three years is equal to the health-state resource use for the CP patients who are progression-free after 18 weeks.
- Bevacizumab usage for the CP arm of the model, based on data from RUBY-1, is redistributed amongst the non-immunotherapy subsequent treatments.
- Removal of oral administration costs for lenvatinib.

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 quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Delaying disease progression.
- Increasing survival.

Overall, the technology is modelled to affect costs by:

- Its higher total cost than current treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- How the costs of subsequent treatments for the CP arm are estimated.

1.3 Summary of the EAG's key issues

Table 2 to Table 5 presents the EAG's key issues. However, the EAG notes that through the use of alternative assumptions, the EAG considers these issues to be resolved. Furthermore, none of the issues highlighted and the associated scenarios [redacted]. The EAG's preferred assumptions increase the company's base case ICER by less than [redacted]. However, these ICERs do not include the confidential PAS discounts for lenvatinib and pembrolizumab. Please see the EAG's confidential appendix to the EAG report.

Table 2. Issue 1: Modelling of time on treatment from cycle one onwards

Report section	4.2.5.2, 4.2.5.3
Description of issue and why the EAG has identified it as important	For the company base case, the company used weighted treatment completion rates for the six treatment cycles (18 weeks) of carboplatin and paclitaxel across both the dostarlimab and placebo arms observed in RUBY-1 for the MMRp/MSS subgroup of the ITT population (pooled data). Treatment completion rates for the first six treatment cycles of dostarlimab were also used. In RUBY-1, the ITT population comprised of all patients randomised even if no study treatment was received. As such, the completion rate for the first treatment cycle in the model is not 100%, as not all patients in the MMRp/MSS subgroup of the ITT population initiated treatment. The EAG considers the use of completion rates for the first six cycles of treatment in either arm for the first cycle in the model does not capture the full cost of starting treatment with CP or dostarlimab + CP.
What alternative approach has the EAG suggested?	TTD KM data for both the dostarlimab and placebo arms from RUBY-1 for the MMRp/MSS subgroup of the ITT population were available and included in the company's economic model. Based on these data, the proportion starting on treatment in each arm was 100%. In the NHS, the full cost of the first treatment cycle is likely to be incurred and as such, the EAG considers that using the TTD KM data for both CP and dostarlimab + CP, with RDI applied from cycle one for dostarlimab is more appropriate.
What is the expected effect on the cost-effectiveness estimates?	The scenario using TTD KM data for both arms of the model and dostarlimab RDI increased the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Use of TTD KM data from cycle one onwards resolves the issue.

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; MMRp, mismatch-repair proficient; MSS, microsatellite stable; TTD, Time-to-treatment discontinuation.

Table 3. Issue 2: Health-state resource use for dostarlimab + CP patients

Report section	4.2.5.5
Description of issue and why the EAG has identified it as important	The EAG's clinical experts considered that once a patient is off immunotherapy and still progression-free, there will likely be a reduction in the monitoring of the patients and so it would not be unreasonable to assume the same health-state resource use as progression-free patients in the CP arm of the model after week 18 (end of CP treatment).
What alternative approach has the EAG suggested?	The EAG suggests that it is reasonable to assume health-state resource use for the dostarlimab + CP arm of the model after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model.
What is the expected effect on the cost-effectiveness estimates?	The scenario reduced the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue.

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

Table 4. Issue 3: Redistribution of bevacizumab usage amongst other subsequent treatments

Report section	4.2.6, 4.2.6.1
Description of issue and why the EAG has identified it as important	In the company's original base case, 8.8% of dostarlimab + CP patients and 5.6% of CP patients were assumed to receive subsequent bevacizumab, based on adjusted data from RUBY-1. Bevacizumab does not have marketing authorisation for use in endometrial cancer and the EAG's clinical experts advised that it would not be used off-label in the NHS. In their updated base case, the company excluded bevacizumab from the subsequent treatment basket for each arm of the model and redistributed the usage amongst the other subsequent treatments. However, the EAG considers that the company's approach to redistribute a proportion of bevacizumab usage to the pembrolizumab and lenvatinib combination treatment (increase of 2.4%) for the CP arm is problematic as a study by Rubinstein *et al*.[1] found that the benefits of treatment with bevacizumab were modest for EC patients. As such, the EAG considers the company's approach increases subsequent treatment costs for the CP arm without similarly increasing the clinical benefit of immunotherapy.
What alternative approach has the EAG suggested?	The EAG suggests that for the CP arm, redistributing the proportion of bevacizumab use among the subsequent treatments, excluding pembrolizumab and lenvatinib, may be more appropriate. This aligns with the redistribution used for the dostarlimab + CP arm of the model. Furthermore, the EAG acknowledges that the proportion of immunotherapy use in the CP arm of the company's original base case (48.8%) was deemed reflective of UK clinical practice, based on advice received by the EAG from the NHS England CDF lead. Therefore, the EAG prefers the use of the unadjusted immunotherapy proportion in the CP arm, based on the observed RUBY-1 data.
What is the expected effect on the cost-effectiveness estimates?	The scenario resulted in an increase in the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Use of the EAG's redistribution of bevacizumab usage among the other subsequent treatments, excluding pembrolizumab and lenvatinib, resolves the issue.

Abbreviations: CP, carboplatin and paclitaxel; CDF, Cancer Drugs Fund; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

Table 5. Issue 4: Inclusion of oral administration cost for lenvatinib

Report section	4.2.6.2, 4.2.6.3
Description of issue and why the EAG has identified it as important	The company assumed an oral treatment administration cost for lenvatinib and considers that it is consistent with the previous appraisals of lenvatinib for other indications (TA498 and T858), as well as the budget impact analysis for cabozantinib in untreated renal cell carcinoma (TA964). The company also considered that use of lenvatinib requires specialist oversight in terms of procurement, prescribing, dispensing and administration. However, based on published advice for patients, the EAG considers that patients are likely to take lenvatinib at home and typically oral oncology drugs are convenient for patients because they do not need to go to hospital for treatment. As such, it is likely that no cost will be incurred to administer lenvatinib in clinical practice. Additionally, inclusion of an oral administration cost for lenvatinib is biased against the comparator, as this treatment is not included in the dostarlimab + CP subsequent treatment basket.
What alternative approach has the EAG suggested?	The EAG considers it is preferable to exclude oral administration costs for lenvatinib
What is the expected effect on the cost-effectiveness estimates?	The scenario resulted in an increase in the ICER from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	The scenario resolves the issue.

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

1.4 Other key issues: summary of the EAG's view

The EAG identified the following two clinical key issues which the EAG considers important to highlight but are currently unresolvable.

Immature overall survival data from RUBY-1

OS data from RUBY-1 are from interim analysis 2 (IA2) and as such are immature, with data maturity of only 54.8% maturity in the MMRp/MSS population. The EAG notes that RUBY-1 is expected to complete in Q3 of 2026 and that no additional interim analysis data cuts are expected. The EAG is concerned about the reliability of the OS data from RUBY-1, in particular the data beyond 30-months due to heavy censoring and the resulting extrapolations used in the company's economic model. Nevertheless, the EAG notes that there are no further data cuts available at present and thus considers these OS data to represent the most appropriate data for use in the model until more mature data become available.

The EAG considers that this issue is unresolvable until data from the final analysis of OS for RUBY-1 becomes available in Q3 2026.

[redacted] **subgroup results from RUBY-1**

The [redacted] with the dostarlimab + CP arm compared to the placebo + CP arm and thus the EAG sought clarification from the company. The EAG notes that geographic region was not a stratification factor in RUBY-1 and in the company response to CQs, baseline characteristics were provided for the Western Europe subgroup [redacted].

The company reported that [redacted].

The EAG considers this issue to be unresolvable based on the data currently available from RUBY-1.

Secondary Issues

The EAG identified some secondary issues that had minimal impact on the ICER but were considered to be more appropriate than the company's base case approach. These are as follows:

- Use of the ONS life tables from 2017-2019, as per guidance in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 23.
- Correct Band 6 nurse and GP costs sourced directly from The Unit Costs of Health and Social Care 2023 Manual.
- Unit cost of carboplatin 450 mg used instead of 600 mg for subsequent treatment cost, based on an assumed dose of 434 mg.

1.5 Summary of EAG's preferred assumptions and resulting ICER

Table 6 presents the EAG's preferred assumptions as well as the EAG deterministic and probabilistic base case ICERs.

Table 6. EAG preferred assumptions

Scenario	Incremental costs	Incremental QALYs	Cumulative ICER (change from company base case
Company base case	[redacted]	**0.75**	[redacted]
ONS life tables from 2017-2019	[redacted]	0.76	[redacted]
TTD KM data from cycle one onwards for both arms of the model	[redacted]	0.76	[redacted]
Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual	[redacted]	0.76	[redacted]
Set health-state resource use for dostarlimab + CP equal to CP after 3 years in the progression-free health state	[redacted]	0.76	[redacted]
Redistribution of bevacizumab usage across non-immunotherapy subsequent treatments	[redacted]	0.76	[redacted]
Removal of oral administration costs for lenvatinib	[redacted]	0.76	[redacted]
Unit cost of carboplatin 450 mg used for subsequent treatment cost	[redacted]	0.76	[redacted]
EAG's preferred deterministic base case - combination of all scenarios	[redacted]	**0.76**	[redacted]
EAG's preferred probabilistic base case - combination of all scenarios	[redacted]	**0.75**	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; TTD, Time-to-treatment discontinuation.

For further details of the exploratory and sensitivity analyses done by the EAG, see Sections 6.1 and 6.3.1.

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of dostarlimab (Jemperli, GlaxoSmithKline) with platinum-based chemotherapy for primary advanced or recurrent endometrial cancer (EC) with microsatellite stability or mismatch repair proficiency (MSS/MMRp).

Dostarlimab was approved by the MHRA in December 2024 for use in combination with platinum-containing chemotherapy (PCC) for the treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy. The EAG notes that prior to this, dostarlimab in combination with PCC was approved for use in only mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) tumours but the December 2024 marketing authorisation has extended to now also include patients with mismatch repair proficient/microsatellite stable (MMRp/MSS) disease.

2.2 Background

Within Section 1 of the company submission (CS), the company provides an overview of EC including:

- disease classification and staging (Section 1.3.1);
- mismatch repair (MMR) molecular classification in EC (Section 1.3.1);
- epidemiology (1.3.2); and
- burden of disease for primary advanced or recurrent EC (1.3.4).

EC originates in the lining of the womb (uterus), known as the endometrium[2] and the focus of this submission is patients with primary advanced or recurrent EC. EC is classified as primary advanced (International Federation of Gynaecology and Obstetrics [FIGO] Stage III or Stage IV), once the cancer has spread beyond the uterus, and the definition of disease recurrence is disease which cannot be detected after primary treatment with curative intent but is radiologically or histologically detected at a later point in time.[3]

EC is the most common gynaecological cancer in England with around 8,200 new cases diagnosed each year. [4] Around 20% of new cases of EC are primary advanced EC and approximately 13% of patients that are initially treated curatively will experience recurrent disease. [4-6]

EC can be classified according to the presence and absence of specific molecular features on biopsy, such as MMR status. The EAG's clinical experts agreed with the company that MMR status is one of the routine tests currently available for patients with primary advanced and recurrent EC in UK clinical practice.

In EC, tumours can be classified as either MMR deficient (dMMR) or MMR proficient (MMRp) depending on the functionality of the MMR system and approximately 75% of EC is MMRp.[6] In dMMR EC, errors during DNA replication are not properly corrected, whereas in MMRp EC, DNA repair mechanisms remain intact and so mutations are corrected.[7-10] Primary advanced or recurrent MMRp/MSS EC is often incurable and associated with a high symptom burden, aggressive disease progression, and low life expectancy.[11-13]

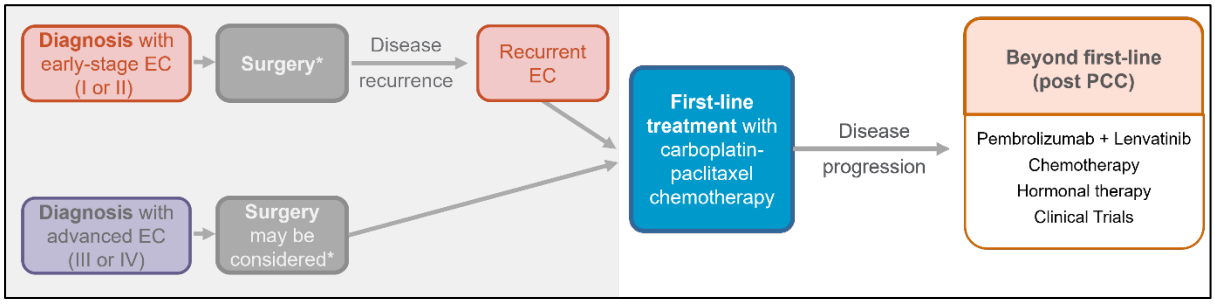
2.2.1 Current treatment pathway and positioning of new treatment(s)

The EAG notes that key clinical guidelines of relevance to UK clinical practice for the management of EC include those from the British Gynaecological Cancer Society (BGCS), European Society for Medical Oncology (ESMO), and European Society for Gynaecological Oncology/European Society for Radiation Oncology/European Society of Pathology (ESGO/ESTRO/ESP).[10, 14, 15] Figure 1 presents the company's overview of the current treatment pathway for primary advanced or recurrent EC in UK clinical practice, which the EAG's clinical experts are broadly in agreement with, although some experts reported that they would expect most Stage III patients in clinical practice to receive surgery plus radiotherapy plus chemotherapy. The EAG notes that newly diagnosed primary advanced or recurrent EC (that is unlikely to be cured by surgery alone) are usually treated via the same treatment pathway in the UK.

The company highlighted that surgery is considered the gold standard initial approach for treating and staging endometrial cancer [14, 15]. However, surgery is generally not curative in patients with primary advanced or recurrent MMRp/MSS EC but it may be performed to reduce tumour burden or alleviate symptoms.[14, 15] Following surgery, patients with recurrent or primary advanced MMRp/MSS endometrial cancer that has not been fully resected are typically treated with first-line systemic therapy (Figure 1).[14, 15] The current standard of care (SoC) in UK clinical practice for first-line systemic therapy is PCC, with the doublet chemotherapy regimen carboplatin in combination with paclitaxel (CP), and this is also recommended in the BGCS guidelines.[14, 15] The EAG's clinical experts were in

agreement with the company, that in the small number of patients where it is deemed not appropriate to use CP, carboplatin monotherapy or hormone therapy may be used as alternatives.

Figure 1. Current treatment pathway excluding dostarlimab in combination with PCC (Reproduced from CS Figure 2)

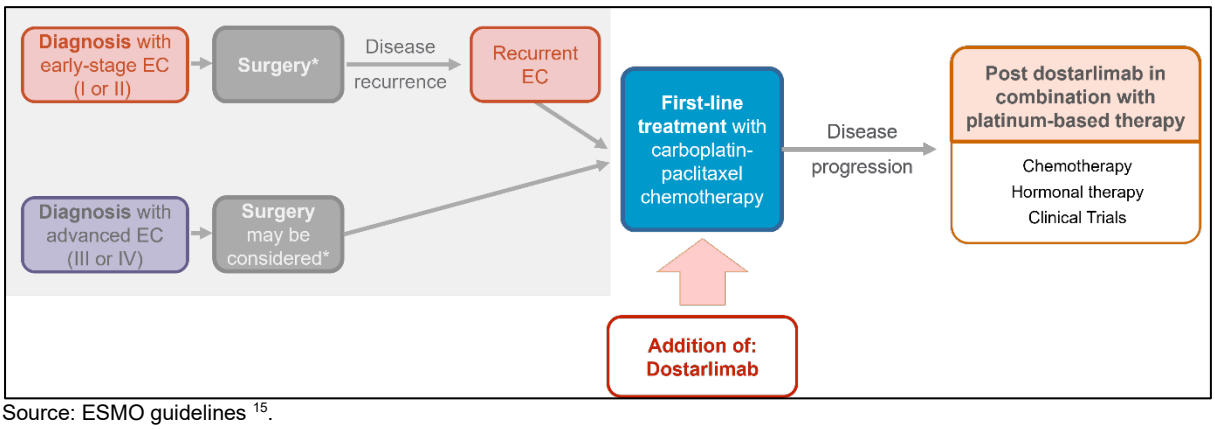


Source: ESMO guidelines, NICE TA779, TA904, and TA914[15-18].
*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery.
Abbreviations: EC, endometrial cancer; PCC, platinum-containing chemotherapy.

2.2.1.1 Positioning of dostarlimab in combination with PCC in the treatment pathway

The company's proposed positioning of dostarlimab in the treatment pathway for primary advanced or recurrent MMRp/MSS EC is outlined in Figure 2. The EAG notes that dostarlimab is expected to be used in addition to PCC and that following completion of PCC, dostarlimab is anticipated to be continued until disease progression or unacceptable toxicity or a maximum of three years of treatment.[15, 19] The EAG also notes that if patients receive dostarlimab as a first-line systemic therapy then they will not be eligible to receive the second-line immunotherapy combination treatment pembrolizumab with lenvatinib given the current funding restrictions for immunotherapies in the NHS.[20, 21]

Figure 2. Proposed treatment pathway including dostarlimab in combination with PCC (Reproduced from CS Figure 2)



Source: ESMO guidelines [15].

*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery.**As per clinical practice and NHS reimbursement, pembrolizumab, an anti-PD-1 therapy, in combination with lenvatinib is not licensed for use following treatment with an anti-PD-(L)1, such as dostarlimab, in the first-line [20, 22, 23].
Abbreviations: EC, endometrial cancer; PCC, platinum-containing chemotherapy; PD-1, programmed death protein 1; PD-(L)1, programmed death-ligand 1.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE[24], together with the rationale for any deviation from it, in Section 1.1 of the CS. This is summarised in Table 7 below and more detailed comments from the EAG are provided in the subsections that follow. Overall, the EAG considers the decision problem addressed, and the evidence used to address it, to be in line with the NICE final scope or any deviations to be reasonable given the rationale provided.

Table 7. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with primary advanced or recurrent endometrial cancer with MMRp/MSS tumours who are candidates for systemic treatment.	As per scope	N/A	The EAG notes that the relevant marketing authorisation is for a broader population (adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy) than that under consideration in this health technology appraisal (people with primary advanced or recurrent EC with MMRp/MSS tumours who are candidates for systemic treatment). However, the EAG considers the population covered in the company submission to reflect that detailed in the NICE final scope. The EAG notes that the MMRp/MSS data from RUBY-1 comprise a subgroup of the overall trial population and, although it was a stratification factor, the trial was not statistically powered for the subgroup. The EAG also notes that the proportion of newly diagnosed primary advanced EC patients with FIGO Stage III disease at diagnosis who were enrolled in the RUBY-1 trial was low compared to the proportion of patients with Stage IV disease (See Section 2.3.1 for further details).

Intervention	Dostarlimab with PCC followed by dostarlimab maintenance.	As per scope	N/A	Aligned with the marketing authorisation for dostarlimab in people with primary advanced or recurrent EC with MMRp/MSS tumours who are candidates for systemic treatment and the clinical trial data from RUBY-1. Further details are provided in CS Section 1.3.6 and Section 2.3.2 below.
Comparator(s)	• Platinum-based chemotherapy (such as paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide) followed by routine surveillance • Hormone therapy (such as medroxyprogesterone acetate and megestrol) followed by routine surveillance • Durvalumab with platinum-based chemotherapy, followed by durvalumab with or without olaparib maintenance (subject to NICE appraisal) • Pembrolizumab with platinum-based chemotherapy, followed by pembrolizumab maintenance (subject to NICE appraisal)	Platinum-containing chemotherapy	GSK do not believe the comparators outlined in the NICE decision problem—hormone therapy, durvalumab in combination with PCC followed by durvalumab with or without olaparib maintenance, and pembrolizumab in combination with PCC followed by pembrolizumab maintenance — are relevant comparators. Hormone therapy is not an alternative treatment in patients eligible for dostarlimab, and durvalumab and pembrolizumab-based regimens are not currently available through routine commissioning within the NHS, and therefore not established standards of care. See CS Section 1.3.4.4 for details.	The EAG's clinical experts agree with the company that the primary comparator of relevance is platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and note this was a comparator in the NICE final scope and the RUBY-1 trial. The EAG's clinical experts also agree with the company that hormone therapy is used in only a small proportion of patients and these patients generally would not be considered suitable for chemotherapy. Based on clinical expert opinion, the EAG considers the company's omission of hormone therapy on the basis it is deemed not a relevant comparator to be reasonable. In addition, the EAG notes that the durvalumab and pembrolizumab treatments listed in the NICE final scope are still subject to ongoing NICE appraisal.

				See Section 2.3.3 for further details.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality-of-life.	As per scope, with the addition of PFS2	PFS2 is an additional secondary efficacy outcome evaluated in the RUBY trial.	All outcomes specified in the NICE final scope were captured in the RUBY-1 trial and reported in the CS. The EAG notes that the data on AEs that were used in the model for the company base case are from the overall safety population rather than the relevant MMRp/MSS subgroup from RUBY-1. However, based on expert opinion the EAG does not consider this to be unreasonable. The EAG is concerned about the reliability of the OS data from RUBY-1 due to its immaturity and notes that the data used in the CS are from interim analysis 2 (IA2), where maturity was only 54.8%. The company reported that RUBY-1 is expected to complete in Q3 2026, and no further interim analyses are planned. See Section 2.3.4 for further details.
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	As per scope	N/A	The economic analysis adheres to the reference case and reflects the final scope.

	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.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Local vs metastatic recurrence • People who have had primary debulking surgery vs those who have not had surgery • Molecular subgroups (such as NSMP, POLε and p53abn).	• Molecular subgroups (POLεmut, TP53mut and NSMP) as per scope. GSK does not believe the subgroups local vs metastatic recurrence and people who had primary debulking surgery vs those who have not had surgery are appropriate for consideration as part of the appraisal.	**Local versus metastatic recurrence**: Within the pivotal RUBY trial which evaluated dostarlimab within the proposed indication, recurrence was captured as a 'yes/no' binary variable and the location of recurrence was not recorded. Subgroup analysis has been performed on patients with recurrent disease but, within this subgroup, further analysis based on the location of the recurrence is not feasible. In addition, guidelines recommend CP for first-line treatment regardless of recurrence location. Therefore, GSK does not believe it is informative for subgroups based on local or metastatic recurrence to be	The EAG notes that the focus of the CS is on the MMRp/MSS subgroup of the RUBY-1 trial and that the company provided results for the molecular subgroups from the overall trial population rather than in the MMRp/MSS subgroup (please see Section 3.3.6.3 for further details). The EAG notes that subgroup data for local vs metastatic recurrence and primary debulking surgery vs no surgery were not reported in the CS for the reasons outlined by the company. The EAG also notes that they were not pre-planned subgroups in RUBY-1.

			considered as part of this technology appraisal. **People who had primary debulking surgery vs people who have not**: GSK does not believe this to be a subgroup of relevance. All patients typically undergo surgery to debulk primary advanced endometrial cancer unless the patient is insufficiently fit. The RUBY trial recruited patients regardless of prior surgical status, however the majority had undergone prior surgery for MMRp endometrial cancer ([redacted]). The small number of patients not receiving surgery would likely prevent any meaningful conclusions from being drawn from a subgroup analysis. Furthermore, it is also unlikely to be feasible to carry out this analysis given how information relating to surgery was collected as part of the RUBY trial. Within the clinical study report, prior anti-cancer surgery for endometrial cancer is captured as a binary 'yes/no' variable and therefore the type and/or	

			outcome of surgery is not readily available.	
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 treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	MHRA marketing authorisation was received on December 13th, 2024, for the following indication: Jemperli is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy.	N/A	N/A

Abbreviations: BGCS, British Gynaecological Cancer Society; CP, carboplatin and paclitaxel; FDA, Food and Drugs Administration; EAG, External Assessment Group; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; MMR, mismatch repair; MMRp, mismatch repair proficient; MSS, microsatellite stability; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSMP: Non-specific molecular profile; PCC; platinum-containing chemotherapy; PFS2, progression-free survival 2; POLε: DNA polymerase epsilon; SmPC, summary of product characteristics; p53abn: TP53mutation.

2.3.1 Population

The population specified in the NICE final scope was people with primary advanced or recurrent EC with MMRp/MSS tumours who are candidates for systemic treatment. The EAG notes that the population enrolled in the RUBY-1 trial, which informs the clinical effectiveness data for dostarlimab in combination with PCC in the company submission (CS), comprised of patients with primary Stage III or Stage IV EC or first recurrent EC that was deemed to have a low potential for cure by radiation therapy or surgery alone or in combination. The overall intention-to-treat (ITT) population in RUBY-1 (N=494) comprised a broader patient population than the MMRp/MSS population (n=376), which is the population under consideration in this single technology appraisal. The EAG considers that the company has submitted data from the appropriate subgroup of RUBY-1 to address the decision problem in the NICE final scope and notes that this subgroup represents the majority of patients enrolled in the RUBY-1 trial (76.1% of the ITT population). In addition, the EAG notes that MMR status was a stratification factor for randomisation in RUBY-1, although the trial was not powered to demonstrate statistical significance within the MMRp/MSS subgroup.

In response to a clarification question, the company stated that in the MMRp/MSS population [redacted]. The EAG's clinical experts reported that the baseline characteristics for the MMRp/MSS subgroup of RUBY-1 suggested the population was [redacted] compared with patients in UK clinical practice (Appendix 8.1). However, they also noted that [redacted], and they did not anticipate the differences in baseline characteristics in RUBY-1 compared with the expected UK patient population to be clinically meaningful treatment effect modifiers.

In the company's economic model, baseline characteristics are based on the MMRp/ MSS subgroup of RUBY-1 (see Section 3.2 for more details of the trial). Table 8 presents the baseline characteristics included in the economic model.

Table 8. Patient baseline characteristics included in the model – RUBY-1 (reproduced from Table 20 of the CS)

Parameter	Value
Mean age (years)	[redacted]
Mean weight (kg)	[redacted]
Mean body surface area (m2)	[redacted]
Glomerular Filtration Rate (ml/min)	[redacted]

Abbreviations: CS, company submission

In summary, the EAG notes that the MMRp/MSS population of interest is a subgroup of the RUBY-1 trial and the EAG considers the population in the NICE final scope to have been addressed appropriately based on the marketing authorisation for dostarlimab in EC.

2.3.2 Intervention

The intervention specified in the NICE final scope was dostarlimab with platinum-based chemotherapy followed by dostarlimab maintenance and this reflects the intervention in both the CS and the RUBY-1 trial. Dostarlimab is an anti-PD-1 therapy which works by blockade of the binding of PD-1 with its ligands, thus preventing immune evasion by the tumour and boosting the anti-tumour immune response.[25]

Dostarlimab (Jemperli) received an extension to its marketing authorisation from the MHRA on 13 December 2024 for use in combination with platinum-containing chemotherapy for treating primary advanced or recurrent EC to include patients with MMRp/MSS disease in addition to those with dMMR/MSI-H. Dostarlimab is approved by the MHRA for use in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. The recommended dosage of dostarlimab is 500 mg intravenously (IV) every 3 weeks for 6 cycles followed by 1000 mg every 6 weeks for all cycles thereafter. Administration of dostarlimab is recommended to continue until disease progression or unacceptable toxicity, or for a maximum duration of up to 3 years.

Based on the advice of its clinical experts, the EAG considers the use of dostarlimab in combination with carboplatin + paclitaxel (CP) in the economic model (dostarlimab + CP) to reflect the expected dosages in UK clinical practice. [redacted]. The EAG notes that TTD was capped at 3-years in the economic model to reflect the treatment-stopping rule in the marketing authorisation for dostarlimab, [redacted].

The EAG notes that there is no requirement for MMR testing prior to commencement of dostarlimab but the EAG's clinical experts report that it is part of the routine management of patients with newly diagnosed primary advanced or recurrent EC.

In addition, the EAG notes that the subsequent treatments used in RUBY-1 are not wholly reflective of UK clinical practice and therefore the results for OS in particular may not accurately reflect outcomes in the UK. The usage of immunotherapies (e.g. pembrolizumab) as subsequent treatments in the dostarlimab + CP trial arm was allowed in RUBY-1, but the EAG notes from NHS England that immunotherapies are not a treatment option in UK NHS clinical practice following dostarlimab treatment. In addition, a representative from NHS England advised the EAG that the biological plausibility that patients who have relapsed on immunotherapy would benefit from further immunotherapy is extremely weak. The EAG considers the impact of subsequent treatment with immunotherapies in the dostarlimab + CP trial arm of RUBY-1 to be uncertain. The EAG's clinical experts also reported that bevacizumab is not used in EC in UK clinical practice, whereas it was a subsequent treatment used by a small proportion (<5%) of patients in both arms of RUBY-1. Subsequent treatments in RUBY-1 are summarised and discussed further in Section 3.2.

In summary, the EAG considers the treatment regimen for dostarlimab in the economic model aligns with the MHRA marketing authorisation [redacted].

2.3.3 Comparators

The NICE final scope lists platinum-based chemotherapy (paclitaxel + carboplatin [CP]) followed by routine surveillance and hormone therapy followed by routine surveillance as comparators of interest. The EAG's clinical experts agree with the company that the primary comparator of relevance is platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and note this reflects the comparator arm in the RUBY-1 trial. In RUBY-1 the treatment regimen for platinum-based chemotherapy was carboplatin AUC, 5 mg/mL/min and paclitaxel 175 mg/m^2 intravenously every three weeks for six cycles and this has been included in the economic model. The EAG's clinical experts reported this is consistent with UK clinical practice.

The EAG's clinical experts agree with the company that hormone therapy is used in only a small proportion of primary advanced or recurrent EC patients, and the patients likely to receive first-line hormone therapy are unlikely to be considered suitable for dostarlimab + CP. The EAG, therefore,

considers the company's decision that hormone therapy is not a relevant comparator to be reasonable.

The EAG is concerned that the subsequent treatments used in RUBY-1 are not wholly reflective of UK clinical practice with some of the EAG's clinical experts reporting that the immunotherapy usage at second-line in MMRp/MSS CP patients may differ slightly in UK clinical practice compared to in RUBY-1. However, estimates from NHS England suggest that immunotherapy usage in the placebo in combination with CP arm of RUBY-1 are reasonably well aligned with current UK NHS clinical practice. Additionally, the EAG's clinical experts reported that bevacizumab is not used in EC in UK clinical practice whereas it was a subsequent treatment used by a small proportion (<5%) of patients in both arms of RUBY-1. Subsequent therapies are discussed in more detail in Sections 3.2 and 4.2.6.

Finally, the EAG notes that durvalumab with platinum-based chemotherapy followed by durvalumab with or without olaparib maintenance (subject to NICE appraisal) and pembrolizumab with platinum-based chemotherapy followed by pembrolizumab maintenance (subject to NICE appraisal) were included as comparators in the NICE final scope. However, the EAG notes that at the time of writing these are still undergoing appraisal by NICE and therefore the EAG is in agreement with the company that they are not relevant comparators at present.[14, 26, 27]

In summary, the EAG agrees with the company that the primary comparator of relevance is platinum-based chemotherapy (PCC) followed by routine surveillance and notes this was a comparator in the NICE final scope and the RUBY-1 trial.

2.3.4 Outcomes

The outcomes specified in the NICE final scope are:

- progression-free survival (PFS);
- overall survival (OS);
- response rates;
- duration of response;
- adverse effects (AEs) of treatment; and
- health-related quality of life (HRQoL).

The EAG notes that data for all of the outcomes specified in the NICE final scope are available for the MMRp/MSS trial population in RUBY-1, and that only data on PFS, OS, HRQoL and AEs are used in

the economic model. The economic model focuses on data from the MMRp/MSS patient population with the exception of AE data which is from the overall trial safety population in the base case. However, AE data for the MMRp/MSS subgroup are presented in the CS appendix D in addition to the overall trial safety population data provided in the CS.

The RUBY-1 trial had two primary endpoints: OS and PFS as assessed by the investigator per RECIST v1.1, and these were statistically powered for the overall population. However, the RUBY-1 study population was stratified by MMR status, and all efficacy outcomes were reported for the MMRp/MSS population albeit some were specified following protocol amendments or defined *post hoc*. The EAG notes that data from RUBY-1 in the CS are reported using one of two interim analyses: interim analysis 1 (IA1; 28 September 2022), and interim analysis 2 (IA2; 22 September 2023). Data for OS, PFS2, and AEs in the CS were from IA2 and the remaining outcomes were based on the IA1 data-cut. In response to clarification questions, the company also provided the results from IA2 for PFS and these are discussed in Section 3.3.1.

Investigator-assessed PFS was one of the primary efficacy endpoints in RUBY-1 and is used to inform PFS in the economic model with blinded independent central review (BICR) PFS included in RUBY-1 as a secondary outcome. The EAG considers the use of investigator-assessed PFS in the economic model to be reasonable, as the trial incorporated a double-blind design for treatments. The trial results for BICR PFS were also provided by the company in the CS appendices for the MMRp/MSS subgroup.

OS data from RUBY-1 are from IA2 and as such are immature with data maturity of only 54.8% maturity in the MMRp/MSS population.[28] The EAG notes that RUBY-1 is expected to complete in Q3 of 2026 and that no additional interim analysis data cuts are expected. The EAG is concerned about the reliability of the OS data from RUBY-1, in particular the data beyond 30-months due to heavy censoring and the resulting extrapolations used in the company's economic model (**Other key issues in Section 1.4**). Nevertheless, the EAG notes that there are no further data-cuts available at present and thus considers these OS data to represent the most appropriate data for use in the model until more mature data become available. Further discussion on the OS results and the modelling of OS are provided in Sections 3.3.2 and 4.2.3.5.

HRQoL was captured in RUBY-1 using EORTC QLQ-C30, QLQ-EN24 and EQ-5D-5L, with the EQ-5D-5L data mapped to EQ-5D-3L for use in the economic model. The results for the EORTC QLQ-C30 global

score and EQ-5D-5L VAS score were provided in the CS and additional HRQoL data provided in response to clarification questions. The results of the HRQoL assessments are discussed further in Section 3.3.5.

Adverse events used in the economic model for the company base case were any AEs of grade ≥3 occurring in ≥2% of patients in at least one of the treatment arms of the RUBY-1 trial with data sourced from the overall trial safety population. The EAG's clinical experts do not consider the occurrence of AEs likely to be related to MMR status and therefore the EAG considers the company's use of the overall safety population for AEs in the model to be reasonable. The EAG notes that the company also provided the AE data for the MMRp/MSS subgroup in CS appendix D, and this is discussed further in Section 3.2.

Additionally, the EAG notes that data from IA2 of RUBY-1 on time to treatment discontinuation (TTD) were also included in the company's economic model. The company also provided results for progression-free survival 2 (PFS2) from IA2 in the CS, although the EAG notes that this was not an outcome specified in the NICE final scope. PFS2 was defined as the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever is earlier. In addition, in response to clarification questions, the company provided PFS2 results for the subgroup of patients who received subsequent therapies. The results for PFS2 are discussed in Section 3.3.3.

In summary, the EAG considers data for all relevant outcomes from the NICE final scope are available from RUBY-1. However, the EAG is concerned about the uncertainty of the data for OS due to its immaturity and the potential differences in subsequent treatments between the trial and UK clinical practice.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR) to identify randomised clinical trials (RCT) evidence reporting on the efficacy and safety of dostarlimab in combination with carboplatin and paclitaxel (CP) and other relevant treatments for primary advanced or recurrent endometrial cancer (EC). The company's SLR was conducted on 10 November 2021 and updated on several occasions up to 16 May 2024 (updates on 22 February 2023, 8 August 2023, 26 October 2023 and 16 May 2024).

In total, the SLR and its updates resulted in the identification of 126 studies that met the inclusion criteria and these related to 60 unique studies. The 60 studies comprised of 51 trials of first-line induction and/or maintenance therapies and 9 trials of adjuvant therapies. One RCT was identified that directly addressed the comparison of interest and investigated the safety and efficacy of dostarlimab + CP versus placebo + CP in patients with primary advanced or recurrent EC: part 1 of the RUBY trial (RUBY-1).[29] This trial was the focus of the company submission (CS) and is discussed further in the sections that follow. The remaining included studies were not used to inform the efficacy or safety data presented in the CS and therefore are not discussed in this report.

Appendix 8.3 provides a summary and the External Assessment Group's (EAG's) critique of the company's SLR. In summary, the EAG considers the methods utilised by the company to be appropriate and that it is unlikely any relevant head-to-head studies have been omitted.

3.2 Critique of the RUBY-1 trial

The RUBY-1 trial (ClinicalTrials.gov number: NCT03981796)[30] was the only study identified in the company's SLR and included in the company submission (CS) to provide evidence on the clinical efficacy and safety of dostarlimab + CP compared with placebo + CP for patients with newly diagnosed primary advanced or recurrent mismatch repair proficient/microsatellite stable (MMRp/MSS) EC.

RUBY-1 is an ongoing Phase III randomised, multicentre, double-blind RCT that enrolled adult female patients with primary Stage III or Stage IV EC or first recurrent EC, with a low potential for cure by radiation therapy or surgery alone or in combination. RUBY-1 was conducted at trial sites across 19

countries worldwide, [redacted] patients in the MMRp/MSS subgroup were enrolled from the UK.

The interventions in RUBY-1 were as follows:

- Dostarlimab 500 mg intravenously (IV) in combination with carboplatin IV AUC 5 mg/ml/min) plus paclitaxel IV (175 mg/m^2) every 3 weeks (Q3W) for six cycles (cycles 1–6), followed by dostarlimab 1,000 mg IV every 6 weeks (Q6W) for cycle 7 onwards (dostarlimab + CP [N=245 ITT; n=192 MMRp/MSS]);
- Placebo IV in combination with carboplatin IV AUC 5 mg/ml/min) plus paclitaxel IV (175 mg/m^2) Q3W for six cycles (cycles 1–6), followed by placebo IV Q6W for cycle 7 onwards (placebo + CP [N=249 ITT; n=184 MMRp/MSS]).

Treatment with dostarlimab was continued until progression of disease or unacceptable toxicity, up to a maximum of 3 years. [redacted]. The EAG notes that TTD was capped at 3-years in the economic model to reflect the treatment-stopping rule in the marketing authorisation for dostarlimab, [redacted].

The EAG notes that randomisation in RUBY-1 was stratified by MMR status. The relevant clinical efficacy data for the MMRp/MSS population of interest is thus limited to subgroup data from RUBY-1, although the AE data used in the company's economic model are from the overall trial safety population. The EAG's critique of the RUBY-1 trial is summarised in Table 10 and the focus of the results discussed in this report are on the MMRp/MSS patient population subgroup of relevance to this appraisal with the exception of AEs.

The EAG considers the immaturity of the OS data from RUBY-1 presented in the CS to be an area of concern; it is noted that at the time of writing, data reported in the CS relate to the second interim analysis. The EAG notes that RUBY-1 is an ongoing study that is expected to complete in Q3 2026, with no further interim analysis data cuts expected prior to study completion (**Other key issues in Section 1.4**).

A further area of concern with regards to RUBY-1 is the subsequent treatment usage not reflecting UK clinical practice. In particular, the EAG is concerned about the usage of immunotherapies as subsequent treatments across both trial arms based on feedback from clinical experts. The usage of immunotherapies (e.g. pembrolizumab) as subsequent treatments in the dostarlimab + CP trial arm was allowed in RUBY-1, but NHS England reported that it is not a treatment option in UK NHS clinical practice following dostarlimab treatment. In addition, some of the EAG's clinical experts reported that immunotherapy usage at second-line in MMRp/MSS CP patients may differ slightly in UK clinical practice compared with RUBY-1. However, estimates from NHS England suggest that immunotherapy usage in the placebo + CP arm of RUBY-1 are reasonably well aligned with current UK NHS clinical practice. The EAG's clinical experts also reported that bevacizumab is not used in EC in UK clinical practice whereas it was a subsequent treatment used by a small proportion (<5%) of patients in both arms of RUBY-1.

The EAG notes that the subsequent treatment data from RUBY-1 that were used in the economic model were from IA1 and that they were calculated as a proportion of the patients who had progressed as subsequent therapies' costs are accrued only by those entering the progressed disease (PD) health state. While the EAG considers it appropriate to use the subsequent treatment data that aligns with the PFS data-cut, the EAG is unclear why the later IA2 data-cut was not used for both PFS and subsequent treatments to align with the OS data from RUBY-1 used in the economic model.

The IA1 subsequent treatments data from RUBY-1 that were used to inform subsequent treatments in the company economic model are summarised in

Table 9 and discussed further in Section 4.2.6. The EAG notes that at IA1, [redacted]. At the time of the IA2 data-cut, [redacted] had received a subsequent anti-cancer therapy (CS Table 15). The EAG considers the impact of [redacted].

Table 9. RUBY-1 IA1 subsequent treatment data in the MMRp/MSS population (Reproduced from CS Table 82)

	Dostarlimab in combination with CP (N=192) (n)	CP (N=184) (n)	Dostarlimab in combination with CP (%)[a]	CP (%)[a]
IA1 progression events	[redacted]	[redacted]	NA	NA
Subsequent treatment (IA1)	[redacted]	[redacted]	92%	100%
No subsequent treatment	[redacted]	[redacted]	8%	0%
Systemic anti-cancer therapy	[redacted]	[redacted]	83%	92%
Immunotherapy	[redacted]	[redacted]	28%	49%
Chemotherapy	[redacted]	[redacted]	55%	43%
Doxorubicin	[redacted]	[redacted]	12%	10%
CP	[redacted]	[redacted]	8%	10%
PLD (doxorubicin)	[redacted]	[redacted]	8%	10%
Paclitaxel	[redacted]	[redacted]	4%	2%
Carboplatin	[redacted]	[redacted]	4%	2%
Cisplatin	[redacted]	[redacted]	2%	2%
Carboplatin/doxorubicin	[redacted]	[redacted]	3%	1%
Hormone therapy	[redacted]	[redacted]	15%	14%
Radiotherapy	[redacted]	[redacted]	21%	14%
Bevacizumab	[redacted]	[redacted]	6%	6%
Total	[redacted]	[redacted]	-	-

[a] Percentages are reported as a percentage of patients with IA1 progression events.

Abbreviations: CP, Carboplatin and paclitaxel; PLD, pegylated liposomal doxorubicin.
Source: CSR, Table 14.1.1.32.

Table 10. EAG's summary of the design, conduct and analysis of RUBY-1

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 2.3.1 and Appendix B.3	**Appropriate** Patients were randomised 1:1 to each of the two study arms with randomisation stratified by MMR/MSI status (proficient vs deficient), disease status (recurrent, primary Stage III, or primary Stage IV), and prior external pelvic radiotherapy (yes or no).
Concealment of treatment allocation	Appendix B.3	**Appropriate** Randomisation was performed in a 1:1 blinded manner using an interactive Web response system (IWRS).

Eligibility criteria	Section 2.2	**Appropriate** The EAG's clinical experts generally considered the RUBY-1 trial inclusion and exclusion criteria to be reasonable but the EAG notes that the MMRp/MSS population of interest for this appraisal is a subgroup of the trial.
Blinding	Section 2.2 and Appendix B.3	**Likely to be appropriate** The study was double-blind and utilised an IWRS to assign treatments with matching placebo dostarlimab given to the control arm. The participant, investigator, study staff, the sponsor study team, and its representatives were blinded to the assigned treatment from the time of randomization until database lock. It is noted that treatment assignment could be unblinded by the investigator for urgent or non-urgent clinical reasons as detailed in the protocol.
Baseline characteristics	Section 2.3.5 and Appendix C.1.2	**No major concerns although it is noted that there are potentially some discrepancies compared to the UK population.** Baseline characteristics were reasonably well balanced between trial arms in the MMRp/MSS population. The EAG's clinical experts considered the population of the trial potentially comprised of [redacted] compared to UK clinical practice (see Appendix 8.1 for the baseline characteristics for the MMRp/MSS population of RUBY-1). It is also noted that [redacted] the trial was not stratified based on geographic region. The Western Europe subgroup is discussed in more detail in Sections 3.3.6.1 and 3.3.6.2.
Dropouts	Section 2.3.6	[redacted] The EAG notes [redacted]
Statistical analysis		
Sample size and power	Section 2.4	**Appears appropriate for the ITT population** The sample size calculations for the RUBY trial were based on the primary efficacy endpoint of PFS (investigator-assessed using RECIST v1.1). A one-sided alpha of 0.02 was initially allocated to hypotheses regarding IA PFS and an alpha level of 0.005 was initially allocated to hypotheses regarding OS. For IA PFS, hypotheses were hierarchically tested in the dMMR–MSI-H population and then in the overall population; OS was tested in the overall population. If the null hypotheses for IA PFS were all rejected, the 0.02 alpha level would be recycled to the hypothesis of OS,

		which would be tested at a one-sided alpha level of 0.025; otherwise, OS would be tested only at the initially allocated one-sided alpha level of 0.005. The power was approximately 89% for testing of hypothesis 1 with a total sample size of 470 patients planned, and approximately 352 patients were expected to be MMRp/MSS. This is because to maintain the natural distribution of MMRp/MSS (75%) and dMMR/MSI-H (25%) in the overall population, the number of participants enrolled with MMRp/MSS or dMMR/MSI-H endometrial cancer was capped at approximately 350 and 120, respectively. In addition, the total number of patients with carcinosarcoma was capped at 50 (approximately 10%) to prevent overrepresentation of this patient population. The EAG notes that the sample size and power calculation are for the ITT population in RUBY-1 and the population of interest to this appraisal is the MMRp/MSS subgroup.
Handling of missing data	Section 2.4	**Appears reasonable** No methods were reported to account for missing data, but efficacy analyses were conducted using the ITT population.
Outcome assessment	Section 2.4	**Appropriate although the relevant MMRp/MSS population is a subgroup of RUBY-1 and the data for OS are immature. In addition, some outcome data are reported in the CS using IA1 data-cut rather than IA2** The EAG considers the outcomes assessed to be appropriate and to have used appropriate methods/questionnaires. The ITT population was used for efficacy analyses, and included all randomised patients (N=494), regardless of treatment received, with 372 patients stratified as MMRp/MSS. The prespecified MMRp/MSS subgroup was determined by source-verified MMR/MSI status and comprised of 192 patients in the dostarlimab + CP arm and 184 in the placebo + CP arm. For the dual-primary efficacy endpoint, PFS (investigator-assessed), the distribution was estimated using the KM method, stratified by MMR/MSI status (dMMR/MSI-H or MMRp/MSS), prior pelvic radiotherapy, and disease status (recurrent, Stage III, or Stage IV). A stratified Cox regression model estimated the PFS hazard ratio (HR) and confidence interval for hypothesis testing. Results reported in the CS are from the IA1 and IA2 data-cuts, with data from IA2 not available for all outcomes. In addition, data for the final analysis of OS are not yet available.

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission; EAG, External Assessment Group; MMR, mismatch repair; IA, interim analysis; ITT, intention-to-treat; dMMR, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stability; OS, overall survival; PFS, progression-free survival

3.3 Critique of the clinical effectiveness analysis and interpretation RUBY-1

The EAG presents the results for the key endpoints of relevance to the decision problem included in the economic model (OS, PFS and HRQoL), focusing on the MMRp/MSS subgroup of RUBY-1. Results

for the ITT population are available in the CS and its appendices. In addition, the results for objective response rate and PFS2 are discussed below with the results for duration of response and other secondary endpoints available in the CS. The only results for the overall trial population that are presented in this report are AEs because they are used in the economic model. Results from the subgroup analyses within the MMRp/MSS population and the molecular subgroup analyses for the overall trial population are also presented below (Section 3.3.6).

The RUBY-1 trial was not powered to specifically test the null hypothesis for PFS and OS within the MMRp/MSS population. As such, the EAG notes that Nominal p-values were used within the company submission to indicate p-values that were derived from analyses of the MMRp/MSS population that have not been subject to formal statistical hypothesis testing.

In the MMRp/MSS population, the median duration of follow-up was [redacted] at the time of the IA1 data cut and 37.5 months at IA2. The EAG notes that the median duration of follow-up at IA2 in the MMRp/MSS population was similar between the dostarlimab + CP arm and the placebo + CP arm at [redacted] and [redacted], respectively.[31]

3.3.1 Investigator-assessed progression-free survival

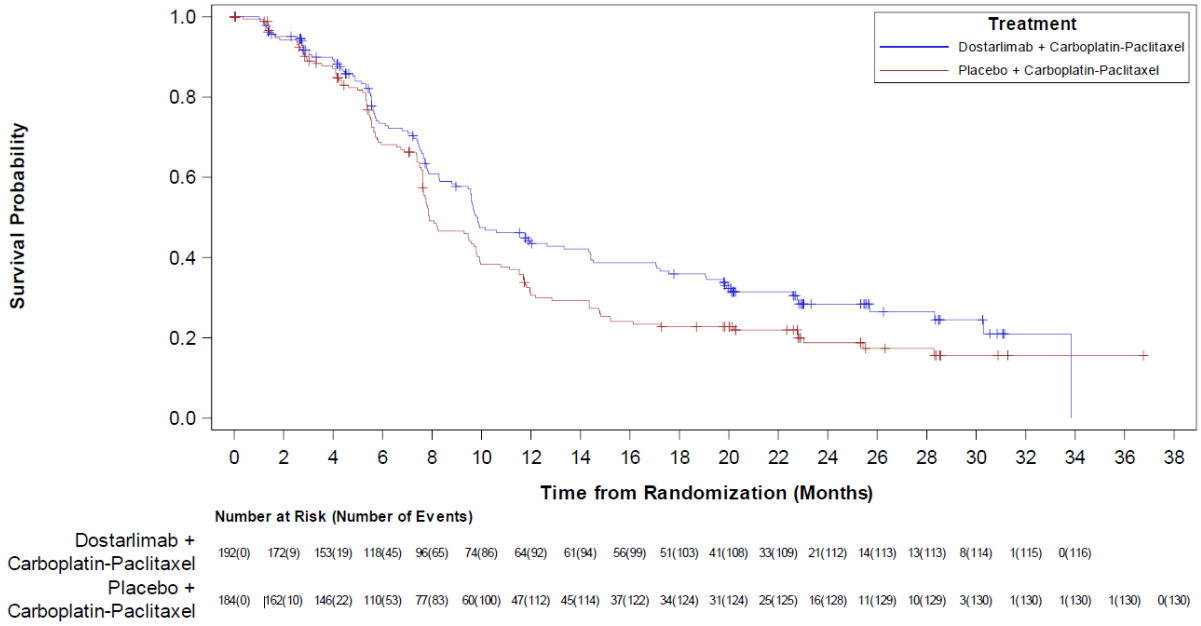
The company reported the results of PFS using IA1 in the CS and used these data in the economic model although in the company response to clarification questions results for investigator-assessed PFS from IA2 were also provided. Figure 3 shows the KM analysis of PFS in the MMRp/MSS population at IA1 and Figure 4 shows PFS at IA2. The EAG notes from the company response to clarification questions Figure 11 that the KM curves [redacted]

The results from IA1 were that dostarlimab in combination with CP reduced the risk of progression or death by 24% compared with CP (HR: 0.76, 95% CI: 0.59 to 0.98, nominal p-value = 0.0177; Figure 3).[29] The HR for PFS from IA2 [redacted] [Figure 4 and Table 12]). [redacted] (Table 11 and Table 12).

The EAG notes that a sensitivity analysis using BICR assessment instead of investigator assessment for PFS was provided in CS Appendix J. The results for BICR assessed PFS were broadly consistent

with the investigator-assessed PFS results, [redacted].

Figure 3. KM curves of IA1 PFS in the MMRp/MSS patient population (Reproduced from CS Figure 5)



Source: IA1 CSR Figure 15.1.1. [32].
Data cut off: 28 September 2022.
Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

Table 11. KM analysis of IA1 PFS in the MMRp/MSS patient population (Reproduced from CS Table 11)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS, months (95% CI)	9.9 (9.0 to 13.3)	7.9 (7.6 to 9.8)
PFS probability (95% CI)		
Month 12	43.5% (35.7% to 51.0%)	30.6% (23.6% to 37.8%)
Month 24	28.4% (21.2% to 36.0%)	18.8% (12.8% to 25.7%)
Hazard ratio (95% CI)	0.76 (0.592 to 0.981)	
Nominal p-value of 1-sided stratified log-rank test	0.0177	

Source: IA1 CSR Table 14.2.1.1 [32].
Data cutoff: 28 September 2022
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

Figure 4. KM curves of IA2 PFS in the MMRp/MSS population (Reproduced from company response to CQs Figure 3)

Data cut off: 22 September 2023.
Abbreviations: IA2, second interim analysis KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-free survival.

Table 12. KM analysis of IA2 PFS in the MMRp/MSS population (Adapted from company response to CQs Table 15)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS, months (95% CI)	[redacted]	[redacted]
PFS status [n (%)]		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
PFS probability (95% CI)		
Month 12	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Month 36	[redacted]	[redacted]
Hazard ratio[b] (95% CI)	[redacted]	

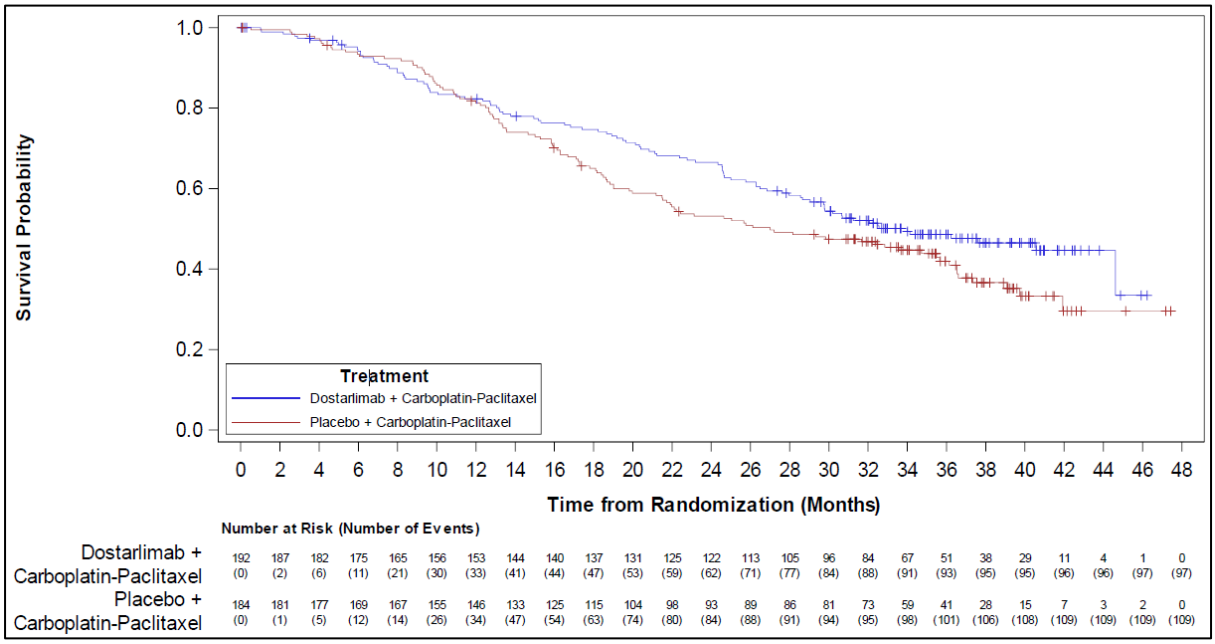
[a] 95% confidence intervals generated using the method of Brookmeyer and Crowley (1982).
[b] Stratified Cox Regression.
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS, progression-fee survival.

3.3.2 *Investigator-assessed overall survival*

The results for OS in the MMRp/MSS population reported in the CS and used in the company's economic model were from IA2 (Figure 5 and Table 13), which differs to the data-cut used for PFS in the economic model (IA1).

In summary, dostarlimab in combination with CP reduced the risk of death by 21% compared with CP alone based on the data from IA2 (HR:0.79, 95% CI: 0.602 to 1.044; nominal p=0.0493).[29] Median OS for the dostarlimab + CP arm was 34.0 months (95% CI: 28.6 to Not Estimable) vs 27.0 months (95% CI: 21.5 to 35.6) for the placebo + CP arm, corresponding to an improvement in median OS of 7 months with dostarlimab (Table 13). The EAG considers there to be heavy censoring in the KM curves for the analysis of OS beyond approximately 30 months and therefore the EAG considers the results for OS beyond this timepoint to be associated with increasing uncertainty and should be interpreted with caution.

Figure 5. KM curves of IA2 OS in the MMRp/MSS patient population (Reproduced from CS Figure 6)



Source: IA2 CSR Figure 15.1.8.[31]
Data cutoff: 22 September 2023.
Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; OS, overall survival.

Table 13. KM analysis of IA2 OS in the MMRp/MSS patient population (Reproduced from CS Table 12)

Category subcategory	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median OS, months (95% CI)	34.0 (28.6 to NE)	27.0 (21.5 to 35.6)
OS probability (95% CI)		
Month 12	82.3% (76.0% to 87.1%)	81.2% (74.7% to 86.2%)
Month 24	66.5% (59.2% to 72.8%)	53.2% (45.6% to 60.2%)
Month 36	48.6% (41.0% to 55.7%)	41.9% (34.3% to 49.4%)
Hazard ratio (95% CI)	0.79 (0.602 to 1.044)	
Nominal p-value of 1-sided stratified log-rank test	0.0493	

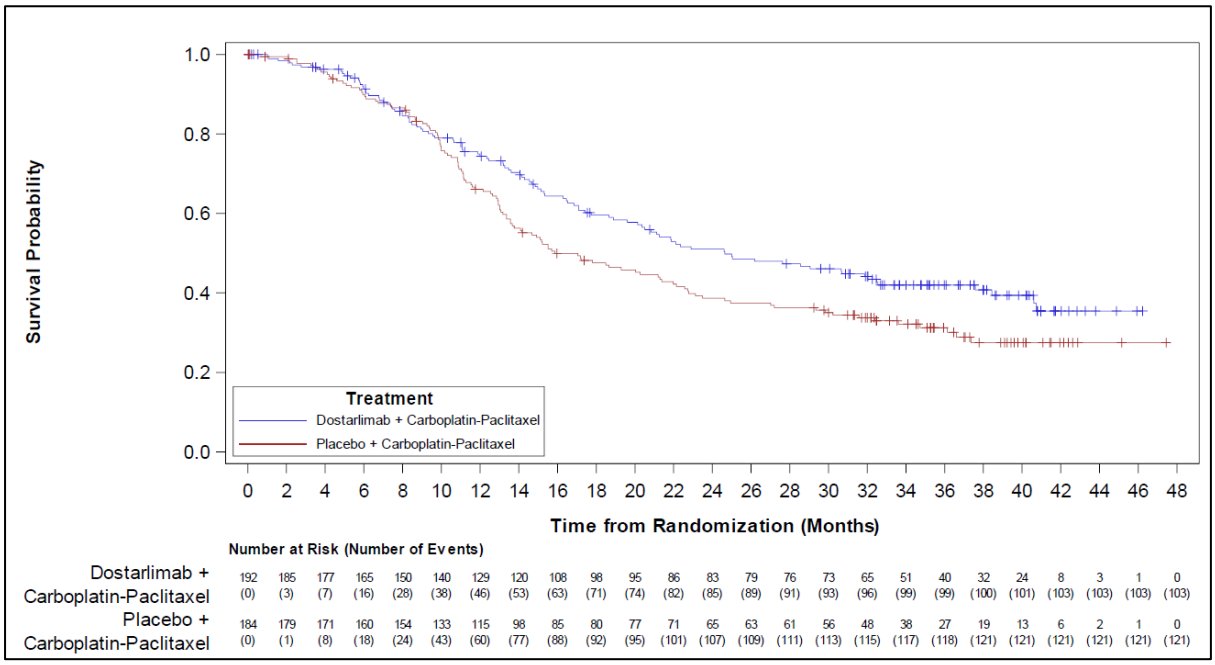
Source: IA2 CSR Table 14.2.1.8 [31] and Powell *et al.*[28]
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival.

3.3.3 *Progression-free survival 2*

The results for PFS2 reported in the CS were from the IA2 data-cut (Figure 6 and Table 14). Dostarlimab in combination with CP demonstrated a reduction in the risk of progression following the first subsequent anticancer therapy or death (PFS2) among patients with MMRp/MSS disease. Median PFS2 was 24.6 months (95% CI: 20.1 to 32.6) in the dostarlimab + CP arm, compared with 15.9 months (95% CI: 13.6 to 22.0) in the placebo + CP arm (HR 0.74; 95% CI: 0.57 to 0.97).[28] The results from the analysis of PFS2 corresponded to a median improvement of 8.7 months in the time to a second progression event for patients in the dostarlimab + CP arm compared with the placebo + CP arm.

In response to clarification questions the company provided an additional *post hoc* analysis of PFS2 in only those MMRp/MSS patients who received a subsequent anti-cancer therapy. The EAG notes that the results of this analysis for patients who received a subsequent anti-cancer therapy [redacted], and HR 0.74; 95% CI: 0.57 to 0.97, respectively). However, it should also be noted that this analysis comprises a *post hoc* subgroup and breaks randomisation, therefore the results should be interpreted with caution.

Figure 6. KM curves of IA2 PFS2 in the MMRp/MSS patient population (Reproduced from CS Figure 7)



Source: IA2 CSR Figure 15.1.11.[31]
Data cutoff: 22 September 2023.

Abbreviations: KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression free survival 2.

Table 14. Summary of IA2 PFS2 in the MMRp/MSS patient population (Reproduced from CS Table 13)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=65)
Hazard ratio (95% CI)	0.74 (0.571 to 0.970)	
Median PFS2, months (95% CI)	24.6 (20.1 to 32.6)	15.9 (13.6 to 22.0)
PFS2 Probability at 24 months (95% CI)	51.0% (43.3% to 58.2%)	38.7% (31.4% to 45.8%)
PFS2 Probability at 36 months (95% CI)	42.0% (34.4% to 49.4%)	31.2% (24.3 to 38.4)

Source: CSR Table 14.2.1.39[31] and Powell *et al.*[28]
Data cutoff: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS2, progression-free survival 2.

3.3.4 Objective response rate

Objective response rate (ORR) in RUBY-1 was defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1). The analysis of ORR reported in the CS (CS Appendix J.2.2.2) was that undertaken regardless of the presence of target or non-target lesions at baseline, although the EAG notes that there was a proportion of patients in each trial arm with most recent Grade of disease not assessable at baseline and that the proportion was [redacted]. The EAG notes that the data for ORR are from IA1 and suggest similar ORR for dostarlimab + CP (57.8%) compared with placebo + CP (55.4%). The absolute risk difference for ORR demonstrates [redacted].

Table 15. Summary of IA1 tumour response in the MMRp/MSS population (Reproduced from company response to CQs Table 1)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Best Overall Response by RECIST v1.1 [n (%)] [a]		
CR	38 (19.8%)	31 (16.8%)
PR	73 (38.0%)	71 (38.6%)
SD	36 (18.8%)	39 (21.2%)
Non-CR/Non-PD	0	0
No disease	27 (14.1%)	22 (12.0%)
PD	7 (3.6%)	12 (6.5%)
Not Evaluable	11 (5.7%)	9 (4.9%)
ORR[a]		
N (%)	111 (57.8%)	102 (55.4%)
95% CI	[redacted]	[redacted]
Absolute Risk Difference of ORR		
Estimate	[redacted]	
95% CI	[redacted]	
p-value	[redacted]	

[a]Denominator is number of patients randomised regardless of presence of target or non-target lesions at baseline.
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; CR, complete response; MMRp, mismatch repair proficient; MSS, microsatellite stable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; SD, stable disease.

3.3.5 Health-related quality of life outcomes

All health-related quality of life outcomes were reported using the IA1 data cut-off.

3.3.5.1 EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) global score results are summarised in Table 16. The EAG notes that higher scores are associated with improved HRQoL.

The least-squared mean (LSM) difference in change from baseline for the dostarlimab + CP arm compared with the placebo + CP arm resulted in no significant difference (LSM difference -1.8; 95% CI: -4.9 to +1.2). In addition, the company reported that estimates for Meaningful Change Thresholds

for global EORTC QLQ-C30 have ranged from 5 to 11 points suggesting that the LSM differences are also not clinically meaningful differences between the treatment groups.[33]

Table 16. EORTC QLQ-C30 comparative data between trial arms for the MMRp/MSS patient population of RUBY-1 (Reproduced from company response to CQs Table 3)

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EORTC Global QoL Score				
Overall	Change from Baseline	N	182	176
		LSM (SE)	-1.1 (1.05)	0.7 (1.14)
		95% CI	-3.2, 0.9	-1.5, 3.0
		Difference from placebo		
		LSM (SE)	-1.8 (1.56)	-
		95% CI	-4.9, 1.2	-
		p-value	0.2420	-

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error; QoL, quality of life.

3.3.5.2 EQ-5D-5L

The European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) visual analogue scale score LSM difference in change from baseline was -3.7 (95% CI: -6.4 to -0.9) for dostarlimab + CP compared to placebo + CP (Table 17). The EAG notes that the company reported this not to be a clinically significant change, but the EAG notes that the resulting p value was statistically significant (p = 0.01).

Table 17. EQ-5D-5L VAS Comparative data between trial arms for the MMRp/MSS patient population of RUBY-1 (Reproduced from company response to CQs Table 4)

Visit	Variable	Statistic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Scale/Item: EQ-5D-5L VAS Score				
Overall	Change from Baseline	N	180	174
		LSM (SE)	0.3 (0.93)	3.9 (1.02)
		95% CI	-1.6 to 2.1	1.9 to 6.0
		Difference from placebo		
		LSM (SE)	-3.7 (1.39)	N/A

		95% CI	-6.4 to -0.9	N/A
		p-value	0.0086	N/A

Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; EQ-5D-5L, European Quality of Life scale, 5-Dimensions, 5-Levels; LSM, Least Square Mean; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error; VAS, Visual Analogue Scale.

EQ-5D was recorded at baseline, each treatment cycle (Q3W in induction phase and Q6W in the maintenance phase), end of treatment, safety follow up (occurring 90 days after the last dose of the study drug) and during the survival follow up period (beginning 90 days after the safety follow up).

The EAG notes that where EQ-5D-5L was analysed for the purpose of deriving utility weights, this was undertaken according to the treatment assigned at randomisation even if no study treatment was received. Patients who were incorrectly stratified at randomisation were analysed according to the stratum assigned at randomisation and all patients in the analysis were required to have a baseline and post-baseline EQ-5D assessment.

The EAG notes that the HRQoL data used in the company's economic model were the EQ-5D-5L responses at each time point and the mean utility, cross-walked to the EQ-5D-3L using the UK value set in the MMRp/MSS population. These results are summarised in Table 18 with more detail provided in Section 4.2.4. In summary, the EAG notes that the resulting EQ-5D-3L values [redacted].

Table 18. EQ-5D-5L data cross-walked to EQ-5D-3L between trial arms from IA1 for the MMRp/MSS patient population of RUBY-1 (Reproduced from company response to CQs Table 8)

Visit	Statistic	Dostarlimab in combination with CP (N=181)	Placebo in combination with CP (N=174)
Scale/Item: EQ-5D-5L Score cross-walked to EQ-5D-3L			
Baseline	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
EOT	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Safety Follow-up[a]	N	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

[a] The Safety Follow-up Visit should occur 90±7 days after the last dose of study drug.

Source: Data on file. ru_uk_t_stat_p3 [34]

Data cut off: 28 September 2022.

Note: Utility analysis for modelling is based off MMR status at randomisation and only included patients with a baseline and post-baseline EQ-5D score, while descriptive analyses are based on source-verified ITT population.

Abbreviations: CP, carboplatin plus paclitaxel; EOT, end of treatment; EQ-5D-3L, European Quality of Life scale, 5-Dimensions, 3 Levels; EQ-5D-5L, European Quality of Life scale, 5-Dimensions, 5 Levels; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; SD, standard deviation; VAS, Visual Analogue Scale.

3.3.5.3 QLQ-EN24

The EAG notes that there is no overall score for the Quality of Life Questionnaire Endometrial Cancer 24-item module (QLQ-EN24) domains but comparative analysis results for the some of the domains were provided in the company response to clarification questions Table 5. The EAG notes that in general, similar changes from baseline were observed in both dostarlimab + CP and placebo + CP study arms with two exceptions. These exceptions were the EN24 Sexual Interest score and the EN24 Tingling/Numbness Score.

EN24 Sexual Interest score was relatively stable over the course of the trial in the dostarlimab + CP arm (-0.5; 95% CI: -2.7 to +1.7) while in the placebo + CP arm it increased (+3.6; 95% CI: +1.3 to +5.9), indicating improvement, resulting in a 4.1 point lower score in the dostarlimab + CP arm compared to placebo + CP. The EN24 Tingling/Numbness Score increased markedly in both the dostarlimab + CP (+31.5; 95% CI: +27.4 to 35.7) and placebo + CP (+23.8; 95% CI: +19.4 to +28.2) arms, suggesting patients suffered increased levels of tingling and numbness. The LSM difference for EN24 Tingling/Numbness Score change from baseline for dostarlimab + CP versus placebo + CP was +7.7 (95% CI: +1.5 to 13.9) suggesting a greater impact of tingling/numbness in the dostarlimab + CP arm.

3.3.6 Subgroup analysis and sensitivity analyses

3.3.6.1 Subgroup analysis of PFS

The results of the subgroup analyses of investigator-assessed PFS from IA1 [redacted] (Figure 7). The EAG notes [redacted]. However, the EAG also notes that some of these subgroups comprise of [redacted].

In addition, it is noted that only disease status and prior external pelvic radiotherapy were stratification factors in RUBY-1.

Figure 7. Forest plot of IA1 PFS and 95% CIs by subgroup for the MMRp/MSS patient population (Reproduced from CS Figure 11)

Source: IA1 CSR Figure 15.2.1[32]
Data cutoff: 28 September 2022.
Note: HRs presented are from unstratified Cox regression model.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; PFS, progression-free survival.

3.3.6.2 Subgroup analysis of overall survival

The results of the subgroup analyses of OS at IA2 in the MMRp/MSS population [redacted] (Figure 8). The EAG notes that analyses of OS [redacted] and as discussed in Section 3.3.2, it is noted that the results for OS are immature.

The EAG also notes [redacted]. The company reported that those with Stage III primary disease status and no disease at baseline are expected to have a better prognosis which the EAG considers reasonable. [redacted] (**Other key issues in Section 1.4**). The EAG notes that geographic region was not a stratification factor in RUBY-1 and in the company response to CQs, baseline

characteristics were provided for the Western Europe subgroup [redacted] (Appendix 8.2).

[redacted]

Figure 8. Forest plot of IA2 OS and 95% CIs by subgroup for the MMRp/MSS patient population (Reproduced from CS Figure 12)

Source: IA2 CSR Figure 15.2.2.[31]
Data cutoff: 22 September 2023.
Note: HRs presented are from unstratified Cox regression model.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival.

3.3.6.3 Molecular subgroup analyses

The NICE final scope specified molecular subgroups (such as non-specific molecular profile [NSMP], POLε and p53abn) to be of interest and the EAG notes that the company conducted exploratory *post hoc* subgroup analyses by molecular subgroup. However, the EAG also notes that the company's molecular subgroup analyses reported in the CS were conducted using the full RUBY-1 trial population with whole exome sequencing results (N=400; 81%) and not just the MMRp/MSS subgroup of the trial and so the EAG is therefore unsure how reflective these are of the MMRp/MSS subgroup. In addition, the EAG notes that there were only 5 patients in the POLεmut subgroup and that approximately 20% of the RUBY-1 trial population (94 patients) lacked sequencing data. The molecular subgroup analyses were also conducted *post hoc* and given the various limitations the EAG considers the results from the molecular subgroup analyses should be interpreted with caution and does not present the results here. In summary, with the exception of the POLεmut subgroup where there were no events, the hazard ratios for PFS and OS for the TP53 mutation and NSMP subgroups were broadly consistent with the overall MMRp/MSS population (HRs <1; CS Table 16).

3.3.7 Safety

In the company's base-case analysis, grade 3 or higher treatment-emergent adverse events (TEAEs) occurring in at least 2% of the safety population from the overall trial population in either treatment arm of RUBY-1 were included in the model (Table 19). In response to a clarification question, the company also included grade 3 or higher immune-related AEs (irAEs) occurring in at least 2% of patients. The company reported that in the ITT population, 241 patients who had received one dose of dostarlimab in combination with CP and 246 patients in the placebo + CP arm were included in the safety analysis (370 of these 487 patients in the safety analyses were from the MMRp/MSS subgroup).

The company also provided safety data for the MMRp/MSS subgroup of RUBY-1 in Appendix D of the CS and reported that they were consistent with the ITT safety population results. In addition, the company reported that the safety results for IA1 and IA2 were both consistent and that the safety profile of the dostarlimab + CP arm was generally consistent with the known safety profiles of the individual agents.[28, 29] The EAG's clinical experts were also in agreement that the AEs were in keeping with the known AEs of dostarlimab and CP.

In summary, Grade ≥3 TEAEs were 12% higher in the dostarlimab + CP arm compared with the placebo + CP arm of the RUBY-1 safety population (72.2% vs 60.2%, respectively). The most frequently reported Grade ≥3 TEAEs in both arms for dostarlimab + CP and placebo + CP were anaemia (14.9% vs 16.7%), neutrophil count decreased (8.3%, 13.8%), neutropenia (9.5% vs 9.3%) and hypertension (7.1% vs 3.3%). IrAEs occurred in 58.5% of patients in the dostarlimab + CP arm and 37.0% of patients in the placebo + CP arm. Grade ≥3 irAEs occurring in ≥2% of patients in the dostarlimab + CP arm were rash, ALT increased, and AST increased but there were no Grade ≥3 irAEs occurring in ≥2% of patients in the placebo + CP arm (Table 19).

Table 19. Adverse events occurring in ≥2% of patients in either arm of RUBY-1 (safety population)

Adverse event	Dostarlimab + CP (N = 241)		CP (N = 246)	
	N	(%)	N	(%)
Treatment-emergent adverse events				
Anaemia	36	14.9%	41	16.7%
Neutropenia	23	9.5%	23	9.3%
Neutrophil count decreased	20	8.3%	34	13.8%
Hypertension	17	7.1%	8	3.3%
White blood cell count decreased	16	6.6%	13	5.3%
Hypokalaemia	12	5.0%	9	3.7%
Pulmonary embolism	14	5.8%	12	4.9%
Lymphocyte count decreased	13	5.4%	18	7.3%
Lipase increased	11	4.6%	3	1.2%
Abdominal pain	9	3.7%	4	1.6%
Urinary tract infection	7	2.9%	4	1.6%
Rash	11	4.6%	3	1.2%
Nausea and hyponatremia	16	6.6%	12	4.9%
Immune-related adverse events				
Rash	16	6.6%	-	-
ALT increased	5	2.1%	-	-
AST increased	5	2.1%	-	-

Abbreviations: ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; CP, carboplatin and paclitaxel; ITT, intention-to-treat.

Estimation of the disutility and costs associated with AEs can be found in Section 4.2.4.1. In response to a clarification question, the company explained that the duration of each AE was assumed to be one-week (one model cycle) but explored a scenario where the duration was assumed to be two-

weeks, but this had minimal impact on the ICER (see Section 5.2.2). The total disutility and costs of AEs were applied in the first model cycle.

The EAG considers the company's approach to inclusion of AEs in the model to be appropriate. With regards to the duration of AEs, the company stated that data were not available from RUBY-1 and thus made a simplifying assumption that duration of AEs would be one-week, with a scenario exploring a duration of two weeks having minimal impact on the ICER. The EAG considers that this is a simplifying assumption, and that the company could have searched the published literature or consulted with their clinical experts to get a more accurate reflection of the duration of AEs. Nonetheless, the EAG considers that generally, AEs are not a primary driver of cost-effectiveness and thus more robust methods to estimate the duration of AEs are unlikely to have a substantial impact on the ICER.

3.4 Conclusions of the clinical effectiveness section

The EAG considers the decision problem addressed by the company to be appropriate, with any differences relating to the National Institute for Health and Care Excellence (NICE) final scope to be reasonable given the rationale provided (see Section 2.3). The SLR performed to identify clinical evidence was reasonable and the EAG considers it unlikely that any relevant head-to-head studies of dostarlimab + CP vs CP to have been missed (see Section 3.1).

The EAG considers the RUBY-1 trial to be at low risk of bias but notes that the key data to inform the relevant population in the CS (MMRp/MSS patients [n=376]) are a subgroup of the RUBY-1 ITT population (N=494), with many of the outcomes for this subgroup comprising *post hoc* analyses (see Section 2.3.1 and 3.2). Feedback from the EAG's clinical experts highlighted that the mean age and baseline ECOG performance status were potentially lower in RUBY-1 compared to UK clinical practice, but otherwise the baseline characteristics of the trial patients were broadly consistent with the UK population (see Section 2.3.1 and Section 3.2) and this was not considered to be an area of major concern.

Based on the advice of its clinical experts, the EAG considers the use of dostarlimab in combination with carboplatin + paclitaxel (CP) in the economic model to reflect the expected dosages in UK clinical practice. [redacted]

[redacted]. The EAG notes that TTD was capped at 3-years in the economic model to reflect the treatment-stopping rule in the marketing authorisation for dostarlimab, [redacted].

The EAG agrees with the company that the primary comparator of relevance for dostarlimab + CP is the platinum-based chemotherapy regimen of carboplatin in combination with paclitaxel (CP) followed by routine surveillance and notes this was a comparator in the NICE final scope and the RUBY-1 trial.

The exclusion of hormone therapy as a comparator is considered to be reasonable by the EAG, with the EAG's clinical experts agreeing with the company that hormone therapy is used in only a small proportion of primary advanced or recurrent EC patients, and the patients likely to receive first-line hormone therapy are unlikely to be considered suitable for dostarlimab + CP. The EAG, therefore, considers the company's decision that hormone therapy is not a relevant comparator to be reasonable (see Section 2.3.3). In addition, the EAG notes that durvalumab with platinum-based chemotherapy followed by durvalumab with or without olaparib maintenance (subject to NICE appraisal) and pembrolizumab with platinum-based chemotherapy followed by pembrolizumab maintenance (subject to NICE appraisal) were included as comparators in the NICE final scope. However, at the time of writing these are still undergoing appraisal by NICE and therefore the EAG is in agreement with the company that they are not relevant comparators at present.

The EAG's clinical experts reported that the subsequent treatments used in RUBY-1 are not wholly reflective of UK clinical practice and, therefore, the EAG considers that the results for OS in particular may not accurately reflect outcomes in the UK. The usage of immunotherapies (e.g. pembrolizumab) as subsequent treatments in the dostarlimab + CP trial arm was allowed in RUBY-1, but the EAG received guidance from NHS England that immunotherapies are not a treatment option in UK NHS clinical practice following dostarlimab treatment. The EAG's clinical experts also reported that bevacizumab is not used in EC in UK clinical practice, whereas it was a subsequent treatment used by a small proportion (<5%) of patients in both arms of RUBY-1.

The EAG notes that data from RUBY-1 in the CS are reported using one of two interim analyses: interim analysis 1 (IA1; 28 September 2022), and interim analysis 2 (IA2; 22 September 2023). Data from RUBY-1 on PFS, OS, HRQoL, AEs and TTD are used in the economic model. The EAG considers that the data used in the economic model should be used from the same analysis, whereas the

company used IA1 for PFS, HRQoL and TTD and IA2 for OS and AEs. This is considered further in Section 4.2.2.

OS data from RUBY-1 IA2 are immature, with data maturity of only 54.8% maturity in the MMRp/MSS population. The EAG is concerned about the reliability of the OS data from RUBY-1, in particular the data beyond 30-months due to heavy censoring and the resulting extrapolations used in the company's economic model (**Other key issues in Section 1.4**). Nevertheless, the EAG notes that there are no further data cuts available at present and thus considers these OS data to represent the most appropriate data for use in the model until more mature data become available (RUBY-1 is expected to complete in Q3 of 2026 and no additional interim analysis data cuts are expected).

Clinical effectiveness results for PFS and OS from RUBY-1 (see Section 3.3) for the MMRp/MSS subgroup generally favour treatment with dostarlimab + CP compared to placebo + CP, [redacted].

In terms of HRQoL in the RUBY 1 MMRp/MSS subgroup, the EAG notes that the resulting EQ-5D-3L values [redacted].

The company used safety data from the safety population of the overall trial ITT population in RUBY 1 in the economic model, although they also provided safety data for the MMRp/MSS subgroup of RUBY-1 in Appendix D of the CS and reported that it was consistent with the ITT safety population results. The EAG's clinical experts were in agreement with the company that the AEs in RUBY 1 were in keeping with the known AEs of dostarlimab and CP. Grade ≥3 TEAEs were 12% higher in the dostarlimab + CP arm compared with the placebo + CP arm of the RUBY-1 safety population (72.2% vs 60.2%) and the most frequently reported Grade ≥3 TEAEs in both arms were anaemia (14.9% vs 16.7%), neutrophil count decreased (8.3%, 13.8%), neutropenia (9.5% vs 9.3%) and hypertension (7.1% vs 3.3% [Section 3.3.7]). The Grade ≥3 irAEs occurring in ≥2% of patients in the dostarlimab + CP arm were rash, ALT increased, and AST increased but there were no Grade ≥3 irAEs occurring in ≥2% of patients in the placebo + CP arm.

Finally, the EAG notes that the [redacted] with the dostarlimab + CP arm compared to the placebo + CP arm and thus the EAG sought clarification from the company (**Other key issues in Section 1.4**). The EAG notes that geographic region was not a

stratification factor in RUBY-1 and, in the company response to CQs, baseline characteristics were provided for the Western Europe subgroup [redacted] (Appendix 8.2). The company reported that [redacted].

4 Cost effectiveness

This section presents a summary and critique of the cost effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation.

Table 20 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case results. Results presented in this document are inclusive of a [redacted] patient access scheme (PAS) discount for dostarlimab.

Table 20. Company's base case results (post clarification)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4.1 EAG comment on the company's review of cost effectiveness evidence

The company conducted a systematic literature review (SLR) to identify cost-effectiveness, health-related quality of life (HRQoL), and cost and resource use evidence for first-line treatments in patients with primary advanced or recurrent endometrial cancer (EC). The company's original SLR was conducted in November 2021 and several updates were made, with the most recent update conducted in May 2024. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 21.

Table 21. EAG's critique of company SLR methods

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E.1.1	Appendix F.1.1	Appendix G.1.1	Appropriate

Inclusion/ exclusion criteria	Appendix E.1.2.1	Appendix F.1.2.1	Appendix G.1.2.1	Appropriate
Screening	Appendix E.1.2.2	Appendix F.1.2.2	Appendix G.1.2.2	Appropriate
Data extraction	Appendix E.1.2.3	Appendix F.1.2.3	Appendix F.1.2.3	Appropriate
Quality assessment of included studies	Appendix E.1.2.4	None reported.	None reported.	Drummond checklist used for the cost-effectiveness evidence, which is appropriate. Checklists such as CASP (recommended in DSU TSD 9) would be preferred for HRQoL evidence.[35]

Abbreviations: CASP, Critical Appraisal Skills Programme; CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

Overall, a total of 12 cost-effectiveness studies, three HRQoL studies and 17 resource and cost use records reporting on 14 unique studies were identified by the SLR.

Of the 12 cost-effectiveness studies identified, four were health technology assessment (HTA) reports of dostarlimab with platinum-based chemotherapy for treating primary advanced or recurrent EC with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), including NICE guidance TA963.[36] The company relied on the existing model for dostarlimab that informed TA963 as the basis for their *de novo* model for the current appraisal.

The EAG notes that none of the identified HRQoL or costs studies were used to inform the economic model and instead data from RUBY-1 and TA963 (identified in the cost-effectiveness SLR) were used and the EAG considers this to be appropriate. Overall, the EAG considers that the company's search was robust and identified relevant studies for the appraisal.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 22 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 22. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the reference case.
Perspective on costs	NHS and PSS	Adheres to the reference case.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Adheres to the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the reference case.
Synthesis of evidence on health effects	Based on systematic literature review	The company performed an appropriate 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.	Base case QALYs estimated using EQ-5D-5L data from RUBY-1, mapped to the EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data obtained directly from patients in RUBY-1, mapped to EQ-5D-3L using the Hernadez-Alava mapping algorithm as recommended by NICE.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in RUBY-1 are generally representative of the UK patient population.[37, 38]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the reference case.
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	Adheres to the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the reference case.

Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

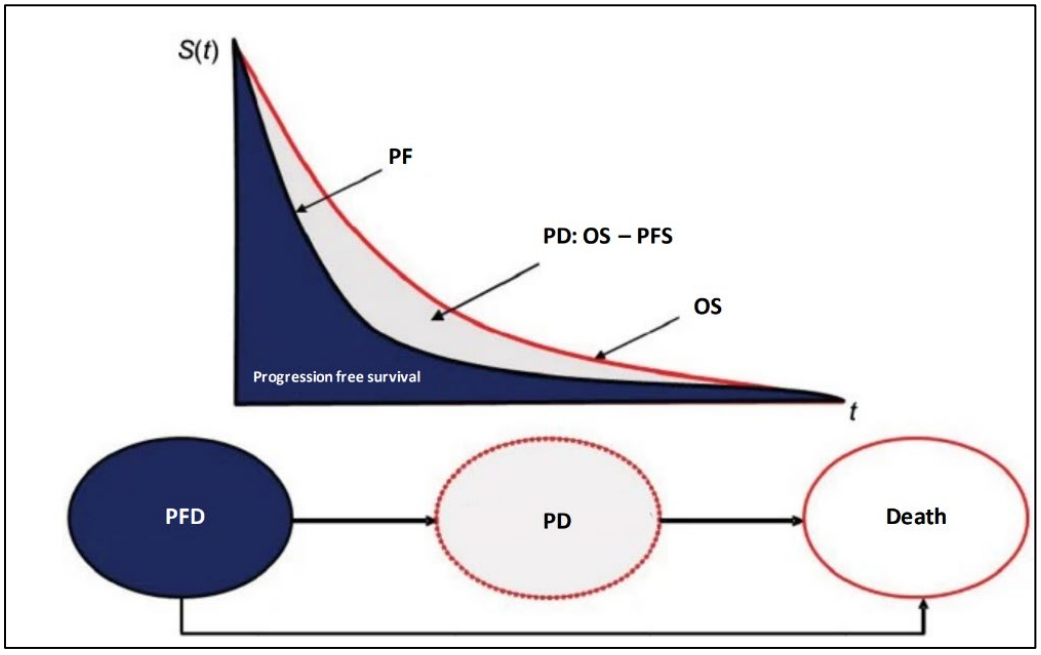
4.2.2 Modelling approach and model structure

A single economic model, adapted from the model informing TA963, was developed in Microsoft© Excel to assess the cost-effectiveness of dostarlimab in addition to platinum-based chemotherapy (carboplatin and paclitaxel, hereafter known as CP) for the treatment of patients with newly

diagnosed primary advanced or recurrent EC that is mismatch repair proficient (MMRp) or microsatellite stable (MSS).

The model uses a partitioned survival analysis model (PSM) structure, with a weekly cycle length and includes three main health states: progression-free, progressed disease and death (Figure 9). The company stated that the chosen model structure is in line with previous HTA EC models (TA779, TA904 and TA963).[16, 17, 36]

Figure 9. Model structure (reproduced from Figure 13 of the company submission)



Abbreviations: PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival; OS, overall survival; S, survival; t, time.

All patients enter the model in the progression-free health state and are assumed to be on either CP or dostarlimab + CP for the first 18 cycles of the model. Dostarlimab patients who occupy the progression-free health state after the first 18 cycles can continue with dostarlimab monotherapy unless they are experiencing unacceptable toxicity or until they have received a maximum of three years of treatment (maximum treatment duration according to the Summary of Product Characteristics [SmPC] for dostarlimab).[39] CP patients who occupy the progression-free health state after the first 18 cycles are considered to have routine surveillance.

Patients can remain in the progression-free health state until disease progression, at which point they transition to the progressed disease health state or die (transitioning to the death health state).

When patients transition into the progressed disease health state, they remain in this health state until death.

The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes of progression-free survival (PFS) (used to model the progression-free health state) and overall survival (OS). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 4.2.3.

As mentioned previously, a model cycle length of one week was implemented in the model for PFS and OS and TTD. The model time horizon was set to 36 years (lifetime). The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.

The EAG considers the company's model structure is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models, especially for EC. The one-week cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment.

4.2.3 Treatment effectiveness

4.2.3.1 Overview of the company's approach to survival analysis

Clinical data for the outcomes of PFS, OS and TTD that inform the economic model are derived from the RUBY-1 trial, described in Section 3.3. To extrapolate the RUBY-1 Kaplan-Meier (KM) data, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[40]

To decide whether to jointly or independently fit survival distributions, the company tested whether the assumption of proportional hazards (PH) held for PFS and OS outcomes by producing log-cumulative hazard, Schoenfeld residual and quantile-quantile (QQ) plots (Figures 14 to 16 and Figures 21 to 23 of the company submission). Based on the diagnostic plots, the company determined that the PH assumption did not hold for PFS or OS and independently fit survival distributions for each treatment arm of the model.

Extrapolations of the KM data were then explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log normal, log-logistic, gamma and generalised gamma). If standard parametric models were considered a poor fit to the observed data, the company explored flexible spline models in accordance with DSU TSD 21.[41] To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using visual inspection of the curves, goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, and clinical plausibility of the extrapolation over the time horizon of the model.

Table 23 presents an overview of the company's survival curve selection for each outcome and Sections 4.2.3.3 and 4.2.3.5 provides more detail on the company's approach to extrapolating PFS and OS. Please refer to Section 4.2.5.1 for further details on TTD.

The EAG notes that the company has implemented the following limits in the model to ensure that model outcomes pass clinical and face validity:

- Risk of progression or mortality risk per cycle cannot fall below age-matched general population mortality, based on ONS life tables from 2020-2022;[42]
- PFS is capped to OS (i.e. PFS cannot exceed OS);
- TTD cannot exceed PFS;
- A treatment duration cap of 18 weeks (six treatment cycles) is applied to the CP arm of the economic model;
- A treatment duration cap of three years is applied to the TTD KM curve for dostarlimab (see Section 4.2.5.1 for further details).

Table 23. Overview of company's survival curve selection by outcome and subgroup

Outcome	CP	Dostarlimab + CP
PFS	Spline Normal, k=2	Spline Odds, k=3
OS	Log-logistic	Lognormal
TTD	Treatment completion rates from RUBY-1	- CP: Treatment completion rates from RUBY-1, capped at 18 weeks. - Dostarlimab: Treatment completion rates for 18 weeks and TTD KM curve from RUBY-1, capped at three years.

Abbreviations: CP, carboplatin paclitaxel; k, knots; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

4.2.3.2 EAG critique

The EAG considers that the company's general approach to survival analysis is appropriate. However, the EAG notes that for PFS and OS, different types of parametric models have been used by the company to extrapolate the KM data for each treatment arm. In response to a clarification question B2), the company explained that use of different parametric models to fit curves to the observed data was considered appropriate because of three factors:

- differentiated mechanism of action of dostarlimab compared with chemotherapy alone,
- longer time on treatment with dostarlimab compared with the limited six cycles of chemotherapy, and
- delayed exposure-response relationship observed with dostarlimab and common with other immunotherapies.

As such, the company considered that these factors contributed to the difference in the trends of the observed hazards in RUBY-1 for each treatment arm (see Figure 3 of the company clarification response). The EAG considers the company's justification for fitting different parametric models for each treatment arm for PFS and OS is not unreasonable.

The company's use of 2020-2022 ONS UK life tables for age-matched general population mortality was identified as a minor issue by the EAG. Guidance in NICE DSU TSD 23 recommends using the ONS life tables from 2017-2019 due to the uncertainty about the long-term impact of Covid-19 on the 2020-2022 data.[43] As such, the EAG ran a scenario using the ONS UK life tables from 2017-2019 (see Section 6.2). The EAG's scenario had minimal impact on the incremental cost-effectiveness ratio (ICER) but is included in the EAG base case for adherence to the guidance in NICE DSU TSD 23.

4.2.3.3 Progression-free survival

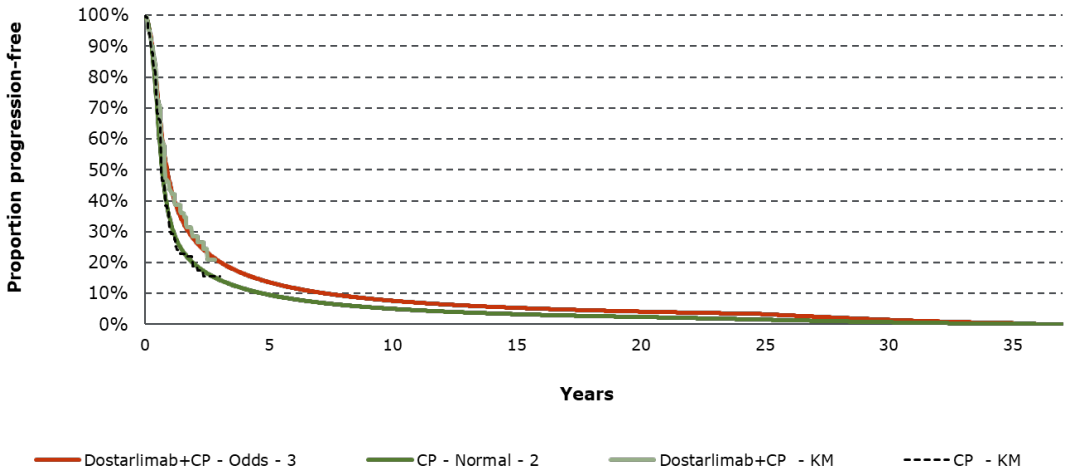
The company explored the observed hazard rate plot for PFS and found that the hazards for CP and dostarlimab + CP were non-monotonic and considered flexible methods for survival analysis (specifically spline models) would be more appropriate than standard parametric extrapolations of the observed PFS data. Consequently, the company explored nine spline models, encompassing normal, hazard, and odds extrapolations with one to three knots.

The company considered the hazard models had poor statistical and visual fit and so were excluded from the curve selection process. Based on statistical fit, visual fit and clinical validation of the PFS

curves, the company selected the normal k=2 spline curve for the CP. The normal k=2 ranked fourth in terms of statistical fit but was within five points of the top three spline curves (see Table 21 of the company submission [CS]), thus indicating similar statistical fit. For the dostarlimab + CP arm, the company selected the odds k=3 spline curve, which ranked one of the lowest in terms of in terms of statistical fit, but all the odds and normal spline models were within five points of each other and so had similar goodness-of-fit to the observed data.

Figure 10 presents the company's preferred PFS curves. Table 24 presents a comparison of the landmark estimates from the company's preferred PFS extrapolations compared with KM data from RUBY-1. The estimated mean discounted life years in the progression-free health state for CP and dostarlimab + CP was [redacted] years and [redacted] years, respectively.

Figure 10. Company base case PFS curves for CP and dostarlimab + CP



Abbreviations: CP, carboplatin and paclitaxel; PFS, progression-free survival.

Table 24. Landmark estimates of progression-free survival

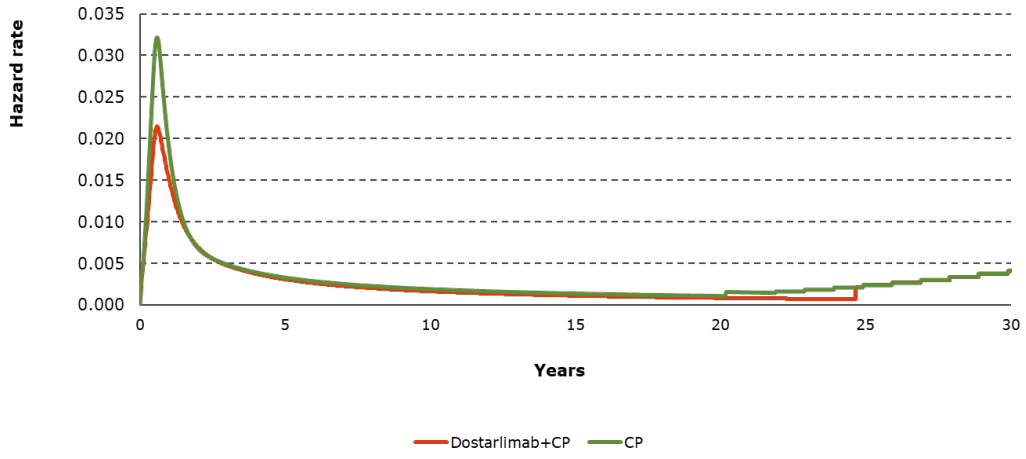
Year	CP		Dostarlimab + CP	
	KM data from RUBY-1	Log-logistic (company base case)	KM data from RUBY-1	Lognormal (company base case)
2	19%	19%	28%	27%
3	16%	14%	-	20%
5	-	10%	-	14%
10	-	5%	-	8%
15	-	3%	-	5%
20	-	2%	-	4%

30	-	0.7%	-	1.5%

Abbreviations: CP, carboplatin and paclitaxel; KM, Kaplan-Meier; PFS, progression-free survival.

The hazard rate plot based on the company's selected PFS curves are presented in Figure 11. The hazard rate plot indicates that the risk of progression is similar for both the dostarlimab + CP and CP arms of the model after approximately two years. Nonetheless, the company included functionality in their model to explore immediate treatment waning (dostarlimab PFS hazards equal the CP arm at the end of the observed period) and gradual waning over user defined timepoints. Both approaches have minimal impact on the ICER (presented in Section 5.2.2), given that in the company base case, the PFS hazards for both arms of the model are similar after two years. As such, the much-discussed issue of treatment effect waning for immunotherapy may not be relevant based on the modelled PFS hazards.

Figure 11. Hazard rate plot over time based on company's preferred PFS curves



Abbreviations: CP, carboplatin and paclitaxel; PFS, progression-free survival.

4.2.3.4 EAG critique

Overall, the EAG considers the company's approach to modelling PFS is appropriate. The PFS data informing the economic model from RUBY-1 are based on the first interim analysis (IA1) data cut (28 September 2022). During the clarification stage, the EAG request the company to present PFS data from the second interim analysis (IA2) data cut (22 September 2023). The company supplied the PFS IA2 KM curves (Figure 3 of the company clarification response and Section 3.3.1 of this report),

which demonstrated that PFS outcomes were stable, but that the tail of the curve (32 months onwards) plateaus for both dostarlimab + CP and placebo + CP.

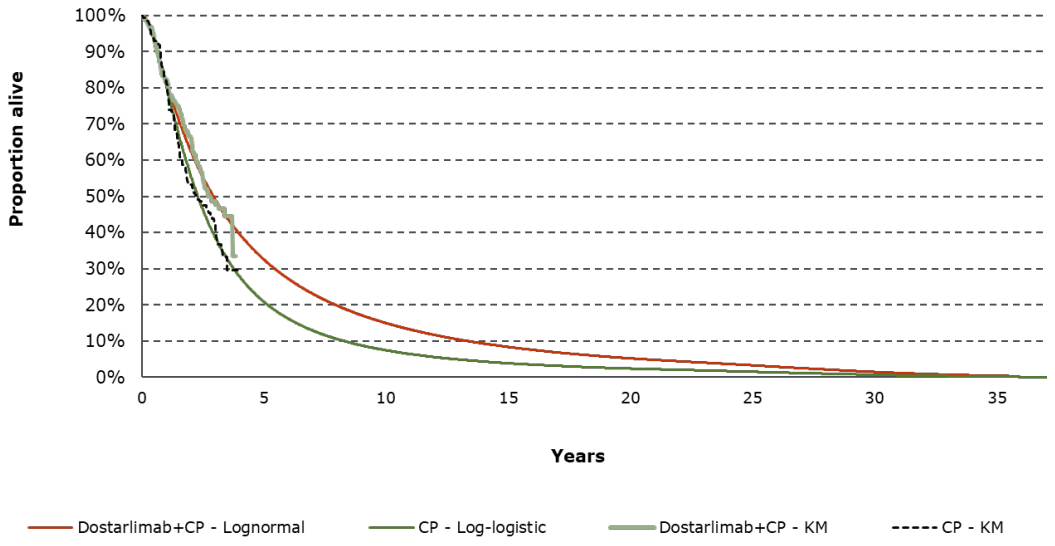
The EAG considers that the tail of the KM curve has a substantial amount of uncertainty due to censoring and that based on advice from its clinical experts, outcomes for MMRp/MSS EC population are poor and so most patients are like to relapse. This is discussed further in Section 3.3.1. As such, the EAG does not consider it appropriate to model a long-term plateau for PFS and therefore the company's base case approach using IA1 PFS and the choice of extrapolation is not unreasonable.

4.2.3.5 Overall survival

Based on statistical fit, visual fit and clinical validation of the OS curves, the company selected the log-logistic distribution for CP and the lognormal distribution for dostarlimab + CP. Figure 12 presents the company's preferred OS curves. Table 25 presents a comparison of the landmark estimates from the company's preferred OS extrapolations compared with KM data from RUBY-1.

The EAG notes that, based on statistical fit (Table 30 of the CS), the lognormal distribution for dostarlimab + CP ranked lower than the log-logistic distribution, which had the best statistical fit of all the standard parametric models, but highlights that both distributions were within five points of each other indicating similar statistical fit. The estimated mean discounted total life years for CP and dostarlimab + CP was [redacted] years and [redacted] years, respectively.

Figure 12. Company base case OS curves for CP and dostarlimab + CP



Abbreviations: CP, carboplatin and paclitaxel; OS, overall survival.

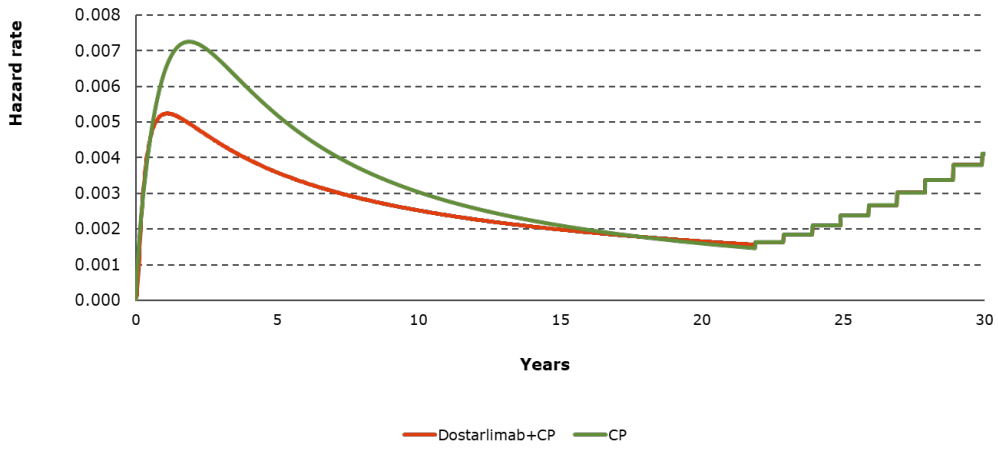
Table 25. Landmark estimates of overall survival

Year	CP		Dostarlimab + CP	
	KM data from RUBY-1	Log-logistic (company base case)	KM data from RUBY-1	Lognormal (company base case)
2	53%	56%	67%	62%
3	42%	39%	49%	49%
5	-	21%	-	33%
10	-	7%	-	15%
15	-	4%	-	8%
20	-	2%	-	5%
30	-	0.7%	-	1.5%

Abbreviations: CP, carboplatin and paclitaxel; KM, Kaplan-Meier; OS, overall survival.

The hazard rate plot based on the company's selected OS curves is presented in Figure 13. The hazard rate plot indicates that over time, the risk of death for CP gradually converges towards the risk of death for dostarlimab + CP until year 15, after which the risk between the two arms is similar. The EAG considers that the reduction in the risk of death for the CP is potentially due to the impact of treatment with a subsequent immunotherapy and that after 15 years, patients in both arms have similar risks due to the substantial length of time since they received immunotherapy.

Figure 13. Hazard rate plot over time based on company's preferred OS curves



Abbreviations: CP, carboplatin and paclitaxel; OS, overall survival.

4.2.3.6 EAG critique

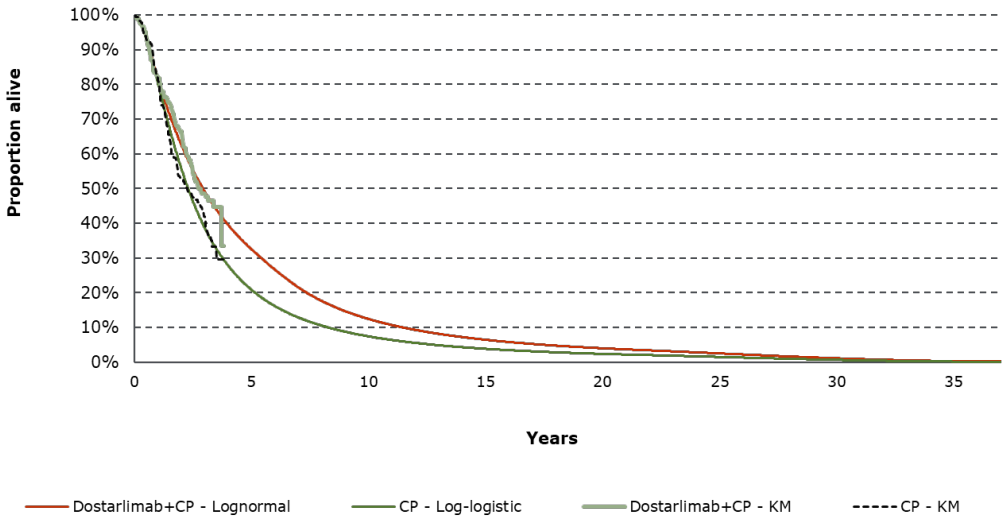
The EAG considers that the company's approach to OS is generally appropriate. The EAG notes that based on an investigation of the OS KM plot, there appears to be a convergence in the dostarlimab +

CP and placebo + CP curves from month 30, with the curves diverging again from month 36 (Figure 6 of the CS and Section 3.3.2 of this report). As such, the EAG considers that it is useful for committee to consider the company's treatment effect gradual waning scenario, where the risk of death for the dostarlimab + CP arm declines towards the risk of death for the CP arm between year five and seven. Figure 14 presents the OS curves and Figure 15 presents the hazard rate plot when gradual waning is applied. Implementation of the gradual waning scenario on OS increases the ICER from [redacted] to [redacted].

The EAG considers that while it is useful to explore the treatment effect waning scenario on OS, it should be noted that the tails of the OS KM curves are associated with considerable uncertainty due to a large amount of censoring. Additionally, as mentioned previously, the convergence in the OS KM curves is not maintained as from 36 months onwards, there is a divergence.

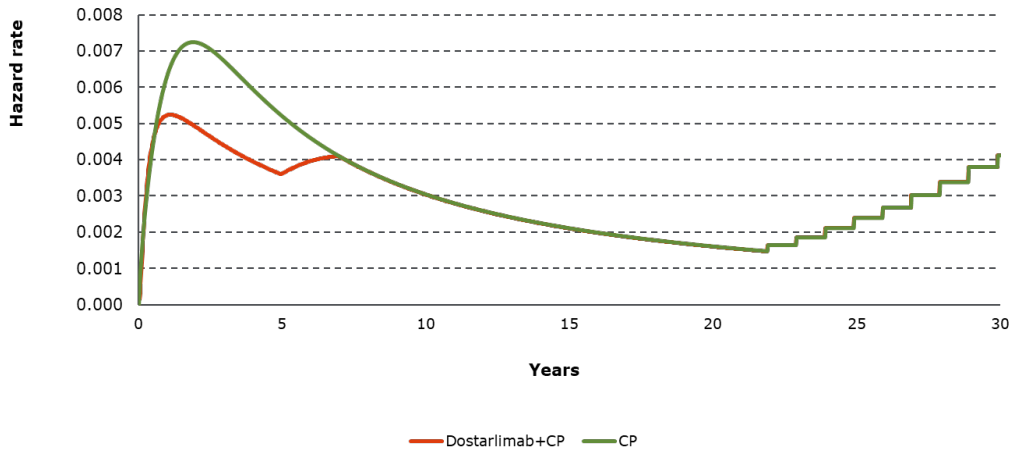
Therefore, the EAG has not included the treatment waning scenario in its preferred assumptions but instead explored it as a scenario around the EAG base case for committee consideration (see Section 6.3.1).

Figure 14. Company's base case overall survival curves with gradual treatment effect waning (between years 5 & 7) applied



Abbreviations: CP, carboplatin and paclitaxel.

Figure 15. Hazard rate plot over time based on company's preferred OS curves and gradual treatment effect waning (between years 5 & 7) applied



Abbreviations: CP, carboplatin and paclitaxel; OS, overall survival.

4.2.4 *Health-related quality of life*

Health state utility values (HSUVs) included in the model were derived from EQ-5D-5L data for the MMRp/MSS subgroup of the ITT population from RUBY-1 and mapped to the EQ-5D-3L using the approach recommended in the NICE manual.[37] Additionally, the company explored a scenario using HSUVs derived from the ITT population of RUBY-1 and found that this had minimal impact on the ICER. The HSUVs for the MMRp/MMS subgroup (company base case values) and the ITT population (scenario analysis only) from RUBY-1 are presented in Table 26.

In RUBY-1, EQ-5D-5L data were collected from the ITT population at baseline, each treatment cycle (every three weeks for the first six treatment cycles, then every six weeks thereafter), end of treatment, safety follow up (90±7 days after the last dose of the study drug), and at survival follow-ups, which occurred every 90±14 days after the safety follow-up visit. The ITT population comprised of patients who were randomised, even if no study treatment was received.

In their clarification response, the company explained that HSUVs were estimated using Generalized Estimating Equations (GEE) and were deemed appropriate as the method can accommodate correlated repeated measures and also directly estimate a population average. The company also clarified that a mixed model for repeated measures (MMRM) was used to analyse the EQ-5D data across different visits. The covariates included in the final GEE model were treatment, progression, and treatment x progression.

Table 26. Health state utility values from RUBY-1 (reproduced from Table 34 of the CS).

Health state	MMRp/MSS, mean (SE)	ITT, mean (SE)
Progression-free disease	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Abbreviations: CS, company submission; ITT, intention-to-treat; MMRp, mismatch repair proficient; MSS, microsatellite stable; SE, standard error.

Utilities in the model were adjusted for age, as per the NICE manual.[37] General population utility values for females adjusted for age were obtained from the HSE 2014 dataset, as recommended by the DSU.[43]

4.2.4.1 Adverse event disutility values

The company applied a utility decrement attributable to AEs in the first cycle of the model to reflect the impact of these events on a patient's HRQoL. Table 27 outlines the disutility associated with each AE included in the model and their source. See Section 3.3.7 for the AE inclusion criteria in the economic model and AE incidence based on RUBY-1 for the intervention and comparators. The total AE disutility impact for each treatment arm is 0.062 for dostarlimab + CP and 0.052 for CP.

Table 27. Adverse event disutilities (reproduced from Table 35 of the company submission)

Adverse event	Disutility	Source
Abdominal pain	-0.069	Swinburn *et al*. Elicitation of health state utilities in metastatic renal cell carcinoma.[44] Assumed equal to mucositis.
Anaemia	-0.119	Swinburn *et al*. Elicitation of health state utilities in metastatic renal cell carcinoma.[44]
ALT/ AST increased	-0.05	NICE TA813[45]
Asthenia	−0.073	Nafees *et al*. Health state utilities for non-small cell lung cancer.[46] Assumed equal to responding plus fatigue.
Hypertension	−0.020	NICE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (TA673).[47]
Hypokalaemia	−0.074	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411).[48]
Lipase increased	−0.010	Assumption
Lymphocyte count decreased	0.000	Assumed to be the same as neutrophil count decreased
Nausea and hyponatremia	-0.0450	NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779).[16]

Neutropenia	−0.090	Nafees *et al*. Health state utilities for non-small cell lung cancer.[46] Assumed equal to responding plus neutropenia
Neutrophil count decreased	0.000	Assumed to have no utility impact
Pulmonary embolism	−0.320	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411).[48]
Rash	−0.116	Assumed equal to hand and foot syndrome, Lloyd (2006).[49]
Urinary tract infection	−0.010	Assumption
White blood cell decreased	0.000	Assumed to have no utility impact

Abbreviations: ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; CP, carboplatin and paclitaxel; ITT, intention-to-treat.

4.2.4.2 EAG critique

The EAG considers the company's approach to utility and disutility values in the model is appropriate and robust.

4.2.5 Resource use and costs

In the economic model, the company included costs relevant to drug acquisition, administration, subsequent treatment, health states, adverse events and terminal care. Drug costs were sourced from the British National Formulary (BNF) or Electronic market information tool (eMIT).[50, 51] Drug administration costs and unit costs for health-state resource use were sourced from NHS 2023/24 National Cost Collection data dashboard and the Unit Costs of Health and Social Care 2023.[52, 53] The NHSCII inflation index from the Unit Costs of Health and Social Care 2023 manual was used to adjust costs to 2023 prices.[53]

The company has a confidential patient access scheme (PAS) discount of [redacted] on the list price of dostarlimab, and all results presented in this report are inclusive of the discount.

A confidential PAS discount is available for pembrolizumab and lenvatinib. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.4 for details on the source of the confidential price for each treatment.

4.2.5.1 *Drug acquisition and administration costs*

The list price of dostarlimab is £5,887.33 per 500 mg/ 10ml vial, and the price inclusive of the PAS discount is [redacted]. The treatment regimen for dostarlimab is 500 mg once every three weeks for the first six treatment cycles and then 1,000 mg once every six weeks, up to a maximum of three years, as per RUBY-1 and the SmPC.[39] The cost per treatment cycle of dostarlimab for the first six cycles is [redacted] and increases to [redacted] per treatment cycle from cycle seven onwards.

In RUBY-1, patients in either arm of the trial received carboplatin (area under curve [AUC] 5 mg/mL/min) and paclitaxel (175 mg/m²) once every three weeks for up to six cycles and this is what has been included in the economic model. Drug acquisition costs for carboplatin and paclitaxel are presented in Table 28, along with dose per cycle which was calculated based on the baseline characteristics for the MMRp/MSS population from RUBY-1 (see Section 2.3.1). Drug wastage was included in the model.

Table 28. Chemotherapy acquisition costs (reproduced from Table 37 of the CS)

Intervention	Unit size	Cost per unit (eMIT)[50]	Dose per treatment cycle	Units per dose	Total per cost per treatment cycle
Carboplatin	450 mg	£23.18	433.58 mg	1	£23.18
Paclitaxel	100 mg	£12.89	333.20 mg	4	£51.54

Abbreviations: eMIT, Drugs and pharmaceutical electronic market information tool.

Drug administration costs for the first 18 model cycles (applied to both treatment arms) and for model cycle 19 onwards (dostarlimab only) are presented in Table 29. Costs were sourced from the NHS 2023/24 National Cost Collection data dashboard.[52]

Table 29. Drug administration costs

Model cycle	Administration cost	Source
Model cycle 1-18	£201.66	NHS 2023/24 National Cost Collection data dashboard - SB13Z: Deliver complex parenteral chemotherapy at first outpatient attendance.[52]
Model cycle 19+	£152.13	NHS 2023/24 National Cost Collection data dashboard - SB12Z: Deliver simple parenteral chemotherapy at first outpatient attendance.[52]

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission.

The EAG considers the company's approach to drug acquisition and administration costs is appropriate.

4.2.5.2 *Treatment duration*

To estimate total drug acquisition and administration costs associated with CP for both arms of the model, the company used weighted completion rates for the six treatment cycles (18 weeks) of carboplatin and paclitaxel across both the dostarlimab and placebo arms observed in RUBY-1 for the MMRp/MSS subgroup of the ITT population (pooled data). Completion rates for carboplatin and paclitaxel are presented in Table 33 of the CS.

The company also used completion rates for the first six treatment cycles of dostarlimab in the model after which observed TTD KM data (presented in Figure 16), adjusted for relative dose intensity (RDI) ([redacted]) from RUBY-1 are used up to the three-year maximum treatment duration. The company ran a scenario where TTD KM data from RUBY-1 for both CP and dostarlimab are used instead of completion rates for the first six treatment cycles in the model. Table 30 presents the completion rates and TTD KM data for CP and dostarlimab from RUBY-1 that are used in the model. It should be noted that in RUBY-1, the ITT population comprised of all patients randomised even if no study treatment was received. As such, the completion rate for the first treatment cycle is not 100%, as not all patients in the MMRp/MSS subgroup of the ITT population initiated treatment.

Figure 16. Time to treatment discontinuation Kaplan-Meier curves from RUBY-1 (reproduced from Figure 4 of the company clarification response)

The EAG notes that TTD KM data from RUBY-1 showed that some patients continued dostarlimab treatment beyond three years and requested further explanation from the company regarding this at the clarification stage. The company explained that in RUBY-1, the investigator could request to continue treatment beyond three years if they believed a patient was still deriving clinical benefit and this request required approval from the study sponsor (Tesaro, GSK). For dostarlimab + CP TTD, the numbers at risk beyond 36 months were [redacted] (see Figure 4 of the company clarification response).

The company assumed the same time on treatment for CP (whether based on completion rates or TTD KM data) in both arms of the model for the first six treatment cycles. The EAG considers that assuming the same CP time on treatment would estimate the same total cost of CP for both treatment arms of the model. For the dostarlimab + CP arm of the model, time on treatment for both dostarlimab and CP is considered (either based on completion rates or TTD KM data) and the company assumed the maximum of the two values is used each cycle for the first six treatment cycles of the model.

Table 30. Comparison of dostarlimab and CP completion rates and TTD from RUBY-1

Treatment cycle	CP		Dostarlimab	
	Weighted completion rate (company base case)	TTD (scenario)	Completion rate (company base case)	TTD (scenario)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; TTD, time to treatment discontinuation

4.2.5.3 EAG critique

As mentioned previously, patients in RUBY-1 could continue receiving treatment beyond the maximum treatment duration if the investigator believed a patient was still deriving clinical benefit and if the study sponsor approved the request (six patients in the dostarlimab + CP arm of the RUBY-1) trial. In their clarification response, the company provided a scenario where the TTD curve for

dostarlimab + CP was not truncated at three-years and included data for the full follow up period, which increased the ICER from [redacted] to [redacted]. The marketing authorisation for dostarlimab states that treatment should not be given beyond three years. Thus, the EAG considers that in clinical practice, treatment beyond three years is unlikely to occur.

Nonetheless, the EAG has provided an extrapolation of dostarlimab + CP TTD data for committee consideration (Figure 17). The EAG reviewed the company's standard parametric curves and considered the Gompertz had good statistical and visual fit to the observed data. Based on the Gompertz curve, at [redacted] almost all patients have discontinued dostarlimab. The resulting ICER for the Gompertz TTD extrapolation is [redacted]. The EAG considers the extrapolation and resulting ICER is only illustrative as it is based on a [redacted] of patients continuing dostarlimab treatment beyond three years and does not align with the marketing authorisation for the drug.

Figure 17. Dostarlimab + CP time-to-treatment discontinuation extrapolation (Gompertz)

The EAG considers the use of completion rates for the first six cycles of treatment in either arm treatment costs for the first cycle in the model does not capture the full cost of starting treatment with CP or dostarlimab + CP (**Key issue 1**, Section 1). The EAG acknowledges that the data from RUBY-1 informing the model for clinical outcomes and TTD are based on the MMRp/MSS subgroup

of the ITT population and so does include a proportion of patients who were randomised but did not initiate treatment, so in that regard treatment costs and outcomes are aligned.

Nonetheless, in the NHS the full cost of the first treatment cycle is likely to be incurred and as such, the EAG considers that using the TTD KM data for both CP and dostarlimab + CP is more appropriate and is still based on the MMRp/MSS subgroup of the ITT population, thus maintaining the alignment with clinical outcomes. The EAG ran a scenario using TTD KM data for both arms of the model and dostarlimab RDI applied from cycle one and this increased the ICER from [redacted] to [redacted] and this scenario has been included in the EAG base case, presented in Section 6.3.

4.2.5.4 Health state resource use

The company elicited health state resource use from six clinicians experienced in the diagnosis and management of patients with primary advanced/recurrent EC in the UK. Unit costs of resources were obtained from the NHS 2023/24 National Cost Collection data dashboard and the Unit Costs of Health and Social Care 2023 Manual.[52, 53] Table 31 presents the company's weekly health state resource use assumptions included in the model.

In response to an EAG clarification question (B23), the company updated their base case to include the costs of investigation tests (thyroid function test, liver function test, kidney function test, cortisol level) for the dostarlimab + CP arm of the model. The cost for each test was £5.30 and taken from the NHS 2023/24 National Cost Collection data dashboard (DAPS03: clinical biochemistry [370 – medical oncology]) and added to the administration cost for dostarlimab to ensure the tests were aligned with treatment administration as per the EAG's clinical expert advice.[52]

Table 31. Health state resource use and costs

Resource	Unit cost	Unit cost source	Resource use per weekly cycle			
			Progression-free (up to week 18) – all treatment arms	Progression-free Carboplatin + paclitaxel (week 19+)	Progression-free Dostarlimab (week 19+)	Progressed disease (all treatment arms)
Outpatient visit	£205.82	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes WF01A-B	0.30	0.08	0.13	0.121

		(Outpatient visit [Oncology], first and follow up).[52]				
CT scan	£118.58	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes RD20A,RD21A, RD22-27Z (CT scan of 1-3+ areas).[52]	0.13	0.05	0.06	0.07
Complete blood count	£8.04	NHS 2023/24 National Cost Collection data dashboard – DAPS05: haematology.[52]	0.33	0.06	0.22	0.09
Specialist nurse visit	£61.01	Unit Costs of Health and Social Care 2023 Manual. Qualified nurse, band 6, uplifted to 2023 prices.[53]	0.11	0.07	0.07	0.10
GP visit	£50.30	Unit Costs of Health and Social Care 2023 Manual. Unit costs of a GP uplifted to 2023 prices.[53]	-	0.01	0.01	0.01
Total cost per weekly cycle	**-**	**-**	**£86.53**	**£27.65**	**£40.41**	**£40.33**
Abbreviations: CT, computed tomography; GP, general practitioner						

4.2.5.5 EAG critique

The EAG explored the company's health-state resource use assumptions with its clinical experts, and they advised that while on CP and immunotherapy, resources like outpatient visits and complete blood counts would be aligned with the treatment cycles. Additionally, computed tomography (CT)

scans would not be as frequent as the company has assumed in its base case (they would likely be once every three months on treatment and once every six months for patients with progressed disease). As such, the EAG requested, and the company supplied a scenario exploring the EAG's clinical expert assumptions (clarification question B23). Implementing the EAG's clinical expert assumptions had a negligible impact on the ICER (see Section 5.2.2).

The EAG considered that once patients discontinued treatment with dostarlimab after the maximum treatment duration of three years, health-state resource use might be reflective of patients in the CP arm who remain progression-free after week 18 in the model (**Key issue 2**, Section 1). The EAG's clinical experts considered that once a patient is off immunotherapy and still progression-free, there will likely be a reduction in the monitoring of the patients and so it would not be unreasonable to assume the same resource use as the CP arm of the model after week 18. As such, the EAG requested, and the company supplied a scenario where health-state resource use for the dostarlimab + CP arm of the model after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model. The requested scenario reduced the ICER from [redacted] to [redacted]. The EAG considers that it is appropriate to assume health-state resource use for the dostarlimab + CP after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model and has included this in the EAG base case, presented in Section 6.3.

The EAG identified minor discrepancies in the unit cost of a Band 6 qualified nurse and cost of a GP visit from the Unit Costs of Health and Social Care 2023 Manual.[53] The correct costs should be £57 per working hour for a Band 6 qualified nurse and £49 per surgery consultation lasting 10 minutes with a GP.[53] The EAG has run a scenario with the correct costs, presented in Section 6.2 and has included these in its preferred base case, presented in Section 6.3

4.2.5.6 Adverse event costs

Adverse event costs were calculated by multiplying the rate of each adverse event (see Section 3.3.7) by its respective unit cost (Table 32 below). Total AE costs per treatment arm were applied as a one-off cost in the first model cycle. The total one-off cost of AEs for the dostarlimab + CP arm of the model was £749.22 and £651.29 for the CP arm.

Table 32. Adverse event unit costs

Adverse event	Unit cost	Source
Anaemia	£612.92	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes SA04G, H, J, K, L (iron Deficiency Anaemia with CC Score 0-14+).[52]
Neutropenia	£560.68	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes SA08G, H, J (Other Haematological or Splenic Disorders, with CC Score 0-6+).[52]
Neutrophil count decreased	£901.96	NHS 2023/24 National Cost Collection data dashboard – RN13Z: nuclear Medicine Infection Scan or White Cell Scan.[52]
Hypertension	£360.74	NHS 2023/24 National Cost Collection data dashboard – EB04Z: hypertension (day case).[52]
White blood cell count decreased	£901.96	Assumed to be the same as neutrophil count decreased
Hypokalaemia	£1,789.88	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes FD04A-E (nutritional Disorders with Interventions, with CC Score 0-2+ and nutritional Disorders without Interventions, with CC Score 0-6+).[52]
Pulmonary embolism	£2,048.26	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes DZ09J-N and DZ09P-Q (pulmonary Embolus with Interventions, with CC Score 0-9+ and pulmonary Embolus without Interventions, with CC Score 0-12+).[52]
Lymphocyte count decreased	£901.96	Assumed to be the same as neutrophil count decreased
Lipase increased	£901.96	Assumed to be the same as neutrophil count decreased
Abdominal pain	£437.01	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes FD05A-B (abdominal Pain with Interventions [non-elective short stay] and abdominal Pain without Interventions [non-elective short stay]).[52]
Urinary tract infection	£2,020.71	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes LA04N, LA04P-S (kidney or Urinary Tract Infections, without Interventions, with CC Score 0-13+).[52]
Rash	£227.88	NHS 2023/24 National Cost Collection data dashboard – JD07K: skin disorders, without intervention, with CC score 0-1.[52]
Nausea and hyponatremia	£564.22	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes FD10J-M (non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-11+).[52]
ALT/ AST increased	£193.89	NHS 2023/24 National Cost Collection data dashboard – HRG code 370 – Medical Oncology consultant-led follow-up visit.[52]

Abbreviations: ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased; HRG, healthcare resource group

The EAG considers that the unit costs for AEs the company has sourced are reasonable and consistent with TA963.[36] Furthermore, changes to the unit costs have minimal impact on the ICER.

4.2.5.7 End of life costs

The company included a one-off end-of-life cost, applied upon transition to the death health state and represents the management costs associated with terminal care. In their updated base case, the company used a cost of £11,508, sourced from the Unit Costs of Health and Social Care Manual, which provides the cost of hospital care in the final year of life for cancer.[53] The EAG considers the company's approach is appropriate.

4.2.6 Subsequent treatments

On disease progression, a proportion of newly progressed patients were assumed to receive further lines of treatment. The types of subsequent treatments included in the economic model and the proportion of patients receiving each treatment were based on data from RUBY-1. Subsequent treatment data from RUBY-1 for the MMRp/MSS population, based on the proportion of patients with progressed disease, are presented in Appendix K.2, Table 82 of the CS and summarised below in Table 33.

In RUBY-1, [redacted] of patients in the dostarlimab + CP arm and [redacted] of patients in the CP arm went on to receive a subsequent line of treatment on progression and this has been included in the model.

Based on data from RUBY-1, patients in either treatment arm received subsequent immunotherapy, chemotherapy, hormone therapy, radiotherapy and bevacizumab. In the NHS, pembrolizumab with lenvatinib is the only second-line immunotherapy approved for use in the MMRp population and has been included in the economic model to represent patients receiving immunotherapy in RUBY-1. To represent chemotherapy, the company assumed the six most common chemotherapy regimens used in the NHS (presented in Table 33) and hormone therapy was assumed to be megestrol acetate.

Rechallenge with immunotherapy is not currently permitted in the NHS based on NHS England Blueteq criteria and so the company adjusted the RUBY-1 data for dostarlimab + CP to exclude immunotherapy use and redistribute the proportion amongst the chemotherapy regimens.

Additionally, bevacizumab does not have marketing authorisation for use in endometrial cancer and the EAG's clinical experts advised that it would not be used off-label in the NHS. In the company's original base case, based on RUBY-1 data, 8.8% of dostarlimab + CP patients and 5.6% of CP patients were assumed to receive subsequent bevacizumab.

During the clarification stage, the EAG advised that bevacizumab should be excluded from the analysis and the company updated base case, to redistribute the proportions assumed to receive bevacizumab across the other treatments. The company used the following calculation to redistribute the bevacizumab proportion across the other subsequent treatments:

$$Updated\ proportion = Original\ proportion \times (1 + \frac{Bevacizumab\ proportion}{Sum\ of\ non - bevacizumab\ treatments})$$

Table 33 presents the proportion of patients receiving each subsequent treatment included in the model.

Table 33. Proportion of patients receiving each subsequent treatment (reproduced from Table 31 of the company clarification response)

Subsequent treatment	Dostarlimab + CP	CP
Carboplatin and doxorubicin	4.80%	0.80%
Carboplatin and paclitaxel	14.40%	10.90%
Paclitaxel	6.40%	2.50%
Doxorubicin (and PLD)	35.10%	21.80%
Carboplatin	6.40%	1.70%
Pembrolizumab and lenvatinib	0.00%	51.20%
Cisplatin	3.20%	2.50%
Hormone therapy	16.00%	14.30%
Radiotherapy	23.00%	15.10%
Bevacizumab	0.00%	0.00%
No treatment	8.30%	0.00%

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission; PLD, Pegylated liposomal doxorubicin.

In the model, the cost and quality-adjusted life year (QALY) impact of subsequent treatments are based drug acquisition and administration costs, as well as disutility and costs associated with adverse events, with further details of each category provided in Sections 4.2.6.2 to 4.2.6.4.

The total costs and disutility impact of subsequent treatments are presented in Table 34 and are applied to newly progressed patients per cycle as a one-off cost and disutility upon health state entry. The estimation of newly progressed patients in described in Section 4.2.6.6.

Table 34. Total costs and disutility impact of subsequent treatments

Treatment arm	Total costs	Total AE disutility
Dostarlimab + CP	£2,054.93	0.051
CP	£48,580.34	0.056

Abbreviations: CP, carboplatin and paclitaxel.

4.2.6.1 EAG critique

The EAG considers that the company's approach to using RUBY-1 data and adjusting the data to reflect NHS practice is reasonable. However, the EAG considers that the company's approach to redistribute a proportion of bevacizumab usage to the pembrolizumab and lenvatinib combination treatment (increase of 2.4%) for the CP arm is problematic (**Key issue 3**, Section 1).

A study by Rubinstein *et al*. found that use of bevacizumab after one prior line of treatment for patients with advanced endometrial cancer (not limited to MMRp/MSS patients) resulted in a median PFS of 3.5 months and the overall conclusions found that the benefits of the treatment were "modest".[1] As such, the EAG considers that the clinical benefits of bevacizumab in the overall survival data from RUBY-1 are unlikely to be profound. Thus, eliminating the costs and but maintaining the benefit is not going to introduce substantial bias in the analysis, and can be considered akin (but to a lesser extent) to the usage of subsequent immunotherapy in the dostarlimab + CP arm of RUBY-1 without the associated costs in the economic model. However, increasing the usage, and thus the costs, of an effective treatment combination (pembrolizumab and lenvatinib) without the subsequent clinical benefits for the CP arm introduces bias in favour of the dostarlimab + CP arm of the model.

The EAG suggests that for the CP arm, redistributing the proportion of bevacizumab use among the other subsequent treatments, excluding pembrolizumab and lenvatinib, may be more appropriate. This aligns with the redistribution used for the dostarlimab + CP arm of the model. Furthermore, the EAG acknowledges that the proportion of immunotherapy use in the CP arm of the company's original base case (48.8%) was deemed reflective of UK clinical practice, based on advice received by

the EAG from the NHS England Cancer Drugs Fund (CDF) lead. Therefore, the EAG prefers the use of the unadjusted immunotherapy proportion in the CP arm, based on the observed RUBY-1 data.

The EAG ran a scenario where bevacizumab usage for the CP arm was redistributed amongst the non-immunotherapy subsequent treatments and results are presented in Section 6.2. The scenario resulted in an increase in the ICER from [redacted] to [redacted] and is included in the EAG base case, presented in Section 6.3.

4.2.6.2 Subsequent treatment acquisition, administration and monitoring costs

The dose regimens and durations of subsequent treatments included in the economic model are presented in Table 35. Drug costs and dose regimens were sourced from the BNF and the drug SmPCs.[51] Durations of each subsequent treatment were generally based on published median PFS data and mean time on treatment for pembrolizumab and lenvatinib.

The EAG notes that the list price for lenvatinib is the same for either 4 mg or 10 mg tablets (£1,437 per pack of 30 tablets). The EAG's clinical experts advised that dose reductions are common for patients on lenvatinib. Based on the flat pricing for lenvatinib, number of tablets rather than dose size has an impact on cost. For example, patients on the recommended dose of lenvatinib (20 mg) would consume two 10 mg tablets, and for the median dose of 13.8 mg given in Makker *et al*. would also result in the consumption of one 10 mg tablet and one 4 mg tablet, thus both doses require two tablets and so the cost would be equal.

Table 35. Subsequent treatment dose regimens, durations and costs included in the economic model

Treatment	Unit and Pack size	List price per pack	Treatment regimen	Dose per administration	Drug acquisition cost per administration	Treatment duration (months)	Number of regimen cycle received (over treatment duration)	Total treatment costs	Source
Paclitaxel	1 x 100 mg / 16.7 ml	£12.89	175 mg/m² once every 3 weeks	333.20 mg	£51.54	3.2	4.64	£239.06	BNF[51] RUBY-1
Doxorubicin	1 x 50 mg / 25 ml vial	£10.06	70 mg/m² once every 3 weeks	133.28 mg	£30.18	2.1	3.04	£91.86	BNF[51] Makker *et al*. 2013[54]
Carboplatin	1 x 600 mg / 60 ml vial	£38.93	AUC 5 mg/mL/min once every 3 weeks	433.58 mg	£38.93	3.2	4.64	£180.58	BNF[51] RUBY-1
Pembrolizumab	1 x 100 mg / 4 ml vial	£2,630.00	200 mg once every 3 weeks	200 mg	£5,260.00	8.3	11.98	£63,019.81	BNF[51] Makker *et al*. 2022 (supplementary material)[55]
Lenvatinib	30 x 10 mg tablets	£1,437.00	20 mg once daily	20 mg	£95.80	8.3	251.80	£24,122.44	BNF[51] Makker *et al*. 2022 (supplementary material)[55]
Cisplatin	1 x 100 mg / 100 ml vial	£37.34	100 mg/m² once every 3 weeks	190.40 mg	£74.68	4.1	6.00	£448.12	BNF[51]
Hormone therapy (megestrol acetate)	30 x 160 mg tablets	£19.52	160.00 mg once daily	160 mg	£0.65	3.2	97.40	£63.37	BNF[51] Mileshkin *et al*. 2019[56]

Radiotherapy	N/A	N/A	N/A	N/A	£3,388.24	6.0	1.00	£3,620.79	NICE TA779[16]

Abbreviations: BNF, British National Formulary; N/A. not available.

Drug administration costs by type of treatment are presented in Table 36. The EAG notes that the company assumed an oral treatment administration cost for lenvatinib but not hormone therapy in the model.

Table 36. Subsequent treatment drug administration costs

Treatment type	Administration cost	Source
Intravenous infusion	£201.66	NHS 2023/24 National Cost Collection data dashboard - SB13Z: Deliver complex parenteral chemotherapy at first outpatient attendance.[52]
Oral	£247.13	NHS 2023/24 National Cost Collection data dashboard - SB11Z – Deliver Exclusively Oral Chemotherapy.[52]

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission.

The total drug acquisition and administration costs for each subsequent treatment are presented in Table 37.

Table 37. Total drug and administration costs of subsequent treatments

Subsequent treatment	Total drug acquisition cost	Total drug administration cost	Overall total costs
Carboplatin and doxorubicin	£272.44	£1,592.28	£1,864.72
Carboplatin and paclitaxel	£419.62	£1,870.64	£2,290.28
Paclitaxel	£239.06	£935.32	£1,174.37
Doxorubicin (and PLD)	£91.86	£656.95	£748.81
Carboplatin	£180.58	£935.32	£1,115.90
Pembrolizumab and lenvatinib	£87,142.25	£4,660.15	£91,802.40
Cisplatin	£448.12	£1,120.07	£1,658.19
Hormone therapy	£63.37	-	£63.37
Radiotherapy	£3,620.79	-	£3,620.79

Abbreviations: PLD, Pegylated liposomal doxorubicin.

As part of their updated base case and to reflect health-state resource assumptions made for dostarlimab, the company included the cost of investigational tests (thyroid function test, liver function test, kidney function test, cortisol level) for pembrolizumab with lenvatinib. The cost for each test was £5.30 and taken from the NHS 2023/24 National Cost Collection data dashboard (DAPS03: clinical biochemistry [370 – medical oncology]).[52] The total cost of monitoring for pembrolizumab with lenvatinib in the company's base was £253.83.

4.2.6.3 EAG critique

The EAG was concerned by the application of an oral administration cost for lenvatinib, as this is biased against the CP arm of the model and in the clarification stage, asked the company to justify the assumption (**Key issue 4**, Section 1). The company explained that inclusion of an oral administration cost is consistent with the previous appraisals of lenvatinib for other indications (TA498 and T858), as well as the budget impact analysis for cabozantinib in untreated renal cell carcinoma (TA964).[57-59] The company also considered that use of lenvatinib requires specialist oversight in terms of procurement, prescribing, dispensing and administration. However, the EAG considers that patients are likely to take lenvatinib at home and typically oral oncology drugs are convenient for patients because they do not need to go to hospital for treatment.[60] As such, the EAG considers it is preferable to exclude oral administration costs for lenvatinib and this is included in the EAG base case, presented in Section 6.3.

The EAG notes a minor issue with the cost used for subsequent carboplatin. In the model, the average dose per administration of subsequent carboplatin was assumed to 433.58 mg, which is the same as the dose assumed for first-line carboplatin in the economic model. However, the company applied the unit cost for carboplatin 600 mg (£38.93) instead of the cheaper, and less wasteful, pack size of 450 mg (£23.18). The EAG ran a scenario using the unit cost of carboplatin 450 mg, presented in Section 6.2 and notes it has minimal impact on the ICER. Nonetheless, for accuracy, the EAG has used the unit cost of carboplatin 450 mg for subsequent treatment costs in its preferred assumptions, presented in Section 6.3.

4.2.6.4 Adverse events for subsequent treatments

The company included the impact of AEs related to subsequent treatments in the model based on published data for each treatment. Adverse events from the published literature were included if they were reported to occur in each treatment in at least 2% of patients. Table 38 outlines the subsequent treatment AEs rates that have been included in the company base case.

The EAG notes that subsequent chemotherapy includes single agent carboplatin, paclitaxel, doxorubicin (including PLD) and cisplatin, as well as combination treatments including carboplatin and doxorubicin, and carboplatin and paclitaxel. Additionally, AEs related to radiotherapy were not included in the economic model due to lack of data availability.

Table 38. Subsequent treatment adverse event rates

Adverse event	Platinum-based chemotherapy (Gladieff *et al.*)[61] (N = 180)		Doxorubicin (and PLD) (Miller *et al.*)[62] (N = 249)		Pembrolizumab and lenvatinib (Makker *et al.*)[55] (N = 246)		Hormone therapy (Mileshkin *et al.*)[56] (N = 82)	
	n	(%)	n	(%)	n	(%)	n	(%)
Anaemia	0	-	38	15.3%	25	6.2%	0	-
Neutropenia	91	50.6%	112	45.0%	0	-	0	-
Neutrophil count decreased	0	-	25	10.0%	0	-	0	-
Hypertension	0	-	0	-	154	37.9%	0	-
White blood cell count decreased	0	-	20	8.0%	0	-	0	-
Asthenia	0	-	14	5.6%	0	-	0	-
Fatigue	15	8.3%	14	5.6%	21	5.2%	7	8.5%
Leukopenia	0	-	45	18.1%	0	-	0	-
Nausea	0	-	13	5.2%	0	-	0	-
Vomiting	0	-	13	5.2%	0	-	0	-
Diarrhoea	0	-	0	-	31	7.6%	0	-
Decreased appetite	0	-	0	-	32	7.9%	0	-
Weight decrease	0	-	0	-	42	10.3%	0	-
Proteinuria	0	-	0	-	22	5.4%	0	-

Abbreviations: CP, carboplatin and paclitaxel; PLD, pegylated liposomal doxorubicin.

Note: Adverse events for platinum-based chemotherapy are taken from a study by Gladieff *et al.* and are for carboplatin and paclitaxel. The company has assumed the same AE rates apply for single agent carboplatin, paclitaxel, and cisplatin, combination carboplatin and doxorubicin. Doxorubicin-related AEs were taken from Miller *et al.*[62] AEs for hormone therapy were assumed by the company to reflect the safety profile of anastrozole.

Table 39 presents the disutilities associated with additional AEs for subsequent treatments not covered in Section 4.2.4.1. Disutilities were sourced from previous NICE guidance for dostarlimab for previously treated advanced or recurrent endometrial cancer with MSI-H or dMMR (TA779) and lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858).[16, 57]

Table 39. Additional subsequent adverse event disutilities

Adverse event	Disutility	Source
Fatigue	0.07	NICE TA779[16]
Leukopenia	0.09	NICE TA779[16]
Nausea	0.05	NICE TA779[16]

Vomiting	0.10	NICE TA779[16]
Diarrhoea	0.26	NICE TA858[57]
Decreased appetite	0.04	NICE TA858[57]
Weight decrease	0.04	NICE TA858[57]
Proteinuria	0.08	NICE TA858[57]

The AE disutility associated with each subsequent treatment estimated using the AE rates presented in Table 38 are available in Appendix K.1 (Table 81) of the CS. The total AE disutility impact for each treatment arm based on the proportion of patients receiving each subsequent treatment (presented in Table 33) is 0.051 for dostarlimab + CP and 0.056 for CP.

Subsequent treatment adverse event costs were calculated by multiplying the rate of each adverse event by its respective unit cost. Unit costs for AEs are presented in Section 4.2.5.5 and in Table 32 for additional AEs not previously described. The cost of AEs associated with each subsequent treatment are presented in Table 44 of the CS.

The total cost of subsequent treatment AEs for each treatment arm based on the proportion of patients receiving each subsequent treatment (presented in Table 33) was £333.04 for dostarlimab + CP and £398.61 for CP.

Table 40. Additional subsequent treatment adverse event unit costs

Adverse event	Unit cost	Source
Fatigue	0.00	NICE TA779[16]
Leukopenia	£560.68	Assumed to be equal to neutropenia.
Nausea	£522.60	NICE TA779[16] Inflated to 2023 prices.
Vomiting	£522.60	NICE TA779[16] Inflated to 2023 prices.
Diarrhoea	£696.19	NICE TA858[57]
Decreased appetite	£822.00	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG LB06N-S (Kidney, Urinary Tract or Prostate Neoplasms, without Interventions, with CC Score 0-13+ [non-elective short stay]).[52]
Weight decrease	£577.55	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG codes FD04A-E (Nutritional Disorders with Interventions, with CC Score 0-2+ [non-elective short stay] and Nutritional Disorders without Interventions, with CC Score 0-6+ [non-elective short stay]).[52]
Proteinuria	£759.80	NHS 2023/24 National Cost Collection data dashboard – weighted average of HRG LA09M-Q (General Renal Disorders without Interventions, with CC Score 0-9+ [non-elective short stay]) and WF01A (Non-Admitted Face-to-Face Attendance, Follow-up).[52]

Abbreviations: HRG, healthcare resource group

4.2.6.5 EAG critique

The company justified the inclusion of subsequent treatment AE costs and disutility as consistent with the approach to include AE impacts for initial treatment, especially as the included subsequent treatments are associated with AEs. The EAG notes that follow-up for OS is nearly four years and so it may not be unreasonable that the impacts of AEs for subsequent treatment may be fully realised in the OS data from RUBY-1. The inclusion of subsequent treatment AE costs and disutility are only relevant to the comparator due to the usage of subsequent immunotherapy. The observed OS in RUBY-1 is too immature to capture the full benefits of subsequent immunotherapy for the CP arm. In particular, the QALY benefits of immunotherapy for the CP arm, in terms of utility associated with PFS2, are not captured as only utility associated with progressed disease is applied in the model. Thus, the company's approach is potentially biased because it only captures the negative impacts of immunotherapy for the CP. As such, the EAG requested, and the company supplied a scenario where AE costs and disutility were excluded and this had minimal impact on the ICER (see Section 5.2.2), demonstrating that it is not a key driver of cost-effectiveness.

4.2.6.6 Estimation of newly progressed patients

To estimate the proportion of newly progressed patients per model cycle, the company assumed that a constant proportion PFS events would be non-fatal progression events ([redacted]). The proportion of non-fatal progression events applied in the model was based on data from RUBY-1, where it was observed that [redacted] of PFS events were fatal ([redacted]) and thus the remainder were non-fatal progression events.

4.2.6.7 EAG critique

During the clarification stage, the EAG requested time-to-progression (TTP) data for the MMRp/MSS subgroup of the ITT population from RUBY-1 to understand the pattern of observed new progressions over the follow-up period. The company provided the TTP KM curves (Figure 6 of the company clarification response) as a breakdown of PFS events categorised by either progression or death (Table 41 below).

Consistent with the EAG's clinical expert advice that disease progression in the MMRp/MSS population occurs early, Table 41 demonstrates that most PFS events are disease progression, predominantly within the first year of follow-up and this is reflected in the modelling of the progressed disease health state, where most progression events occur in by 1.2 years. The EAG notes that based on the data from RUBY-1, OS events predominantly occur after disease progression. Furthermore, subsequent treatment costs for newly progressed patients, based on the company's constant proportion of [redacted] for non-fatal events, peak at around six months for both arms of the model.

The EAG considers, that based on the evidence provided by the company, the use of a constant proportion for non-fatal progression events to estimate newly progressed patients per cycle is not an unreasonable simplification, especially as the company's modelled risk of progression for both arms of the model declines over time (see Section 4.2.3.3).

Table 41. Progression events categorised by progression and death events - MMRp/MSS population (reproduced from Table 27 of the company clarification response)

Month	Dostarlimab + CP (N=192)			Placebo + CP (N=184)		
	PFS events	No. of progressions (%)	No. of deaths (%)	PFS events	No. of progressions (%)	No. of deaths (%)
0	0	[redacted]	[redacted]	0	[redacted]	[redacted]
2	9	[redacted]	[redacted]	10	[redacted]	[redacted]
4	10	[redacted]	[redacted]	12	[redacted]	[redacted]
6	26	[redacted]	[redacted]	31	[redacted]	[redacted]
8	20	[redacted]	[redacted]	30	[redacted]	[redacted]
10	21	[redacted]	[redacted]	17	[redacted]	[redacted]
12	6	[redacted]	[redacted]	12	[redacted]	[redacted]
14	2	[redacted]	[redacted]	2	[redacted]	[redacted]
16	5	[redacted]	[redacted]	8	[redacted]	[redacted]
18	4	[redacted]	[redacted]	2	[redacted]	[redacted]
20	5	[redacted]	[redacted]	0	[redacted]	[redacted]
22	1	[redacted]	[redacted]	1	[redacted]	[redacted]
24	3	[redacted]	[redacted]	3	[redacted]	[redacted]
26	1	[redacted]	[redacted]	1	[redacted]	[redacted]
28	0	[redacted]	[redacted]	0	[redacted]	[redacted]
30	1	[redacted]	[redacted]	1	[redacted]	[redacted]
32	1	[redacted]	[redacted]	0	[redacted]	[redacted]
34	1	[redacted]	[redacted]	0	[redacted]	[redacted]

Abbreviations: CP, carboplatin plus paclitaxel; PFS, progression-free survival.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 42 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of 0.76 over carboplatin and paclitaxel (CP) along with [redacted] for dostarlimab + CP, generates an incremental cost-effectiveness ratio (ICER) of [redacted]. The net health benefit (NHB) based on the probabilistic results using the £20,000 and £30,000 threshold is [redacted] and [redacted] respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 42. Company's base case results (post clarification)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

A PSA scatterplot is presented in Figure 18 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 19.

Figure 18. Scatterplot of PSA estimates on a cost-effectiveness plane (reproduced from Figure 13 of the company clarification response

Figure 19. Cost-effectiveness acceptability curve (reproduced from Figure 14 of the company clarification response)

5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagram presented in Figure 20.

The ICER was most sensitive to the dostarlimab completion rates per cycle and the number of outpatient visits associated with the progression-free (week 19+) and progressed disease health states.

Figure 20. Tornado plot (reproduced from Figure 15 of the company clarification response)

5.2.2 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 43. In addition, the company conducted several additional scenario analyses requested by the External Assessment Group (EAG), also presented in the tables below.

Table 43. Company deterministic scenario analysis

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	**Company base case**	[redacted]	**0.755**	[redacted]
1	Starting age - 65.5 (UK RWE)	[redacted]	0.748	[redacted]
2	Annual discount rate for costs and QALYs – 1.5%	[redacted]	0.905	[redacted]
3	Annual discount rate for costs and QALYs – 5%	[redacted]	0.666	[redacted]
4	PFS Curve selection (CP) - Odds, k=2 flexible spline model	[redacted]	0.750	[redacted]
5	PFS curve selection (dostarlimab+CP) - Normal, k=2 flexible spline model	[redacted]	0.747	[redacted]
6	PFS curve selection - Independent models (CP, log-logistic; dostarlimab, generalised gamma)	[redacted]	0.745	[redacted]
7	OS curve selection (dostarlimab+CP) - Independent, log-logistic	[redacted]	0.650	[redacted]
8	Treatment effect waning: OS and PFS - Waning from 8-10 years	[redacted]	0.711	[redacted]
9	Treatment effect waning: OS and PFS - Waning from 5-7 years	[redacted]	0.615	[redacted]
10	TTD Completion rates – TTD KM data used instead of completion rates	[redacted]	0.755	[redacted]
11	Vial wastage – no vial wastage	[redacted]	0.755	[redacted]
12	Adverse event threshold - Grade 3+ AEs ≥5% in either arm of RUBY-1	[redacted]	0.755	[redacted]
13	Subsequent treatment assumptions - Equal proportion receiving no treatment (set to dostarlimab proportion for both)	[redacted]	0.755	[redacted]
14	Subsequent treatment assumptions - 75% market share assumed for PEM+LEN in CP proportions	[redacted]	0.755	[redacted]
15	Utility values - ITT RUBY-1 source	[redacted]	0.752	[redacted]
16	AE disutilities excluded	[redacted]	0.755	[redacted]
17	No age adjustment for utilities	[redacted]	0.797	[redacted]
EAG requested scenarios				
B6	TTD KM used for full follow-up period (Up to cycle 187)	[redacted]	0.755	[redacted]
B10	Doubled AE rates in both arms (1L and 2L)	[redacted]	0.755	[redacted]
B11	Exclude AE disutilities for subsequent treatments	[redacted]	0.755	[redacted]
B12	Exclude AE costs for subsequent treatments	[redacted]	0.755	[redacted]
B15	Use dostarlimab+CP arm completion rates for CP	[redacted]	0.755	[redacted]
B20	Exclude Admin cost for Lenvatinib	[redacted]	0.755	[redacted]
B22	Set resource use equal after 3 years in the PF state	[redacted]	0.755	[redacted]
B23	Use EAG clinical expert resource use	[redacted]	0.755	[redacted]

B26	Apply PSSRU end of life cost to those dying from PD only	[redacted]	0.755	[redacted]
B28	Equal TTD to PFS	[redacted]	0.755	[redacted]

Abbreviations: 1L, first-line; 2L, second-line; AE, adverse events; CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RWE, real-world evidence; TTD, time-to-treatment discontinuation.

5.3 Model validation and face validity check

Section 3.13 in the company submission outlines the company's approach to the validation of the economic model. Generally, the EAG is satisfied that the company's approach to model validation was robust.

6 Additional economic analysis undertaken by the EAG

6.1 Exploratory and sensitivity analyses undertaken by the EAG

In Section 4 of this report, the External Assessment Group (EAG) describes several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The scenarios that the EAG performed are as follows:

1. Use of the ONS life tables from 2017-2019, as per guidance in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 23 – Section 4.2.3.2.
2. Correct unit costs from The Unit Costs of Health and Social Care 2023 Manual (£57 per working hour for a Band 6 qualified nurse and £49 per surgery consultation lasting 10 minutes with a GP) – Section 4.2.5.5.
3. Time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one – Section 4.2.5.3
4. Bevacizumab usage for the carboplatin and paclitaxel (CP) arm of the model redistributed amongst the non-immunotherapy subsequent treatments – Section 4.2.6.1.
5. Unit cost of carboplatin 450 mg used for subsequent treatment cost – Section 4.2.6.3.
6. Full time-to-treatment discontinuation (TTD) extrapolation (Gompertz) used for dostarlimab + CP arm of the model – Section 4.2.5.3.

6.2 EAG scenario analysis

Table 44 presents the results of the EAG exploratory analyses described in Section 6.1. Results reported include the company's patient access scheme (PAS) discount on the list price of [redacted] for dostarlimab.

Confidential PAS discounts are available for pembrolizumab and lenvatinib, which are included in the model as subsequent treatments. As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

Table 44. Results of the EAG's deterministic scenario analyses

	Results per patient	Dostarlimab + CP	CP	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
1	ONS life tables from 2017-2019			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.76
	ICER (£/QALY)	-	-	[redacted]
2	Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
3	TTD KM data for both treatment arms and dostarlimab RDI applied from cycle one			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
4	Redistribution of bevacizumab usage across non-immunotherapy subsequent treatments			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
5	Unit cost of carboplatin 450 mg used for subsequent treatment cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
6	TTD Gompertz extrapolation for Dostarlimab + CP			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred base case for the cost-effectiveness of dostarlimab in addition to platinum-based chemotherapy (dostarlimab + CP) for the treatment of patients with newly diagnosed primary advanced or recurrent endometrial cancer (EC) that is mismatch repair proficient (MMRp) or microsatellite stable (MSS). The assumptions that form the EAG's preferred base case are listed below.

- Use of the ONS life tables from 2017-2019, as per guidance in the NICE DSU TSD 23.

- Time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one.
- Correct nurse and GP costs sourced directly from The Unit Costs of Health and Social Care 2023 Manual.
- Health-state resource use for the dostarlimab + CP after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model.
- Bevacizumab usage for the CP arm of the model redistributed amongst the non-immunotherapy subsequent treatments.
- Removal of oral administration costs for lenvatinib.
- Unit cost of carboplatin 450 mg used for subsequent treatment cost.

Table 45 presents the deterministic EAG base case. Probabilistic results for the EAG base case are presented in Table 46. Results of the scenarios around the EAG base case (Section 6.3.1) are deterministic as performing probabilistic sensitivity analysis (PSA) in the company's model is time intensive. However, the EAG considers that, based on the base case results, deterministic and probabilistic results are consistent with each other.

Table 45. EAG's preferred model assumptions (deterministic)

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case	-	[redacted]	0.75	[redacted]
ONS life tables from 2017-2019	4.2.3.2	[redacted]	0.76	[redacted]
TTD KM data for both treatment arms and dostarlimab RDI applied from cycle one	4.2.5.3	[redacted]	0.76	[redacted]
Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual	4.2.5.5	[redacted]	0.76	[redacted]
Set health-state resource use for dostarlimab + CP equal to CP after 3 years in the PF health state	4.2.5.5	[redacted]	0.76	[redacted]
Redistribution of bevacizumab usage across non-immunotherapy subsequent treatments	4.2.6.1	[redacted]	0.76	[redacted]
Removal of oral administration costs for lenvatinib	4.2.6.3	[redacted]	0.76	[redacted]
Unit cost of carboplatin 450 mg used for subsequent treatment cost	4.2.6.3	[redacted]	0.76	[redacted]
EAG preferred base case	**-**	[redacted]	**0.76**	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

Table 46. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

6.3.1 Scenarios around the EAG base case

The EAG has explored the assumption of gradual treatment effect waning on overall survival around its preferred base case to assess the impact on the ICER. Results of the EAG's scenario are presented in Table 47.

Table 47. Deterministic results of the EAG's scenario around the EAG base case

	Results per patient	Dostarlimab + CP	CP	Incremental value
0	EAG base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.76
	ICER (£/QALY)	-	-	[redacted]
1	Gradual treatment effect waning on overall survival (5-7 years)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.62
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.4 Conclusions of the cost effectiveness sections

The EAG considers the company's submitted cost-effectiveness analysis adheres to the decision problem defined in the NICE final scope.[24] The EAG's preferred assumptions increase the company's base case ICER by less than [redacted] and [redacted]

[redacted]. However, these ICERs do not include the confidential PAS discounts for lenvatinib and pembrolizumab. Please see the EAG's confidential appendix to the EAG report.

Three key assumptions in the EAG base case are relatively more important for decision making. These include the approach to modelling TTD from the start of the model time horizon, health-state resource use for dostarlimab + CP patients who are progression-free after the maximum treatment duration of three years, and assumptions informing subsequent treatment costs for the CP arm of the model. Nevertheless, the alternative assumptions implemented in the EAG's base case have addressed the issues the EAG identified with the company's approach.

7 References

1. Rubinstein MM, Dickinson S, Narayan P, Zhou Q, Iasonos A, Ma W, et al. Bevacizumab in advanced endometrial cancer. *Gynecol Oncol* 2021; **161**: 720-6.
2. Cancer Research UK. Uterine cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence. Date accessed: March 2025.
3. Jeppesen MM, Mogensen O, Hansen DG, Iachina M, Korsholm M, Jensen PT. Detection of recurrence in early stage endometrial cancer - the role of symptoms and routine follow-up. *Acta Oncol* 2017; **56**: 262-9.
4. National Health Service England. Cancer Registration Statistics, England, 2022., 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2022#. Date accessed: March 2025.
5. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. *Gynecol Oncol* 2006; **101**: 520-9.
6. Ryan NAJ, McMahon R, Tobi S, Snowsill T, Esquibel S, Wallace AJ, et al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. *PLoS Med* 2020; **17**: e1003263.
7. Pećina-Šlaus N, Kafka A, Salamon I, Bukovac A. Mismatch Repair Pathway, Genome Stability and Cancer. *Front Mol Biosci* 2020; **7**: 122.
8. Mulet-Margalef N, Linares J, Badia-Ramentol J, Jimeno M, Sanz Monte C, Manzano Mozo JL, et al. Challenges and Therapeutic Opportunities in the dMMR/MSI-H Colorectal Cancer Landscape. *Cancers (Basel)* 2023; **15**.
9. Li G-M. Mechanisms and functions of DNA mismatch repair. *Cell Research* 2008; **18**: 85-98.
10. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *International Journal of Gynecologic Cancer* 2021; **31**: 12-39.
11. Kalampokas E, Giannis G, Kalampokas T, Papathanasiou AA, Mitsopoulou D, Tsironi E, et al. Current Approaches to the Management of Patients with Endometrial Cancer. *Cancers (Basel)* 2022; **14**.
12. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *J Clin Oncol* 2020; **38**: 3841-50.
13. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2008; **18**: 803-8.
14. Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: Recommendations for practice. *European journal of obstetrics, gynecology, and reproductive biology* 2022; **270**: 50-89.
15. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology* 2022; **33**: 860-77.
16. National Institute for Health and Care Excellence. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779], 2022. Available from: https://www.nice.org.uk/guidance/ta779/documents/committee-papers Date accessed: March 2025.

17. National Institute for Health and Care Excellence. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer [TA904], 2023. Available from: https://www.nice.org.uk/guidance/ta904 Date accessed: March 2025.
18. National Institute for Health and Care Excellence. Technology appraisal guidance [TA914] Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency, 2023. Available from: https://www.nice.org.uk/guidance/ta914. Date accessed: March 2025.
19. Medicines & Healthcare products Regulatory Agency (MHRA). Jemperli (Dostarlimab) Summary of Product Characteristics, 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/b929cf3b61f35467e313e286bfc12c919929e963. Date accessed: March 2025.
20. National Health Service England. National Cancer Drugs Fund, 2025. Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Date accessed: March 2025.
21. National Institute for Health and Care Excellence. Technology appraisal guidance [TA904] Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer., 2023. Available from: https://www.nice.org.uk/guidance/ta904 Date accessed: March 2025.
22. Oaknin A, Pothuri B, Gilbert L, Sabatier R, Brown J, Ghamande S, et al. Safety, Efficacy, and Biomarker Analyses of Dostarlimab in Patients with Endometrial Cancer: Interim Results of the Phase I GARNET Study. *Clinical Cancer Research* 2023; **29**: 4564-74.
23. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. *J Clin Oncol* 2020; **38**: 2981-92.
24. National Institute for Health and Care Excellence. Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency - Final Scope [ID6415], 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11503/documents/final-scope. Date accessed: March 2025.
25. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 2008; **26**: 677-704.
26. Wagner VM, Backes FJ. Do Not Forget about Hormonal Therapy for Recurrent Endometrial Cancer: A Review of Options, Updates, and New Combinations. *Cancers (Basel)* 2023; **15**.
27. National institute for Health and Care Excellence. NICE health technology evaluations: the manual. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 (accessed on: January 2025). 2022.
28. Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. *Annals of Oncology* 2024.
29. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. *The New England journal of medicine* 2023; **388**: 2145-58.
30. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY) [Internet]. 2019. Available from: https://clinicaltrials.gov/study/NCT03981796.
31. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 19-Janurary-2024 (data cut off: 22-SEP-2023).
32. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in

Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 07-March-2023 (data cut off: 28-SEP-2022).
33. Clarke NA, Braverman J, Worthy G, Shaw JW, Bennett B, Dhanda D, et al. A Review of Meaningful Change Thresholds for EORTC QLQ-C30 and FACT-G Within Oncology. *Value in Health* 2024; **27**: 458-68.
34. GSK. Data on file. ru_uk_t_stat_p3.
35. Papaioannou D, Brazier, J.E., Paisley, S. NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature, 2011. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: March 2025.
36. National Institute for Health and Care Excellence. Dostarlimab with platinum-containing chemotherapy for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA963], 2024. Available from: https://www.nice.org.uk/guidance/ta963 Date accessed: March 2025.
37. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 Date accessed: March 2025.
38. Hernández-Alava M, Pudney S. Mapping between EQ-5D-3L and EQ-5D-5L: A survey experiment on the validity of multi-instrument data. *Health Economics* 2022; **31**: 923-39.
39. European Medicines Agency. Imfinzi Summary of Product Characteristics, 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Date accessed: March 2025.
40. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data, 2011. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: March 2025.
41. Rutherford M, Lamber, P., Sweeting, MJ., Pennington, B., Crowther, MJ., Abrams, KR., Latimer, NR. NICE DSU technical support document 21: Flexible Methods for Survival Analysis., 2020. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: March 2025.
42. Office of National Statistics. National life tables – life expectancy in the UK: 2020 to 2022. 2024. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2020to2022. Date accessed: March 2025.
43. Wailoo A. A guide to calculating burden of illness for NICE Evaluations: Technical Support Document 23, 2024. Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list. Date accessed: March 2025.
44. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin* 2010; **26**: 1091-6.
45. National Institute for Health and Care Excellence. Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [TA813], 2022. Available from: https://www.nice.org.uk/guidance/ta813/history. Date accessed: March 2025.
46. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008; **6**: 84.
47. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy, 2021. Available from: https://www.nice.org.uk/guidance/ta673/history. Date accessed.
48. National Institute for Health and Care Excellence. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer [TA411]. 2016. Available from: https://www.nice.org.uk/guidance/ta411 Date accessed: March 2025.

49. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer* 2006; **95**: 683-90.
50. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2023. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: March 2025.
51. National Institute for Health and Care Excellence. British National Formulary. 2025. Available from: https://bnf.nice.org.uk/. Date accessed: March 2025.
52. NHS England. National Schedule of NHS Costs 2023/24. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Date accessed: March 2025.
53. PSSRU. Unit Costs of Health and Social Care Programme (2022–2027). 2024. Available from: https://www.pssru.ac.uk/unitcostsreport/. Date accessed: March 2025.
54. Makker V, Hensley ML, Zhou Q, Iasonos A, Aghajanian CA. Treatment of advanced or recurrent endometrial carcinoma with doxorubicin in patients progressing after paclitaxel/carboplatin: Memorial Sloan-Kettering Cancer Center experience from 1995 to 2009. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2013; **23**: 929-34.
55. Makker V, Colombo N, Casado Herraez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *The New England journal of medicine* 2022; **386**: 437-48.
56. Mileshkin L, Edmondson R, O'Connell RL, Sjoquist KM, Andrews J, Jyothirmayi R, et al. Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial - ANZGOG 0903. *Gynecol Oncol* 2019; **154**: 29-37.
57. National Institute for Health and Care Excellence. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [TA858], 2023. Available from: https://www.nice.org.uk/guidance/ta858/history. Date accessed: March 2025.
58. National Institute for Health and Care Excellence. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [TA498], 2018. Available from: https://www.nice.org.uk/guidance/ta498/history. Date accessed: March 2025.
59. National Institute for Health and Care Excellence. Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [TA964], 2024. Available from: https://www.nice.org.uk/guidance/ta964/history. Date accessed: March 2025.
60. Macmillan Cancer Support. Lenvatinib. 2025. Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/lenvatinib. Date accessed: March 2025.
61. Gladieff L, Ferrero A, De Rauglaudre G, Brown C, Vasey P, Reinthaller A, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. *Ann Oncol* 2012; **23**: 1185-9.
62. Miller DS, Scambia G, Bondarenko I, Westermann AM, Oaknin A, Oza AM, et al. ZoptEC: Phase III randomized controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (NCT01767155). *Journal of Clinical Oncology* 2018; **36**: 5503-.
63. National Institute for Health and Care Excellence (NICE). Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template, 2015. Available from: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-and-highly-specialised-technologies-evaluation-user-guide-for-company-evidence-submission-template-pdf-72286715419333. Date accessed: March 2025.

8 Appendices

8.1 Baseline characteristics for the MMRp/MSS population in RUBY-1

Table 48. Summary of baseline characteristics in the MMRp/MSS population of RUBY-1 (Reproduced from CS Table 5)

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Age Group, n (%)		
19–64	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Weight (kg)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Height (cm)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BMI (kg/m^2)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BSA (m^2)		
Mean (SD)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ECOG PS, n (%)		
0	[redacted]	[redacted]

1	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.15 [32].
Abbreviations: BMI, body mass index; BSA, body surface area; CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; MMRp, mismatch repair proficient; MSS, microsatellite stability; PS, performance status; SD, standard deviation.

Table 49. Summary of disease history in MMRp/MSS population (Reproduced from CS Table 6)

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
FIGO stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at diagnosis		
Carcinosarcoma	[redacted]	[redacted]
Clear cell adenocarcinoma	[redacted]	[redacted]
Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]
Mucinous adenocarcinoma	[redacted]	[redacted]
Other	[redacted]	[redacted]
Serous adenocarcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[redacted]	[redacted]
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Most recent grade of disease		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not accessible	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.17 [32]
Abbreviations: CP, carboplatin plus paclitaxel; FIGO, Federation of Gynaecology and Obstetrics; MMRp, mismatch repair proficient; MSS, microsatellite stability.

Table 50. Prognostic stratification factors in MMRp/MSS population (Reproduced from CS Table 7)

Category, n (%)	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Previous external pelvic radiotherapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Disease status		
Primary Stage III	[redacted]	[redacted]
Primary Stage IV	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]

Source: IA1 CSR Table 14.1.1.10 [32]
Abbreviations: CP, carboplatin plus paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable.

8.2 Baseline characteristics for the Western Europe subgroup of RUBY-1

Table 51. Summary of baseline characteristics for WE subgroup (MMRp/MSS population [Reproduced from company response to CQs Table 11])

Characteristic	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Number of patients in the subgroup	[redacted]	[redacted]	[redacted]
Race [n (%)]			
N	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Mixed Race	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]
Age (years)			
N	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
BMI (kg/m^2) [a]			

N	[redacted]	[redacted]	[redacted]
Mean (std)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Histology [n (%)]			
N	[redacted]	[redacted]	[redacted]
Endometrioid carcinoma (adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]	[redacted]
Serous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Clear Cell Adenocarcinoma	[redacted]	[redacted]	[redacted]
Mucinous Adenocarcinoma	[redacted]	[redacted]	[redacted]
Undifferentiated Carcinoma	[redacted]	[redacted]	[redacted]
Neuroendocrine tumors	[redacted]	[redacted]	[redacted]
Carcinosarcoma	[redacted]	[redacted]	[redacted]
Mixed carcinoma with ≥10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]	[redacted]
Mixed Carcinoma, Other	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
ECOG Performance Status [n (%)]			
N	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Prior EPR [n (%)]			
N	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Endometrial cancer disease status [n (%)]			
N	[redacted]	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]	[redacted]
Primary Stage III	[redacted]	[redacted]	[redacted]
Primary Stage IV	[redacted]	[redacted]	[redacted]
Evaluable Disease at Baseline [n (%)]			

N	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Measurable Disease at Baseline [n (%)]			
N	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
PD-L1 Status [n (%)]			
N	[redacted]	[redacted]	[redacted]
PD-L1+	[redacted]	[redacted]	[redacted]
PD-L1-	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; EPR, oestrogen and progesterone receptor; Max, maximum; Min, minimum; MMRp, mismatch repair proficient; MSS, microsatellite stable; PD-L1, programmed death-ligand 1.

8.3 Summary of the EAG critique of company's SLR

Table 52. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix B.1.1	**Appropriate**. The following databases were searched on 10 November 2021 for the original SLR with updates searches conducted on 22 February 2023, 8 August 2023, 26 October 2023 and 16 May 2024: • MEDLINE; • Embase; • Cochrane Database of Systematic Reviews (CDSR); and • Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the abstracts of the following gynaecological cancer-related conference proceedings from the past four years prior to the original search date (2021) or up to the most recent search date, i.e., May 2024: • American Association for Cancer Research; • American Society of Clinical Oncology; • European Society for Medical Oncology; • International Society for Pharmacoeconomics and Outcomes Research; • European Society of Gynaecological Oncology Annual Meeting; • International Gynecologic Cancer Society Annual Global Meeting; • National Comprehensive Cancer Network Annual Conference; • Society of Gynecologic Oncology Annual Meeting; • Society for Immunotherapy of Cancer Annual Meeting; and

		• British Gynaecological Cancer Society. The websites of select HTA bodies (NICE, Scottish Medicines Consortium, Canada's Drug Agency, Haute Autorité de santé, Institute for Clinical and Economic Review, Gemeinsamer Bundesausschuss, and Pharmaceutical Benefits Advisory Committee) that publish appraisal reports online were searched for relevant data or references not identified in the other searches. The ClinicalTrials.gov trial registry was searched to identify ongoing phase II/III RCTs and/or RCTs with results not published in medical journals or scientific congresses. The bibliographies of all relevant SLRs identified during the SLR were also hand-searched.
Search strategies	Appendix B.1.1	**Appropriate** Searches were broad and appropriately limited by disease stage (advanced and recurrent endometrial cancer) and study design (clinical trials). Limits were defined using both keywords and subject heading terms.
Inclusion criteria	Appendix B.1.2.1	**Appears appropriate** The EAG considers the inclusion criteria to align with the final scope issued by NICE and the decision problem addressed by the company in the CS. The EAG considers it unlikely that any studies relevant to the decision problem have been missed, although the EAG notes that studies were required to be published in the English language.
Screening	Appendix B.1.2.3	**Appropriate** Title/abstract review and full-text review were completed by two independent reviewers, with a third reviewer resolving any discrepancies.
Data extraction	Appendix B.1.2.3	**Appears reasonable** Data from the included studies for the SLR were extracted into individual data extraction tables designed in Microsoft Excel®. Relevant data from each study were extracted by one reviewer and verified by a second independent reviewer. Any discrepancies were resolved by discussion or the involvement of a third reviewer.
Tool for quality assessment of included study or studies	Appendix B.1.2.4 and B.3, Table 10 of the CS	**Appropriate** The quality of included randomised controlled trials (RCTs) was assessed using the quality assessment tool conducted using the risk of bias checklist provided in the NICE STA user guide for company evidence submission.[63] The EAG performed its own assessment of risk of bias in RUBY-1 in Section 3.2.

Abbreviations: CS, company submission; EAG, External Assessment Group; HTA, health technology appraisal; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review; STA, single technology appraisal.

8.4 Price sources for treatments included in the confidential appendix

Table 53. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Pembrolizumab	Simple PAS
Lenvatinib	Simple PAS

Abbreviations: PAS, patient access scheme.

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

EAG report addendum – Patient Access Scheme discount update

June 2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 172882.

1 Introduction

The External Assessment Group (EAG) has produced an addendum to the EAG report to reflect an update to the company's patient access scheme (PAS) discount that was agreed as part of the Cancer Drugs Fund (CDF) exit review of TA963 (dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability [MSI-H] or mismatch repair deficiency [MMRd]). The updated PAS discount for dostarlimab is now [redacted], which equates to [redacted] per vial.

2 Updated company cost-effectiveness results

2.1 Company's cost effectiveness results

Table 1 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of 0.75 over carboplatin and paclitaxel (CP) along with [redacted] for dostarlimab + CP, generates an incremental cost-effectiveness ratio (ICER) of [redacted]. The net health benefit (NHB) based on the probabilistic results using the £20,000 and £30,000 threshold is [redacted] and [redacted], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 1. Company's base case results (post FAC)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

A PSA scatterplot is presented in Figure 1 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 2.

Figure 1. Scatterplot of PSA estimates on a cost-effectiveness plane

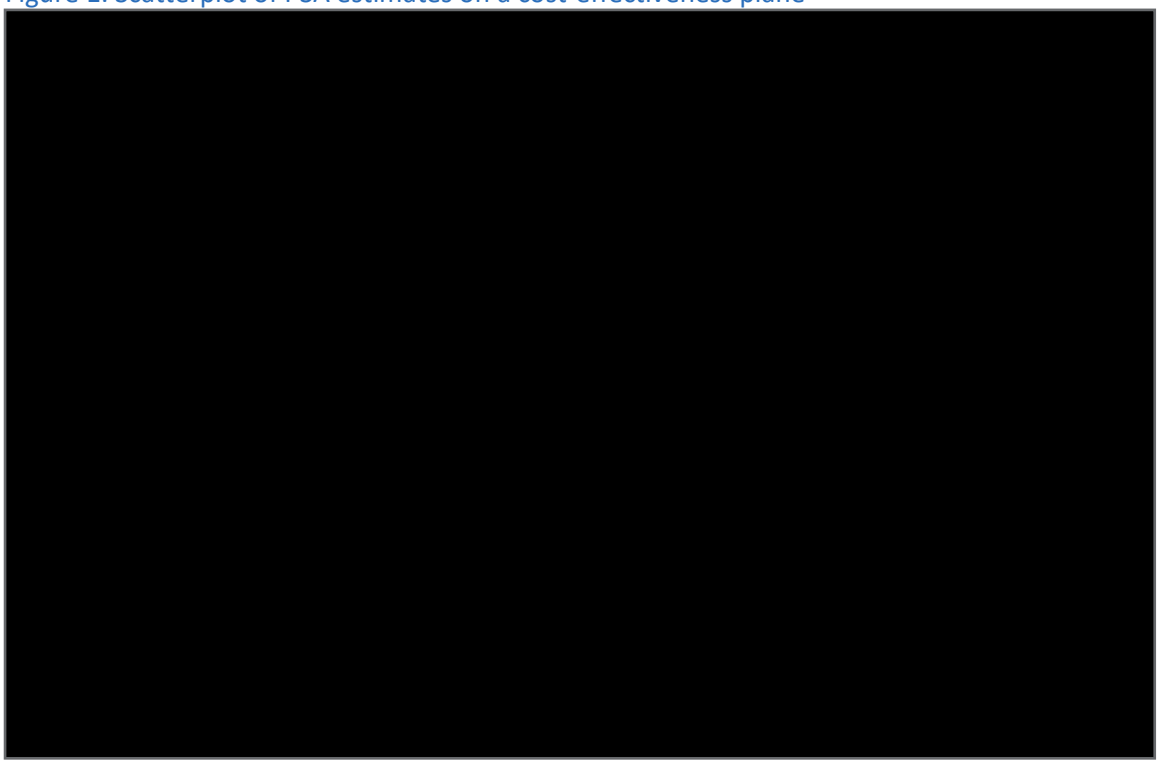
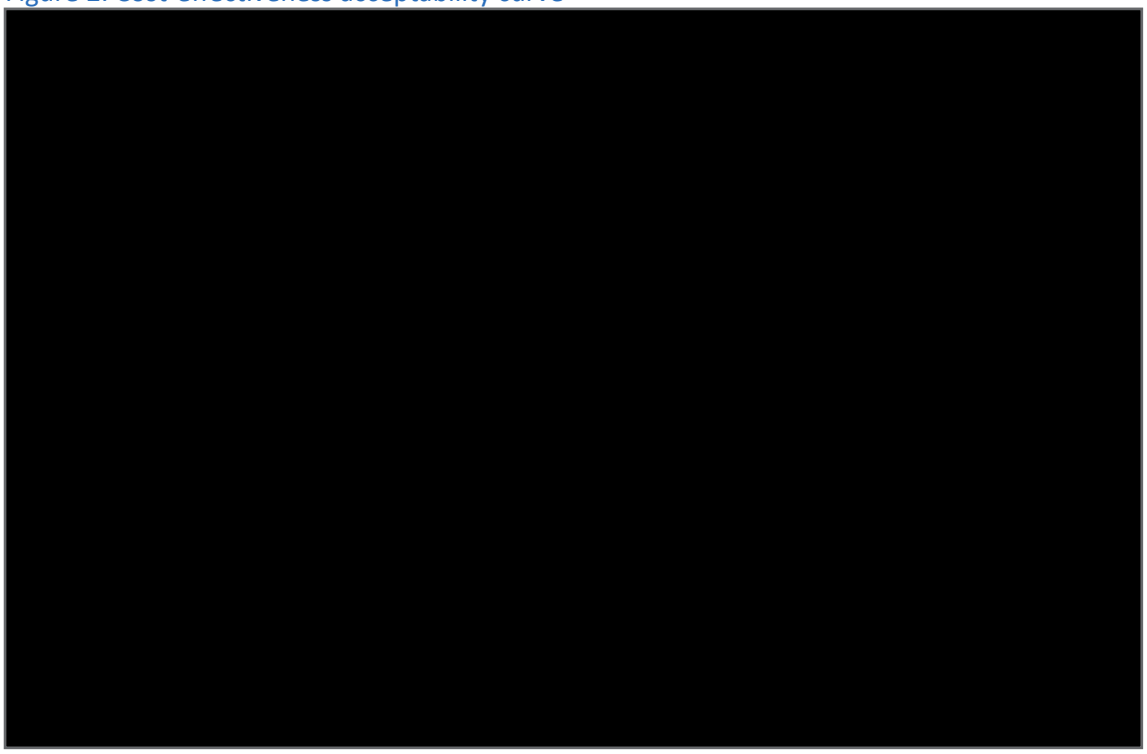


Figure 2. Cost-effectiveness acceptability curve



2.2 Company's sensitivity analyses

2.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagram presented in Figure 3.

The ICER was most sensitive to the number of outpatient visits associated with the progression-free (week 19+), outpatient visit unit cost and dostarlimab completion rates per cycle (week 10).

Figure 3. Tornado plot

2.2.2 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 2. In addition, the company conducted several additional scenario analyses requested by the External Assessment Group (EAG), also presented in the tables below.

Table 2. Company deterministic scenario analysis

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	**Company base case**	[redacted]	0.76	[redacted]
1	Starting age - 65.5 (UK RWE)	[redacted]	0.75	[redacted]
2	Annual discount rate for costs and QALYs – 1.5%	[redacted]	0.91	[redacted]
3	Annual discount rate for costs and QALYs – 5%	[redacted]	0.67	[redacted]
4	PFS Curve selection (CP) - Odds, k=2 flexible spline model	[redacted]	0.75	[redacted]
5	PFS curve selection (dostarlimab+CP) - Normal, k=2 flexible spline model	[redacted]	0.75	[redacted]
6	PFS curve selection - Independent models (CP, log-logistic; dostarlimab, generalised gamma)	[redacted]	0.76	[redacted]
7	OS curve selection (dostarlimab+CP) - Independent, log-logistic	[redacted]	0.65	[redacted]
8	Treatment effect waning: OS and PFS - Waning from 8-10 years	[redacted]	0.71	[redacted]
9	Treatment effect waning: OS and PFS - Waning from 5-7 years	[redacted]	0.62	[redacted]
10	TTD Completion rates – TTD KM data used instead of completion rates	[redacted]	0.76	[redacted]
11	Vial wastage – no vial wastage	[redacted]	0.76	[redacted]
12	Adverse event threshold - Grade 3+ AEs ≥5% in either arm of RUBY-1	[redacted]	0.76	[redacted]
13	Subsequent treatment assumptions - Equal proportion receiving no treatment (set to dostarlimab proportion for both)	[redacted]	0.76	[redacted]
14	Subsequent treatment assumptions - 75% market share assumed for PEM+LEN in CP proportions	[redacted]	0.76	[redacted]
15	Utility values - ITT RUBY-1 source	[redacted]	0.75	[redacted]
16	AE disutilities excluded	[redacted]	0.76	[redacted]
17	No age adjustment for utilities	[redacted]	0.80	[redacted]
EAG requested scenarios				
B6	TTD KM used for full follow-up period (Up to cycle 187)	[redacted]	0.76	[redacted]
B10	Doubled AE rates in both arms (1L and 2L)	[redacted]	0.76	[redacted]
B11	Exclude AE disutilities for subsequent treatments	[redacted]	0.76	[redacted]
B12	Exclude AE costs for subsequent treatments	[redacted]	0.76	[redacted]
B15	Use dostarlimab+CP arm completion rates for CP	[redacted]	0.76	[redacted]
B20	Exclude Admin cost for Lenvatinib	[redacted]	0.76	[redacted]
B22	Set resource use equal after 3 years in the PF state	[redacted]	0.76	[redacted]
B23	Use EAG clinical expert resource use	[redacted]	0.76	[redacted]

B26	Apply PSSRU end of life cost to those dying from PD only	[redacted]	0.76	[redacted]
B28	Equal TTD to PFS	[redacted]	0.76	[redacted]

Abbreviations: 1L, first-line; 2L, second-line; AE, adverse events; CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; QALY, quality-adjusted life-year; RWE, real-world evidence; TTD, time-to-treatment discontinuation.

3 Additional economic analysis undertaken by the EAG

3.1 Exploratory and sensitivity analyses undertaken by the EAG

In Section 4 of the External Assessment Group (EAG) report, the EAG describes several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The scenarios that the EAG performed are as follows:

1. Use of the ONS life tables from 2017-2019, as per guidance in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 23 – Section 4.2.3.2.
2. Correct unit costs from The Unit Costs of Health and Social Care 2023 Manual (£57 per working hour for a Band 6 qualified nurse and £49 per surgery consultation lasting 10 minutes with a GP) – Section 4.2.5.5.
3. Time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one – Section 4.2.5.3.
4. Bevacizumab usage for the carboplatin and paclitaxel (CP) arm of the model redistributed amongst the non-immunotherapy subsequent treatments – Section 4.2.6.1.
5. Unit cost of carboplatin 450 mg used for subsequent treatment cost – Section 4.2.6.3.
6. Full time-to-treatment discontinuation (TTD) extrapolation (Gompertz) used for dostarlimab + CP arm of the model – Section 4.2.5.3.

3.2 EAG scenario analysis

Table 3 presents the results of the EAG exploratory analyses described in Section 3.1. Results reported include the company's patient access scheme (PAS) discount on the list price of [redacted] for dostarlimab.

Confidential PAS discounts are available for pembrolizumab and lenvatinib, which are included in the model as subsequent treatments. As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

Table 3. Results of the EAG's deterministic scenario analyses

	Results per patient	Dostarlimab + CP	CP	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
1	ONS life tables from 2017-2019			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.76
	ICER (£/QALY)	-	-	[redacted]
2	Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
3	TTD KM data for both treatment arms and dostarlimab RDI applied from cycle one			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
4	Redistribution of bevacizumab usage across non-immunotherapy subsequent treatments			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
5	Unit cost of carboplatin 450 mg used for subsequent treatment cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
6	TTD Gompertz extrapolation for Dostarlimab + CP			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

3.3 EAG preferred assumptions

In this section, the EAG presents its preferred base case for the cost-effectiveness of dostarlimab in addition to platinum-based chemotherapy (dostarlimab + CP) for the treatment of patients with newly diagnosed primary advanced or recurrent endometrial cancer (EC) that is mismatch repair proficient (MMRp) or microsatellite stable (MSS). The assumptions that form the EAG's preferred base case are listed below.

- Use of the ONS life tables from 2017-2019, as per guidance in the NICE DSU TSD 23.

- Time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one.
- Correct nurse and GP costs sourced directly from The Unit Costs of Health and Social Care 2023 Manual.
- Health-state resource use for the dostarlimab + CP after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model.
- Bevacizumab usage for the CP arm of the model redistributed amongst the non-immunotherapy subsequent treatments.
- Removal of oral administration costs for lenvatinib.
- Unit cost of carboplatin 450 mg used for subsequent treatment cost.

Table 4 presents the deterministic EAG base case. Probabilistic results for the EAG base case are presented in Table 5. Results of the scenarios around the EAG base case (Section 3.3.1) are deterministic as performing probabilistic sensitivity analysis (PSA) in the company's model is time intensive. However, the EAG considers that, based on the base case results, deterministic and probabilistic results are consistent with each other.

Table 4. EAG's preferred model assumptions (deterministic)

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case	-	[redacted]	0.75	[redacted]
ONS life tables from 2017-2019	4.2.3.2	[redacted]	0.76	[redacted]
TTD KM data for both treatment arms and dostarlimab RDI applied from cycle one	4.2.5.3	[redacted]	0.76	[redacted]
Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual	4.2.5.5	[redacted]	0.76	[redacted]
Set health-state resource use for dostarlimab + CP equal to CP after 3 years in the PF health state	4.2.5.5	[redacted]	0.76	[redacted]
Redistribution of bevacizumab usage across non-immunotherapy subsequent treatments	4.2.6.1	[redacted]	0.76	[redacted]
Removal of oral administration costs for lenvatinib	4.2.6.3	[redacted]	0.76	[redacted]
Unit cost of carboplatin 450 mg used for subsequent treatment cost	4.2.6.3	[redacted]	0.76	[redacted]
EAG preferred base case	**-**	[redacted]	**0.76**	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; KM, Kaplan-Meier; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDI, relative dose intensity; TTD, time-to-treatment discontinuation.

Table 5. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

3.3.1 Scenarios around the EAG base case

The EAG has explored the assumption of gradual treatment effect waning on overall survival around its preferred base case to assess the impact on the ICER. Results of the EAG's scenario are presented in Table 6.

Table 6. Deterministic results of the EAG's scenario around the EAG base case

	Results per patient	Dostarlimab + CP	CP	Incremental value
0	EAG base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.76
	ICER (£/QALY)	-	-	[redacted]
1	Gradual treatment effect waning on overall survival (5-7 years)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.62
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

3.4 Conclusions of the cost effectiveness sections

The EAG considers the company's submitted cost-effectiveness analysis adheres to the decision problem defined in the NICE final scope.[1] The EAG's preferred assumptions increase the company's base case ICER by less than [redacted] and [redacted]

[redacted]. However, these ICERs do not include the confidential PAS discounts for lenvatinib and pembrolizumab. Please see the EAG's confidential appendix to the EAG report.

Three key assumptions in the EAG base case are relatively more important for decision making. These include the approach to modelling TTD from the start of the model time horizon, health-state resource use for dostarlimab + CP patients who are progression-free after the maximum treatment duration of three years, and assumptions informing subsequent treatment costs for the CP arm of the model. Nevertheless, the alternative assumptions implemented in the EAG's base case have addressed the issues the EAG identified with the company's approach.

4 References

1. National Institute for Health and Care Excellence. Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency - Final Scope [ID6415], 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11503/documents/final-scope. Date accessed: March 2025.

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 Thursday 24 April 2025** 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 information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of modelling approaches

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2, page 67 "A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of dostarlimab in addition to platinum-based chemotherapy (carboplatin and paclitaxel, hereafter known as CP) for the treatment of patients with newly diagnosed advanced or recurrent EC that is mismatch repair proficient (MMRp) or microsatellite stable (MSS)."	Update text to: "A single economic model (adapted from the model accepted as part of TA963) was developed in Microsoft© Excel to assess the cost-effectiveness of dostarlimab in addition to platinum-based chemotherapy (carboplatin and paclitaxel, hereafter known as CP) for the treatment of patients with newly diagnosed advanced or recurrent EC that is mismatch repair proficient (MMRp) or microsatellite stable (MSS)."	This update adds important context to more accurately reflect the model development process. The model was based on the model submitted as part of TA963. GSK therefore suggest a revision to the exiting text which clarifies this.	Thank you for highlighting this amendment. The EAG report has been updated accordingly.
Section 4.2.2, page 67 "The model uses a partitioned survival analysis model (PSM) structure, with a weekly cycle length and includes three main health states: progression-free, progressed disease and death (Figure 9). The progression-free health state is further sub-divided into progression-free on treatment and progression-free off treatment, with proportions determined by time to treatment discontinuation (TTD) data (see Section 4.2.5.1). The company stated that the chosen model	Update text to: "The model uses a partitioned survival analysis model (PSM) structure, with a weekly cycle length and includes three main health states: progression-free, progressed disease and death (Figure 9). ~~The progression-free health state is further sub-divided into progression-free on treatment and progression-free off treatment, with proportions determined by time to treatment discontinuation (TTD) data (see Section 4.2.5.1).~~ The company stated that the chosen model structure is in line with previous HTA	The PSM does not split the progression free health state into those on treatment and those off treatment. TTD is also modelled independently of PFS. The amendment ensures the description of the model structure is accurate and reflective. Furthermore, as part of the company submission, it was stated that the chosen model structure aligned with TA779, TA904 and TA963. GSK therefore suggest that TA963 is added for completeness.	Thank you for highlighting this issue. The EAG report has been amended. As health state resource use is categorised by time in the model and progression status, that can be considered akin to being PFS on or off treatment, especially when taking into account the EAG's preferred assumption of reduced resource use for dostarlimab patients who remain progression-free after the maximum treatment duration. However, the EAG considers

structure is in line with previous HTA EC models (TA779 and TA904).(1, 2)"	EC models (TA779, TA904 and TA963).(1, 2)"		that the company's suggested amendment is appropriate as the categorisation of resource use costs is not explicitly defined by being on or off treatment.

Abbreviations: CP, carboplatin and paclitaxel; dMMR, deficient mismatch repair; EAG, Evidence Appraisal Group; EC, endometrial cancer; HTA, health technology assessment; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PSM, partitioned survival analysis model; TA, technology appraisal; TTD, time to treatment discontinuation

Issue 2 Errors in reporting of economic model results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.3.6, page 75 "Implementation of the gradual waning scenario on OS increases the ICER from [redacted] to [redacted]."	Update text to: "Implementation of the gradual waning scenario on OS increases the ICER from [redacted] to [redacted]"	The ICER reported in table 54 of the clarification questions responses for this scenario differs to that reported by the EAG.	Thank you for highlighting this error. The EAG report has been amended.

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PLD, Pegylated liposomal doxorubicin

Issue 3 Inaccurate description of concerns regarding administration costs and bias in economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG have suggested that inclusion of administration costs, AE costs or disutilities associated with the counterfactual pathway results in a bias. GSK understands this to be factually inaccurate and believes it is appropriate that intervention and	**Section 1.3, Table 5, page 16** ~~*Additionally, inclusion of an oral administration cost for lenvatinib is biased against the comparator, as this treatment is not included in the*~~	GSK acknowledges the EAG's disagreement regarding the suitability of lenvatinib administration costs, and whether the costs included reflect the economic cost of lenvatinib use. However, GSK do not believe the inclusion of a bona fide cost which is	The EAG does not consider this to be a factual inaccuracy, given the context of the application of an oral administration cost is not considered to be incurred in UK clinical practice and thus is a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
comparator arms of the economic analysis will accrue different costs, reflecting the costs and outcomes of their respective pathways and outcomes. **Section 1.3, Table 5, page 20** "Additionally, inclusion of an oral administration cost for lenvatinib is biased against the comparator, as this treatment is not included in the dostarlimab + CP subsequent treatment basket." **Section 4.2.6.3, page 94** "The EAG was concerned by the application of an oral administration cost for lenvatinib, as this is biased against the CP arm of the model and in the clarification stage, asked the company to justify the assumption (Key issue 4, Section 1)." **Section 4.2.6.5, page 97** "However, inclusion of subsequent treatment AE costs and disutility is potentially biased against the comparator due to the usage of subsequent immunotherapy.	~~*dostarlimab + CP subsequent treatment basket*~~. **Section 4.2.6.3, page 94** *The EAG was concerned by the application of an oral administration cost for lenvatinib, as this is ~~biased against~~ only relevant for the CP arm of the model and in the clarification stage, asked the company to justify the assumption.* **Section 4.2.6.5, page 97** *However, inclusion of subsequent treatment AE costs and disutility ~~is potentially biased against~~ are only relevant to the comparator due to the usage of subsequent immunotherapy.*	relevant for only one arm constitutes a bias, but instead represents a legitimate cost-offset. GSK therefore request that any wording implying a bias in the adopted approach be amended.	potential source of bias in the analysis. With regards to the last point about subsequent treatment AE costs and disutility, the EAG has amended its report to include the context that only negative impacts of immunotherapy for CP are captured in the analysis and not the potential PFS2 QALYs. Thus, the company's approach is potentially biased against the comparator.

Abbreviations: AE, adverse event; CP, carboplatin and paclitaxel; CS, company submission; EAG, External Assessment Group; NHS, National Health Service,

Issue 4 General inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout EAG report	Please note that the CS follows the latest NICE template, in which sections in the main CS no longer start with the letter "B", therefore these should be removed throughout	To align with the latest NICE CS template	Thank you for highlighting this oversight. The EAG report has been corrected accordingly.
Throughout EAG report	Please note that throughout the EAG report the use of "advanced or recurrent EC" should be changed to "primary advanced or recurrent EC"	For consistency and as per the CS	Thank you for highlighting this amendment. The EAG report has been updated accordingly.
Section 2.1, page 23 "The EAG notes that prior to this, dostarlimab was approved for use in only mismatch repair deficient (MMRd)/microsatellite instability-high (MSI-H) tumours but the December 2024 marketing authorisation has extended to now also include patients with mismatch repair proficient/microsatellite stable (MMRp/MSS) disease."	Update text to: "The EAG notes that prior to this, dostarlimab in combination with PCC was approved for use in only mismatch repair deficient (MMRd)/microsatellite instability-high (MSI-H) tumours but the December 2024 marketing authorisation has extended to now also include patients with mismatch repair proficient/microsatellite stable (MMRp/MSS) disease."	It should be clarified that dostarlimab is used in combination with PCC, as dostarlimab monotherapy was approved as a separate indication in 2022, for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 2.2, page 23 "mismatch repair (MMR) molecular classification in EC (Section B.1.3.1.5);"	Update text to: "mismatch repair (MMR) molecular classification in EC (Section 1.3.1);"	Incorrect cross reference	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 3.1, page 39 "The company's SLR was conducted on 10 November 2021 and updated on several occasions up to 16 May 2024	Update text to: "The company's SLR was conducted on 10 November 2021 and updated on several occasions up to 16 May 2024	The original SLR was conducted on the 10th November 2021, therefore that date should be removed from the list of updates	Thank you for highlighting this correction. The EAG report has been updated accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
(updates on 10 November 2021, 22 February 2023, 8 August 2023, 26 October 2023 and 16 May 2024)”	(updates on ~~10 November 2021~~, 22 February 2023, 8 August 2023, 26 October 2023 and 16 May 2024)”		
Section 4.2.6.4, table 40 The costs for nausea and vomiting are incorrectly reported as £489.18.	The correct costs for nausea and vomiting should be £522.60	As part of the clarification questions, the EAG requested that updated inflation indices were used. As a result, the company base case was updated using the 2022/2023 updated PSSRU indices (3) The cost reported is the cost from the original model, whereas the adjustment reflects the use of the updated inflation indices within the updated company base case provided in response to clarification questions.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 3.2, table 10, page 42, first row “Randomisation" “Section 2.2 and Appendix B.3”	Update text to: Section 2.3.1 and Appendix B.3	Randomisation is described in depth in Section 2.3.1, whereas Section 2.2 only gives an overview of the trial design	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 3.2, table 10, page 43 “[redacted]”.	Update text to: “[redacted]”.	Incorrect figure- the figures given in the EAG report are for death due to disease progression, not death from any cause.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 3.3.1, page 45 [redacted]	Update text to: [redacted]	Incorrect figure	Thank you for highlighting this correction. The EAG report has been updated accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.4, page 51 "was "[redacted]".	Update text to: "was "[redacted]".	Incorrect figure- the figures provided should be updated to align with Table 6 Summary of disease history in MMRp/MSS population in main CS (page 44)	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.3.1, table 23, page 69 "- Dostarlimab: TTD KM curve from RUBY-1, capped at three years."	Update text to: "- Dostarlimab: Treatment completion rates for 18 weeks and TTD KM curve from RUBY-1, capped at three years."	The dostarlimab arm also includes the use of treatment completion rates for six treatment cycles (18 weeks) followed by the KM capped at 3 years.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.3.6, page 75 "Figure 13 presents the OS curves and Figure 15 presents the hazard rate plot"	Update text to: Figure 14 presents the OS curves and Figure 15 presents the hazard rate plot	Incorrect cross reference	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.6.2, table 37, page 91 Some of the costs within the table do not match the post clarification questions version of the model. • Carboplatin and doxorubicin, reported as £1821.57 • Doxorubicin (and PLD), reported as £705.66 • Pembrolizumab and Lenvatinib, reported as £91,632.55	Update costs: • Carboplatin and doxorubicin should be updated to £1,864.72 • Doxorubicin (and PLD) should be updated to £748.81 • Pembrolizumab and Lenvatinib should be updated to £91,802.40	As part of the clarification questions, the EAG requested that updated inflation indices were used. As a result, the company base case was updated using the 2022/2023 updated PSSRU indices (3) The cost reported is the cost from the original model, whereas the adjustment reflects the use of the updated inflation indices within the updated company base case provided in response to clarification questions.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.6.2, table 35, page 92 The cost of radiotherapy in the table is incorrectly reported as £3,388.24.	Update results: The correct costs should be £3,620.79	As above, costs do not reflect the use of the updated inflation indices	Thank you for highlighting this correction. The EAG report has been updated accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		and therefore, the latest version of the model (3)	

Abbreviations: CP, carboplatin and paclitaxel; CS, company submission; EAG, Evidence Appraisal Group; EC, endometrial cancer; KM, Kaplan-Meier; MMR, mismatch repair; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PCC, platinum-based chemotherapy; PLD, Pegylated liposomal doxorubicin; SLR, systematic literature review; TTD, time to treatment discontinuation

Issue 5 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout EAG report The EAG has repeatedly abbreviated to the mismatch repair deficient/ microsatellite instability-high population to '*MMRd/MSI-H'.* This does not align with the dostarlimab license which refers to it as dMMR/MSI-H	Please update throughout to dMMR/MSI-H	The amendment ensures that the abbreviation aligns with the Dostarlimab license, other NICE appraisals in the indication and published guidelines (including ESMO (4))	The abbreviation was used to be consistent with the approach for MMRp included in the CS. However, the EAG report has been amended as per the company request.
Section 2.3, table 7, page 29 • "Molecular subgroups (POLεmut, TP53mut and NSPM) as per scope."	Update text to: • Molecular subgroups (POLεmut, TP53mut and NSMP) as per scope.	Typographical error	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 3.2, table 10, page 44 "In addition, some outcome data are reported in the CS using IA2 data-cut rather than IA2"	Update text to: "In addition, some outcome data are reported in the CS using IA1 data-cut rather than IA2"	Typographical error	Thank you for highlighting this correction. The EAG report has been updated accordingly.

Section 3.3.5.3, page 55 "(-0.5; 95% CI: -.2.7 to +1.7)"	Update text to: "(-0.5; 95% CI: -2.7 to +1.7)"	Typographical error originating from Company's response to CQs	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.6, page 83, "The EAG acknowledges that the data from RUBY-1 informing the model for clinical outcomes and TTD are based on the MMRp/MSS subgroup of the ITT population and so does include a proportion of patient who were randomised but did not initiate treatment, so in that regard treatment costs and outcomes are aligned."	Update text to: "The EAG acknowledges that the data from RUBY-1 informing the model for clinical outcomes and TTD are based on the MMRp/MSS subgroup of the ITT population and so does include a proportion of patients who were randomised but did not initiate treatment, so in that regard treatment costs and outcomes are aligned."	The amendment is for grammatical consistency- patients are plural.	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.6, page 88 $"Updated\ proportion = Original\ proportion \times (1 + \frac{Bevacizumab\ proportion}{Sum\ of\ non-bevacacizumab\ treatments})"$	Update text to: $Updated\ proportion = Original\ proportion \times (1 + \frac{Bevacizumab\ proportion}{Sum\ of\ non-bevacizumab\ treatments})$	Spelling error	Thank you for highlighting this correction. The EAG report has been updated accordingly.
Section 4.2.6, page 89 "A study by Rubinstein *et al*. found that use of bevacizumab after one prior line of treatment for patients with endometrial cancer (not limited to MMRp/MSS patients) resulted in a median PFS of 3.5 months and the overall conclusions found that the benefits of the treatment were "modest".(5)"	Update text to: "A study by Rubinstein *et al*. found that use of bevacizumab after one prior line of treatment for patients with advanced endometrial cancer (not limited to MMRp/MSS patients) resulted in a median PFS of 3.5 months and the overall conclusions found that the benefits of the treatment were "modest".(5)"	The amendment ensures that the description of the population described is accurate and complete.	Thank you for highlighting this amendment. The EAG report has been updated accordingly.

Abbreviations: CQ, clarification question; CS, company submission; dMMR, mismatch repair deficient; EAG, Evidence Appraisal Group; ESMO, European Society for Medical Oncology; ITT, intention-to-treat; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; TTD, time to deterioration

Issue 6 Incorrect confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, table 7, page 27 [redacted] (adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy) [redacted] notes that the MMRp/MSS data from RUBY-1 comprise a subgroup of the overall trial population and, although it was a stratification factor, the trial was not statistically powered for the subgroup. The EAG also notes that the proportion of newly diagnosed advanced EC patients with FIGO Stage III disease at diagnosis who were enrolled in the RUBY-1 trial was low compared to the proportion of patients with Stage IV disease (See Section 2.3.1 for further details)."	Confidential marking to be removed	This information is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.
Section 2.3.2, page 35 In addition, the EAG notes that the subsequent treatments used in RUBY-1 are not wholly reflective of UK clinical practice and therefore the results for OS in particular may	Confidential marking to be removed	This information is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.

not accurately reflect outcomes in the UK [redacted]			
Section 2.3.3, page 36 The EAG is concerned that the subsequent treatments used in RUBY-1 are not wholly reflective of UK clinical practice with some of the EAG's clinical experts reporting that [redacted] Subsequent therapies are discussed in more detail in Sections 3.2 and 4.2.6.	Confidential marking to be removed	This information is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.
Section 2.3.4, page 37 The EAG is concerned about the reliability of the OS data from RUBY-1, in particular the data beyond [redacted]	Confidential marking to be removed	This information is not commercially sensitive, and	Confidential mark-up has been removed in the updated EAG report.

[redacted] and the resulting extrapolations used in the company's economic model (**Other key issues in Section 1.4**).		therefore, confidential marking is not required.	
Section 3.2, page 41 A further area of concern with regards to RUBY-1 is the subsequent treatment usage not reflecting UK clinical practice. [redacted]	Confidential marking to be removed	This information is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.
Section 3.4, page 61 "The usage of immunotherapies (e.g. pembrolizumab) as subsequent treatments [redacted]	Confidential marking to be removed	This information is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.

[redacted]"			
Section 3.4, page 62 The EAG is concerned about the reliability of the OS data from RUBY-1, in particular the data beyond [redacted] and the resulting extrapolations used in the company's economic model (**Other key issues in Section 1.4**).	Confidential marking to be removed	The OS curve is not commercially sensitive, and therefore, confidential marking is not required.	Confidential mark-up has been removed in the updated EAG report.

Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; EAG, Evidence Appraisal Group; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; IA, interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; UK, United Kingdom

References

1. National Institute for Health and Care Excellence. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [TA779]. Available at: https://www.nice.org.uk/guidance/ta779/documents/committee-papers (accessed on: December 2024). 2022.
2. National institute for Health and Care Excellence. NICE guidance. TA904. Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Published 21 June 2023. Available at: https://www.nice.org.uk/guidance/ta904 (last accessed: March 2025). 2023.
3. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care programme (2022 – 2027). Available at: https://www.pssru.ac.uk/unitcostsreport/ (last accessed March 2025). . 2024.
4. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(9):860-77.
5. Rubinstein MM, Dickinson S, Narayan P, Zhou Q, Iasonos A, Ma W, et al. Bevacizumab in advanced endometrial cancer. Gynecol Oncol. 2021;161(3):720-6.