NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (MA review of TA963) [ID6426]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (MA review of TA963) [ID6426]

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 GlaxoKilneSmith:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

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

4. **Expert personal perspectives** from:
   a. Dr Andrew Clamp, nominated by GSK
   b. Gemma EMINOWICZ nominated by GSK
   c. Phillippa Hentsch nominated by Peaches Womb Cancer Trust

5. **External Assessment Report** prepared by University of Warwick

6. **External Assessment Group response to factual accuracy check of EAR**

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 high microsatellite instability or mismatch repair deficiency [ID6426]

Document B

Company evidence submission

October 2024

File name	Version	Contains confidential information	Date
ID6426_Dostarlimab+PC_EC_DocB-Final-[REDACTED]	1.0	Redacted	2nd October 2024

Instructions for companies

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

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Abbreviations

AE	Adverse event
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
CSR	Clinical study report
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
ESGO/ESTRO/ESP	European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology
ESMO	European Society for Medical Oncology
FIGO	International Federation of Gynaecological and Obstetrics
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	First interim analysis
IA2	Second interim analysis
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LY	Life year
MAA	Managed access agreement
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
NSMP	No 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
PFS	Progression-free survival
PFS2	Progression-free survival 2
PH	Proportional hazards
POLE	polymerase epsilon
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
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

TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
WTP	Willingness to pay

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

Overview of endometrial cancer epidemiology, and burden

- Dostarlimab is currently reimbursed via the Cancer Drugs Fund (CDF) in combination with platinum containing chemotherapy (PCC) for mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer patients who are candidates for systemic therapy. Before the introduction of dostarlimab, this group of patients received chemotherapy alone as standard of care (SoC) and typically experienced short-lived treatment responses and extremely poor survival outcomes.
- Patients with primary advanced or recurrent endometrial cancer have an extremely poor prognosis, with almost 50% of patients diagnosed with Stage III endometrial cancer surviving for 5 years or more after diagnosis, dropping to just 15% when diagnosed with Stage IV (1). Recurrent disease is difficult to treat, with only 20% patients surviving over 5 years (2-4).
- These patients experience a range of debilitating and often severe symptoms such as vaginal bleeding, painful intercourse, persistent pelvic pain, and unintended weight loss (5-9).

Current clinical pathway of care and unmet need

- Without dostarlimab, SoC for the treatment of primary advanced or recurrent endometrial cancer is PCC, with the most common regimen being carboplatin plus paclitaxel (CP) given every 3 weeks (Q3W) for six cycles.
- PCC became the SoC in the early 90s, and there have been few meaningful therapeutic advancements in this time until the recent reimbursement of dostarlimab via the CDF (10-12).
- Despite clinical responses of 50–70% with PCC irrespective of mismatch repair (MMR)/microsatellite instability (MSI) status, disease progression is almost inevitable with 75% of dMMR/MSI-H patients expected to progress within 12 months of treatment with chemotherapy alone (12, 13).
- While immunotherapies have improved outcomes for eligible patients in later lines of therapy, a significant unmet need remains for effective first-line treatment in baseline commissioning (14-16).

Dostarlimab in combination with CP

- Dostarlimab in combination with CP represents a practice-changing addition to the treatment pathway for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer, who would otherwise face a very poor prognosis with limited life expectancy, significant detriments to health-related quality of life (HRQoL), and minimal prospects of receiving effective treatment (5-7, 17-19).

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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
Population	People with primary advanced or recurrent endometrial cancer with MSI-H or dMMR	As per scope	N/A
Intervention	Dostarlimab with PCC	As per scope	N/A
Comparator	Platinum-based doublet chemotherapy	PCC, CP	N/A
Outcomes	The outcome measures to be considered include: • Progression-free survival • Time to second objective disease progression • Overall survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality-of-life.	As per scope, with the addition of progression free survival 2 (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. 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.	As per scope	N/A
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.	Dostarlimab has already received marketing authorisation from the MHRA (2nd October 2023) for the indication covered by this submission.	N/A

Abbreviations: dMMR, DNA mismatch repair; MHRA, Medicines and Healthcare products Regulatory Agency; MSI-H, microsatellite instability high; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PFS2, time to second objective disease progression.

B.1.2. Description of the technology

The summary of product characteristics or information for use, and the United Kingdom (UK) public assessment report, scientific discussion or drafts are provided in Appendix C.

A description of the technology being evaluated 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 immunoglobulin G4 (lgG4) isotype that binds to programmed death 1 (PD-1) receptors. The interaction of PD1 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, programmed death-ligand 1 and 2 (PD-L1 and PD-L2), potentiating T-cell responses, including anti-tumour immune-responses (20).
Marketing authorisation/ CE mark status	• On the 2nd October 2023, via project ORBIS, the Medicines and Healthcare products Regulatory Agency (MHRA) authorised a new indication for dostarlimab. ○ JEMPERLI is indicated in combination with platinum-containing chemotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. • As of the 3rd April 2024, dostarlimab with PCC is recommended by NICE with managed access under the Cancer Drug Fund (CDF) as an option for treating primary advanced or recurrent endometrial cancer with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) in adults who are candidates for systemic therapy.
Indications and any restriction(s) as described in the summary of product characteristics	Dostarlimab is indicated in combination with PCC for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. Other existing indications include: Dostarlimab 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 (20).

<table>
<tr><td>Method of administration and dosage</td><td>Dostarlimab dosage (20):
Dostarlimab 500 mg IV every 3 weeks (Q3W) for 6 cycles followed by 1,000 mg every 6 weeks (Q6W) 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 Summary of Product Characteristics (SmPC) of the combination product(s) for further information on administration, safety aspects, and pharmaceutical particulars.</td></tr>
<tr><td>Additional tests or investigations</td><td>The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS) (20). NICE diagnostics guidance DG42 supports testing all patients with endometrial cancer for MMR status (21).</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 (22).
The list price of carboplatin is £168.85 per 450 mg vial (23).
The list price of paclitaxel is £87.50 per 100 mg vial (24).
CP is administered Q3W for a maximum of six cycles. As per the indication above, dostarlimab is administered in combination with PCC for a maximum of six cycles. As per the RUBY-1 trial protocol dostarlimab may be continued until progression of disease or unacceptable toxicity, up to a maximum of 3 years.
The acquisition costs per treatment cycles (Q3W) are shown in the table below:
<table>
<tr><th rowspan="2">Cycle (week)</th><th colspan="2">Acquisition cost per treatment cycle (£)</th></tr>
<tr><th>Dostarlimab</th><th>CP</th></tr>
<tr><td>Cycle ≤18</td><td>[redacted]</td><td>518.85</td></tr>
<tr><td>Cycle ≥19</td><td>[redacted]</td><td>0.00</td></tr>
</table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A confidential simple PAS discount application is approved by Patient Access Schemes Liaison Unit (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>

Abbreviations: CDF, Cancer Drugs Fund; CP, carboplatin plus paclitaxel; dMMR, DNA mismatch repair deficient; GSK, GlaxoSmithKline; IHC, immunohistochemistry; IgG4, immunoglobulin G4; MHRA, Medicines and Healthcare products Regulatory Agency; MMR, mismatch repair; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; PASLU, Patient Access Scheme Liaison Unit; PCC, platinum-containing chemotherapy; PCR, polymerase chain reaction; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; Q3W, every 3 weeks; Q6W, every 6 weeks; UK, United Kingdom.

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

B.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 (25). The majority of these are adenocarcinomas, originating in glandular epithelial cells of the endometrium. Other relatively rare subtypes include carcinosarcoma, an aggressive high-grade malignancy which is more likely to be diagnosed at advanced stages and associated with poorer prognosis (26-28).

Upon diagnosis, endometrial cancer is generally surgically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system (29-31). The FIGO staging system is based on the spread of the tumour from its initial location in the endometrium to other tissues or organs. 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 (25, 32, 33).

Advanced stage endometrial cancer refers to patients who present with primary Stage III or Stage IV cancer and have not undergone complete surgical resection or have at least some residual tumour (34).

Irrespective of stage at diagnosis, patients with endometrial cancer can experience disease recurrence, defined as a malignancy that cannot be detected after primary treatment but is radiologically or histologically detected at a later point in time (35).

Patients with advanced or recurrent disease have poorer outcomes than those diagnosed with primary local disease. Patients with advanced or recurrent disease are treated with a low potential for cure by radiotherapy, surgery or, a combination of both (36).

Within the group of patients classified as having advanced or recurrent endometrial cancer, grade of tumour, histology of tumour and molecular classification (among other patient-specific factors) impact disease severity, and therefore influence the expected outcomes and most appropriate treatment option for the individual patient (37, 38).

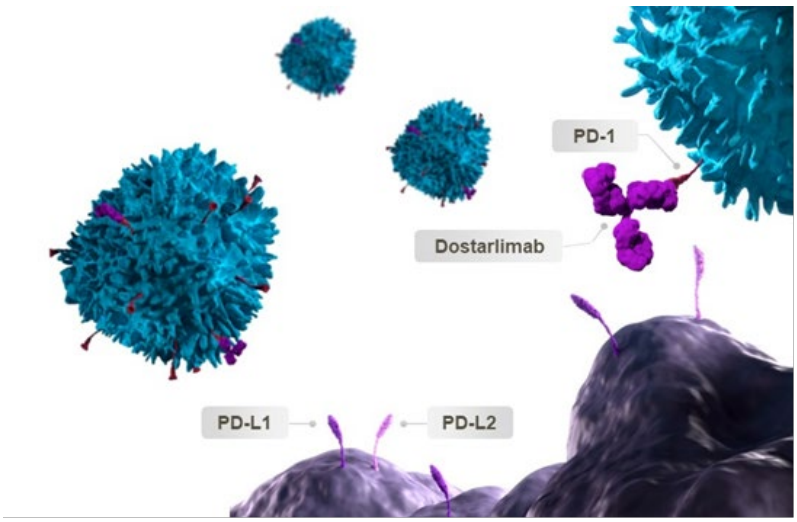
B.1.3.1.1. Molecular classification

Within the European Society for Medical Oncology (ESMO) clinical practice guideline and the subsequent European Society for Gynaecological Oncology / European Society for Radiation Oncology / European Society of Pathology (ESGO/ESTRO/ESP) guidelines for the management of patients with endometrial carcinoma, risk classification also includes molecular classification based on four distinct molecular subgroups polymerase epsilon (POLE)-mutant, dMMR/MSI-H, no specific molecular profile (NSMP) and TP53-mutant (11, 34). This submission focuses on the dMMR/MSI-H molecular subgroup that comprises approximately 25–30% of patients (34).

Endometrial cancer is reported to have the highest incidence of dMMR/MSI-H across all solid tumours, with 25–30% of endometrial cancer cases classified as dMMR/MSI-H (21, 34, 39-41). As part of the National Institute of Health and Care Excellence (NICE) diagnostics guidance DG42, all patients with endometrial cancer are now tested for dMMR/MSI-H at diagnosis (21).

dMMR/MSI-H endometrial cancer is highly immunogenic, exhibiting high levels of tumour-specific neoantigens and tumour-infiltrating T cells, conferring susceptibility to programmed cell death protein 1 (PD-1) blockade (42). Anti-PD-1 therapies, such as dostarlimab, block the PD-1/ programmed death-ligand 1 (PD-L1) pathway, preventing immune evasion by the tumour and boosting the anti-tumour immune response (43). The combination of increased T-cell activity coupled with increased PD-1/PD-L1 expression, makes dMMR/MSI-H endometrial cancer an effective target for dostarlimab. The mechanism of action for dostarlimab is shown in Figure 1.

Figure 1: **Mechanism of action of dostarlimab**



Source; Dostarlimab mechanism of action (44)
Abbreviations: PD-1, programmed death protein 1; PD-L1, programmed death ligand-1.

B.1.3.2. Epidemiology

In the UK, there are approximately 9,800 cases of endometrial cancer diagnosed annually, making it the fourth most common cancer amongst women and the most common gynaecological cancer (45).

Incidence increases with age; in the UK between 2017 and 2019, 52% of all endometrial cancer deaths were in females aged 75 and over (25, 45). High body mass index is a common risk factor for endometrial cancer, with 34% of uterine cancer cases in the UK attributable to obesity (46). Prolonged or unopposed exposure to oestrogen can increase the likelihood of endometrial cancer (11, 47). With rates of obesity rising alongside increased use of hormone replacement therapy in women experiencing menopause, it makes it increasingly important to diagnose and treat early (48, 49).

Of the 8,323 cases of endometrial cancer diagnosed annually in England, approximately 2,454 patients are diagnosed with primary advanced or recurrent endometrial disease (50). Approximately 539 patients will experience dMMR/MSI-H endometrial cancer and receive frontline treatment and are therefore the relevant population for this appraisal decision problem (50). The budget impact analysis (BIA) document outlines full details of the eligible population size.

B.1.3.3. Burden of endometrial cancer

B.1.3.3.1. Clinical burden

Primary advanced or recurrent endometrial cancer is typically incurable, with a survival expectation of 3 years or less (12, 51-53). 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 (12, 51-53).

The lack of durable responses to frontline therapies like carboplatin plus paclitaxel (CP) often leads to repeated, taxing rounds of chemotherapy (54). Prolonged treatment with doublet chemotherapy results in significant toxicities for patients, including blood disorders, fatigue, and neuropathy (12).

B.1.3.3.2. Humanistic burden

Primary advanced or recurrent endometrial cancer imposes a profound humanistic burden, severely impacting physical functioning and health-related quality of life (HRQoL) (5, 8, 19). Symptoms include heavy vaginal bleeding, pain, abdominal distension, and changes in bowel or bladder function, causing significant discomfort and distress (5-9).

Patients often feel unprepared for the psychological and physical toll of chemotherapy, with limited treatment options exacerbating their sense of hopelessness (55).

This burden is especially acute for younger patients who struggle to balance work, family responsibilities, and health, as well as for older patients losing precious retirement time (56). The need for new treatments that effectively combat cancer while preserving HRQoL is critical, as current therapies often fail to provide durable relief and can leave patients feeling overwhelmed and unsupported (7, 12). The availability of dostarlimab through the Cancer Drugs Fund (CDF) currently helps to alleviate this heavy burden faced by patients and therefore it is paramount to move dostarlimab into routine commissioning as a permanent option for patients.

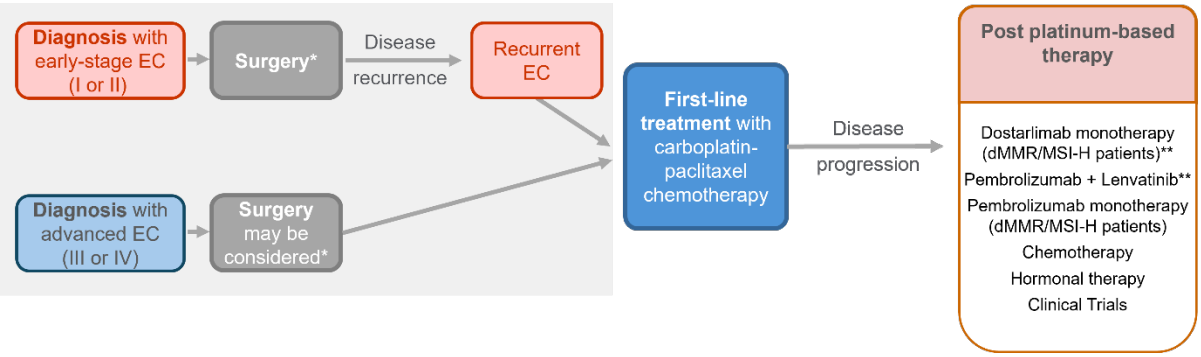
B.1.3.4. Prognosis and current NHS care pathway for the management of endometrial cancer

B.1.3.4.1. Current management pathway for endometrial cancer

The key clinical guidelines available for the management of endometrial cancer include the: British Gynaecological Cancer Society (BGCS), ESMO, and ESGO/ESTRO/ESP (11, 34, 57). There are no recently published NICE guidelines for endometrial cancer treatment outside of laparoscopic hysterectomy (58).

Approximately 20% of patients with endometrial cancer are diagnosed at advanced Stage III and IV with approximately a further 14% experiencing a recurrence (3, 4, 25, 32, 33). Patients with advanced and recurrent endometrial cancer follow the same treatment pathway (Figure 2) (11, 57).

Figure 2: Current treatment pathway excluding dostarlimab in combination with PCC (11, 59-61)



*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery; **As per pivotal trial inclusion/exclusion criteria, anti-PD-L1 / PD-1 not used in post platinum setting if treated with anti-PD-(L)1 in the first-line (15, 62, 63).
Abbreviations: ACM, appraisal committee meeting; dMMR, DNA mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability high; PCC, platinum containing chemotherapy.

B.1.3.4.2. Treatment pathway for advanced and recurrent endometrial cancer

B.1.3.4.2.1 Platinum containing chemotherapy (PCC)

Current clinical guidelines recommend the platinum-containing doublet chemotherapy CP for the first-line treatment of primary advanced and recurrent endometrial cancer (11). This existing preferred regimen is based on the Phase 3 trial GOG0209 (NCT00063999) study which established that CP was not inferior to the cisplatin–doxorubicin–paclitaxel (TAP) regimen with regard to efficacy (objective response rate [ORR] of 40–50%; median progression-free survival [PFS] and overall survival [OS] of 13.2 and 37 months, respectively) and was associated with a more favourable toxicity profile (12).

B.1.3.4.2.2 Post PCC immunotherapies

Dostarlimab monotherapy is recommended for patients with previously treated advanced or recurrent dMMR/MSI-H endometrial cancer via the CDF (59). Pembrolizumab monotherapy is recommended for previously treated dMMR/MSI-H endometrial cancer (61). Additionally, pembrolizumab in combination with lenvatinib is recommended for all previously treated patients with endometrial cancer (64).

B.1.3.4.3. Unmet need

Survival outcomes remain poor for patients with primary advanced or recurrent endometrial cancer. Over 92% of patients diagnosed with Stage I endometrial cancer will survive for 5 years or more, however, this figure drops to 15% in patients diagnosed with Stage IV disease (45). Recurrent endometrial cancer is regarded as an incurable disease, characterised by limited disease-free durations following early-stage treatment, with only 20% of patients surviving beyond 5 years (2, 65). These survival outcomes underscore the

urgent need for new, innovative treatment options that offer durable responses and improve patients' quality of life (QoL).

Prior to dostarlimab availability, chemotherapy had been the mainstay of treatment for decades, with a paucity of meaningful advancements throughout this period. PCC became the standard of care (SoC) in the early 1990s when it resulted in improved response rates and PFS, although notably without any OS benefit. A minor improvement in OS was only achieved following the addition of paclitaxel to PCC, resulting in an additional 3 months of survival (10, 66, 67).

Chemotherapy is used as a first-line treatment option in this group of patients. Despite response rates of 50–70%, the duration of response is typically relatively low with an expected median PFS of only 8–13 months (12, 66, 67).

Therapeutic advancements in first-line treatment options for patients with primary advanced and recurrent endometrial cancer are severely lacking. In contrast, other patient populations have benefited from advancements in cancer care that have markedly improved survival outcomes, leaving patients with endometrial cancer underserved until recently (68, 69). Dostarlimab is a highly innovative therapy within this patient population which has begun to transform how this disease is managed and the outcomes patients can expect in both the relapsed setting (TA779) and more recently in the first-line setting (TA963) (11, 57, 59, 70).

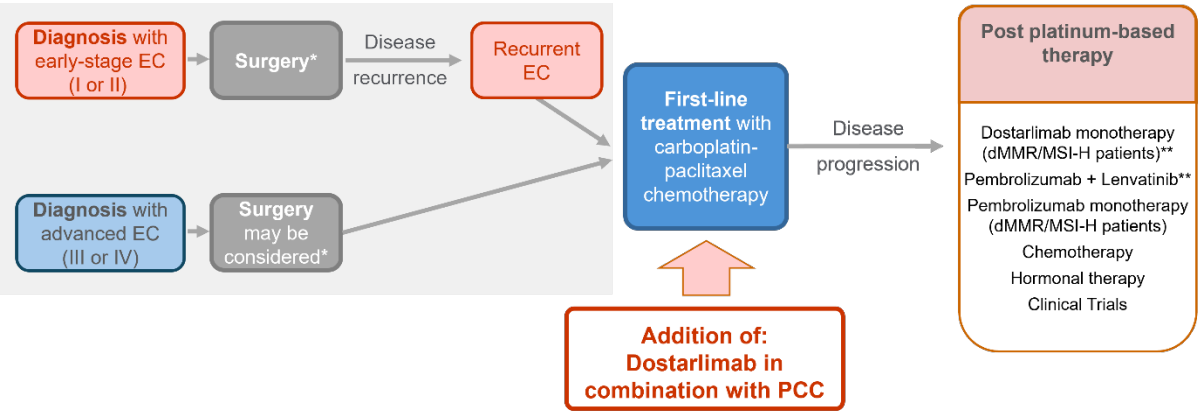
It is therefore imperative that dostarlimab remains available as an effective and permanent treatment option in the primary advanced and recurrent endometrial cancer treatment paradigm.

B.1.3.4.4. Positioning of dostarlimab in combination with PCC in the management of endometrial cancer

Dostarlimab in combination with PCC is recommended by NICE under a managed access agreement (MAA) within the CDF (71). Dostarlimab is now established within the clinical care pathway as an addition to the existing SoC pathway (Figure 3).

As an addition to the established SoC, the combination of dostarlimab with CP ensures that clinicians have the existing confidence and familiarity with the efficacy and side effects of the chemotherapy regimen when making a prescribing decision. Bringing access to immunotherapies earlier from second line into a primary setting has allowed dostarlimab to have additional impact on survival outcomes.

Figure 3: Current treatment pathway including dostarlimab in combination with PCC (11, 59-61)



*At any stage, patients may receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery. **As per pivotal trial inclusion/exclusion criteria, anti-PD-(L)1 not used in post platinum setting if treated with anti-PD-(L)1 in the first-line (15, 62, 63).
Abbreviations: ACM, appraisal committee meeting; dMMR, DNA mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability high; PCC, platinum containing chemotherapy.

B.1.4. Equality considerations

In the UK, endometrial cancer survival outcomes are associated with socio-economic deprivation. After adjusting for demographic and clinical predictors, women from the middle and most deprived socio-economic groups were more likely to die from endometrial cancer, with a two-fold and a 53% increased risk respectively, compared with the least deprived women (72).

Additionally, ethnicity impacts endometrial cancer survival outcomes. One study demonstrated significant differences in demographic characteristics between co-located patients of South Asian and White ethnicity diagnosed with endometrial cancer (73). Specifically, the South Asian patient group were diagnosed at a younger age and had a greater proportion of premenopausal cases (73). Therefore, there may be disparities in the suspected cancer referral criteria between patients of South Asian and White ethnicity.

Recently, the Office for National Statistics (ONS) published data showing substantial disparities in endometrial cancer mortality, with Black ethnic groups having substantially higher mortality rates than other ethnic groups in the UK (74). Late-stage diagnosis of endometrial cancer appears to be increased among women who are Black Caribbean and Black African, compared with women from other ethnic groups (74).

Access to innovative treatment for late stage disease at a national level can help to address the severe inequalities existing in survival outcomes experienced amongst patients with

endometrial cancer of different ethnicities or experiencing different levels of socio-economic deprivation (25, 46). The introduction of new efficacious treatment options for a historically underserved gynaecological cancer raises the profile of the disease amongst the clinical community and increases patient awareness.

B.2. Clinical effectiveness

Dostarlimab plus chemotherapy 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. The greatest benefit was observed in the mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) population.

RUBY-1 trial design

- Part 1 of the RUBY trial (RUBY-1) (NCT03981796) investigates the addition of dostarlimab to the current standard of care (SoC) carboplatin and paclitaxel (CP) in patients with primary advanced or recurrent endometrial cancer (75).
- This submission focuses on the second interim analysis (IA2) of the RUBY-1 trial. Endpoints reported on as part of this analysis are the dual-primary endpoint, OS, the secondary endpoint, progression-free survival 2 (PFS2) and safety. Statistical significance of the other dual-primary endpoint, progression-free survival (PFS) was met in the first interim analysis (IA1) and therefore not recut as part of IA2.
- The dual-primary endpoint of PFS was tested hierarchically in the dMMR/MSI-H population and then in the ITT population. OS was tested for in the ITT population. The RUBY-1 trial was stratified by mismatch repair (MMR) status and OS for the dMMR/MSI-H population was a pre-specified subgroup analysis.

RUBY-1 OS and PFS2 for patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer

- OS:
  - Dostarlimab in combination with CP resulted in both a statistically and clinically significant improvement in the ITT OS compared with placebo in combination with CP (hazard ratio [HR]: 0.69 [95% CI 0.54, 0.89]; p=0.002) (76).
  - The OS benefit was most pronounced in the pre-specified dMMR/MSI-H subgroup (HR: 0.32; 95% CI: 0.17, 0.63; nominal p=0.0002) (40.2% maturity) (76).
- PFS2:
  - Dostarlimab in combination with CP reduced the risk of progression following first subsequent anticancer therapy or death (PFS2) in the dMMR/MSI-H population (HR 0.33; 95% CI: 0.18, 0.63) (76).
  - This improvement in PFS2 demonstrates that the benefits of improving PFS with dostarlimab extends across later lines of treatment. Notably, these results are observed despite the significant second-line use of immunotherapies in the placebo arm, demonstrating that optimal outcomes are achieved when dostarlimab is used earlier in the treatment pathway.

Safety analysis for dMMR/MSI-H primary advanced or recurrent patients

- Dostarlimab in combination with CP has a manageable safety profile consistent with the known profiles of the individual agents with no new safety signals observed at the second interim analysis.

Conclusion

- Dostarlimab has provided a step change in care for patients with dMMR/MSI-H endometrial cancer, resulting in durable responses indicative of long-term remission in this previously underserved patient population.
- It is therefore paramount that dostarlimab continues to remain available for these patients.

B.2.1. Identification and selection of evidence

A systematic literature review (SLR) was conducted on 10 November 2021 (with a refresh on 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 D.

B.2.2. List of relevant clinical effectiveness evidence

As per Section B.1.3.4, CP is the SoC treatment option in the primary advanced or recurrent endometrial cancer population. Fourteen trials were identified to have investigated CP in this population. These trials are summarised in Appendix D. However, no RCTs provided direct head-to-head evidence of dostarlimab in combination with CP compared with CP relevant to the decision problem. Additionally, there is no evidence focused on the CP regimen in the dMMR/MSI-H patient population.

The SLR (see Appendix D) identified RUBY as the only RCT that evaluated the efficacy and safety of dostarlimab in combination with CP as a treatment in female adult patients with primary advanced or recurrent endometrial cancer. RUBY (ClinicalTrials.gov number: NCT03981796) was a pivotal Phase 3 trial investigating dostarlimab in combination with CP as a treatment in female adult patients with primary advanced or recurrent endometrial cancer. The clinical data and cost-effectiveness analyses are based on this study. Table 3 provides a brief overview of the clinical evidence to support the use of dostarlimab in combination with CP in patients with 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 appropriate comparator for this appraisal.

Table 3: Clinical effectiveness evidence

Study	RUBY (ClinicalTrials.gov number: NCT03981796) (75).
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) [dMMR/MSI-H n=118]*
Intervention(s)	Dostarlimab in combination with CP (N=245) [n=53 dMMR/MSI-H]
Comparator(s)	Placebo in combination with CP (N=249) [n=65 dMMR/MSI-H]

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 are provided below. Full details of the eligibility criteria are presented within the study protocol (77) Key inclusion criteria: • Female patient is at least 18 years of age • 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 • Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 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, had 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 intravenous (IV) in combination with carboplatin IV (area under curve (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 all cycles thereafter (cycle 7 onwards) • Dostarlimab is administered prior to chemotherapy on the same day. Treatment 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)	Progression-free survival (PFS) [primary outcome in dMMR/MSI-H population and ITT population] • PFS was assessed by investigator assessment per RECIST v1.1 with sensitivity analysis by blinded independent central review (BICR) o Radiographic scans were conducted prior to the signing of the informed consent as part of routine clinical management and were accepted as initial tumour imaging, provided they were of diagnostic quality and performed within 28 days before the first dose o Patients were evaluated radiographically to assess the extent of disease Q6W until Week 25 (±7 days) followed by Q9W until Week 52 (±7 days). o Subsequent tumour imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment followed by one additional imaging assessment 4-6 weeks later, or when subsequent anticancer therapy was started, whichever occurred first • Overall survival (OS) [primary outcome in ITT population, prespecified subgroup analysis in dMMR/MSI-H population]
Secondary and exploratory outcomes (including scoring methods and timings of assessments)	• PFS based on blinded independent central review (BICR) assessment • Objective response rate (ORR) based on BICR and investigator assessment • Duration of response (DOR) based on BICR and investigator assessment • Disease control rate (DCR) based on BICR and investigator assessment • Patient reported outcomes (PROs) o European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) [mapped to EQ-5D-3L] o European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (C30 [Core; QLQ-C30]) o Endometrial Cancer Module [QLQ-EN24]) o PROs were assessed at every clinic visit and during every survival follow-up assessment • Progression-free survival 2 (PFS2) o 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 adverse events (AEs), serious AEs, AEs of special interests, suspected unexpected serious

	adverse reaction and treatment emergent adverse events (TEAEs)
Prespecified subgroup analyses	• OS in the dMMR/MSI-H population was a pre-specified sub-group analysis. • Exploratory subgroup analyses on the primary endpoints (investigator assessed PFS and OS) were also performed on the dMMR/MSI-H population to explore the homogeneity of the treatment effect across relevant participant subsets: o Age (< 65 years or ≥ 65 years) o Race (white or other) o Region (North America or Europe or Western Europe or Eastern Europe) o Histology (endometrioid carcinoma or other) o Disease status at baseline (recurrent, primary stage III, or primary stage IV), according to the eCRF (source verified classification) o Prior external pelvic radiotherapy (yes or no), according to the eCRF (source verified classification) o Patients with “No disease” at baseline

*N refers to the ITT population while n refers to the dMMR-MSI-H population.
Abbreviations: AE, adverse events; AUC, area under curve; BICR, blinded independent central review; CP, carboplatin and 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; N/A, not applicable; 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; PRO, patient reported outcomes; QLQ-C30, Quality of Life Questionnaire C30 (Core); QLQ-EN25, Quality of Life Questionnaire Endometrial Cancer Module; TEAE, treatment emergent adverse event; UK, United Kingdom; US, United States.

B.2.2.1. UK real-world evidence

A real-world evidence (RWE) study was conducted using the National Cancer Registration and Analysis Service (NCRAS) data for diagnosis between 2013 and 2019 (78). The analysis studied patient characteristics, treatment pathways, and health outcomes in real-world English patients with primary advanced or recurrent endometrial cancer. The results of this study were included in the previous NICE single technology appraisal (STA) submission [ID3986] and reviewed by the committee (79). An update to the RWE NCRAS study was performed in December 2023 to include NCRAS data for diagnosis between 2013 and 2021 (80). The study identified [redacted] patients who received first line systemic treatment for advanced or recurrent endometrial cancer and were eligible for immune checkpoint inhibitors (ICI). Of these patients, [redacted] were treated with CP, highlighting that CP is still the current SoC for these patients (80).

The update was also able to identify patients who were tested for MMR status. This search was restricted to patients whose original diagnosis date was between 2019 and 2021, as this

is when data on MMR status became available within the NCRAS database (80). Of the [redacted] ICI eligible patients diagnosed between 2019 and 2021, [redacted] received an MMR test. Of the patients who received an MMR test, [redacted] were dMMR and [redacted] were mismatch repair proficient (MMRp), in line with the expected split for this population (11, 21). Most patients in this dMMR/MSI-H population were White [redacted] with a mean age of [redacted] at advanced diagnosis or recurrence (80). These demographics are similar to those reported in part 1 of the RUBY trial (RUBY-1), which form the basis of the efficacy data for this submission (Section B.2.3.5). The results provide an insight into the poor prognosis for dMMR/MSI-H patients in the UK. The full report of this NCRAS RWE study is included in Appendix M.

B.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]). 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
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.
*IA1 data was collected for each outcome, however IA2 will be used to inform the economic model.
**Subgroups presented as forest plot only to demonstrate the observed treatment effect is robust across subgroups with none differing significantly from the overall population.
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; Sep, September.

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

B.2.3.1. Summary of study methodology

B.2.3.1.1. Study design

RUBY is a Phase 3, randomised, double-blind, multicentre study aiming to evaluate the efficacy and safety of treatment with dostarlimab in combination with CP followed by dostarlimab versus treatment with placebo and CP. 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:

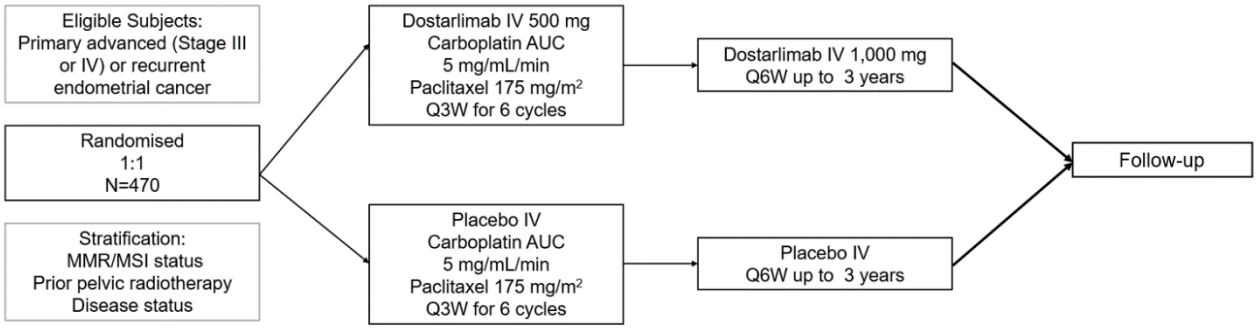
- Intervention arm (dostarlimab arm): Patients received dostarlimab 500 mg intravenous (IV) in combination with CP followed by dostarlimab monotherapy 1,000 mg IV
- Comparator arm (placebo arm): Patients received placebo IV in combination with CP followed by placebo IV.

Patients were stratified by MMR and MSI status as dMMR/MSI-H or MMRp/microsatellite stable (MSS), 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.

B.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 B.2.2, Table 3.

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.

B.2.3.2. Settings and locations

The study was carried out in 19 countries; the US, UK, Belarus, Belgium, Canada, Czechia, Denmark, Finland, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Sweden, Turkey, and Ukraine.

B.2.3.3. Trial drugs and concomitant medications

Dostarlimab was administered IV at a unit dose of 500 mg every three weeks (Q3W) for six cycles (Cycles 1-6), then at 1000 mg every six weeks (Q6W) for all cycles thereafter (Cycle 7 onwards). Placebo was also administered IV Q3W for six cycles (Cycles 1–6) and then every Q6W for all cycles thereafter (Cycle 7 onwards). 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 Q3W. Paclitaxel was administered IV at a unit dose of 175 mg/m^2 Q3W.

Any medication that the patient used during the study other than the study interventions, including herbal and other non-traditional remedies, was considered a concomitant medication. At screening, patients were asked what medications they had taken during the last 30 days. At each subsequent study visit, patients were asked what concomitant medications they were currently taking or had taken since the previous visit. Prior medications that excluded a patient from the study are described in the exclusion criteria in Section B.2.2, Table 5.

B.2.3.4. Study outcomes

The dual primary objectives of RUBY-1, in the intention-to-treat (ITT) population, were to compare the OS and PFS (PFS was assessed by the Investigator per Response Evaluation

Criteria in Solid Tumours version 1.1, RECIST v1.1) observed in the dostarlimab arm to that in the placebo arm. PFS was hierarchically tested in both the dMMR/MSI-H population and the overall population. OS was tested in the ITT population. Additionally, OS in the dMMR/MSI-H population was examined as a pre-specified exploratory analysis. Secondary objectives included the comparison of PFS based on blinded independent central review (BICR) assessment, ORR, duration of response (DOR), disease control rate (DCR), patient-reported outcomes (PRO), PFS2, safety and tolerability endpoints between patients of both treatment arms. Section B.2.2.2 specifies the objectives that were analysed at IA1 (28th September 2022), and at IA2 (22nd September 2023). Relevant clinical effectiveness evidence from IA1 that was used to support the original NICE submission (TA963) and was accepted by the committee has not been duplicated in this submission but can be found in Appendix N (70, 79). This submission will present new clinical effectiveness data from the IA2 to address outstanding uncertainties.

B.2.3.5. Patient demographics and clinical baseline characteristics

Table 5 presents a summary of the demographic baseline characteristics of patients in the dMMR/MSI-H population. There were 53 patients in the dostarlimab arm while 65 patients were in the placebo arm. Most patients were White with a median age of 64.0 years (84.7%) and baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of [redacted]. The median patient age was 61.0 years in the dostarlimab arm and 66.0 years in the placebo arm, however the mean age was comparable in each arm, [redacted] and [redacted] years, respectively. The percentages of patients in the ≥65 years age group and the 19 to 64 years age groups were largely similar between the treatment arms.

At study entry, the mean weight and body mass index (BMI) was slightly higher in the placebo arm compared with the dostarlimab arm ([redacted]). In the previous NICE STA submission [ID3986], an additional analysis determined that these disparities in BMI between the two arms did not affect the hazard ratio (HR) (79). ECOG status was worse in the dostarlimab arm as less patients had a PS of 0 compared with the placebo arm (53.8% vs 60.0%). In total, 46.2% of patients in the dostarlimab arm and 40.0% of patients in the placebo arm had an ECOG PS of 1. In general, the patients baseline characteristics between treatment arms were considered well balanced (81).

Table 5: Summary of demographic characteristics in the dMMR/MSI-H population

Characteristic	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Race, n (%)		
White	44 (83.0)	56 (86.2)
Black or African American	4 (7.5)	6 (9.2)
Asian	2 (3.8)	0
American Indian or Alaska Native	0	1 (1.5)
Native Hawaiian or other Pacific Islander	1 (1.9)	0
Unknown	1 (1.9)	1 (1.5)
Not Reported	1 (1.9)	1 (1.5)
Ethnicity, n (%)		
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median	61.0	66.0
Q1, Q3	[redacted]	[redacted]

Characteristic	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Min, Max	[redacted]	[redacted]
Age Group, n (%)		
19-64	[redacted]	[redacted]
≥65	[redacted]	[redacted]
Weight (kg)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Height (cm)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BMI (kg/m^2)		
Mean (SD)	[redacted]	[redacted]
Median	30.55	35.50
Q1, Q3	[redacted]	[redacted]
Min, Max	20.1, 54.4	17.9, 58.1
BSA (m^2)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ECOG PS, n (%)		
0	28 (53.8)	39 (60.0)
1	24 (46.2)	26 (40.0)

Source: IA1 CSR Table 14.1.1.15.
Abbreviations: BMI, body mass index; BSA, body surface area; CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; PS, performance status; SD, standard deviation.

Table 6 presents a summary of the disease history of patients in the dMMR/MSI-H population, while Table 7 shows a summary of the prognostic stratification factors in dMMR/MSI-H patients. FIGO stage at initial diagnosis was generally similar between the treatment arms. As expected, the most frequent histology type at diagnosis was endometrioid histology (83.0% of patients in the dostarlimab arm and 86.2% in the placebo arm). This was similar for the most recent histology, with 84.9% and 83.1% of patients in the dostarlimab arm and placebo arm presenting with this histology, respectively. Both treatment arms contained a relatively low number of patients with carcinosarcoma histology, however this histology was found in a larger proportion of patients in the dostarlimab arm compared

with the placebo arm (7.5% versus 1.5%). In general, the patients' disease history between treatment arms were considered well balanced (81).

Table 6: Summary of disease history in dMMR/MSI-H population

Category, n (%)	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
FIGO stage at initial diagnosis		
Stage I	18 (34.0)	22 (33.8)
Stage II	3 (5.7)	5 (7.7)
Stage III	14 (26.4)	20 (30.8)
Stage IV	14 (26.4)	15 (23.1)
Unknown	4 (7.5)	3 (4.6)
Histology at diagnosis		
Carcinosarcoma	4 (7.5)	1 (1.5)
Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	44 (83.0)	56 (86.2)
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	2 (3.8)	4 (6.2)
Other	2 (3.8)	3 (4.6)
Serous adenocarcinoma	1 (1.9)	1 (1.5)
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Most recent histology		
Carcinosarcoma	[redacted]	[redacted]
Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]
Other	[redacted]	[redacted]
Serous adenocarcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[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]
Recurrence of endometrial cancer		
Yes	27 (50.9)	32 (49.2)
No	26 (49.1)	33 (50.8)

Source: IA1 CSR Table 14.1.1.17 (82).
Abbreviations: CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; FIGO, Federation of Gynaecology and Obstetrics; MSI-H, microsatellite instability-high.

Table 7: Prognostic stratification factors in dMMR/MSI-H population

Category, n (%)	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
MMR/MSI status		
dMMR/MSI-H	[redacted]	[redacted]
pMMR/MSS	[redacted]	[redacted]
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: IA2 CSR Table 14.1.1.10 (83).
Abbreviations: CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, mismatch repair proficient.

A CONSORT diagram showing the patient flow for RUBY-1 is provided in Section D.5 of Appendix D.

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

No changes to the statistical analysis plan (SAP) were made between the previous data cut (IA1) and the more recent data cut (IA2). Full details of RUBY-1, including a summary of the statistical analyses, are provided in Appendix N, Table 1.

Full details on the definition of endpoints are provided in the IA1 clinical study report (CSR) and IA2 CSR (82, 83). In addition, further details on the assessments performed for RUBY-1 as well as the number of patients that discontinued or withdrew treatment are available in the CSR (83).

B.2.4.1. Analysis populations

B.2.4.1.1. dMMR/MSI-H subset of analysis population

Analyses of dMMR/MSI-H populations were based on source verified classifications of MMR/MSI status collected in the electronic case report form (eCRF). Sensitivity analysis was undertaken based on MMR/MSI classification entered for randomisation.

There are two different classifications of MMR/MSI status due to the datapoint values for MMR/MSI status being captured at two timepoints. Of these, classification based on the source verified value of MMR/MSI status collected in the eCRF, which reflects the actual MMR/MSI status, was chosen for the prespecified primary analysis to reduce the impact of misclassification on the dMMR/MSI-H population.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment for the RUBY-1 trial is provided in Section D.6 of Appendix D.

B.2.6. Clinical effectiveness results of RUBY-1

The following sections present the clinical effectiveness results for the dMMR/MSI-H population. All results for the ITT population are included in the IA1 and IA2 CSRs (82, 83).

The clinical effectiveness of IA1 was appraised as part of TA963, where the committee concluded that RUBY-1 is appropriate for decision making and that dostarlimab is clinically effective in the dMMR/MSI-H population (70). The submission for TA963 included PFS, OS and PFS2 data from IA1, with PFS reaching statistical significance in the dMMR/MSI-H population and the overall population (70). However, due to the immaturity of the available OS data, dostarlimab was recommended only as part of a MAA through the CDF (70, 71). This uncertainty resulted from limited follow-up and a lower number of survival events in the dostarlimab arm during IA1 (70, 71).

With further maturity at IA2, OS has now reached statistical significance in the ITT population, with a median OS of 44.6 months in the dostarlimab arm compared with 28.2 months in the placebo arm (HR: 0.69; 95% confidence interval [CI]: 0.539, 0.890; stratified log-rank test p-value=0.002) (83). The KM analysis of OS in the ITT population can be found in Appendix N. No additional PFS data were collected, as statistical significance was met at IA1 for the dMMR/MSI-H population, in accordance with the statistical analysis plan. The IA2 results validate the trend in OS and PFS observed at IA1 which formed the basis of NICE's earlier appraisal of this indication (70, 71, 79). Table 4 details which data cut is used to inform each endpoint within this submission.

Both efficacy data from the IA1 and IA2 data cut-offs demonstrate the consistent and durable efficacy of the dostarlimab arm on OS. IA1 PFS outcomes are summarised in Appendix N.

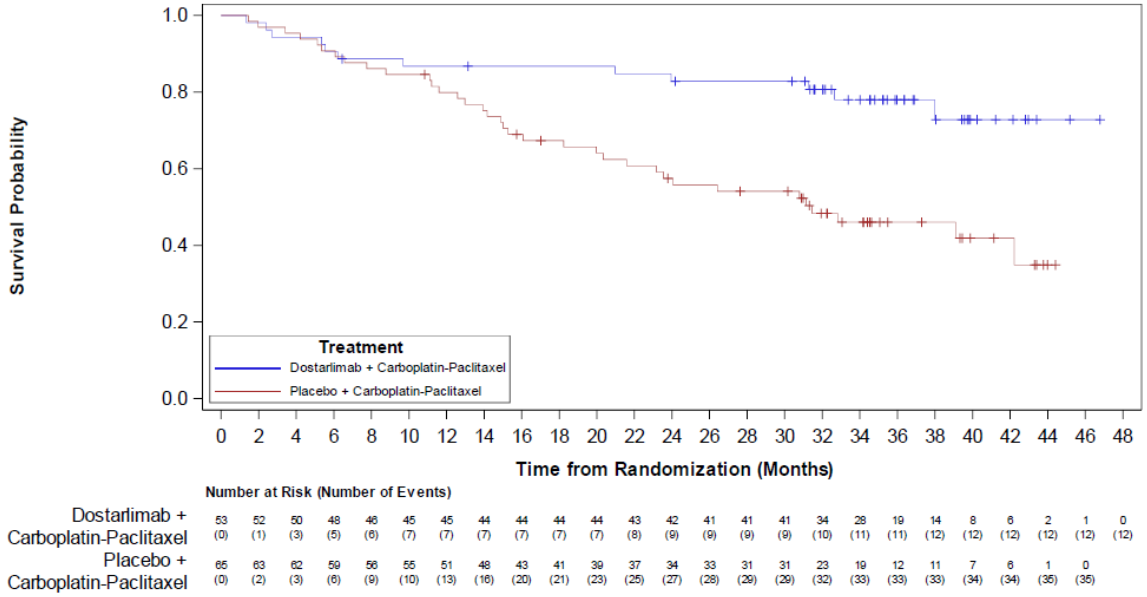
B.2.6.1. OS

Figure 5 shows the Kaplan-Meier (KM) analysis of OS in the prespecified dMMR/MSI-H - subgroup at IA2. At 40.2% OS maturity, there was a 68% reduction in risk of death in the dostarlimab arm compared with the placebo arm (HR: 0.32; 95% CI: 0.166, 0.629; nominal p-value=0.0002). Median OS was 31.4 months for the placebo arm and was not reached for the dostarlimab arm (Table 8).

In the dostarlimab arm there were [redacted], whilst in the placebo arm [redacted] were observed. A clear, early and sustained separation of the survival curves began around 6 months and maintained over the trial period.

The KM probability of survival at 24 months was 57.5% (95% CI: 44.4, 68.6) in the placebo arm versus 82.8% (95% CI: 69.5, 90.7) in the dostarlimab arm (Table 8). At 36 months, the KM probability of survival was 46.0% (95% CI: 32.9%, 58.2%) in the placebo arm versus 78.0% (95% CI: 63.6%, 87.3%) in the dostarlimab arm (76, 84) (Table 8).

Figure 5: IA2 KM analysis OS (dMMR/MSI-H population)



Source: IA2 CSR Figure 15.1.8. (83)
Data cut-off: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Table 8: IA2 KM analysis of OS (dMMR/MSI-H population)

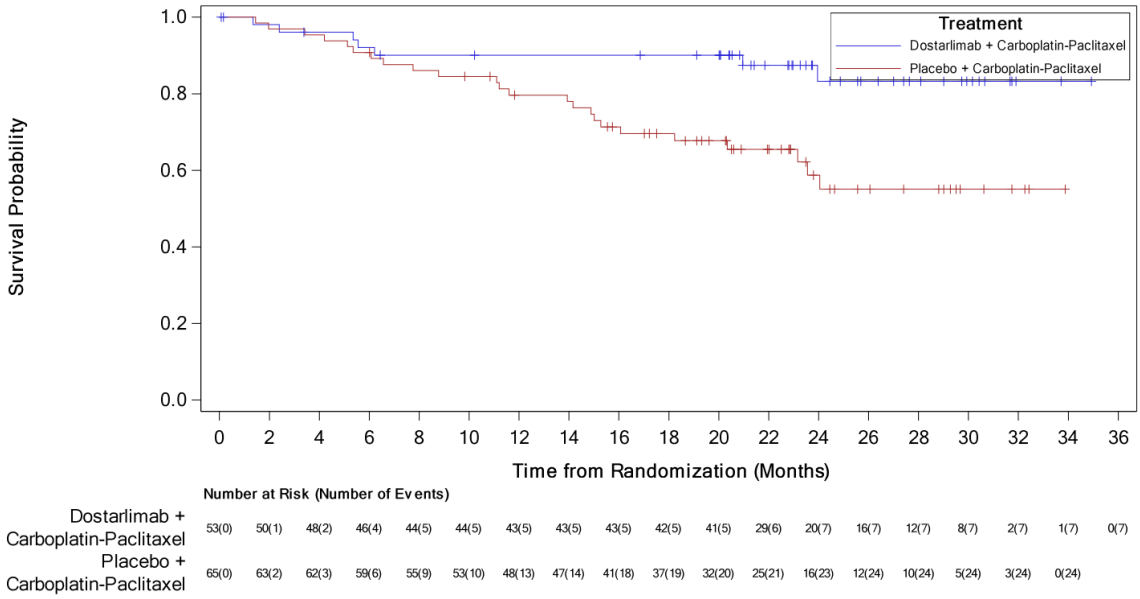
Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
OS status, n (%)		
Events observed	[redacted]	[redacted]

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Censored	[redacted]	[redacted]
OS (months) Quartile (95% CI)[a]		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
OS probability (95% CI)		
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	82.8% (69.5%, 90.7%)	57.5% (44.4%, 68.6%)
Month 30	[redacted]	[redacted]
Month 36	78.0% (63.6%, 87.3%)	46.0% (32.9%, 58.2%)
Month 42	[redacted]	[redacted]
HR (95% CI)[b]	0.32 (0.166, 0.629)	
Nominal p-value of 1-sided stratified log-rank test	0.0002	

Source: Data on file summary of KM analysis of OS (84). Month 36 data from Powell et al. (76).
Data cut-off: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; NR, not reported; OS, overall survival.

Figure 6 shows the KM analysis of OS in the dMMR/MSI-H population from IA1 at 26% OS maturity presented as part of TA963, and Table 14 presents the data from the KM analysis of OS for both IA1 and IA2. The censoring at months 20–24 in the IA1 curve does not occur in the IA2 curve, however, the KM curve retains the same shape, demonstrating that the trend in the probability of survival for the dostarlimab arm in IA1 is validated by the more mature IA2 data. Overall, the KM analyses of OS across both IA1 and IA2 showed a consistent, sustained treatment effect on OS, and durable survival outcomes in the dostarlimab arm.

Figure 6: IA1 KM analysis OS (dMMR/MSI-H population)



Source: IA1 CSR Figure 15.1.8. (82).
Data cut-off: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Table 14: Summary of KM of IA1 and IA2 (dMMR/MSI-H population)

	IA1		IA2	
Category subcategory	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
OS status, n (%)				
Events observed	7 (13.2%)	24 (36.9%)	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]
OS (months) Quartile (95% CI)				
25%	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]
OS probability (95% CI)				
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	83.3% (66.8%, 92.0%)	58.7% (43.4%, 71.2%)	82.8% (69.5%, 90.7%)	57.5% (44.4%, 68.6%)
Month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	NA	NA	78.0% (63.6%, 87.3%)	46.0% (32.9%, 58.2%)
Month 42	NA	NA	[redacted]	[redacted]
HR (95% CI)	0.30 (0.13, 0.70)		0.32 (0.166, 0.629)	

	IA1		IA2	
Category subcategory	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Nominal p-value of 1-sided stratified log-rank test	[redacted]		0.0002	
Median follow-up, months	24.79		36.6	

Source: IA1 and IA2 CSR Table 14.1.1.34 (82, 83). Month 36 data from Powell et al. (76).
Data cut-off: 28 September 2022 and 22 September 2023
Abbreviations: CI, confidence interval; CP, CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; HR, hazard ratio; IA1, first interim analysis; IA2, second interim analysis; ITT, intention-to-treat; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; NA, not available; NR, not reported; OS, overall survival.

B.2.6.2. Secondary efficacy outcomes

The clinical benefit of adding dostarlimab to CP was consistently observed across all secondary efficacy endpoints in the dMMR/MSI-H population including PFS by BICR, PFS2, ORR, DCR, and DOR (Appendix N).

B.2.6.2.1. PFS2

The improvements seen in PFS2 data further support the observed OS benefit by depicting a clinical benefit beyond the first progression for patients in the dostarlimab arm (76, 85).

PFS2, or time from randomisation to death or progression on the first subsequent anticancer therapy, investigates whether the benefits of improved PFS at one line of therapy is maintained across later lines of therapy (76, 85).

Figure 7 shows the KM curves of PFS2 in the dMMR/MSI-H population. An increased time to PFS2 was seen for patients in the dostarlimab arm compared with those in the placebo arm. Median PFS2 was 21.6 months [redacted] in the placebo arm whereas median PFS2 was not reached for patients in the dostarlimab arm, even at 48 months (76, 85). Similar to OS, a separation in PFS2 curves is observed at approximately 6 months, with relatively durable event-free survival in the dostarlimab arm over the follow-up period. This corresponds to a reduction of 67% in the risk of death or progression following the first subsequent anticancer therapy (HR: 0.33; 95% CI: 0.175, 0.627) (Table 9) (76, 85).

The longer PFS2 in the dostarlimab arm demonstrates that the treatment benefits observed with first-line immunotherapy extend beyond the first episode of disease progression. Notably, these strong PFS2 outcomes were achieved despite the significant use of immunotherapy in later lines of treatment in the placebo arm: 41.5% of patients randomised to the placebo arm received subsequent immunotherapy (76)

Figure 7: KM curves of PFS2 (dMMR/MSI-H population)

Source: IA2 CSR Figure 15.1.11 (83).
Data cut-off: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

Table 9: Summary of KM of PFS2 (dMMR/MSI-H population)

	Dostarlimab in combination with CP N=53)	Placebo in combination with CP (N=65)
HR (95% CI)	0.33 (0.175, 0.627)	
Median PFS2, months (95% CI)	[redacted]	21.6 [redacted]
PFS2 probability at 24 months (95% CI)	76.6% (63.1%, 86.9%)	46.8% (33.9%, 58.6%)

Source: IA2 CSR Table 14.2.1.39 (83) and Powell et al. (76).
Data cut-off: 22 September 2023.
Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair deficient; HR, hazard ratio; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

B.2.7. Subgroup analysis of OS

To explore the homogeneity of the treatment effect across relevant participant subsets, subgroup analyses of OS were performed (Figure 8). These results should be interpreted with caution given the smaller sample size in subgroups, low data maturity in some subgroups, and that the analyses were not powered to detect treatment differences in any subgroup.

A forest plot of OS in the dMMR/MSI-H population demonstrates the observed treatment effect is robust across subgroups. The point estimate of the treatment effect is very favourable (HR<0.5) for almost all subgroups, despite the low number of observed OS events and small sample sizes in the individual subgroups (Figure 8). The only exceptions were for the histology category “other” [redacted], and Stage III primary disease status [redacted] These exceptions were discussed during the previous NICE STA submission [TA963] where it was concluded that there was unlikely to be any meaningful difference in treatment effect across relevant subgroups due to small patient numbers being treated (70).

Figure 8: Forest plot of OS and 95% CIs by subgroup (dMMR-MSI-H population)

Source: IA2 CSR Figure 15.2.2. (83).
Data cut-off: 22 September 2023.
Note: HRs presented are from unstratified Cox regression model. HR estimation with 95% CI is displayed as 'Not Applicable' for the subgroup where there are less than five events in a subgroup or there is no event in one treatment arm.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; dMMR, DNA mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

B.2.8. Meta-analysis

RUBY-1 is the only RCT identified evaluating dostarlimab in combination with CP versus CP in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer, as such no meta-analysis is required (Section B.2.2).

B.2.9. Indirect and mixed treatment comparisons

Expert clinical input has confirmed that the CP regimen utilised within the RUBY-1 trial reflects the SoC in the UK for treating patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer (81). This mirrors the pathway described as part of TA963. The recent reimbursement of dostarlimab in this indication via the CDF has led to a growing adoption of this regimen. However, in the absence of dostarlimab, CP alone remains the SoC in this setting. RUBY-1 offers robust head-to-head evidence compared with the UK SoC; therefore, indirect evidence to support this submission is not required.

B.2.10. Adverse reactions

In RUBY-1, the safety profile of dostarlimab in combination with CP was evaluated based on reported adverse events (AE), which were captured as a secondary endpoint. This safety data comprises data from IA2 of RUBY-1. The safety population consists of all participants who received at least one dose of study intervention (N=487); 117 of these participants were stratified as dMMR/MSI-H. Of the 487 participants comprising the safety population, 241 patients were enrolled in the dostarlimab arm (52 of these were dMMR/MSI-H). Safety data are presented for the dMMR/MSI-H population.

Overall, the safety profile for the dostarlimab arm was generally consistent with the known safety profiles of the individual agents in the overall population (n=241) and the dMMR/MSI-H (n=52) populations (Table 10). Safety results were generally consistent with those described for IA1. The safety profile of the proposed regimen was acceptable with generally manageable toxicities in the indicated population. No new safety signals were observed with additional follow-up.

B.2.10.1. Summary of treatment emergent adverse events (TEAE)

A total of 52 patients had received at least one dose of dostarlimab in combination with CP and were included in the safety analysis, while 65 patients in the placebo arm were included. All patients (100%) experienced at least one treatment emergent adverse event (TEAE) across both arms.

The overall summary of TEAEs experienced by patients in the dMMR/MSI-H population can be found in Table 10. Incidences of participants experiencing Grade ≥3 TEAEs related to any treatment, and TEAEs leading to infusion interruption were >10% higher in the dostarlimab arm compared with the placebo arm. The incidence of participants experiencing any immune-related TEAEs and treatment-related immune-related TEAEs were notably

higher (≥35%) in the dostarlimab arm compared with the placebo arm. TEAEs leading to death were reported in two patients, both in the dostarlimab arm and assessed by the Investigator as related to the study treatment (Table 10).

Table 10: Overall summary of TEAEs (dMMR/MSI-H population)

AE category, n (%)	Dostarlimab in combination with CP (N=52)	Placebo in combination with CP (N=65)	Total (N=117)
Any TEAE	[redacted]	[redacted]	[redacted]
Any Grade ≥3 TEAEs	[redacted]	[redacted]	[redacted]
Treatment-related Grade ≥3 TEAEs	[redacted]	[redacted]	[redacted]
Any TEAE with outcome of death	[redacted]	[redacted]	[redacted]
Any SAEs	[redacted]	[redacted]	[redacted]
Treatment-related SAEs	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
Any immune-related TEAEs	[redacted]	[redacted]	[redacted]
Any dostarlimab- or placebo-related immune-related TEAEs	[redacted]	[redacted]	[redacted]
Any infusion-related reactions	[redacted]	[redacted]	[redacted]

Source: CSR Table 14.3.1.1 (83).
Data cut-off: 22 September 2023.
Abbreviations: AE, adverse event; CP, carboplatin and paclitaxel; dMMR, DNA mismatch repair-deficient; MSI-H, microsatellite instability-high; SAE, serious adverse event; TEAE, treatment emergent adverse event.

B.2.10.2. Any grade TEAEs

In the dMMR/MSI-H population, all participants in both treatment arms had at least one TEAE. The most frequently reported TEAEs regardless of causality (≥20% of participants in any arm) are summarised for the dMMR/MSI-H population in Figure 9.

The incidences of TEAEs by specific system organ classes (SOC) and preferred terms (PT) were comparable (≤10% difference) between participants in the two treatment arms. Exceptions were incidences of nausea, rash, hypertension, hypothyroidism, maculo-papular, and pyrexia which were higher in the dostarlimab arm compared with the placebo arm; while anaemia, dyspnoea, urinary tract infection, neutrophil count decreased, dizziness, and white blood cell decreased were higher in the placebo arm compared with the dostarlimab arm. Most TEAEs were Grade 1 or 2, except for anaemia, which had a TEAE incidence of 34.6% and was primarily Grade 2 and 3. An overall summary of TEAEs and their incidences can be found in Appendix F, Table 3.

B.2.10.3. Grade ≥3 TEAEs

Safety results for Grade ≥3 TEAEs were generally consistent between IA1 and IA2. In the dostarlimab arm, [redacted] Grade ≥3 TEAEs occurred during the additional follow up of IA2 [redacted] and [redacted] occurred in the placebo arm [redacted]. The most frequently reported Grade ≥3 TEAEs regardless of causality (≥20% of participants in any arm) are summarised for the dMMR/MSI-H population in Figure 9.

TEAEs were <10% higher in participants in the dostarlimab arm compared with the placebo arm. Incidences of the majority of Grade ≥3 TEAEs by SOC and PT were comparable (<5% difference) in participants between treatment arms. Exceptions between the dostarlimab arm and the placebo arm included: neutrophil count decreased anaemia, white blood cell count decreased, urinary tract infection, lipase increased, and rash (see Appendix F, Table 8). The most frequently reported Grade 4 TEAEs (>2%) in the dostarlimab arm [redacted] while those in the placebo arm were neutrophil count decreased and neutropenia (see Appendix F, Table 8). Grade 5 TEAEs were reported in [redacted] in the dostarlimab arm and related to study treatment. An overall summary of TEAEs and their incidences can be found in Appendix F, Table 9.

From Cycle 7, during the dostarlimab monotherapy phase, a decrease in Grade ≥3 TEAEs was observed in the dostarlimab arm [redacted] after Cycle 7, suggesting that Grade ≥3 TEAEs are reduced when patients receive dostarlimab monotherapy in comparison with the combination phase (see Appendix F, Tables 9, 10 and 11).

Figure 9: TEAEs in ≥20% of patients (dMMR/MSI-H population)

Source: CSR Table 14.3.1.2 (83), and Powell et al. SGO 2024 (76)
Data cut-off: 22 September 2023.

Abbreviations: dMMR, DNA mismatch repair-deficient; MSI-H, microsatellite instability-high; TEAE, treatment emergent adverse event.

B.2.10.4. Grade ≥3 treatment-related TEAEs

The incidence of treatment-related Grade ≥3 TEAEs was generally comparable (<10% differences) between the treatment arms, with the exception of neutrophil count decreased which was higher in the placebo arm [redacted]. Treatment-related TEAEs of Grade ≥3, not related to carboplatin or paclitaxel and related to dostarlimab only, were higher in patients in the dostarlimab arm compared with the placebo arm [redacted]. Differences in incidence of treatment-related TEAEs of Grade ≥3 not related to carboplatin or paclitaxel and related to dostarlimab only were <5% between arms; with the exception of the SOCs for skin and subcutaneous tissue disorders [redacted] and gastrointestinal disorders [redacted], which had the largest differences between arms included. For a more comprehensive list of Grade ≥3 treatment related TEAEs, refer to Appendix F, Table 13.

B.2.10.5. Deaths and serious AEs

There were no new TEAEs leading to deaths at IA2 (Table 10). The two TEAEs leading to death at IA1 were myelosuppression and hypovolemic shock. One patient in the dMMR/MSI-H population had an AE/other cause that was not treatment-emergent and lead to death and occurred more than 90 days after the last dose of study treatment. A dMMR/MSI-H patient in the placebo arm experienced a stroke leading to death 405 days after the last dose. This case is newly reported as of IA2.

A summary of serious adverse events (SAE) experienced by patients in the dMMR/MSI-H population is provided in Appendix F, Table 14. The overall incidence of patients experiencing SAEs was comparable between the dostarlimab arm and the placebo arm ([redacted] vs [redacted]). The most frequently reported SAE (≥2% of patients) which was higher in patients in the dostarlimab arm versus the placebo arm was sepsis ([redacted] vs [redacted]).

The most frequently reported SAEs (≥2% of patients) which were higher in patients in the placebo arm versus the dostarlimab arm were urinary tract infection ([redacted] vs [redacted]), anaemia ([redacted] vs [redacted]), asthenia ([redacted] vs [redacted]), pulmonary embolism ([redacted] vs [redacted]) and colitis ([redacted] vs [redacted]).

B.2.10.6. 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.

As would be expected with an immunotherapy, more irAEs were seen in the dostarlimab arm compared with the placebo arm (75.0% versus 40.0%) of which 55.8% were dostarlimab related.

The most frequently reported dostarlimab or placebo related irAE was hypothyroidism in the dostarlimab arm ([redacted]) and hypothyroidism, arthralgia, and colitis in the placebo arm ([redacted]). Refer to Appendix F (Tables 15, 16 and 17) for a comprehensive list of irAEs.

B.2.10.7. Safety overview

No new safety signals were observed with extended follow-up; the safety profile was similar to that reported in IA1 (76). Overall, dostarlimab in combination with CP has a generally manageable safety profile in dMMR/MSI-H primary advanced or recurrent endometrial cancer (76). Severe and serious TEAEs were approximately 10% higher in dMMR/MSI-H patients in the dostarlimab arm compared with the placebo arm (76). In addition, irAEs were also higher in the dostarlimab arm of the study. This is not entirely unexpected as irAEs are a known side effect profile of immunotherapies (86, 87). Furthermore, most irAEs were not severe, with only 23.1% being Grade ≥3. Serious irAEs were reported in only 5.8% of patients, and only 7.7% of irAEs led to treatment discontinuation (83).

B.2.11. 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 with final readouts of OS and safety.

B.2.12. Interpretation of the clinical effectiveness and safety

Conventional chemotherapy has been the SoC in this treatment setting for over 40 years with no additional major advancements in first-line treatment (10). Without dostarlimab, the primary advanced and recurrent endometrial cancer population experiences poor long-term treatment outcomes with a median OS of 3 years or less, despite the 50–60% response rate to SoC CP (12).

The direct treatment effect of dostarlimab in improving PFS was demonstrated at IA1, with over 60% of dostarlimab arm patients being progression-free and alive at 24 months compared with only 15.7% in the placebo arm (13). This strong data at IA1 meant that PFS met its primary endpoint and so was not re-analysed at IA2.

The analysis of OS in the dMMR/MSI-H population was pre-specified and demonstrated that the addition of dostarlimab to CP resulted in a substantial improvement in survival. There

was an unprecedented reduction in the risk of death by 68% (HR: 0.32; 95% CI: 0.17, 0.63) in the dMMR/MSI-H population, supporting the use of dostarlimab to achieve long-term remission and to improve survival (13). UK clinical experts considered the magnitude of the benefit of the regimen in the dMMR/MSI-H population to be "**impressive"** and **"highly compelling"**, with sufficient data maturity to guide decision-making (81).

In the latest data cut, OS met statistical significance in the overall population, with the greatest magnitude of benefit in the pre-specified dMMR/MSI-H population. These IA2 results validate the trend in improved survival outcomes observed within the earlier IA1 analysis as presented in the original submission (70). This improvement in OS for the dMMR/MSI-H population treated with dostarlimab over a longer period, addresses a key concern set out by the committee within the managed access agreement. In both IA1 and IA2, a clear, early and sustained separation of the survival curves began around 6 months, suggesting that these patients are at high risk of poor outcomes and that upfront use of dostarlimab in combination with chemotherapy leads to a clinically meaningful impact (13, 76).

The observed OS benefit was further supported by the improvements in PFS2, which depicted a clinical benefit beyond the first progression in patients receiving dostarlimab in this population (76, 85). Notably, these strong PFS2 outcomes were achieved despite the significant use of immunotherapy in later lines of treatment in the placebo arm: 41.5% of patients randomised to the placebo arm received subsequent immunotherapy (76). This suggests that dostarlimab provides a durable benefit in delaying disease progression, even when patients in the placebo group eventually had access to immunotherapy. The sustained OS and PFS2 advantages highlight the ability of dostarlimab to provide meaningful, long-term clinical benefits in this population, reinforcing its role as a vital therapeutic option.

The consistent improvement of OS observed across IA1 and IA2, and PFS2 underpin the consistent benefits of dostarlimab for endometrial cancer patients, thereby reducing the uncertainty for the decision makers.

B.2.13. Strengths of the clinical evidence

- The RUBY-1 trial provides a direct, head-to-head comparison to the current SoC used within UK clinical practice and includes a population reflective of real-world patients (81).

- 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 (81).

- Assessed OS, a gold standard in oncology trials, as a dual-primary endpoint in the ITT population and as a pre-specified subgroup in the dMMR/MSI-H population.
    - It is the only trial in primary advanced or recurrent endometrial cancer to show statistical significance for OS in the overall population, with the greatest benefit seen in the dMMR/MSI-H group (76).

- All trial results indicate a durable response through the addition of dostarlimab to the current SoC, as evidenced by IA1 PFS, and IA2 OS and PFS2 data (13, 76).
    - The observed OS benefit was further supported by the improvements in PFS2, which depict a clinical benefit beyond the first progression in patients receiving dostarlimab plus CP in this population.
    - UK clinicians expect a long-lasting effect, consistent with the response observed in the dostarlimab arm of the RUBY-1 trial (88).

B.2.14. Limitations of the clinical evidence

- The OS data in the RUBY-1 trial have not yet reached maturity. At the time of IA2, the trial reached only 40.2% maturity of the OS data in the dMMR/MSI-H population (76).
    - Despite this, the strong PFS and PFS2 results exhibit the same sustained benefit seen in the OS results, underscoring the robustness of the RUBY-1 data (76).
    - Given the strength of the available data, it would be unethical to delay access for this group of patients with limited treatment options until full data maturity is reached.

- Although the trial demonstrated a statistically significant OS benefit in the overall population, it was not powered to show significance within the dMMR/MSI-H subgroup.
    - Nonetheless, the OS benefit appears greatest in the dMMR/MSI-H population, which is consistent across all efficacy endpoints, including the primary endpoint of PFS, for which the dMMR/MSI-H population was specifically powered.

- Additionally, after achieving statistically significant PFS results in the dMMR/MSI-H population during IA1, no additional PFS data were collected during IA2, as per the statistical analysis plan.
    - While no additional PFS data were collected at IA2, updated PFS2 data were available at IA2 and further support the trends seen in the original PFS data.
- The submission focuses on a smaller subgroup of patients with dMMR/MSI-H tumour status, resulting in a limited population size.
    - This sample, however, was sufficient to demonstrate statistically significant PFS results.

B.2.15. Innovation

- The addition of dostarlimab to the current SoC for patients with primary advanced or recurrent endometrial cancer has provided a step change in care for an otherwise underserved population.
    - Conventional chemotherapy has been the SoC for these patients for over 40 years with no additional major advancements in first-line treatment (10).
    - Dostarlimab is the first and only available treatment which provides hope for long-term remission for an otherwise incurable patient population.
- A patient living with endometrial cancer who has received dostarlimab in combination with CP treatment expressed that '*Dostarlimab has made a big difference for me. It has helped me to stay positive and hopeful that I will have a decent quality of life for a good few years yet.' 'I feel so fortunate to have received this treatment – it has given me hope for the future. Cancer patients like me need hope'* (89).
- Dostarlimab is the only available first-line treatment for primary advanced or recurrent endometrial cancer that uniquely mobilises the immune system of the host rather than relying on chemotoxicity. This results in a durable anti-cancer response in dMMR/MSI-H tumours (13, 76).
    - Compared with innovative immunotherapies available in other disease areas, dostarlimab has a differentiated pharmacokinetic and pharmacodynamic profile, contributing to its exceptional efficacy in endometrial cancer (90, 91).

B.2.16. Conclusion

Data from the latest cut off (IA2, 22 September 2023) of RUBY-1 demonstrates that the addition of dostarlimab to CP/SOC consistently improves OS and PFS2 in the dMMR/MSI-H population over time. The consistency in OS between IA1 and IA2, alongside the substantially reduced risk of disease progression and death observed in the dostarlimab arm demonstrates the increased benefit that dostarlimab would have for dMMR/MSI-H patients in first-line treatment. The more mature dostarlimab data continues to demonstrate a survival advantage in dMMR/MSI-H patients compared with CP and placebo. This provides reassurance regarding the longer term survival benefit and addresses the concerns set out by the committee within the MAA, particularly relating to uncertainty in longer term OS data (71). The efficacy and safety data from IA1 and the updated data readouts from IA2 demonstrate that the addition of dostarlimab to the SoC improves patient outcomes, with respect to both OS and PFS compared with CP and placebo in the dMMR/MSI-H primary advanced or recurrent endometrial cancer population.

As a direct head-to-head RCT aligned with the decision problem, this is the most robust source of evidence. The introduction of dostarlimab in combination with PCC in the treatment pathway of patients with primary advanced or recurrent endometrial cancer is a step change in treatment in this area of high unmet medical need where existing therapy confers modest but often short-lived benefits.

Maintaining the availability of an immunotherapy in earlier line settings will allow patients to be offered treatment sooner in their care pathway, which is expected to delay disease progression and reduce the strain on the healthcare system.

B.3. **Cost effectiveness**

Summary of cost-effectiveness analysis

- A *de novo* partitioned survival model with three health states (progression-free survival [PFS], progressed disease [PD] and death) was part of the original submission (TA963) (79). This existing model has been updated for this Cancer Drugs Fund (CDF) exit submission. The cost-effectiveness model (CEM) evaluated the cost-effectiveness of dostarlimab in combination with carboplatin and paclitaxel (CP) versus CP for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer.

- The analysis was consistent with the National Institute for Health and Care Excellence (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 (92).

- Clinical outcomes (PFS, overall survival [OS] and time to treatment discontinuation [TTD]) were based on the dMMR/MSI-H population of the RUBY-1 trial, with more mature OS data from the second interim analysis (IA2) incorporated into the updated CEM.

- Health-state utilities for PFS and PD were informed by EQ-5D-5L data collected in the RUBY-1 study, cross-walked to EQ-5D-3L.

- 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, dostarlimab in combination with CP was associated with [redacted] incremental costs and 4.42 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 a [redacted] chance of being cost effective.

- The results from the deterministic sensitivity analysis show that the cost-effectiveness results are robust to changes in model structure and inputs, with all ICERs remaining below [redacted] per QALY gained for dostarlimab in combination with CP versus CP across all scenarios.

B.3.1. Published cost-effectiveness studies

An economic SLR was undertaken on 10 November 2021 (with an update on 16 May 2024) to identify existing cost-effectiveness studies relevant to the decision problem. Full details of the methodology used to identify all relevant studies, as well as results and quality assessment of the identified studies, are presented in Appendix G. Table 11 provides a summary of the identified published cost-effectiveness studies. New studies identified in the search update since the original submission, are all studies in Table 11 except Ackroyd et al., 2021 (93) and Batman et al., 2021 (94).

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

All models were US-based, except one, which was based in China, and all models used the doublet carboplatin/paclitaxel as the reference arm.

All published models used a Markov structure, except for Benjamin et al., 2024 (95) (not reported) and Francoeur et al., 2024 (95, 96) (partitioned survival model), and all models included three health states except for Benjamin et al., 2024 (95) (health states were not reported).

The time horizon in the models by Ackroyd et al., 2021 (93), Kim et al., 2023 (97) and Francoeur et al., 2024 (96) was three years. The time horizon was four years in the Batman et al., 2021 model (94), and 20 years in the You et al., 2023 model (98). While a lifetime time horizon was adopted by Huo et al., 2024a (99), it was set between the ages of 64 and 82 by Huo et al., 2024b (100). The time horizon was not reported by Benjamin et al., 2024 (95) and Francoeur et al., 2024 (96).

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

- The majority were Markov models, which might be less suitable and do not capture all survival benefits.
- 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 (99), this was a Markov model from a US perspective, making it less relevant.

- The use of medians or aggregate trial data rather than individual patient data, as well as the use of naïve comparisons by some studies 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 four models that specifically evaluated dostarlimab, each had significant limitations (95-98). 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. Important factors such as time to treatment discontinuation and the use of additional treatments in later lines of therapy were absent from the model (98). Benjamin et al., 2024 focused solely on drug acquisition costs, neglecting critical cost components, such as subsequent treatments after disease progression (95). Moreover, the use of expected-value life years gained instead of QALYs failed to account for the quality of life during those years, and the study did not specify the time horizon used (95). The methods for comparing trial data also lacked robustness, relying on median PFS and OS from the RUBY-1 trial without appropriate extrapolation to inform survival predictions (95). Kim et al., 2023 used a Markov model with a one-year cycle length and three-year time horizon (97). The analysis relied on naïve comparisons between trials (RUBY-1, GY018, and GOG0209), without comprehensive assessment of feasibility or consideration of potential heterogeneity (97). Lastly, Francoeur et al., 2024 used a three-year time horizon, relying on published aggregate trial data rather than individual-level data (96). 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 (96).

In addition to the published economic evaluations identified, the SLR identified four HTA reports in relation to dostarlimab. These are also reported in Table 11.

Table 11: Summary list of published cost-effectiveness studies

Study	Summary of model	Patient population*	Intervention	Comparator	Incremental QALYs	Incremental costs	ICER (per QALY gained)
Ackroyd, 2021 (93)	- Markov model - US Healthcare perspective - Three-year horizon - Costs and utilities were discounted annually at 3%.	Advanced or recurrent endometrial cancer, 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, subgroup: MSI-high			0.11	$313,487	$2,849,882/ QALY, USD inflated to 2020
Batman, 2021 (94)	- 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, subgroup: NA	CB + PAC + TRA	CB + PAC	2,065	$144,335,895	$69,903/ QALY, USD inflated to 2019
You, 2023 (98)	- 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
Benjamin, 2024 (95)	NR	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	DOS + CB + PAC	CB + PAC	1.60	$249,807	$155,865/QALY
Huo, 2024a (99)	- 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	Incremental QALYs	Incremental costs	ICER (per QALY gained)
	- Lifetime horizon - Costs and utilities were discounted annually at 3%	Advanced or recurrent endometrial cancer, subgroups: pMMR			0.93	$83,661	$90,284.80/QALY
Huo, 2024b (100)	- 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: pMMR			0.50	$140,502	$279,239.72/QALY
Kim, 2023 (97)	- Markov model - Perspective: NR - Three-year horizon - Costs and utilities were discounted annually at 3%	Advanced or recurrent endometrial cancer, subgroups: dMMR-MSI-H	PEM + CB + PAC	CB + PAC	NR	NR	$377,718/QALY
			DOS + CB + PAC		NR	NR	$401,859/QALY (Absolute dominance)
Francoeur, 2024 (96)	- 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: pMMR			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: pMMR			0.325	$156,601	$481,845/QALY

Study	Summary of model	Patient population*	Intervention	Comparator	Incremental QALYs	Incremental costs	ICER (per QALY gained)
CDA-AMC, 2024 (101)	- 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
NICE, 2024 (79)	- 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 (102)	- 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 (103)	- 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

*Specific stages regarding the population were not reported

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.

B.3.2. Economic analysis

A cost-effectiveness model (CEM) evaluating dostarlimab in combination with CP (referred to as the dostarlimab arm) versus placebo in combination with CP (referred to as the CP arm) was part of the original submission (TA963) and was previously accepted by NICE (79). This CEM has been updated for this CDF exit submission.

Four 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 B.3.1.

B.3.2.1. Patient population

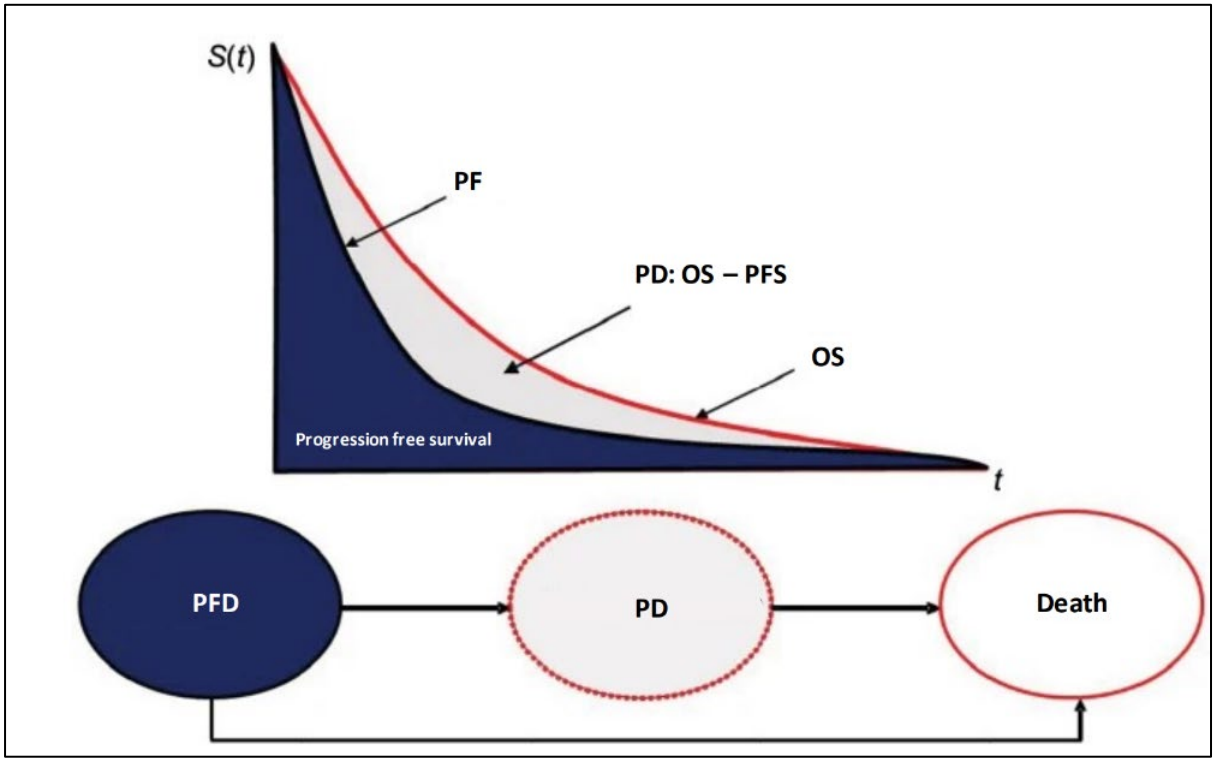
In line with the decision problem, the cost-effectiveness analysis conducted for this appraisal considered adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer.

B.3.2.2. Model structure

A partitioned survival model (PSM) was used in the previous NICE appraisal for dostarlimab in this indication (TA963) (79). It was considered appropriate for decision making and therefore has been used for the CDF exit submission.

The model estimates the proportion of a cohort in each state based upon parametric survival equations. In the PSM, PFS and OS data from the trial are used to model state occupancy using “progression-free disease”, “progressed disease” and “death” health states as shown in Figure 10 and Table 12.

Figure 10: PSM structure schematic



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

Table 12: 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 is 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 is estimated by extrapolating OS KM curves (i.e. death = 1 - OS)	

Note: PFS data comes from IA1 (September 28 2022), and OS data comes from IA2 (September 22 2023).
Abbreviations: IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PD, progressed disease; TTD, time to death.

The model structure does not allow patients to improve their health state, which reflects the progressive nature of advanced or recurrent endometrial cancer, and the death state is an absorbing health state. PFS and PD health states capture the differences in costs and HRQoL within endometrial cancer. PFS and OS curves were modelled as described in Section B.3.3.2.1 and Section B.3.3.2.2. Time to treatment discontinuation (TTD) curves were also modelled directly, informing the proportion of patients on treatment as described in Section B.3.3.2.3.

Costs, life years (LY) and quality-adjusted life years (QALY) 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, respectively. The incremental cost-effectiveness ratio (ICER) of dostarlimab in combination with CP versus CP was evaluated in terms of the incremental cost per QALY and LY gained.

B.3.2.3. Intervention technology and comparators

Dostarlimab is administered through IV infusion. The dose of dostarlimab incorporated in the economic model is aligned with the summary of product characteristics (SmPC) (Appendix C) and the RUBY-1 study. In the intervention arm of the RUBY-1 study, patients received 500 mg of dostarlimab plus AUC 5 mg/ml/min of carboplatin and 175 mg/m^2 of paclitaxel Q3W for six cycles (i.e. Weeks 1, 4, 7, 10, 12, 16), followed by (i.e. from Week 19 onwards) 1,000 mg of dostarlimab Q6W until disease progression, unacceptable toxicity, or up to 3 years.

The comparator is carboplatin in combination with paclitaxel (CP). As outlined in the scope, CP is the SoC in the UK in the absence of dostarlimab and reflects the comparator arm of the RUBY-1 trial. In the comparator arm of the RUBY-1 trial, patients received placebo plus AUC 5 mg/ml/min of carboplatin and 175 mg/m^2 of paclitaxel Q3W for six cycles (i.e. Weeks 1, 4, 7, 10, 12, 16), followed by (i.e. from Week 19 onwards) placebo Q6W for up to 3 years or until patient progression.

B.3.3. Clinical parameters and variables

B.3.3.1. Baseline characteristics

The patient baseline characteristics used as inputs in the CEM are provided in Table 13. The mean age recorded in the RUBY-1 trial, [redacted] years, is used as the starting age for the model. During the previous appraisal, the committee preferred a higher mean age for the model, [redacted], however since then, several sources of RWE have been collected that indicate the mean patient age in the RUBY-1 trial is representative of clinical practice in the NHS in England. RWE using NCRAS data (Section B.2.2.1) as well as RWE collected from the early access to medicines scheme (EAMS) for dostarlimab reported patients mean age of [redacted] years and [redacted] years, respectively (104). A scenario analysis has been performed using the mean age from the NCRAS RWE. Other model baseline characteristics also align with the dMMR/MSI-H population in the RUBY-1 trial.

Table 13: Patient baseline characteristics for the base-case economic analysis

Parameter	Value	Reference
Mean age (years)	[redacted]	RUBY-1 trial (75)
Mean weight (kg)	[redacted]	RUBY-1 trial (75)
Mean body surface area (m2)	[redacted]	
GFR (ml/min)	[redacted]	Calculation based on RUBY-1 trial (75)

*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; NCRAS, National Cancer Registration and Analysis Service; RWE, Real World Evidence.

B.3.3.2. Survival analyses

For all outcomes in the RUBY-1 trial, PFS, OS, and TTD, 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 (105). Survival analyses were conducted in weeks due to the model cycle length.

This aligns with the approach taken as part of TA963 (79). The more mature OS data from IA2 has been incorporated into the updated CEM. No additional PFS or TTD data are available as part of IA2, therefore these model inputs have not been revised.

B.3.3.2.1. Progression-free survival

As no further PFS data was collected, the approach to PFS remains the same as the original submission and is briefly outlined below for completeness. Detailed PFS results from IA1 of the RUBY-1 trial are reported in Appendix N.

B.3.3.2.1.1 CP progression-free survival

PFS is modelled in accordance with the external assessment group (EAG) and the NICE committee's preferences from TA963 (79). No further evidence has been identified which might justify a divergence from the base-case of TA963. The Odds k=2 flexible spline model was selected as the most robust approach for the base case PFS extrapolation of CP. A comprehensive description of appropriate curve selection developed as part of TA963 is outlined in Appendix O. This aligns with the NICE committee’s preferences from TA963 (79).

B.3.3.2.1.2 Dostarlimab in combination with CP progression-free survival

The Odds k=1 flexible spline model was selected as the most robust approach for the base case PFS extrapolation for dostarlimab following a full assessment of suitability aligned with that made for CP. A comprehensive description of appropriate curve selection developed as

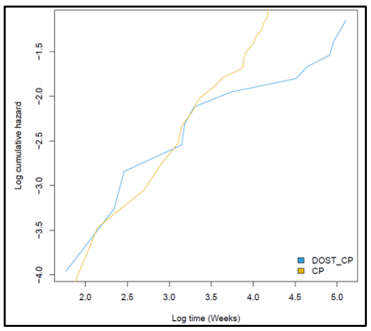
part of TA963 is outlined in Appendix O. This aligns with the NICE committee's preferences from TA963 (79).

B.3.3.2.2. Overall Survival

Analysis of OS has been updated with the IA2 data cut (see Section B.2.6.1). The observed data shows a similar OS trajectory between dostarlimab and CP for the first 6 months of treatment. Following this period, separation begins, with a pronounced sustained treatment benefit for dostarlimab observed from 10 months (see Section B.2.6.1, Figure 5).

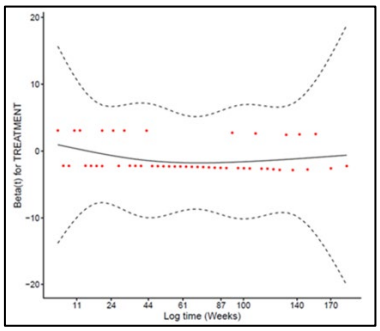
Several statistical tests were conducted to understand if the proportional hazards assumption and constant accelerated failure time (AFT) assumptions would be violated. These tests are presented in Figure 11, Figure 12, and Figure 13.

Figure 11: Log-cumulative hazards plot for IA2 OS



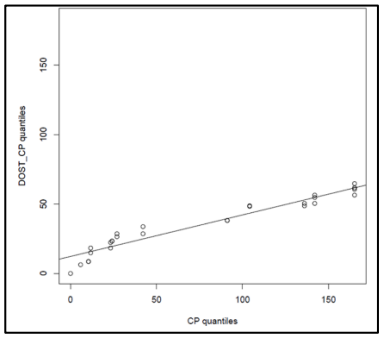
Abbreviations: CP, carboplatin plus paclitaxel; OS. overall survival

Figure 12: Schoenfeld residuals plot for IA2 OS



Abbreviations: OS. overall survival

Figure 13: Quantile-quantile plot for IA2 OS



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

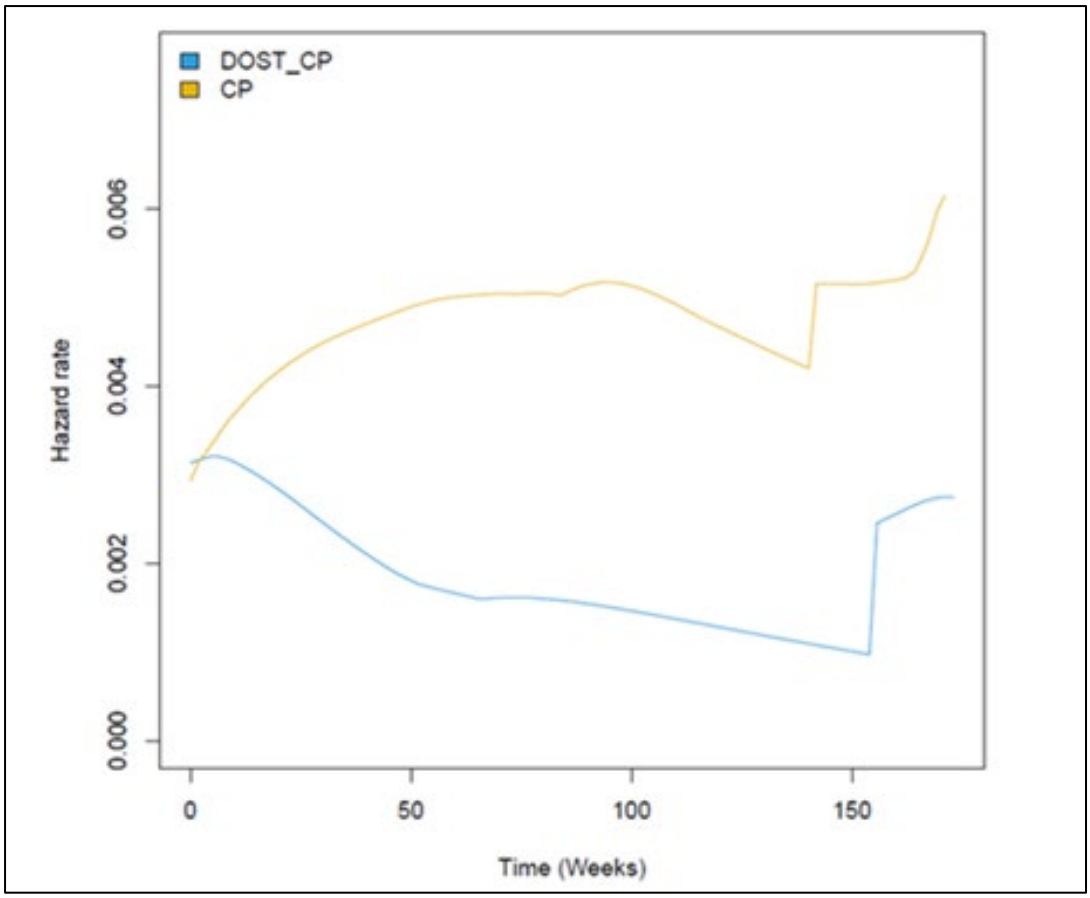
Inspection of the log-cumulative hazards (Figure 11), Schoenfeld residual plot (Figure 12), and the quantile-quantile plot (Figure 13) suggest that the relative hazards are likely to vary over time, and as such, it is not possible to conclude that the proportional hazards (PH) assumption holds. Whilst the Schoenfeld test p-value of >0.05 means that the null hypothesis of proportional hazards cannot formally be rejected, the Schoenfeld test plot suggests a non-random pattern against time and the log-cumulative hazard plot (Figure 12) lines intersect, which is highly indicative of a violation of the PH assumption. Figure 13 indicates that the quantiles do not lie on a straight line, suggesting that the treatment does not have a multiplicative effect with respect to time, and therefore provides evidence of violation of the AFT assumption.

Overall, the statistical tests and subsequent diagnostic plots indicate that the PH assumption does not hold. Expert advice has confirmed that this is consistent with clinical expectations due to the mechanism of action of immunotherapies which, in contrast to traditional chemotherapies, do not have an immediate chemotoxic mechanism of action. Based on this,

applying a proportional treatment effect was not considered appropriate and independent models were selected for the base case.

A fixed treatment effect is explored in a scenario analysis by applying the HR observed in RUBY-1 (see Table 8) for the dostarlimab arm to the OS extrapolation of the CP arm only to ensure consistency with the original submission. This is considered a conservative assumption considering the early and durable plateau seen in the RUBY-1 dostarlimab arm OS KM and the mechanism of action of immunotherapies.

Figure 14: Hazard rate plot for IA2 OS



Abbreviations: IA2, second interim analysis; OS. overall survival.

The hazard rate plot (Figure 14) shows a monotonically decreasing empirical hazard for the dostarlimab arm over time. This is consistent with the similarly observed monotonically decreasing hazards for the dostarlimab arm observed in PFS (Appendix O). The empirical hazard plot for the CP arm shows a non-monotonic hazard that is consistently higher than the dostarlimab arm and has a turning point. A sudden increase in the hazard rate is observed at approximately Week 150 for both arms, however, advice received from both clinical and health economic experts (July 2024) suggests this is not clinically relevant and can be explained by the single OS event observed at this time point (106). Clinical advisors

also confirmed that an increasing hazard at this time point is not plausible given the totality of clinical evidence as demonstrated by strong and consistent PFS and PFS2 outcomes (106). Given the observed shapes of the empirical hazard plots, survival modelling methods which accommodate a turning point for the CP arm, and a monotonically decreasing hazard for the dostarlimab arm, are considered most appropriate.

B.3.3.2.2.1 CP overall survival

Standard parametric distributions were fitted to OS from RUBY-1 IA2 for the CP arm. The choice of curve in the base case was selected by visual analysis, considering UK clinical opinion and consideration of external data sources, alongside analysis of goodness-of-fit statistics such as Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Table 14 summarises the AIC and BIC values for each parametric model fitted to the OS of the CP arm. All distributions were within 2 points by AIC rank, with the lognormal, log-logistic and exponential distributions having the lowest AIC and BIC (best statistical fit). The generalised gamma curve had the worst statistical fit for both AIC and BIC statistics. Overall, the lognormal, loglogistic, and exponential distributions produced the best statistical fits by AIC and BIC values.

Table 14: Summary of goodness-of-fit data for CP for OS (standard parametric independent models)

OS	CP			
Distribution	**AIC**	**Ranking**	**BIC**	**Ranking**
Exponential	[redacted]	2	[redacted]	1
Weibull	[redacted]	5	[redacted]	5
Gompertz	[redacted]	6	[redacted]	6
Log-logistic	[redacted]	3	[redacted]	3
Lognormal	[redacted]	1	[redacted]	2
Generalised gamma	[redacted]	7	[redacted]	7
Gamma	[redacted]	4	[redacted]	4

Note: A low AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin and paclitaxel; IA, investigator assessment; OS, overall survival.

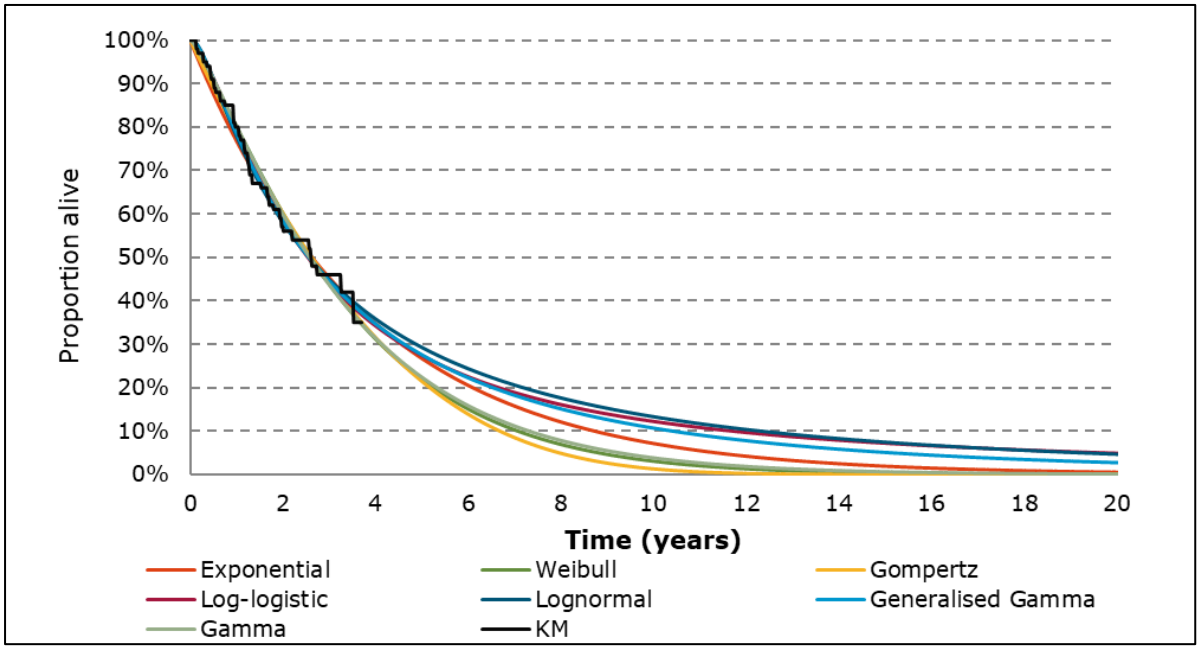
In line with the previous appraisal (TA963), clinical opinion was sought to estimate OS for patients treated with CP (79). The full results can be found in Appendix O. Table 15 presents the overall mean estimate of this clinical opinion alongside the proportions estimated through standard parametric extrapolations. Figure 15 presents graphically, the standard parametric extrapolations with the observed CP RUBY-1 data.

Table 15: Advisor mean estimates and standard parametric estimates of the proportion of patients who would be alive at landmark time points in dMMR/MSI-H population in the RUBY-1 trial treated with CP

Months (years)	Advisors' mean	CP						
		Exp	Weibull	Gomp	Log-logistic	Log-normal	Gen Gamma	Gamma
60 (5)	21%	27%	22%	22%	27%	29%	28%	23%
120 (10)	9%	7%	3%	1%	12%	13%	11%	4%
180 (15)	5%	2%	0%	0%	7%	7%	5%	1%
240 (20)	4%	1%	0%	0%	5%	5%	3%	0%

Abbreviations: dMMR, DNA mismatch repair deficiency; exp, exponential; MSI-H, microsatellite-instability high; CP, carboplatin and paclitaxel.

Figure 15: Standard parametric survival analyses for CP for OS



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

Consistent with the assessment of statistical fit above, experts at a UK advisory board (July 2024) agreed that all curves provide a similar fit to the observed data and produce plausible landmark estimates for CP OS (106). Based on values elicited using clinical expert opinion, the log-logistic, log-normal, and generalised gamma curves provide the most plausible OS estimates particularly at 10 and 20 years compared with the other distributions. A constant hazard implied by the exponential function is inconsistent with the non-monotonic hazard illustrated in Figure 14 and described in Section B.3.3.2.2. This supports the consideration of the log-logistic, log-normal, and generalised gamma curves, which allow a non-monotonic hazard rate, as the most appropriate parametric extrapolations.

Therefore, **the log-logistic curve is chosen for the base case extrapolation of OS in the CP arm**. The log-logistic curve provides a good visual and statistical fit to the observed data

and produces estimates of CP OS at landmark timepoints that are consistent with clinical expert opinion. Furthermore, during the previous appraisal (TA963), after the committee discussion, the log-logistic curve was selected as the preferred choice to model the CP arm (79).

Upon applying OS in the model, a rule was also applied to both treatment arms whereby the OS curve could not exceed general population mortality.

B.3.3.2.2.2 Dostarlimab in combination with CP OS

Standard parametric distributions were also fitted to OS from RUBY-1 for the dostarlimab arm. As highlighted in B.3.3.2.2, the PH tests suggest that the PH assumption does not hold. As a result, independent curves have been assessed in the base case.

The choice of 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 AIC and BIC. Table 16 summarises the AIC and BIC values for each extrapolation. The AIC values were all within 2 points of each other, with a slightly wider spread for the BIC values although the rankings between distributions remained consistent. The generalised gamma distribution provided the worst statistical fit, particularly by BIC value. The exponential, log-normal, and log-logistic curves have the lowest AIC/BIC values.

Table 16: Summary of goodness-of-fit data for dostarlimab arm for OS (standard parametric independent models)

OS	Dostarlimab in combination with CP			
Distribution	**AIC**	**Ranking**	**BIC**	**Ranking**
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	4	[redacted]	4
Gompertz	[redacted]	6	[redacted]	6
Log-logistic	[redacted]	3	[redacted]	3
Lognormal	[redacted]	2	[redacted]	2
Generalised gamma	[redacted]	7	[redacted]	7
Gamma	[redacted]	5	[redacted]	5

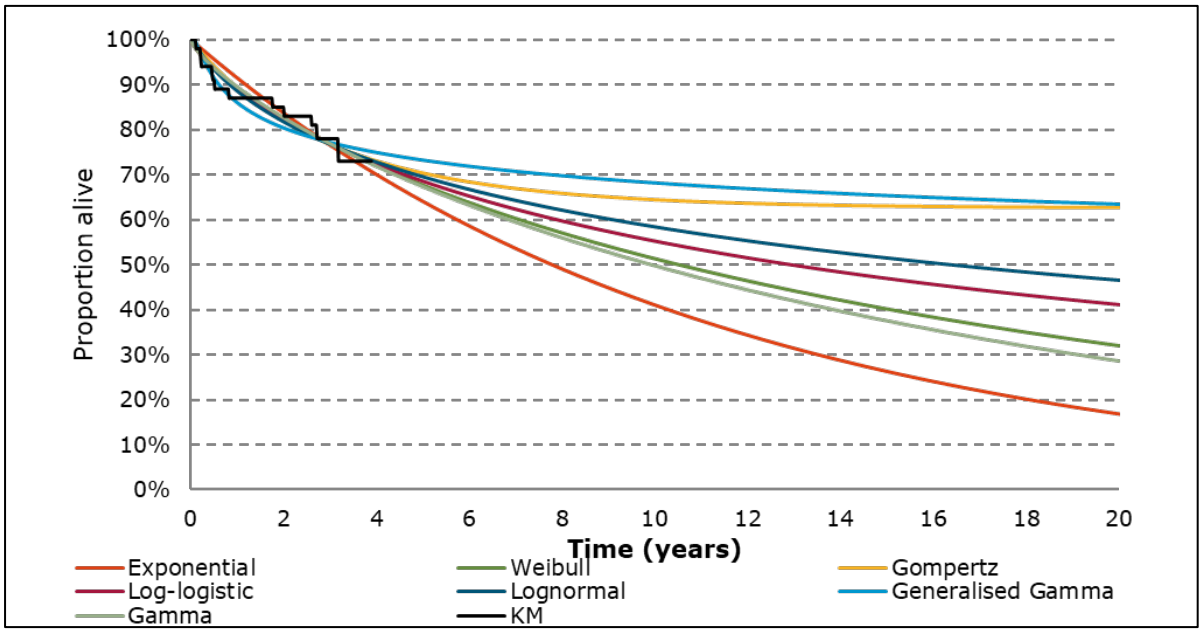
Note: A low AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CP, carboplatin and paclitaxel; IA, investigator assessment; OS, overall survival.

Figure 16 presents the standard parametric extrapolations of the dostarlimab arm with the observed RUBY-1 IA2 data. Landmark OS estimates for each distribution are provided in Table 17. None of the parametric curves provided a particularly strong visual fit to the observed data. The generalised gamma curve provided a good initial fit and then considerably underpredicted OS up to around 3 years, before overpredicting the tail of the

KM curve. The Gompertz also overpredicts the tail of the KM. The other distributions provide a poor initial fit to the observed data (overpredicting between 0–2 years), however, provide a better fit to the tail of the KM curve.

Considering that the shape of the hazard function for the dostarlimab arm is monotonically decreasing, the exponential distribution which assumes a constant hazard is not considered appropriate. Of the remaining curves (log-normal, gamma, Weibull, and log-logistic), the log-normal and log-logistic had the best statistical fits. **The log-logistic distribution was selected for the base case extrapolation of dostarlimab OS** as it produces more conservative survival estimates than the log-normal. Scenario analysis is performed using the gamma and the Weibull curves.

Figure 16: Standard parametric survival analyses for dostarlimab



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

Table 17: Proportion of patients alive at landmark time points in dMMR/MSI-H population in the RUBY-1 trial treated with dostarlimab

Months (years)	Dostarlimab						
	Exp	Weibull	Gomp	Log-logistic	Log-normal	Gen Gamma	Gamma
60 (5)	64%	68%	70%	69%	70%	73%	67%
120 (10)	41%	51%	64%	55%	58%	68%	50%
180 (15)	26%	40%	63%	47%	52%	65%	38%
240 (20)	17%	32%	63%	41%	47%	63%	29%

Abbreviations: dMMR, DNA mismatch repair deficiency; MSI-H, microsatellite-instability high.

B.3.3.2.2.3 Treatment effect waning

As highlighted in Section B.2.6.1, a sustained treatment benefit over the CP arm is observed for the dostarlimab arm in both the IA1 and IA2 OS data cuts. Notably in IA2, with longer follow-up (median follow-up ~4 years), a sustained benefit is observed beyond the treatment stopping rule for the dostarlimab arm (3 years).

Clinical experts at a UK advisory board (April 2024) expressed that “the benefit of dostarlimab is likely to be very durable” and would expect this benefit to be sustained in the long term (88). More recent advice from UK clinical experts at an advisory board in July 2024 supported the expectation of the potential for long-term remission in this indication following treatment with dostarlimab (106). Furthermore, as outlined in the trial publication the unprecedented PFS and PFS2 results in the dMMR/MSI-H population are indicative of long-term remission.

Waning was considered by UK clinicians at the July 2024 advisory board to be an “artificial way of producing plausible survival curves” compared with using the available data directly. Any material convergence of mortality is expected to be driven by the background mortality risk of this elderly population (106). The selection of independent models is expected to implicitly capture any waning effect seen in the dostarlimab arm. In the base case (independent log-logistic extrapolations), the treatment effect, i.e. the HR, implied by the preferred survival curves (Figure 17) is maximised at approximately 3 years, after which it begins to decrease until the treatment effect is equal between the dostarlimab arm and CP arm. Towards the end of the survival curves, as OS tends to 0 in the CP arm, the implied HR for the dostarlimab arm tends to 1. Based on this rationale, no additional treatment effect waning is included within the base case for dostarlimab.

Figure 17: OS hazard ratio over time

Abbreviations: OS, overall survival.

The precedent of the treatment effect waning in NICE appraisals of anti-PD1 therapies in this therapy area, is considered to be highly relevant as it relates to the treatment effect of a comparable anti-PD1 therapy in endometrial cancer. This was explored in the recent appraisal of pembrolizumab for use as a second-line treatment option for patients with dMMR/MSI-H tumours (TA914) (61). Notably, this is in the second-line setting where the patient population is more refractory to existing treatments. It was agreed by the committee that a treatment waning effect should be applied from 7–9 years for pembrolizumab in this setting where it has a 2-year stopping rule (61). Clinicians have confirmed that the treatment effect waning of dostarlimab in first-line endometrial cancer treatment, which has a 3-year stopping rule in place, should not have a more restricted treatment effect waning assumption than that accepted for the comparable second-line population in TA914 (61).

To consider treatment effect waning in a scenario analysis a waning effect is applied to the dostarlimab OS extrapolation from 8–10 years, similar to the horizon assumed in TA914 (7–9 years) but accounting for the additional year of treatment that patients on dostarlimab would receive compared with pembrolizumab (61). It should be noted that this scenario is considered conservative, given the reasons outlined above regarding stopping rules and line of therapy, and given that the NICE committee called it “potentially conservative” in TA914 (61). Landmark estimates applying treatment effect waning between 8 and 10 years compared with the base case OS curve are presented in Table 18.

Table 18: OS estimates across scenarios

Months (years)	OS estimates	
	Base-case OS curve	OS treatment waning scenario (8–10 years)
120 (10)	55%	50%
180 (15)	47%	30%
240 (20)	38%	20%

Abbreviations: dMMR, DNA mismatch repair deficiency; MSI-H, microsatellite-instability high; OS, overall survival.

B.3.3.2.3. Time to treatment discontinuation

Similarly to PFS, TTD is modelled in accordance with the external assessment group (EAG) and the NICE committee's preferences from TA963 (79). No further evidence has been identified which might justify a divergence from the base case of TA963. TTD from the RUBY-1 trial is directly used to inform treatment discontinuation within the CEM (84). The approach is briefly outlined below for completeness, with more detail available in Appendix O.

B.3.3.2.3.1 CP TTD

In line with TA963, patients on CP are given six treatment cycles (where one treatment cycle is 3 weeks) with response monitored after three treatment cycles (11). The CP arm TTD KM data includes time on treatment for three treatments: carboplatin, paclitaxel, and placebo;

- Placebo: beyond Week 18, the KM curve is used for the follow-up period and subsequently, the Weibull standard parametric curve.

- Carboplatin and paclitaxel: the completion rates from RUBY-1 were applied for the first six treatment cycles (Table 19) (where one treatment cycle is 3 weeks), with placebo continuing until Year 3.

B.3.3.2.3.2 Dostarlimab in combination with CP TTD

In line with TA963, completion rates from RUBY-1 were applied for the first six treatment cycles (Table 19), followed by the KM for the follow-up period and subsequently the Weibull standard parametric curve (79). In addition, a stopping rule of 3 years was applied to align with the SmPC and the RUBY trial protocol.

Table 19: Completion rates for dostarlimab in combination with CP and CP per treatment cycle

Dostarlimab completion rates per treatment cycle	Proportion receiving dose of dostarlimab (%)	Weighted average across carboplatin/paclitaxel (%)
1	[redacted]	[redacted]
2	[redacted]	[redacted]

Dostarlimab completion rates per treatment cycle	Proportion receiving dose of dostarlimab (%)	Weighted average across carboplatin/paclitaxel (%)
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel.

B.3.4. Measurement and valuation of health effects

B.3.4.1. HRQoL data from clinical trials

Utility values used in the model are aligned with those outlined in the original submission. These are summarised within Table 20. More detail on methodology and inputs are outlined in Appendix O.

EQ-5D-5L data were collected within the RUBY-1 trial, and aligned with NICE preference, were mapped to EQ-5D-3L using the cross-walk approach (107). The ITT population is the preferred source of HRQoL, rather than the dMMR/MSI-H population data, due to the larger sample of patient data, particularly in the PD health state. This approach was supported previously in the original submission (TA963) due to the inherent sample size advantages (79).

Table 20: Health state utility values from RUBY trial

Health state	dMMR/MSI-H, mean (SE)	ITT, mean (SE)	Source:
PFS	[redacted]	[redacted]	RUBY-1 trial (82, 83)
PD	[redacted]	[redacted]	

Abbreviations: dMMR, DNA mismatch repair deficient; ITT, intention-to-treat; MSI-H, microsatellite instability-high; PD, progressive disease; PFS, progression-free survival; SE, standard error.

B.3.4.2. Mapping

EQ-5D-5L were mapped to EQ-5D-3L. 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. and Pudney S., 2017, as recommended in the NICE manual, 2022) (92, 107).

B.3.4.3. Health-related quality of life studies

An HRQoL SLR was undertaken on 10 November 2021 (with an update on 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 H.

The HRQoL SLR identified two studies evaluating health utilities in patients with advanced or recurrent endometrial cancer. Both were questionnaire-based studies. The study by Ackroyd et al, 2023 (108) was identified in the search update, this has been detailed below.

Ackroyd et al, 2023 (108) 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. 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. Utility values for specific regimens under each treatment class were also reported, e.g. 0.76 (0.27, 1.00) in the 12 patients treated with CP.

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.

B.3.4.4. Adverse reactions

Section B.2.10 includes details of the AE data collected in IA2 of the RUBY-1 trial. Based on committee preferences from the original submission (TA963) (70), AEs of Grade ≥3 affecting at least 2% of patients and occurring more frequently in the dostarlimab arm, were included in the model (Section B.3.5.4). AEs from the ITT population were the preferred source, since more patient data was available (Appendix F, Table 12). AEs were updated using the IA2 data cut in the model, however, rates were highly comparable to IA1 with few additional events recorded (Section B.2.10). In addition, minimal differences were observed between the AEs observed in the ITT population and dMMR-MSI-H population (Appendix F, Tables 8 and 12).

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. This was supported by the AEs observed during RUBY-1, as events were more likely to occur during the combination phase versus during the monotherapy phase (Appendix F, Tables 9, 10 and 11).

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 21).

Table 21: AE disutilities

AE	Disutility	Source
Abdominal pain	–0.069	Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin 2010;26:1091-6 (109). Assumed equal to mucositis.
Anaemia	–0.119	Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin 2010;26:1091-6 (109).
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). Published 17 February 2021. Available from: https://www.nice.org.uk/guidance/ta673/history. Accessed August 2024 (110)
Hypokalaemia	−0.074	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). Published 28 September 2016. Available from: https://www.nice.org.uk/guidance/ta411. Accessed August 2024 (111)
Lipase increased	−0.010	Assumption
Lymphocyte count decreased	0.000	Assumed to be the same as neutrophil count decreased
Neutropenia	−0.090	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84 (112). 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). Published 28 September 2016. Available from: https://www.nice.org.uk/guidance/ta411. Accessed August 2024 (111)
Urinary tract infection	−0.010	Assumption
White blood cell decreased	0.000	Assumed to have no utility impact
Rash	−0.116	Assumed equal to hand and foot syndrome, Lloyd (2006) (113)
Amylase increased	−0.069	Assumed equal to abdominal pain
Hyponatraemia	−0.045	Assumed equal to nausea
Nausea	−0.045	NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779). Published 16 March 2022. Available from: https://www.nice.org.uk/guidance/ta779 Accessed August 2024 (59) Lloyd (2006) (113)

AE	Disutility	Source
Relevant to subsequent treatments only		
Asthenia	−0.073	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84 (112). Assumed equal to responding plus fatigue
Fatigue	−0.073	Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84 (112). Assumed equal to responding plus fatigue
Leukopenia	−0.090	NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779). Published 16 March 2022. Available from: https://www.nice.org.uk/guidance/ta779 Accessed August 2024 (59)
Vomiting	−0.103	NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779). Published 16 March 2022. Available from: https://www.nice.org.uk/guidance/ta779 Accessed August 2024 (59)
Diarrhoea	−0.261	NICE. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). Published 11 January 2023. Available from: https://www.nice.org.uk/guidance/ta858 Accessed August 2024 (114)
Decreased appetite	−0.038	NICE. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). Published 11 January 2023. Available from: https://www.nice.org.uk/guidance/ta858 Accessed August 2024 (114)
Weight decrease	−0.038	NICE. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). Published 11 January 2023. Available from: https://www.nice.org.uk/guidance/ta858 Accessed August 2024 (114)
Proteinuria	−0.081	NICE. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). Published 11 January 2023. Available from: https://www.nice.org.uk/guidance/ta858 Accessed August 2024 (114)

Abbreviations: AE, adverse event; NICE, National Institute for Health and Care Excellence.

In line with TA963, AE disutilities related to subsequent treatment were added as a one-off utility decrement, at the start of subsequent treatment upon progression into the PD state (79). Full details of this can be found in Appendix P.

B.3.4.5. HRQoL data used in the cost-effectiveness model

Table 22 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 (107).

Table 22: 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 (ITT): [redacted]	[redacted]	Section B.3.4.1 (Page 74) • Health-related quality-of-life data from clinical trials Section B.3.4.5 (Page 77) • HRQoL data used in the CEM	EQ-5D-5L data from RUBY-1 trial were mapped to EQ-5D-3L aligned with NICE guidelines (92). ITT data were used because there were four-fold more data available versus the dMMR/MSI-H subgroup
PD	Base case (ITT): [redacted]	[redacted]		
Age-adjusted utilities	Base case: included			Age adjusted utilities were applied to align with NICE guidelines (92)
AEs				
AEs	Base case: included	Section B.3.4.4 (Page 75) • 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; dMMR, DNA mismatch repair deficient; HRQoL, health-related quality-of-life; ITT, intention-to-treat; MSI-H, microsatellite instability-high; PD, progressed disease; PFS, progression free survival.

B.3.5. Cost and healthcare resource use identification, measurement

An economic SLR was undertaken on 10 November 2021 (with an update on 16 May 2024) to identify existing HCRU evidence relevant to the decision problem. Full details of the methodology used to identify all relevant studies and results are presented in Appendix I.

The economic SLR identified thirteen publications from eleven unique studies reporting on HCRU that met the inclusion criteria. Three publications representing three unique studies were identified within the search update (115-117)

All studies enrolled adult women diagnosed with endometrial cancer. Seven studies were conducted in the US, with four studies carried out in Denmark, Germany, Italy, and the UK.

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 (118). The mean length of inpatient hospitalisation among patients with endometrial cancer was reported in three studies (119, 120). Two were US studies; In Galaznik et al. 2019 this was in a predominantly Medicare fee-for-service population (119); and in Kebede et al. 2022, the mean length of stay increased gradually with increasing lines of therapy (120). Only Pennington et al. 2016 reported UK resource use data, detailing the number and proportion of patients who received medical procedures and prescription drugs (121).

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 British National Formulary (BNF) and National Health Service (NHS) reference costs where applicable.

B.3.5.1. Costs included in the model

As the CEM was built from the perspective of the NHS and personal social service (PSS), and in line with the NICE reference case (92), NHS reference costs were deemed an appropriate source for the HCRU cost inputs. Treatment costs were sourced from 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 2022/23 cost year using inflation indices annual percentage increase for adult services published by Personal Social Services Research Unit (PSSRU) (122).

B.3.5.2. Intervention and comparators' costs and resource use

B.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 scheduled for the dostarlimab arm, and the CP arm. Treatment prices were sourced from the BNF (123).

Cost per unit was multiplied by dose per treatment cycle (where one treatment cycle is 3 weeks) 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 B.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.

B.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 B.3.3.2.2.3). 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. The cost of 50 mg, 150 mg, 450 mg and 600 mg were £20.20, £56.92, £168.85, and £232.64, 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 £200.35. Paclitaxel is administered intravenously at a unit dose of 175 mg/m^2 Q3W (Table 23).

B.3.5.2.1.2 CP

Carboplatin and paclitaxel are administered intravenously for the first six cycles only. Table 23 and Table 24 summarise the treatment acquisition cost for dostarlimab in combination with CP and CP.

Table 23: 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	20.20	444.57	0	0	0	0
	150	56.92		0	0	0	0
	450	168.85		1	168.85	0	0
	600	232.64		0	0	0	0
Paclitaxel	100	200.35	343.35	4	801.40	0	0

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

Table 24: 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)	970.25
Cycle ≥19	11,774.66 (list price) [redacted] (PAS price)	0.00

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

B.3.5.2.2. Treatment administration cost

Administration costs for both dostarlimab in combination with CP and CP were sourced from NHS national cost collection data publication 2021/22 and inflated to the most recent cost year (2023) (Table 25). Treatment administration costs were applied in addition to treatment acquisition costs to derive the total cost per treatment cycle (Table 25).

Table 25: 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	£363.63 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£294.81 [SB12Z -Deliver Simple Parenteral Chemotherapy at First Attendance, Total HRGs]	£7,343.68 (list price) [redacted] (PAS price)	£12,186.65 (list price) [redacted] (PAS price)	NHS. National Cost Collection Data Publication 2021/2022. https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ Accessed August 2024 (124) NICE. British National Formulary (BNF). https://bnf.nice.org.uk/. Accessed August 2024 (124)
CP	£363.63 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£0.00	£1,465.35	£0.00	NHS. National Cost Collection Data Publication 2021/2022. https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ Accessed August 2024 (124)

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

B.3.5.3. Health-state unit costs and resource use

B.3.5.3.1. Monitoring costs

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 B.3.3.2.1) and PD health state (based on the difference between the PFS and OS modelled as described in Section B.3.3.2.1 and B.3.3.2.2, respectively).

There have been no recent changes to clinical practice or the management of this patient group since the publication of TA963 therefore estimates of resource use included within the model remain unchanged. The inputs were initially derived based on rates provided by UK clinical experts (70). 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 2021/22 (124). HCRU per weekly cycle applied per health state for dostarlimab in combination with CP and CP are presented in Table 26.

Table 26: Cost and resource use per weekly model cycle for dostarlimab in combination with CP, and CP

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	193.70	PFS	0.30	0.13	0.30	0.08	48.07	20.83	48.07	12.82
		PD	0.12	0.12	0.12	0.12	19.23	19.23	19.23	19.23
CT scan	139.47	PFS	0.13	0.06	0.13	0.05	19.10	8.81	19.10	7.34
		PD	0.07	0.07	0.07	0.07	10.28	10.28	10.28	10.28
Complete blood count	3.04	PFS	0.33	0.22	0.33	0.06	0.99	0.66	0.99	0.18
		PD	0.09	0.09	0.09	0.09	0.27	0.27	0.27	0.27
Specialist nurse visit	58.55	PFS	0.11	0.07	0.11	0.07	6.44	4.10	6.44	4.10
		PD	0.10	0.10	0.10	0.10	5.86	5.86	5.86	5.86
GP visit	47.25	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.

B.3.5.3.2. End of life costs

Healthcare costs substantially increase at 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 (79). Costs were taken from Guest et al, 2006 and inflated to the 2023 cost year (125). Guest et al, 2006 estimated the costs of palliative care associated with ovarian cancer to be £4,789 (2000/2001 UK setting) (125). 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 (59).

B.3.5.4. Adverse reaction unit costs and resource use

Based on the original submission committee preferences, Grade ≥3 AEs affecting at least 2% of patients and occurring more frequently in the dostarlimab arm were included in the model. AE data is 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 dMMR/MSI-H population (Section B.2.10).

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 (see Table 10).

Table 27 summarises the costs for each AE and AE incidence in the dostarlimab arm and CP arm, included in the cost-effectiveness analysis.

Table 27: 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	620.17	14.9%	16.7%	83.94	93.66	NHS. National Cost Collection Data Publication 2021/22 (124)
Neutropenia	557.74	9.5%	9.3%	50.34	49.31	
Neutrophil count decreased	771.32	8.3%	13.8%	78.26	130.33	
Hypertension	401.48	7.1%	3.3%	25.25	11.64	
White blood cell count decreased	771.32	6.6%	5.3%	62.61	49.83	Assumed same as neutrophil count decreased
Hypokalemia	1,972.12	5.0%	3.7%	96.83	71.15	NHS. National Cost Collection Data Publication 2021/22 (124)
Pulmonary embolism	1,957.76	5.8%	4.9%	117.93	99.02	
Lymphocyte count decreased	771.32	5.4%	7.3%	50.87	69.00	Assumed same as neutrophil count decreased
Lipase increased	771.32	4.6%	1.2%	17.98	4.81	Assumed same as lymphocyte count decreased
Amylase increased	472.48	3.7%	1.6%	33.06	14.40	NHS. National Cost Collection Data Publication 2021/22 (124)
Hyponatraemia	584.57	4.6%	3.3%	37.24[a]	27.36[a]	
Nausea	584.57	2.9%	1.6%			
Urinary tract infection	592.95	2.9%	1.6%	60.55	33.90	
Rash	398.55	4.6%	1.2%	34.90	9.32	
TOTAL				**669.99**	**600.11**	

Abbreviations: AE, adverse event; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; CP, carboplatin and paclitaxel.
[a]Grouped together as have same cost and disutility.

B.3.5.5. Subsequent treatment costs

The cost of subsequent treatments were included to account for the costs of treatment sequencing (see Appendix P for subsequent treatment costs). During the original appraisal of TA963, some of the innovative therapies utilised in later lines of therapy within the RUBY-1 trial were not available for patients receiving care via the NHS (79). This treatment landscape has since changed with the availability of pembrolizumab monotherapy (TA914) in addition to the pembrolizumab-lenvatinib regimen (TA904) previously available (61, 126). As a result, the subsequent treatment pathway for NHS patients who progress following treatment with CP now better resembles that of the RUBY-1 trial. In the CDF submission for TA963, opinions from UK clinical experts were used to inform the exact subsequent treatment regimens for these patients within the model for the base case (79). At the time, this was representative of approved SoC in England but, as the treatment landscape has changed, updated clinical insight was sought to inform the updated version of the model.

The subsequent treatments used within the base case do not include treatments currently available via the CDF (notably dostarlimab in previously treated patients). Although some use of dostarlimab monotherapy following CP was part of the clinical expert opinion, this immunotherapy use has been replaced with pembrolizumab monotherapy, an analogous PD-1 targeting immunotherapy licensed and reimbursed in this second-line setting.

A scenario has been included where data from RUBY-1 IA2 is used to inform subsequent treatments, which includes dostarlimab as a subsequent treatment option for patients who have not received prior immunotherapy treatment, as outlined in Appendix P.

Table 28 presents the cost of and percentage of patients treated with each subsequent treatment. The percentages for each subsequent treatment were reweighted to ensure the total sum of percentages for all subsequent treatments doesn't exceed 100%. 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 B.3.4.4. The list price for all subsequent treatments were used and their time on treatment is informed by the literature or a fixed number of cycles. A scenario has been included where a 25%, 50%, and 75% discount has been applied to list prices of lenvatinib and pembrolizumab in Appendix K.

The total subsequent treatment costs, inclusive of drugs at list prices and AE costs, of dostarlimab in combination with CP were £5,038.97. Total subsequent treatment costs of CP were £46,129.16 (127).

Table 28: Subsequent treatments (HCP Opinion with no CDF options available)

Second-line treatment	CP	Pembrolizumab	Doxorubicin	Bevacizumab	Pembrolizumab and lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	No treatment
Total cost per class for average total treatment duration (£)	8,169.07	95,617.69	7,403.24	21,364.43	72,382.70	4.17	190.48	3,388.24	0.00
Total cost of AEs during subsequent treatment (£)	281.87	116.98	636.66	67.23	422.30	0.00	0.00	0.00	0.00
Percentage usage post dostarlimab in combination with CP	35.1%	0.0%	19.6%	0.0%	0.0%	5.2%	5.2%	14.1%	20.5%
Percentage usage post CP	13.1%	42.6%	6.2%	1.4%	[redacted]	3.8%	3.8%	10.0%	[redacted]

Abbreviations: AE, adverse event; CDF, cancer drugs fund; CP, carboplatin and paclitaxel; HCP, healthcare professional.

B.3.5.6. Miscellaneous units costs and resource use

NICE diagnostic guidance DG42 recommends that all patients with endometrial cancer should be tested using immunohistochemistry to identify tumours with dMMR/MSI-H status (21). As such and in line with the previous submission of TA963, dMMR/MSI-H testing is SoC for all patients with endometrial cancer and dMMR testing costs were not included within the base case economic analysis. NHS England is in the process of implementing widespread testing pathways nationally, which has been ongoing since 2021 (21).

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

B.3.6. Severity

The lifetime QALY gain of patients in the CP arm of the CEM and corresponding age and sex from the RUBY-1 trial (see Table 29) was used to understand the extent to which the disease impacts the remaining QALYs of patients. Utility data are outlined in Section B.3.4.1 (Table 20).

Patients with primary advanced or recurrent endometrial cancer experience dire health outcomes, demonstrated by the absolute shortfall of almost 9 QALYs, which is a 76% proportional shortfall compared with patients in the general population (Table 31). 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 29: 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 B.3.3.1

Abbreviations: QALY, quality-adjusted life year.

Table 30: 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 31: 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	11.76	[redacted]	[redacted]	[redacted]

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

B.3.7. Uncertainty

The updated IA2 data cut for OS provided more mature data than was available in the original submission. This showed a pronounced sustained treatment benefit for dostarlimab observed from 10 months (see Section B.2.6.1, Figure 5). Statistical tests suggested that it was not possible to conclude that the PH assumption holds. Therefore, independent models were selected for the base case. Various scenario analyses were undertaken around the OS for dostarlimab, including testing alternative survival distributions, assuming more conservative estimates of treatment effect by modelling a fixed treatment effect, and exploring the waning of the treatment effect over time.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 32.

Table 32: 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]	-	B.3.3.2
Age at baseline (years)	[redacted]	-	B.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%	-	B.3
Clinical inputs			
PFS (dostarlimab arm)	IA PFS, flexible Odds K=1	Each survival analysis sheet	B.3.3.2.1.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PFS (CP)	IA PFS, flexible Odds K=2	contains a calculation for probabilistic analysis	B.3.3.2.1.1
OS ((dostarlimab arm)	Log-logistic		B.3.3.2.2.2
OS (CP)	Log-logistic		B.3.3.2.2.1
OS HR	[redacted]	[redacted] Log-normal	B.3.3.2.2
TTD (dostarlimab arm)	Weibull (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	B.3.3.2.3.2
TTD (CP)	Weibull (KM for full follow up period) three year stopping rule and completion rates applied		B.3.3.2.3.1
Cost inputs			
Dostarlimab cost (up to cycle 18)	[redacted]	-	B.3.5.2.1
Dostarlimab cost (up to cycle 19+)	[redacted]	-	
Carboplatin and paclitaxel cost (up to cycle 18)	£970.25	-	
Admin cost up to cycle 18 Dostarlimab+CP	£363.63	235.32, 519.41 Gamma	B.3.5.2.2
Admin cost cycle 19+ Dostarlimab	£294.81	190.78, 421.10 Gamma	
Administration cost per cycle with CP (up to cycle 18)	£363.63	235.32, 519.41 Gamma	
Outpatient visit unit cost	£193.70	125.35, 276.68 Gamma	B.3.5.3
CT scan unit cost	£139.47	90.26, 199.23 Gamma	
Complete blood count unit cost	£3.04	1.97, 4.34 Gamma	
Blood pressure and heart rate unit cost	£222.27	143.84, 317.49 Gamma	
Specialist nurse visit unit cost	£58.55	37.89, 83.63 Gamma	
GP visit unit cost	£47.25	30.58, 67.49 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Resource use frequency			
Outpatient visit Dostarlimab+CP in PF state up to cycle 18	0.30	0.19, 0.43 Gamma	B.3.5.3
Outpatient visit Dostarlimab+CP in PD state up to cycle 18	0.12	0.08, 0.17 Gamma	
CT scan Dostarlimab+CP in PF state up to cycle 18	0.13	0.08,0.19 Gamma	
CT scan Dostarlimab+CP in PD state up to cycle 18	0.07	0.05, 0.10 Gamma	
Complete blood count Dostarlimab+CP in PF state up to cycle 18	0.33	0.21, 0.47 Gamma	
Complete blood count Dostarlimab+CP in PD state up to cycle 18	0.09	0.06, 0.13 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	0.07, 0.16 Gamma	
Specialist nurse visit Dostarlimab+CP in PD state up to cycle 18	0.10	0.06, 0.14 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	
Outpatient visit Dostarlimab+CP in PF state from cycle 19+	0.13	0.08, 0.19 Gamma	
Outpatient visit Dostarlimab+CP in PD state from cycle 19+	0.12	0.08, 0.17 Gamma	
CT scan Dostarlimab+CP in PF state from cycle 19+	0.06	0.04, 0.09 Gamma	
CT scan Dostarlimab+CP in PD state from cycle 19+	0.07	0.05, 0.10 Gamma	
Complete blood count Dostarlimab+CP in PF state from cycle 19+	0.22	0.14, 0.31 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 Dostarlimab+CP in PD state from cycle 19+	0.09	0.06, 0.13 Gamma	
Blood pressure and heart rate Dostarlimab+CP in PF state from cycle 19+	0.00	0.00, 0.00 Gamma	
Blood pressure and heart rate Dostarlimab+CP in PD state from cycle 19+	0.00	0.00, 0.00 Gamma	
Specialist nurse visit Dostarlimab+CP in PF state from cycle 19+	0.07	0.05, 0.10 Gamma	
Specialist nurse visit Dostarlimab+CP in PD state from cycle 19+	0.10	0.06, 0.14 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	0.19, 0.43 Gamma	
Outpatient visit CP in PD state up to cycle 18	0.12	0.08, 0.17 Gamma	
CT scan CP in PF state up to cycle 18	0.13	0.08, 0.19 Gamma	
CT scan CP in PD state up to cycle 18	0.07	0.05, 0.10 Gamma	
Complete blood count CP in PF state up to cycle 18	0.33	0.21, 0.47 Gamma	
Complete blood count CP in PD state up to cycle 18	0.09	0.06, 0.13 Gamma	
Blood pressure and heart rate CP in PF state up to cycle 18	0.00	0.00, 0.00 Gamma	
Blood pressure and heart rate CP in PD state up to cycle 18	0.00	0.00, 0.00 Gamma	
Specialist nurse visit CP in PF state up to cycle 18	0.11	0.07, 0.16 Gamma	
Specialist nurse visit CP in PD state up to cycle 18	0.10	0.06, 0.14 Gamma	
GP visit CP in PF state up to cycle 18	0.00	0.00, 0.00 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 PD state up to cycle 18	0.01	0.01, 0.01 Gamma	
Outpatient visit CP in PF state from cycle 19+	0.08	0.05, 0.11 Gamma	
Outpatient visit CP in PD state from cycle 19+	0.12	0.08, 0.17 Gamma	
CT scan CP in PF state from cycle 19+	0.05	0.03, 0.07 Gamma	
CT scan CP in PD state from cycle 19+	0.07	0.05, 0.10 Gamma	
Complete blood count CP in PF state from cycle 19+	0.06	0.04, 0.09 Gamma	
Complete blood count CP in PD state from cycle 19+	0.09	0.06, 0.13 Gamma	
Blood pressure and heart rate CP in PF state from cycle 19+	0.00	0.00, 0.00 Gamma	
Blood pressure and heart rate CP in PD state from cycle 19+	0.00	0.00, 0.00 Gamma	
Specialist nurse visit CP in PF state from cycle 19+	0.07	0.05, 0.10 Gamma	
Specialist nurse visit CP in PD state from cycle 19+	0.10	0.06, 0.14 Gamma	
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	
Adverse event costs			
Anaemia unit cost	620.17	401.34, 885.86 Gamma	B.3.5.4
Neutropenia unit cost	557.54	360.81, 796.39 Gamma	
Neutrophil count decreased unit cost	771.32	499.16, 1,101.76 Gamma	
Hypertension unit cost	401.48	259.81, 573.47 Gamma	
White blood cell count decreased unit cost	771.32	499.16, 1,101.76 Gamma	
Hypokalemia unit cost	1,972.12	1,276.25, 2,816.99 Gamma	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Pulmonary embolism unit cost	1,957.76	1,266.96, 2,796.47 Gamma	
Lymphocyte count decreased unit cost	771.32	499.16, 1,101.76 Gamma	
Lipase increased unit cost	771.32		
Abdominal pain and amylase increased unit cost	472.48	305.76, 674.89 Gamma	
Urinary tract infection unit cost	592.95	383.72, 846.97 Gamma	
Nausea and hyponatremia unit cost	584.57	378.30, 835.00 Gamma	
Rash unit cost	398.55	257.92, 569.30 Gamma	
AE probabilities			
Anaemia Dostarlimab+CP up to cycle 18	0.15	0.10, 0.21 Beta	B.3.5.4
Neutropenia Dostarlimab+CP up to cycle 18	0.10	0.06, 0.14 Beta	
Neutrophil count decreased Dostarlimab+CP up to cycle 18	0.08	0.05, 0.12 Beta	
Hypertension Dostarlimab+CP up to cycle 18	0.07	0.05, 0.10 Beta	
White blood cell count decreased Dostarlimab+CP up to cycle 18	0.07	0.04, 0.09 Beta	
Hypokalemia Dostarlimab+CP up to cycle 18	0.05	0.03, 0.07 Beta	
Pulmonary embolism Dostarlimab+CP up to cycle 18	0.06	0.04, 0.08 Beta	
Lymphocyte count decreased Dostarlimab+CP up to cycle 18	0.05	0.03, 0.08 Beta	
Lipase increased Dostarlimab+CP up to cycle 18	0.05	0.03, 0.07 Beta	
Abdominal pain and amylase increased Dostarlimab+CP up to cycle 18	0.04	0.02, 0.05 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	0.04, 0.09 Beta	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Rash Dostarlimab+CP up to cycle 18	0.05	0.03, 0.07 Beta	
Anaemia CP up to cycle 18	0.17	0.11, 0.24 Beta	
Neutropenia CP up to cycle 18	0.09	0.06, 0.13 Beta	
Neutrophil count decreased CP up to cycle 18	0.14	0.09, 0.20 Beta	
Hypertension CP up to cycle 18	0.03	0.02, 0.05 Beta	
White blood cell count decreased CP up to cycle 18	0.05	0.03, 0.08 Beta	
Hypokalemia CP up to cycle 18	0.04	0.02, 0.05 Beta	
Pulmonary embolism CP up to cycle 18	0.05	0.03, 0.07 Beta	
Lymphocyte count decreased CP up to cycle 18	0.07	0.05, 0.10 Beta	
Lipase increased CP up to cycle 18	0.01	0.01, 0.02 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	0.03, 0.07 Beta	
Rash CP up to cycle 18	0.01	0.01, 0.02 Beta	
Subsequent treatment			
Proportion receiving Carboplatin and paclitaxel following discontinuation from Dostarlimab	0.35	0.22, 0.49 Dirichlet	B.3.5.5
Proportion receiving Pembrolizumab following discontinuation from Dostarlimab	0.00	0.00, 0.00 Dirichlet	
Proportion receiving Doxorubicin following discontinuation from Dostarlimab	0.20	0.13, 0.28 Dirichlet	
Proportion receiving Bevacizumab following discontinuation from Dostarlimab	0.00	0.00, 0.00 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 Pembrolizumab and lenvatinib following discontinuation from Dostarlimab	0.00	0.00, 0.00 Dirichlet	
Proportion receiving Letrozole following discontinuation from Dostarlimab	0.05	0.03, 0.07 Dirichlet	
Proportion receiving Medroxyprogesterone acetate following discontinuation from Dostarlimab	0.05	0.03, 0.07 Dirichlet	
Proportion receiving Radiotherapy following discontinuation from Dostarlimab	0.14	0.09, 0.20 Dirichlet	
Proportion receiving No treatment following discontinuation from Dostarlimab	0.21	0.13 , 0.29 Dirichlet	
Proportion receiving Carboplatin and paclitaxel following discontinuation from CP	0.13	0.08, 0.19 Dirichlet	
Proportion receiving Pembrolizumab following discontinuation from CP	0.43	0.26, 0.60 Dirichlet	
Proportion receiving Doxorubicin following discontinuation from CP	0.06	0.04, 0.09 Dirichlet	
Proportion receiving Bevacizumab following discontinuation from CP	0.01	0.01, 0.02 Dirichlet	
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP	[redacted]	[redacted] Dirichlet	
Proportion receiving Letrozole following discontinuation from CP	0.04	0.02, 0.05 Dirichlet	
Proportion receiving Medroxyprogesterone acetate following discontinuation from CP	0.04	0.02, 0.05 Dirichlet	
Proportion receiving Radiotherapy following discontinuation from CP	0.10	0.06, 0.14 Dirichlet	
Proportion receiving No treatment following discontinuation from CP	[redacted]	[redacted] Dirichlet	
Subsequent treatment cost Dostarlimab+CP	5,038.97	-	
Subsequent treatment cost CP	46,129.16	-	
Quality of life			
Utility: PF	[redacted]	[redacted]	B.3.4.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
		Beta	
Utility: PD	[redacted]	[redacted] Beta	
Anaemia disutility	0.12	0.08, 0.17 Beta	B.3.4.4
Neutropenia disutility	0.09	0.06, 0.13 Beta	
Neutrophil count decreased disutility	0.00	0.00, 0.00 Beta	
Hypertension disutility	0.02	0.01, 0.03 Beta	
White blood cell count decreased disutility	0.00	0.00, 0.00 Beta	
Hypokalemia disutility	0.07	0.05, 0.10 Beta	
Pulmonary embolism disutility	0.32	0.20, 0.45 Beta	
Lymphocyte count decreased disutility	0.00	0.00, 0.00 Beta	
Lipase increased disutility	0.01	0.01, 0.01 Beta	
Abdominal pain and amylase increased disutility	0.10	0.05, 0.10 Beta	
Urinary tract infection disutility	0.01	0.01, 0.01 Beta	
Nausea and hyponatremia disutility	0.05	0.03, 0.07 Beta	
Rash disutility	0.12	0.08, 0.17 Beta	

Abbreviations: CP, carboplatin plus paclitaxel; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.8.2. Assumptions

A summary of the assumptions made in the model are presented in Table 33.

Table 33: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Population and comparators	Adult patients with primary advanced or recurrent DNA mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) endometrial cancer and who are candidates for systemic therapy	This is aligned with the decision problem for this appraisal and confirmed as part of the NICE TA963 submission (70)
	Carboplatin/paclitaxel (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 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 dMMR/MSI-H 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
	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 estimated by UK clinical experts, and do not include treatments currently within the CDF. For CP, dostarlimab use has been replaced with pembrolizumab	This is expected to best reflect 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; dMMR, mismatch repair deficient; EQ-5D, euro-qol 5 dimensions; MSI-H, microsatellite Stable- high; NHS, National Health System; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressed disease; PFD, progression-free disease; SmPC, Summary of Product Characteristics; UK, United Kingdom; QALYs, quality-adjusted life years

B.3.9. Base-case results

B.3.9.1. Base-case incremental cost-effectiveness analysis results

The base-case results are presented using the list price for CP and the PAS discount of [redacted] with a net price of [redacted] for dostarlimab as described in Section B.1.2.

Total costs, LYs, QALYs, and the ICER for dostarlimab in combination with CP versus CP are presented in Table 34. In the deterministic base-case analysis, dostarlimab was associated with [redacted] incremental costs and 4.418 incremental QALYs compared with CP, which corresponds to an ICER of [redacted] per QALY gained i.e., <£20,000 per QALY gained. Disaggregated base-case results are presented in Appendix J.

The net health benefit (NHB) is displayed in Table 35. The NHB at £20,000 and £30,000 of [redacted] and [redacted], respectively, implies that overall population health would be increased as a result of introducing dostarlimab.

Table 34: 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]	4.418	[redacted]

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

Table 35: 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]	4.418	[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.

B.3.10. Exploring uncertainty

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

B.3.10.1. Probabilistic sensitivity analysis

PSA involves drawing a value at random for each variable from its uncertainty distribution (see Table 32). This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'; 1,000 simulations were performed, which give a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results.

For costs and resource use estimates a gamma distribution was fitted to prevent values less than zero. For utilities and probabilities, a beta distribution was used to restrict draws to between 0 and 1. Treatment costs for primary advanced or recurrent endometrial cancer remained fixed. Treatment cost for subsequent treatments, and incidence of usage, are varied. An incremental cost-effectiveness plane (ICEP) scatterplot (Figure 18) and cost-effectiveness acceptability curve (CEAC) (Figure 19) were produced to graphically illustrate the level of variability and uncertainty in the results.

Probabilistic results are presented in Table 36 and are highly congruent with the deterministic base-case results (Table 34). At a willingness to pay (WTP) threshold of £20,000 and £30,000 per QALY, [redacted] of dostarlimab simulations were cost-effective.

Table 36: 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]	4.339	[redacted]

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

Figure 18: Scatterplot of probabilistic results

Abbreviations: CP, carboplatin plus paclitaxel; PSA, probabilistic sensitivity analysis.

Figure 19: Cost-effectiveness acceptability curve

Abbreviations: CP, carboplatin plus paclitaxel.

B.3.10.2. Deterministic sensitivity analysis

The OWSA varied one parameter at a time and assessed the subsequent impact on the incremental QALYs and incremental costs.

The OWSA is programmed to assign a lower and upper bound to each parameter; the low value is the lower bound of the 95% CI, and the high value is the upper bound of the 95% CI of the pre-specified probabilistic distributions assigned to each parameter.

In the absence of CI data, a standard error of +/- 20% of the mean for each parameter was assumed and the lower and upper bounds were estimated by applying the appropriate distribution (gamma for parameters that must be greater than or equal to zero or beta for parameters that must be bounded between 0 and 1). Table 32 presents the mean, upper bound, and lower bound values for each variable.

A tornado diagram was developed to graphically present the parameters which have the greatest effect on the ICER. The top 10 most sensitive parameters for dostarlimab versus CP is presented in Figure 20, with tabulated results presented in Table 37. The model was most sensitive to the parameters of the selected OS distribution for dostarlimab, followed by the subsequent treatment costs of pembrolizumab, and the completion rates per cycle associated with the dostarlimab arm.

Figure 20: OWSA results: tornado diagram

Abbreviations: CP, carboplatin plus paclitaxel; ICER, incremental cost-effectiveness ratio; OS, overall survival; OWSA, one-way sensitivity analysis; PF, progression-free.

Table 37: Tabulated OWSA results

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Dostarlimab+CP - OS	[redacted]	[redacted]	[redacted]
Total cost for average total treatment duration (£) Pembrolizumab	[redacted]	[redacted]	[redacted]
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 16)	[redacted]	[redacted]	[redacted]
Proportion receiving Pembrolizumab following discontinuation from CP	[redacted]	[redacted]	[redacted]
Outpatient visit Dostarlimab+CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit unit cost	[redacted]	[redacted]	[redacted]
CP - OS	[redacted]	[redacted]	[redacted]
Proportion receiving No treatment following discontinuation from CP	[redacted]	[redacted]	[redacted]
CT scan Dostarlimab+CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Admin cost cycle 19+ (£) Dostarlimab	[redacted]	[redacted]	[redacted]

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

B.3.10.3. Scenario analysis

Scenario analyses were conducted to test structural and parametric uncertainty. The results of these scenarios are summarised in Table 38. The results from the scenario analyses show that the cost-effectiveness results are robust to changes in model structure and inputs, with ICERs remaining below [redacted] per QALY gained for the dostarlimab arm compared with CP across all scenarios. In addition, the probabilistic results from the scenario analysis were aligned with the deterministic results, showing that the scenarios were robust to probabilistic uncertainty. The scenarios with the greatest impact on incremental results are applying treatment effect waning between 8-10 years and applying a 50% and 75% discount on the price of pembrolizumab/lenvatinib.

A scenario was explored whereby a fixed treatment effect is assumed for dostarlimab by applying the HR observed in RUBY-1 for the dostarlimab in combination with CP arm to the OS extrapolation of the CP arm. This is considered a conservative assumption, considering the early and durable plateau observed in the OS KM curve from the RUBY-1 dostarlimab arm, as well as the mechanism of action of immunotherapies. However, it has been included for consistency with the original submission regarding the OS data of dostarlimab.

As described in Section B.3.3.2.2.3, although the company consider treatment warning to be implicitly captured within OS extrapolations by fitting independent log-logistic curves, a scenario exploring treatment waning has been included. In the recent appraisal of pembrolizumab for use as a second-line treatment option for patients with dMMR/MSI-H tumours (TA914), the committee agreed on a waning of treatment effect from 7-9 years. This was in a setting where the treatment had a 2-year stopping rule (61). Based on this, the waning of the treatment effect for dostarlimab is applied from 8-10 years to account for the additional year of treatment patients on dostarlimab would receive.

Table 38: 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]	4.418	[redacted]	[redacted]
2	Starting age	[redacted] (RUBY-1)	[redacted] (NCRAS)	[redacted]	[redacted]	4.285	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs	3.50%	1.50%	[redacted]	[redacted]	5.633	[redacted]	[redacted]
4	Subsequent treatment source	UK expert opinion	RUBY data source	[redacted]	[redacted]	4.418	[redacted]	[redacted]
5	OS extrapolation	Dostarlimab arm extrapolated using log-logistic curve	Gen gamma	[redacted]	[redacted]	5.353	[redacted]	[redacted]
6	OS extrapolation	Dostarlimab arm extrapolated using log-logistic curve	Weibull	[redacted]	[redacted]	3.991	[redacted]	[redacted]
7	OS extrapolation	Independent models	HR applied to CP arm	[redacted]	[redacted]	4.141	[redacted]	[redacted]
8	Treatment waning	No treatment waning applied	Treatment waning 8-10 years applied to base case curve	[redacted]	[redacted]	3.422	[redacted]	[redacted]
9	Subsequent treatment cost	0% discount on list price of lenvatinib and pembrolizumab	25% discount on list price of lenvatinib and pembrolizumab	[redacted]	[redacted]	4.418	[redacted]	[redacted]
10	Subsequent treatment cost	0% discount on list price of lenvatinib and pembrolizumab	50% discount on list price of lenvatinib and pembrolizumab	[redacted]	[redacted]	4.418	[redacted]	[redacted]
11	Subsequent treatment cost	0% discount on list price of lenvatinib and pembrolizumab	75% discount on list price of lenvatinib and pembrolizumab	[redacted]	[redacted]	4.418	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years.

B.3.11. Subgroup analysis

Subgroup analysis was not performed as part of this submission because dMMR/MSI-H was already a pre-specified population of the RUBY-1 trial.

B.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 (128-130).

Patients with primary advanced or recurrent endometrial cancer experience dire health outcomes, demonstrated by the absolute shortfall of almost 9 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 endometrial cancer. Currently, innovative treatment options for patients with primary advanced or recurrent endometrial cancer are restricted to patients who have experienced disease relapse.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

B.3.13.1.1. Validation of OS curve for dostarlimab in combination with CP using PFS2

The company 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 (88, 106). An advisory board (July 2024) was specifically run to understand appropriate modelling methods and curve selection for the economic model (106).

During this session, the lack of additional PFS data was highlighted as a limitation of the evidence (106). Although the primary endpoint of PFS in the dMMR/MSI-H group was reached during IA1, the data have not yet reached maturity. Experts suggested that the more mature PFS2 data could be used to justify the curve choice for OS (106). PFS2 has been shown to demonstrate a positive correlation in several solid tumours across oncology treatments (127, 131). Further to this, as outlined in Section B.2.6.2.1, a correlation between PFS2 and OS in the RUBY IA2 trial data has been observed, with median PFS2 not being

reached in the dostarlimab arm compared with median PFS2 of 21.6 months [redacted] in the CP arm indicating prolonged disease control following treatment with dostarlimab.

In order to explore this suggestion, the KM data for PFS2 was overlayed onto the base case OS and PFS extrapolations for the dostarlimab arm. As seen in Figure 21, the PFS2 KM sits between the extrapolations of OS and PFS, which would be consistent with the expected correlation of PFS2, PFS and OS. Furthermore, at around 4 years, the PFS2 KM data begins to intersect with the extrapolated OS curve suggesting that the chosen OS curve is not only appropriate but potentially conservative.

Figure 21: Base case OS and PFS extrapolations presented with PFS2 KM data

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

B.3.14. Interpretation and conclusions of economic evidence

B.3.14.1. Summary of cost-effectiveness analysis

Over a lifetime time horizon, at the dostarlimab PAS price, deterministic base-case results showed that dostarlimab accrued incremental QALYs of 4.418 with an incremental cost of [redacted] compared with CP. The resulting ICER in the base case was [redacted] per QALY, which is significantly below the NICE threshold of £30,000 per QALY.

Based on 1,000 simulations, the mean PSA results were highly congruent with the deterministic base case results. Dostarlimab, at the PAS price, was associated with an additional 4.333 QALYs and [redacted] incremental costs versus PCC which resulted in an ICER of [redacted] per QALY gained, significantly below the NICE threshold. The probability

that dostarlimab (with PAS) is cost-effective at a £30,000 and £20,000 WTP threshold is [redacted].

In the OWSA, the parameters with the greatest effect on the base case ICER were the parameters of the OS distribution for dostarlimab, followed by the subsequent treatment cost of pembrolizumab and the completion rates per cycle associated with dostarlimab. Several scenario analyses investigated variation in model settings and approaches, and all resulted in dostarlimab being cost-effective at the £30,000 per QALY threshold with the ICER remaining below the [redacted] per QALY across all scenarios. The PSA results of the scenario analyses were aligned with the deterministic scenario analyses results further demonstrating that the results were robust to changes in model structure and inputs.

B.3.14.2. Generalisability of the cost-effectiveness analysis

The economic evaluation is based on the patient population from the RUBY-1 trial, which is considered representative of patients with primary advanced or recurrent endometrial cancer. 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.

The population included in the model is the dMMR/MSI-H population which aligns with the anticipated marketing authorisation and is therefore representative of the patients who are anticipated to be eligible for treatment. As per the NICE reference case, the analysis was conducted from an NHS and PSS perspective (92).

B.3.14.3. Strengths of cost-effectiveness analysis

The economic evaluation is based on the dMMR/MSI-H 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 B.2.2). The dMMR/MSI-H population was a predefined population in the RUBY-1 trial, avoiding post-hoc bias.

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.

B.3.14.4. Limitations of cost-effectiveness analysis

A limitation of the economic analysis is that despite OS data being more mature from the IA2 data cut, median had still not been reached in the dostarlimab arm. To overcome this limitation, alternative approaches to modelling the treatment effect in the dostarlimab arm were explored. In addition, a conservative approach was taken to extrapolate the OS curves for dostarlimab.

B.3.15. Conclusion

Currently, innovative treatment options for patients with primary advanced or recurrent endometrial cancer are restricted to patients who have experienced disease relapse. These patients describe facing a constant fear of recurrence, with one patient speaking to this worry “There’s always a chance that the microscopic cells could pop up and wreak havoc, and it’s preventing me from thinking about my future.” (132). Expanding treatment regimens to patients earlier in the treatment pathway would aim to further improve outcomes in the primary setting and provide the benefit of innovative treatments.

Dostarlimab has been a viable treatment option for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer since guidance published by NICE in April 2024 (70). Without dostarlimab, these patients face a poor prognosis with limited treatment options.

Maintaining access to dostarlimab ensures patients continue to have the opportunity to receive the only licensed immunotherapy reimbursed by NICE for the treatment for primary advanced or recurrent endometrial cancer. This access to innovative treatment options in earlier lines of therapy increases the chances of survival for patients and improves their outcomes.

The results from the cost-effectiveness analysis demonstrate dostarlimab to be a cost-effective use of NHS resources, considering a willingness to pay threshold of £30,000 per QALY gained when provided at the PAS price. Both deterministic and probabilistic results indicated the ICER is <£20,000 per QALY gain. The results of the sensitivity and scenario analysis support the robustness of the base case analysis. There was a [redacted] chance of

dostarlimab being cost-effective at both a £20,000 per QALY and £30,000 per QALY WTP threshold.

For patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer, dostarlimab represents a step change in the clinical management of this condition. UK experts noted that the medical community will be keen to use dostarlimab for treatment of patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer, rather than waiting for patients to relapse (102).

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Appendices

The following appendices are provided in a standalone document:

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analyses
- Appendix F: Ruby-1 adverse event data
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality of life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Price details of treatments included in the submission
- Appendix L: Checklist of confidential information
- Appendix M: National Cancer Registration and Analysis Service (NCRAS) real world evidence (RWE) study
- Appendix N: First interim analysis clinical effectiveness
- Appendix O: Additional detail to Section B3
- Appendix P: Subsequent treatment information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

Summary of Information for Patients (SIP)

October 2024

File name	Version	Contains confidential information	Date
ID6426_Dostarlimab+PC_EC_SIP	**3.0 (Final)**	**No**	**20th September 2024**

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 that is either '**primary advanced**', where upon diagnosis the cancer has either spread outside of the womb, perhaps to the ovaries, lymph nodes or to organs further away, such as the lungs, or the cancer has not spread beyond the womb but is considered too difficult to cure with surgery and supportive therapies (1) or diagnosed with endometrial cancer that is considered '**recurrent**', meaning it has returned when it previously could no longer be detected, after treatment (which includes surgery, chemotherapy or radiotherapy) (2). Patients must **also** have endometrial cancer that is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) **and** who are considered appropriate to receive systemic chemotherapy.

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 2nd Oct 2023 the MHRA authorised a new use for dostarlimab through project ORBIS which is a programme to review and approve promising cancer drugs helping patients access treatments faster. This new indication for JEMPERLI recommends it in combination with platinum-containing chemotherapy for the treatment of adult patients with mismatch repair deficient/ microsatellite instability-high primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy. The full details on this authorisation can be found in this link to the SmPC (summary of product characteristics) for Jemperli https://mhraproducts4853.blob.core.windows.net/docs/027861b3342ec89d7cf5c51d7a3ae0590403e8bd

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 the patient information leaflet for dostarlimab to ensure it is written and designed in a patient friendly format and language. Peaches 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 organization, 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 is a type of cancer found in the lining of the womb, known as the endometrium, and is the most common type of womb cancer (3). dMMR/MSI-H is a specific defect in the genetic code (DNA) of the cancer cells. This defect results in the normal DNA matching process not functioning properly. This can also be associated with a high number of mutations (or DNA changes) which is referred to as microsatellite instability. Cancers with these defects are referred to as mismatch repair deficient/microsatellite instability-high, which is then shortened to dMMR/MSI-H. These genetic defects can be found by taking samples (a biopsy) of the cancer and running tests in a laboratory. Primary advanced endometrial cancer is where upon first diagnosis the cancer has either spread outside of the womb, perhaps to the ovaries, lymph nodes or to organs further away, such as the lungs, or the cancer

has not spread beyond the womb but is considered too difficult to cure with surgery and supportive therapies (1).

Recurrent endometrial cancer is where the cancer has returned after treatment when it previously could no longer be detected (2).

It is estimated that approximately 9,800 patients are diagnosed with endometrial cancer each year in the UK (4). Of the 8,323 cases of endometrial cancer diagnosed each year in England, around 2,454 are diagnosed with advanced or recurrent disease. It is estimated that approximately 539 patients are diagnosed with primary advanced or recurrent dMMR/MSI-H endometrial cancer each year in England (4-9).

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 (10)

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 or happens between periods
- a vaginal discharge that might vary in colour from pink and watery to dark and foul smelling.

About 9 out of 10 womb cancers, including endometrial cancer (90%), are picked up because of post-menopausal or irregular vaginal bleeding. Therefore, endometrial cancer is often diagnosed at an early stage of its growth. While this means the majority of endometrial cancer is caught early, unfortunately, some patients are only diagnosed with advanced disease which is difficult to treat.

Less common symptoms of endometrial cancer include blood in the urine (haematuria) with either:

- low red blood cell level (anaemia)
- high platelet count (thrombocytosis)
- high blood sugar level.

Diagnosis (11)

It is important to get checked by your doctor (GP) if any of the above symptoms occur. 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 can feel a lump (mass) in the tummy (abdomen) or pelvis. The doctor then decides 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(12):

- ultrasound (procedure that uses high frequency sound waves to create a picture of the womb)
- biopsy of the womb lining (take a sample of the tissue known as the endometrium that lines the womb)
- blood tests for endometrial cancer (for example blood cell levels and how well the liver and kidneys are working)

- 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)
- 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. A patient's doctor will look for specific genes, proteins or other types of molecules (biomarkers) in your tissues or blood to understand what type of tumour you have. The dMMR/MSI-H biomarker can be identified by a laboratory test that examines the tumour cells after a biopsy is taken. This test is standard practice in the NHS in England and is where a small sample of the cancer cells are analysed in a laboratory to determine if they contain the dMMR/MSI-H biomarker (13).

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 (14)

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 main treatment is surgery.

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

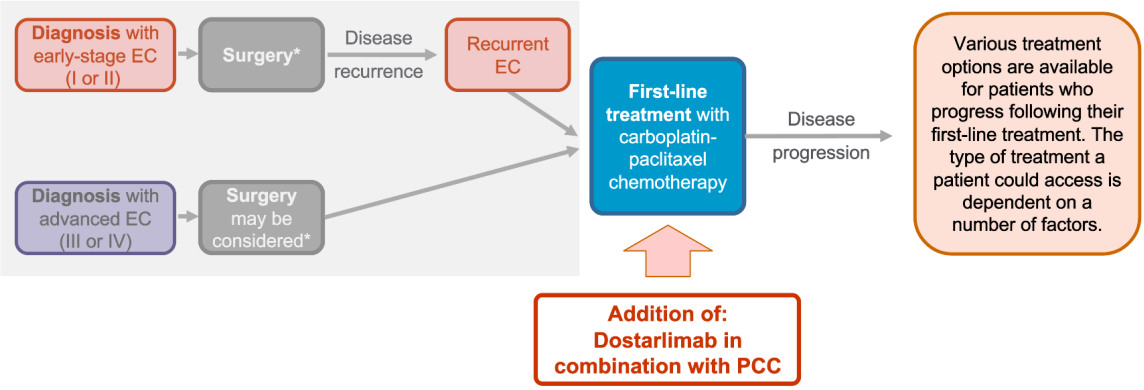
Treatment for primary advanced or recurrent endometrial cancer (15)

For patients who are able to receive chemotherapy, the most common treatment following surgery is a combination of two chemotherapy drugs – carboplatin and paclitaxel (16). These drugs destroy rapidly dividing cells, such as cancer cells (17).

Currently, dostarlimab is available via the Cancer Drugs Fund (CDF) as an add on to this chemotherapy treatment. NICE reviewed the evidence for dostarlimab in early 2024 and recommended that dostarlimab was a cost-effective use of NHS funding and patients should be able to access it. There was some uncertainty in this decision however as patients from the trial had only been followed up for a limited amount of time. Due to this, funding for dostarlimab is currently provided through the CDF. This new, updated submission for dostarlimab in combination with chemotherapy includes data with a longer follow up in order to allow a permanent decision to be made about how patients can access treatment.

It is important that dostarlimab remains available as an effective and permanent treatment option for patients with primary advanced and recurrent endometrial cancer.

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



Abbreviations: EC, endometrial cancer; PCC, platinum-containing chemotherapy.

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 B.1.5 in 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 patient-based evidence (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" (18). 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 (19).

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 impacts on quality of life and social functioning which may persist for years following treatment (20).

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 (21).

Patients 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. These patients are often 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 (19).

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

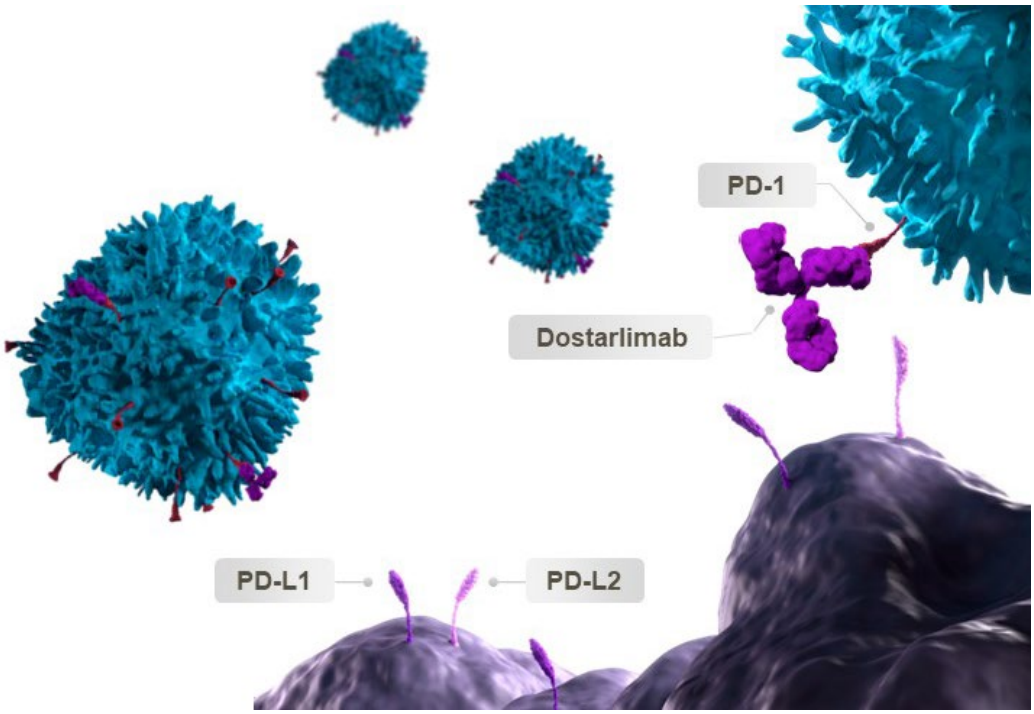
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

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 an immuno-oncology treatment that works by enhancing the body's own immune response to target the tumour (cancer). It does this by binding to a receptor called PD-1 on the surface of a type of white blood cell called a T-cell (22). In endometrial cancer, PD-1 is responsible for dampening (reducing) the body's anti-cancer immune response (23-25). Dampening prevents the T-cells from killing the tumour cells, meaning the tumour is allowed to grow unrestricted.

Dostarlimab works by preventing this process, leading to an increased anti-tumour response from the body. As a result, more cancer cells are killed, and further growth of the tumour becomes restricted.

Figure 2: Mechanism of action for dostarlimab (26)



Abbreviations: PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2.

dMMR/MSI-H tumours result in increased T-cells; dostarlimab is therefore particularly effective for this particular type of endometrial cancer because there are more PD-1 receptors (27).

Dostarlimab is different to the current treatment options available for patients in this setting, as it is an immuno-oncology treatment, rather than chemotherapy or hormone therapy. Dostarlimab is the only treatment in this setting that targets a specific process in the immune system and enhances the body's own immune response against the tumour.

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 current standard of care for people with primary advanced or recurrent endometrial cancer (28).

As explained in section 2c, for patients 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 (15). This standard of care treatment is widely available.

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 (29).

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 (30).

When carboplatin and paclitaxel are used together, they can have a more powerful effect on cancer cells than when used individually (16). They target different aspects of cell division and growth, making the treatment more effective in killing cancer cells and reducing tumour size (17).

Dostarlimab works alongside these chemotherapies and helps the body's natural immune defences to also target and destroy cancer cells as explained in section 3a. As dostarlimab works with the body's immune system, treatment with dostarlimab is continued after chemotherapy to help create a durable (long-lasting) response to treatment.

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. (28, 31)

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

Cycles (doses) 6+: Following this, dostarlimab is given as a dose of 1,000mg every 6 weeks afterwards. The doctor will decide how many treatments of dostarlimab you need. In the clinical trial RUBY, patients were given dostarlimab for a maximum of three years. Table 1 below demonstrates the dosing regimen.

Table 1: Dose regimen for dostarlimab in combination with platinum containing chemotherapy (PCC)

	500 mg once every 3 weeks in combination with PCC[a] (1 Cycle = 3 weeks)							1000 mg once every 6 weeks until disease progression or unacceptable (1 Cycle = 6 weeks)			
Cycle	1	2	3	4	5	6		7	8	9	Continue dosing Q6W
Week	1	4	7	10	13	16		19	25	31	

3 weeks between cycle 6 and cycle 7

[a]During the administration of dostarlimab with PCC, each cycle should start with the infusion of dostarlimab before PCC on the same day

As dostarlimab is administered at the same time 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 standard of care 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 touch point with their HCPs.

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 carboplatin paclitaxel (CP) is supported by the RUBY trial (NCT03981796): a Phase 3, randomised, double-blind, multicentre study (32). The RUBY study has 2 parts, for this submission and indication of dostarlimab the clinical evidence used has come from Part 1 of the study.

Part 1 of the RUBY trial looks at the efficacy and safety of dostarlimab plus CP for the treatment of primary advanced of recurrent endometrial cancer.

The trial included 494 adult patients in Part 1, of which 118 had the dMMR/MSI-H biomarker. 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
- They provided a tumour tissue sample to test their biomarker status
- They were deemed fit enough to participate (had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1).

Patients were excluded from the trial if:

- They had undergone anticancer therapy before the main treatment 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 their endometrial cancer
    - They had received treatment with an anti-PD-1, anti-PD-1L, or anti-PD-L2 agent before
    - 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 trial has two primary end points, progression-free survival (PFS) and overall survival (OS) for the overall population included in the RUBY trial.

People were recruited across 164 centres including five UK sites.

The RUBY trial is still ongoing in both the population of dMMR/MSI-H patients as well as the full population.

The RUBY trial is registered on ClinicTrials.gov under NCT03981796.

For further information on the RUBY trial, **please see the following publication**:
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.

Two important objectives of part 1 of the RUBY study were to compare progression free survival and overall survival of patients treated with dostarlimab plus carboplatin paclitaxel (CP) against those who only had carboplatin paclitaxel.

Progression-free Survival

Progression free survival (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 their disease progressing.

In the dMMR/MSI-H population, the Kaplan-Meier curves, which show the probability of a patient being progression free over time, demonstrated promising results. When the data was analysed (when 56% of patients in the trial had experienced a PFS outcome as outlined above), patients in the dostarlimab plus carboplatin paclitaxel group showed a significant reduction in the risk of disease progression or death indicated by a hazard ratio of 0.28. A hazard ratio represents the likelihood of an event happening. This hazard ratio of 0.28 suggests that there is a 72% reduced risk of a patient’s cancer coming back or getting worse when receiving dostarlimab plus carboplatin paclitaxel compared to the patients who were only receiving carboplatin paclitaxel.

The data collected suggests that dostarlimab in combination with platinum containing chemotherapy had a notable impact in increasing PFS compared to the carboplatin plus paclitaxel alone in the dMMR/MSI-H patient population.

Overall Survival (Section B.2.6.1 of the company submission)

Overall survival represents the duration a patient lives from the start of treatment until their death, regardless of whether the cause of death is related to the disease being treated or not. Overall survival is an important outcome measure used in clinical trials and medical research to assess the effectiveness of treatments and evaluate the impact on patients’ survival rates.

At the time when the data was analysed, the overall survival results showed a trend favouring the dMMR/MSI-H patients who were receiving dostarlimab plus carboplatin paclitaxel. The analysis was performed when 40% of the patients had reached the exploratory endpoint of overall survival. In the dMMR/MSI-H subgroup, there was a reduction in the number of deaths indicated by a hazard ratio of 0.32. This hazard ratio of 0.32 suggests that for dMMR/MSI-H patients there is a 68% reduced risk of death for those receiving dostarlimab plus carboplatin paclitaxel compared to the patients who were only receiving carboplatin paclitaxel.

Progression Free Survival 2 (Section B.2.6.2.1 of the company submission)

PFS2 is the length of time during and after the treatment that a patient lives with their cancer without it getting worse for the second time. It starts from the time a patient begins their first treatment until the cancer worsens after a second line of treatment. In other words, PFS2 helps us understand how long a treatment can keep the cancer from growing or spreading again after the patient has already been treated once. Based on the RUBY trial dostarlimab resulted in a hazard ratio of 0.33. This hazard ratio suggests that for dMMR/MSI-H patients there is a 67% reduction in the risk of death or progression following the first subsequent anticancer therapy, compared to the patients who were receiving carboplatin paclitaxel. Longer PFS2 in the dostarlimab arm means that treatment benefits seen when treating with an immunotherapy in the first-line, extend beyond the first episode of disease progression.

Limitations of the data

The limitations to this data are that the OS data is not fully mature. The trial needs to continue to run and to follow up these patients to collect longer term information. The data collected so far suggests that dostarlimab had a notable impact in increasing survival compared to the carboplatin plus paclitaxel alone in the dMMR/MSI-H patient population.

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 specially to assess the quality of life of cancer patients (33). The EQ-5D-5L Visual Analogue Scale (VAS) was also captured during this trial which records the patient's self-rated-health on a vertical visual analogue 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 (34).

During the chemotherapy period, there were no significant differences observed between the patients receiving dostarlimab and carboplatin plus paclitaxel compared to patients receiving only carboplatin plus paclitaxel. This means the impact on the overall well-being and quality of life for patients during the chemotherapy period of the trial, the first 18 weeks, were similar in both groups, and no significant differences were detected when comparing the scores of the two groups using the assessment tools.

Broader quality of life benefits

As discussed in Section 2d) patients experience increased anxiety, depression, and psychological problems when they are diagnosed with endometrial cancer. Maintaining access to more treatment options that potentially can extend the amount of time a patient has before their disease progresses could help to combat this anxiety as well as increasing the amount of time patients can spend with their families, friends, and as full members of society. As noted in Section 2c) dostarlimab is currently established within the clinical care pathway via the CDF, as an add on to chemotherapy treatment. This submission aims to secure the exit of dostarlimab from the CDF and to ensure patients can access this treatment through routine NHS commissioning.

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 carboplatin plus paclitaxel treatment 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 dMMR/MSI-H 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 dMMR/MSI-H). In these patients, the most common adverse reactions that happened in more than 10% of patients were:

- Rash, flat discoloured areas of skin (22.8%),
- Maculopapular rash, a mix of flat discoloured areas of skin and small raised bumps (14.1%)

- Hypothyroidism, when the thyroid gland does not make enough thyroid hormones to meet the body's demand (14.1%)
- Alanine aminotransferase (ALT) increased, indicating damage or injury to the cells in the liver (12.9 %)
- Aspartate aminotransferase increased, indicating damage or injury to the cells in the liver or heart (12.0 %)
- Pyrexia, or fever (12.0 %)
- Dry skin (10.4 %) (28).

As dostarlimab is an immune checkpoint inhibitor, immune related adverse events are of special interest in the RUBY trial and were evaluated as well. Immune related adverse events are known to be more common with the class of drugs (PD-1 inhibitors) that dostarlimab is a part of. Immune related adverse events 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 adverse reactions, most of which were immune related events (28). Adverse reactions were serious in 5.8% of patients; most serious adverse reactions were immune-related adverse reactions (28).

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 for patients is that dostarlimab has been shown to increase progression free survival (a primary endpoint) and increase overall survival (a prespecified exploratory end point) when used in combination with carboplatin plus paclitaxel when compared to carboplatin plus paclitaxel alone, in this specific dMMR/MSI-H advanced or recurrent endometrial cancer patient group. For these dMMR/MSI-H patients, there was a reduction in the risk of death of 68% (HR ¼ 0.32, 95% CI 0.17-0.63) , supporting the use of dostarlimab to achieve long-term remission and to improve survival (35). The benefit seen with dostarlimab has also been shown to extend into later lines of therapy when looking at the end point of PFS2. Results from the RUBY-1 trial suggest that patients who received dostarlimab as their first line of treatment had better outcomes during their next line of treatment than those who received CP.

This improvement in patients' health comes at no cost to a patient's quality of life. Overall, safety analyses from the RUBY trial indicate that dostarlimab in combination with CP followed by dostarlimab monotherapy has an acceptable safety profile, and the side effects of the medicine are generally manageable (35, 36). Also, the safety profile of dostarlimab in combination with CP was similar to the known safety profiles of the individual medicines.

There is a lack of innovative treatments available to the people in this patient group. Therefore, maintaining an additional option for patients to have dostarlimab first in combination with chemotherapy, followed by dostarlimab on its own for up to 3 years afterwards is imperative. Dostarlimab is currently established within the clinical care pathway via the CDF, as an add on to chemotherapy treatment. This submission aims

to secure the exit of dostarlimab from the CDF and to ensure patients can access this treatment through routine NHS commissioning.

Dostarlimab is different to the current treatment options available for patients in this setting, as it is an immuno-oncology treatment, rather than chemotherapy or hormone therapy.

Dostarlimab is the only current treatment in this setting that targets a specific process in the immune system and enhances the body's pre-existing immune response to cause an anti-tumour response.

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 has meant that patients spend more time attending hospital appointments due to:

- The additional 30 minutes of time it takes for a dostarlimab infusion on top of the standard infusion time for platinum containing chemotherapy (28, 31).

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 increase in travel to and from appointments (28, 31).

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's important to look beyond the duration of the RUBY clinical trial and consider its long-term impact. In this NICE submission, a partition survival model was used. Partitioned survival 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 shown to improve the length of time that primary advanced or recurrent dMMR/MSI-H patients spend in the progression free health state when compared to those receiving standard of care.

This improvement in progression free survival comes at no cost to patient's quality of life when compared to the current standard of care treatment.

These health outcomes have positive impact both personally for patients and their families but also to wider society. Patients may require less help from family members and carers in their life.

Although dostarlimab is associated with higher costs, these have been shown using the company's economic model to be cost-effective for the increase in quality adjusted life years that dostarlimab provides.

Uncertainty

As mentioned in Section 3e), there is limited long term data available for dostarlimab in this primary advanced or recurrent dMMR/MSI-H population. There are only a maximum of 49 months of data available from the RUBY trial, so any longer-term outcomes have been estimated out into the future creating some uncertainty. However, the efficacy and safety data from IA1 and the updated data readouts from IA2 continue to demonstrate that the addition of dostarlimab to standard of care improves patient outcomes compared with standard of care alone. This reduces previous uncertainty surrounding the survival benefits associated with dostarlimab in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer.

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 carboplatin and paclitaxel would be considered as offering a good use of NHS resources, as a new treatment for patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer.

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 step-change in the management of dMMR/MSI-H primary advanced and recurrent endometrial cancer patients who are candidates for systemic therapy. Currently this patient population experiences poor long-term treatment outcomes despite 50-60% of patient responding to the standard of care chemotherapy.

The combination of dostarlimab with carboplatin and paclitaxel has the following innovative characteristics, which are meaningful to both patients & the NHS:

- Compared with the current standard of care of platinum containing chemotherapy, dostarlimab is an immunotherapy with a different, innovative, way of working (as described in section 3a), and different toxicity profile. This allows dostarlimab to be used both in combination with carboplatin and paclitaxel and continually after on its own for up to three years in total, to suppress any remaining disease and extend the length of time patients spend disease free.
- dMMR/MSI-H endometrial cancer triggers a strong immune response in the body. This means that it is more likely to respond well to a PD-1 blockade by drugs like dostarlimab. The combination of increased activity of immune cells (T cells) and the presence of PD-1/PD-L1 proteins in dMMR/MSI-H endometrial cancer makes it a promising target for dostarlimab. This drug has shown to be effective in boosting the immune system's response against cancer cells in other types of cancer where patients have dMMR/MSI-H expression (37).
- There is a need to address an inequality in access to innovative therapies in endometrial cancer compared with other cancer types. While Immunotherapies have been available for several years in second line for advanced/recurrent endometrial cancer patients, access in earlier lines of therapy for cancers such as melanoma (skin cancer), renal cell carcinoma (cancer in the kidney) and, lung cancer has been shown to make a significant impact (38-40). Ensuring that patients can continue to access dostarlimab in the first line will help to address these inequalities.

Dostarlimab is currently established within the clinical care pathway via the CDF, as an add on to chemotherapy treatment. This submission aims to secure the exit of dostarlimab from the CDF and to ensure patients can access this treatment through routine NHS commissioning.

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

Dostarlimab, when used with platinum-containing chemotherapy, could be an alternative treatment option for patients dealing with primary advanced or recurrent endometrial cancer that test positive for the dMMR/MSI-H biomarker.

The survival rates for this group of patients are very low, with a high number of deaths within five years (4, 41).

There are significant differences in survival rates among different ethnicities and socioeconomic backgrounds among patients with endometrial cancer (4, 42). To address these inequalities, it's important to make innovative treatments widely available throughout the UK.

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 (43).

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 or feel a decrease in your muscle strength.

Aspartate aminotransferase (AST): AST is an enzyme that, when increase, is often associate with signs of liver or heart 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.

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.

Haematuria: Blood in your urine

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 into 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

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: 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

Pyrexia: Also known as fever, when body temperature increases in a person beyond the normal range

Quality of life: The way that symptoms impact on the way that people experience 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 natural immune system

Thrombocytosis: When the body produces too many platelets

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
ID6426_Dostarlimab+PC_EC_GSK response to EAG clarification questions_Final_v1.0_Redacted	1.0	Redacted	13th November 2024

Notes for company

Highlighting in the template

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.

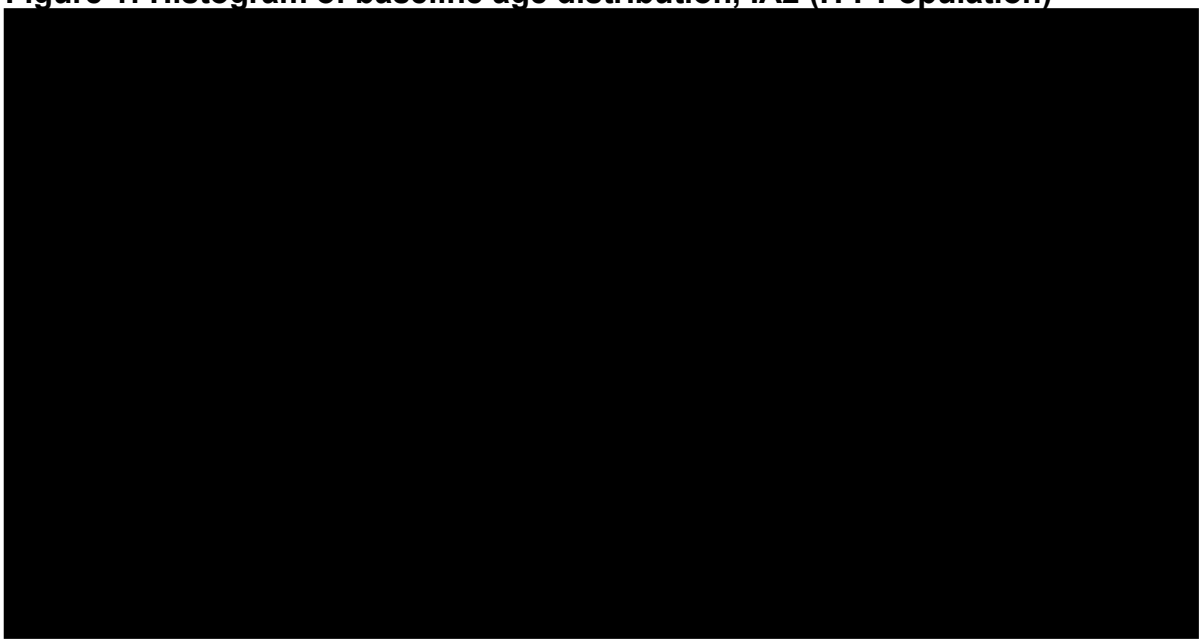
To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Please provide the histogram of the distribution of age at baseline of the RUBY ITT population and of the RUBY dMMR/MSI-H subgroup.

Figure 1 and Figure 2 present the histogram of the distribution of age at baseline for the RUBY ITT population and the dMMR/MSI-H population respectively.

Figure 1: Histogram of baseline age distribution, IA2 (ITT Population)



Source: REQ0381_F_10_01_AGE
Data cutoff: 22 September 2023. Treatment 1 = dostarlimab + carboplatin and paclitaxel. Treatment 2 = Placebo + carboplatin and paclitaxel

Abbreviations: ITT, intention to treat.

Figure 2: Histogram of baseline age distribution, IA2 (dMMR/MSI-H Population)

Source: REQ0381_F_10_02_AGE
Data cutoff: 22 September 2023. Treatment 1 = dostarlimab + carboplatin and paclitaxel. Treatment 2 = Placebo + carboplatin and paclitaxel
Abbreviations: dMMR, DNA mismatch repair deficient; MSI-H, microsatellite instability high.

A2. Please confirm whether IA2 was a pre-planned interim analysis and what protocol conditions were met for this to occur?

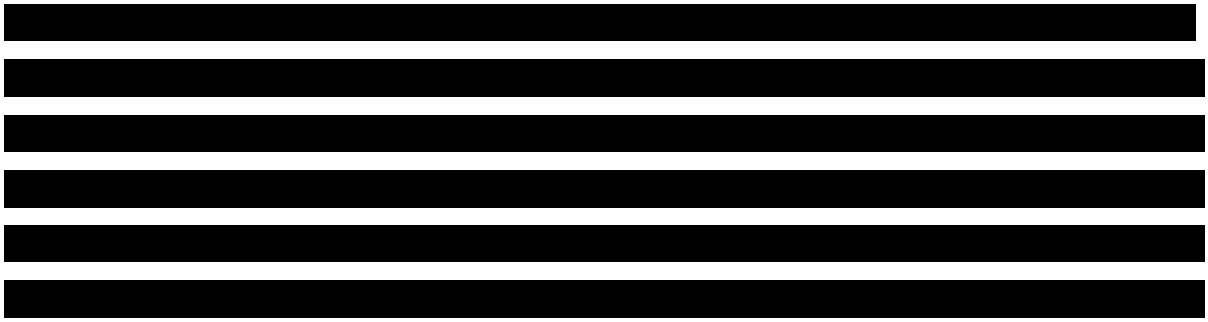
The second interim analysis (IA2) was a pre-planned interim analysis for the dual primary endpoint of overall survival (OS) in the intention-to-treat (ITT) population. IA2 was planned to occur when approximately 221 OS events had occurred, per Table 21 in the protocol (Protocol Amendment 5). The planned number of OS events for IA2 was observed by the data cut-off (DCO) of 22 September 2023, however, as part of the survival follow-up strategy, additional survival status information was obtained from public records, where permitted, between DCO and database lock for participants who discontinued from study due to any reasons other than death. Thus, there were 253 OS events identified at the DCO on 22 September 2023, surpassing the planned number of expected events for OS for IA2 (221 events).

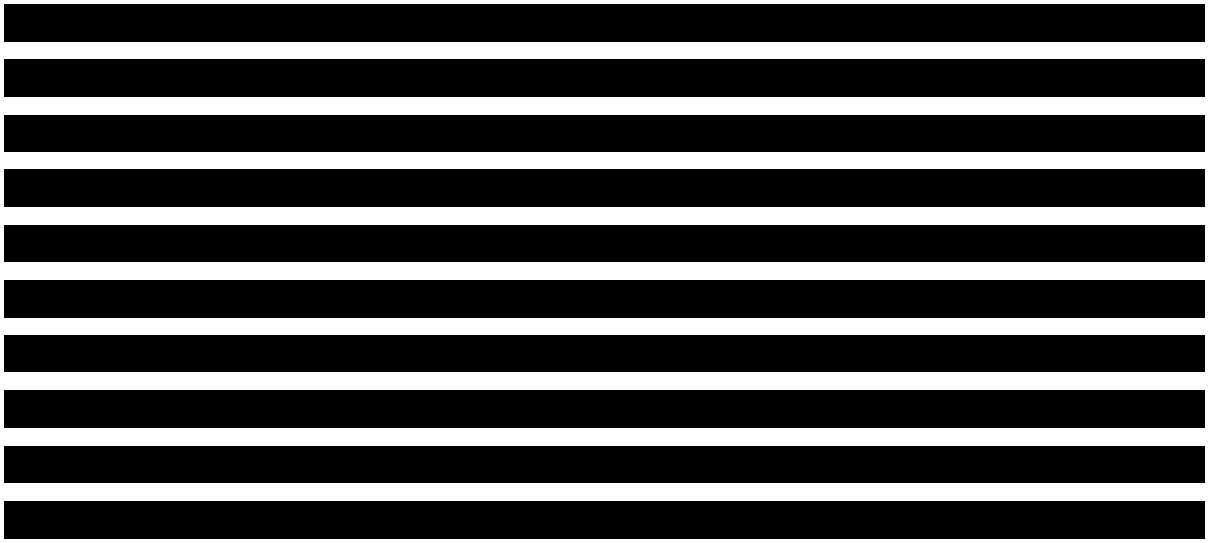
A3. Please explain how PFS2 data are available from IA2 but a lack of monitoring for disease progression from IA1 meant PFS data were not

updated. If PFS data are available, but were just not tested, please provide an overview of the updated data (Kaplan-Meier, hazard ratio estimate).

Progression-free survival 2 (PFS2) was defined as the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following the study intervention or death from any cause, whichever occurred earlier. According to this definition, a progression-free survival (PFS) event does not need to be re-analysed to record a PFS2 event, provided a subsequent anticancer therapy has been initiated.

At IA1 (DCO 28 September 2022), RUBY Part 1 met the PFS dual-primary endpoint by demonstrating that dostarlimab in combination with carboplatin-paclitaxel reduced the risk of progression or death by 72% in dMMR/MSI-H primary advanced or recurrent EC, and by reducing the risk of progression or death by 36% in the overall population, which includes participants enrolled regardless of MMR/MSI status. Given that statistical significance for pre-specified PFS analysis was crossed at IA1, no further inferential analyses of PFS were to be performed for RUBY Part 1.





[redacted]

Figure 3 : KM Plot of PFS per investigator assessment, IA2 (dMMR/MSI-H population)

Source: f_15_2_1_1d_kmplot_pfs
Data cutoff: 22 September 2023
Abbreviations: dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; PFS – progression-free survival.

Table 1: KM analysis of PFS per investigator assessment, IA2 (dMMR/MSI-H population)

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
PFS status, n (%)		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
PFS (months) Quartile (95% CI)		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
PFS distribution function (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 (95% CI)	[redacted]	
p-value of 1-sided stratified log-rank test	[redacted]	

Source: t_14_2_1_1d_km_pfs
Data cutoff: 22 September 2023
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MMRp – mismatch repair proficient; MSI-H – microsatellite instability-high; MSS – microsatellite stable; PFS – progression-free survival.

A4. Please perform an analysis and Kaplan Meier plot of PFS2 but only including people who received subsequent therapy.

In the RUBY trial, 60% (n=39/65) of patients randomised to the placebo arm went on to receive a subsequent therapy compared to only 28% (n=15/53) in the dostarlimab arm in DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) population. The time from randomisation to PFS2 for this group of patients is illustrated in Figure 4.

A higher proportion of patients in the placebo arm received an immune checkpoint inhibitor (IO) in the second-line setting (69.2%, or 27 out of 39 patients) compared to the dostarlimab arm (53.3%, or 8 out of 15 patients). Given that IO therapy is generally associated with improved outcomes in the second line, it could be expected that PFS2 with respect to subsequent therapy would be more favourable in the placebo arm compared to the dostarlimab arm. There is however no clear separation between the two arms suggesting that patients are experiencing

comparable PFS2 despite the lower rate of subsequent IO therapy in the dostarlimab arm.

It is important to note that this is an inherently biased analysis given the subgroup is selected based on a negative prognostic post-baseline event. Nevertheless, it is notable that fewer dostarlimab arm patients required a subsequent line of therapy than placebo arm.

Figure 4: KM analysis of PFS2, for patients who received at least one FUACT (dMMR/MSI-H population)

Source: REQ0381_F_08_01_KM_PFS2_FUACT.rtf

Data cutoff: 22 September 2023

Abbreviations: dMMR, DNA mismatch repair-deficient; FUCAT, follow-up anti-cancer therapy; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

A5. Page 22 of reference 80 refers to tables and spreadsheets, these have not been submitted. Please provide these.

The tables and spreadsheets referenced on page 22 of reference 80 were intended to support the detailed data analyses discussed in the document. However, these supporting materials were not submitted initially. We apologise for this oversight and have uploaded the relevant tables and spreadsheets to the NICE portal for your review.

A6. Please present PFS, OS, TTD and PFS2 Kaplan-Meier plots from RUBY-1 only including people with recurrent disease or stage 4 disease at baseline

The KM plots stratified by disease status, patients with recurrent or Stage IV disease for PFS (Figure 5), OS (Figure 6), TTD (Figure 7), and PFS2 (Figure 8) from RUBY-1 have been provided in the figures below. The company notes that running these analyses yields smaller patient numbers, as each represents a subgroup of the dMMR/MSI-H population. Consequently, these results should be interpreted with caution, as the study was not powered to detect a treatment difference within these subgroups.

Figure 5: KM analysis of PFS, Stage IV or recurrent disease IA1 (dMMR/MSI-H population)

Source: REQ0381_F_04_01_KM_PFS_RS4
Data cutoff: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Figure 6: KM analysis of OS, Stage IV or recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_04_02_KM_OS_RS4
Data cutoff: 22 September 2023.

Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Figure 7: KM analysis of TTD, Stage IV or recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_04_04_KM_TTD_RS4

Data cutoff: 22 September 2023 Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; TTD, time to treatment discontinuation.

Figure 8: KM analysis of PFS2, Stage IV or recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_04_03_KM_PFS2_RS4
Data cutoff: 22 September 2023 Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

A7. Please explain how date limits were applied (or other method used) to identify new studies from MEDLINE, Embase and Cochrane in updates #2, #3 and #4 for the clinical SLR. The final few lines of the search strategies reported in Appendix D1.1.4 tables 2-4 are confusing and also do not match the numbers for update #4 as recorded in the PRISMA diagram (Figure 1); MEDLINE (n = 99), Embase (n = 372), Cochrane (n = 19).

The original SLR was searched on the date of November 10, 2021. The SLR update #1 included an overlap of three months with the timeframe of the original SLRs searches (i.e. covering literature from August 1, 2021 - February 22, 2023) to account for any delay between entry of articles into the databases of interest and time-to-indexing with Medical Subject Heading/Emtree terms. The same approach was applied to the clinical efficacy and safety SLR Update #2 (i.e., covering literature from January 1, 2023- August 8, 2023), SLR Update #3 (i.e., covering the literature from May 1, 2023 – October 26, 2023 for the clinical SLR update, and literature from January 1, 2023-October 26, 2023 for the utilities, economic burden, and economic evaluation SLRs), and SLR Update #4 (i.e., covering literature from July 1, 2023-May 16, 2024). It is worth noting that during SLR update #2, only the efficacy and safety SLR was updated.

The figures in Appendix D, Figure 1 align with those in the original SLR report. We apologise for the oversight in which certain rows in Tables 2–4 of Appendix D were omitted, resulting in a misalignment with Figure 1. Updated versions of Tables 2-4 are provided below.

Updated Table 2: MEDLINE search strategy (via OvidSP)

Search number	Search terms	Results (Original SLR – 10 November 2021)	SLR Update #1 (22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
1	exp endometrial neoplasms/ or ((endometrial or endometrium or uterine or uterus) adj3 (cancer$ or neoplasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.	59,567	63,417	64,794	65,425	67,030
2	exp Neoplasm Metastasis/ or (recurrent or recurrence or relaps$ or advanced or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage iii$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab.	2,165,817	2,348,567	2,411,286	2,438,926	2,517,334
3	1 and 2	17,930	19,370	19,865	20,104	20,684
4*	Randomised Controlled Trials as Topic/ or randomised controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or Placebos/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomised controlled trial.pt. or multicentre study.pt. or clinical trial.pt. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or (placebo$ or randomly allocated).tw. or (allocated adj2 random$).tw.	1,764,731	1,885,633	1,921,156	1,936,403	1,981,494
5	Review.pt.	2,876,482	3,109,679	3,189,834	3,225,649	3,322,358
6	Systematic Review.pt. or Systematic Reviews as Topic/ or Meta-Analysis.pt. or exp Network Meta-Analysis/ or exp Meta-Analysis as Topic/ or Cochrane Database of Systematic Reviews.jn.	265,459	328,516	345,703	354,249	377,780
7	(systematic$ or systematic or pubmed or medline or Embase or Cochrane or metaanalysis or meta analysis or metaanalysis or meta-analyses or meta analyses or metaanalyses or meta-analyzed or meta analyzed or	743,736	865,809	908,557	928,283	982,303

Search number	Search terms	Results (Original SLR – 10 November 2021)	SLR Update #1 (22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
	metaanalyzed or meta-analysed or meta analysed or metaanalysed or ((indirect or mixed or multiple) and treatment comparison)).ti,ab.					
8	5 not (6 or 7)	2,611,129	2,797,002	2,859,418	2,887,124	2,961,595
9	case reports/ or case study/ or case report$.jw. or Editorial.pt. or Letter.pt. or Note.pt.	3,764,163	3,969,420	4,038,349	4,068,330	4,149,500
10	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,148,598	3,301,741	3,356,783	3,380,780	3,436,679
11	or/8-10	8,237,413	8,695,000	8,849,791	8,918,137	9,097,656
12	4 not 11	1,482,308	1,586,727	1,617,446	1,630,503	1,669,541
13	3 and 12	1,811	1,977	2,016	2,036	2,096
14	13 not ((exp animal/ or nonhuman/) not exp human/)	1,808	1,974	2,013	2,033	2,093
15	(202108$ or 202109$ or 202110$ or 202111$ or 202112$ or 2022$ or 2023$).ed,dt.	--	3,072,865	--	--	--
15	2023$.ed,dt.	--	--	1,124,384	--	--
15	(202305$ or 202306$ or 202307$ or 202308$ or 202309$ or 202310$).ed,dt.	--	--	--	903,631	--
15	(202307$ or 202308$ or 202309$ or 202310$ or 202311$ or 202312$ or 2024$).ed,dt.	--	--	--	--	1,533,808
16	14 and 15	--	213	65	54	99

Updated Table 3: EMBASE search strategy (via OvidSP)

Search number	Search terms	Results (Original SLR – 10 November 2021)	Results (SLR Update #1 – 22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
1	exp endometrium cancer/ or ((endometrial or endometrium or uterine or uterus) adj3 (cancer$ or neoplasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.	87,398	96,222	100,545	101,979	105,691
2	exp Metastasis/ or (advanced or recurrent or recurrence or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage iii$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab.	2,850,546	3,168,459	3,213,846	3,253,336	3,375,533
3	1 and 2	29,480	33,132	34,929	35,554	37,119
4*	Clinical Trial/ or Randomised Controlled Trial/ or controlled clinical trial/ or multicentre study/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp Randomisation/ or Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/ or Placebo/ or Prospective Study/ or (randomi?ed controlled trial$ or rct or placebo$).tw. or (random$ adj2 allocat$).tw. or (single blind$ or double blind$).tw. or ((treble or triple) adj blind$).tw.	2,579,051	2,900,530	2,923,306	2,962,677	3,054,880
5	Review.pt.	2,803,212	3,054,496	3,106,547	3,135,728	3,225,500
6	exp "systematic review"/ or exp "systemic review (topic)"/ or exp meta analysis/ or exp network meta-analysis/ or exp "meta-analysis (topic)"/ or Cochrane Database of Systematic Reviews.jn.	472,103	593,903	598,032	611,842	650,854
7	(systematic$ or systematic or pubmed or medline or Embase or Cochrane or meta-analysis or meta analysis or meta-analysis or meta-analyses or meta analyses or meta-analyses or meta-analysed or meta analysed or meta-analysed or meta-analysed	922,822	1,103,458	1,122,787	1,145,604	1,214,280

Search number	Search terms	Results (Original SLR – 10 November 2021)	Results (SLR Update #1 – 22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
	or meta analysed or meta-analysed or ((indirect or mixed or multiple) and treatment comparison)).ti,ab.					
8	5 not (6 or 7)	2,503,274	2,686,228	2,724,737	2,745,860	2,811,109
9	case reports/ or case study/ or case report$.jx. or case report$.jw. or Editorial.pt. or Letter.pt. or Note.pt.	2,927,864	3,178,467	3,294,695	3,324,601	3,416,701
10	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,409,394	3,679,904	3,702,764	3,735,148	3,831,078
11	or/8-10	7,915,824	8,537,387	8,681,971	8,755,433	8,977,569
12	4 not 11	2,242,623	2,545,631	2,558,325	2,595,464	2,682,017
13	3 and 12	3,060	3,660	3,786	3,904	4,078
14	13 not ((exp animal/ or nonhuman/) not exp human/)	3,057	3,657	3,783	3,901	4,074
15	conference abstract.pt.	4,223,186	4,685,222	4,844,767	4,929,238	5,151,096
16	14 not 15	2,004	2,268	2,360	2,391	2,486
17	aacr.cf,cg.	82,103	85,475	85,805	85,805	88,864
18	asco.cf,cg.	61,780	70,639	72,182	72,229	76,236
19	esmo.cf,cg.	29,699	32,788	33,886	36,470	37,597
20	Society of Gynecologic Oncology.cf,cg.	5,023	5,656	5,696	6,216	6,216
21	ESGO.cf,cg.	5,743	7,424	7,424	7,424	8,275
22	International Gynecologic Cancer Society.cf,cg.	5,419	6,383	6,383	6,383	6,892
23	NCCN.cf,cg.	197	213	213	226	239

Search number	Search terms	Results (Original SLR – 10 November 2021)	Results (SLR Update #1 – 22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
24	or/17-23	189,964	208,578	211,589	214,753	224,319
25	limit 24 to yr="2019-current"	42,383	60,996	63,929	67,029	76,595
26	ispor.cf,cg.	46,409	51,328	53,356	53,357	55,871
27	Society for Immunotherapy of Cancer.cf,cg.	4,985	4,985	4,985	4,985	4,985
28	26 or 27	51,394	56,314	58,341	58,342	60,856
29	limit 28 to yr="2018-current"	15,332	20,252	22,279	22,280	24,793
30	14 and (25 or 29)	289	527	534	596	659
31	16 or 30	2,293	2,795	2,894	2,987	3,145
32	(202108$ or 202109$ or 202110$ or 202111$ or 202112$ or 2022$ or 2023$).em,dc.	--	3,915,102	--	--	--
32	2023$.em,dc.	--	--	1,673,062	--	--
32	202305$ or 202306$ or 202307$ or 202308$ or 202309$ or 202310$).em,dc.	--	--	--	1,466,910	--
32	(202307$ or 202308$ or 202309$ or 202310$ or 202311$ or 202312$ or 2024$).em,dc.	--	--	--	--	2,522,329
33	31 and 32	--	632	197	201	372

Updated Table 4:Cochrane systematic reviews and trials (via Ovid)

Search number	Search terms	Results (Original SLR – 10 November 2021)	SLR Update #1 (22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
1	exp endometrial neoplasms/	652	968	1,005	1,014	1,192
2	((endometrial or endometrium or uterine or uterus) adj3 (cancer$ or neoplasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab.	3,597	3,438	3,572	3,594	3,749
3	1 or 2	3,741	3,467	3,786	3,811	3,994
4	exp Neoplasm Metastasis/	5,383	6,490	6,543	6,557	7,558
5	(recurrent or recurrence or relaps$ or advanced or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab.	201,575	205,547	213,114	214,479	224,617
6	4 or 5	202,598	206,819	214,397	215,766	226,038
7	3 and 6	1,464	1,495	1,550	1,559	1,655
8	(EUCTR$ or NCT$ or ICTRP$ or CTRI$ or ISRCTN$ or chictr$ or actrn$ or IRCT$ or NTR$).en.	327,547	487,993	526,870	535,153	584,874
9*	(journal conference abstract or journal conference paper or "journal conference review").pt.	189,557	214,901	224,121	224,635	239,911
10	7 not (8 or 9)	982	847	858	858	866
11	remove duplicates from 10	947	821	832	832	824
12	limit 11 to randomised controlled trial [Limit not valid in CDSR; records were retained]	312	821	832	832	--
13	(202108$ or 202109 or 202110$ or 202111$ or 202112$ or 2022$ or 2023$).up.	--	1,974,383	589,161	--	474,727

Search number	Search terms	Results (Original SLR – 10 November 2021)	SLR Update #1 (22 February 2023)	SLR Update #2 (08 Aug 2023)	SLR Update #3 (26 Oct 2023)	SLR Update #4 (16 May 2024)
13	(202305$ or 202306$ or 202307$ or 202308$ or 202309$ or 202310$).up.	--	--	--	74,916	--
14	12 and 13	--	807	252	14	--
14	Limit 13 to yr=”2023-current”	--	--	--	--	134
15	14 use cocz	--	7	6	--	--
16	Limit 12 to yr=”2021-Current”	--	53	--	--	19
16	limit 12 to yr="2023 -Current"	--	--	12	--	--
17	15 or 16	--	60	18	--	--

A8. PRIORITY Please provide the Kaplan Meier data separately by arm for OS (IA1), OS (IA2), PFS(IA1), PFS2(IA2), PFS(BICR) (IA1), TTD (IA1) carboplatin + paclitaxel (10 tables) and the TTD (IA1) dostarlimab for the dostarlimab arm (1 table) in same format as the hypothetical data of the table below, splitting censoring into censoring events due to the data cut and censoring events due to other reasons. Please also provide the median follow-up for each set of KM data when this median is not within the economic model.

Due to time constraints and data availability, the Kaplan Meier data which splits the cause of censoring events by censored due to the data cut and censored due to other reasons are only reported for each requested endpoint in two-monthly time intervals. However, to ensure the question is fully addressed we have also provided Kaplan Meier survival data which details at which timepoint each event and censor was recorded as part of the reference pack.

The following analyses by arm are presented below:

- OS (IA1) (Table 4 and Table 5)
- OS (IA2) (Table 6 and Table 7)
- PFS per investigator assessment (INV) (IA1) (Table 8 and Table 9)
- PFS by blinded independent central review (BICR) (IA1) (Table 10 and Table 11)
- PFS2 (IA2) (Table 12 and Table 13)
- TTD for the dostarlimab arm (IA1) (Table 14 and Table 15)

The TTD for carboplatin and paclitaxel by arm from IA1 has been requested, but due to the analysis method used, this information is not available separately from the overall TTD. The company has provided completion rate data for each chemotherapy agent by arm as part of the response to B7.

Table 16 includes the median duration of follow up for each end point requested.

Table 4: KM analysis of OS in the dostarlimab arm, IA1 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]						
2							
4							
6							
8							
10							
12							
14							
16							
18							
20							
22							
24							
26							
28							
30							
32							
34							
36							

Source: REQ0381_T_01_01_KM_OS_IA1_DOST.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Table 5: KM analysis of OS in the placebo arm, IA1 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]						
2							
4							

Month	N at risk	N events (cumulative)	N events	Censored		P(event)	S(t)
				Follow-up ongoing	Follow-up ended		
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_02_KM_OS_IA1_PL.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Table 6: KM analysis of OS in the dostarlimab arm, IA2 (dMMR/MSI-H population)

Month	N at risk	N events (cumulative)	N events	Censored		P(event)	S(t)
				Follow-up ongoing	Follow-up ended		
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_03_KM_OS_IA2_DOST.
Data cutoff: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair deficient; IA2, second interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Table 7: KM analysis of OS in the placebo arm, IA2 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_04_KM_OS_IA2_PL.
Data cutoff: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair deficient; IA2, second interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Table 8: KM analysis of PFS per investigator assessment in the dostarlimab arm, IA1 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month	N at risk	N events (cumulative)	N events	Censored		P(event)	S(t)
				Follow-up ongoing	Follow-up ended		
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_05_KM_PFS_IA1_DOST.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Table 9: KM analysis of PFS per investigator assessment in the placebo arm, IA1 (dMMR/MSI-H population)

Month	N at risk	N events (cumulative)	N events	Censored		P(event)	S(t)
				Follow-up ongoing	Follow-up ended		
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month	N at risk	N events (cumulative)	N events	Censored: Follow-up ongoing	Censored: Follow-up ended	P(event)	S(t)
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_06_KM_PFS_IA1_PL.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Table 10: KM analysis of PFS BICR in the dostarlimab arm, IA1 (dMMR/MSI-H population)

Month	N at risk	N events (cumulative)	N events	Censored: Follow-up ongoing	Censored: Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_09_KM_PFSB_IA1_DOST.
Data cutoff: 28 September 2022.
Abbreviations: BICR, blinded independent central review; dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Table 11: KM analysis of PFS BICR in the placebo arm, IA1 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_10_KM_PFSB_IA1_PL.
Data cutoff: 28 September 2022.

Abbreviations: BICR, blinded independent central review; dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Table 12: KM analysis of PFS2 in the dostarlimab arm, IA2 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_07_KM_PFS2_IA2_DOST.
Data cutoff: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair deficient; IA2, second interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

Table 13: KM analysis of PFS2 in the placebo arm, IA2 (dMMR/MSI-H population)

				Censored			
Month	N at risk	N events (cumulative)	N events	Follow-up ongoing	Follow-up ended	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month	N at risk	N events (cumulative)	N events	Censored		P(event)	S(t)
				Follow-up ongoing	Follow-up ended		
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Source: REQ0381_T_01_08_KM_PFS2_IA2_PL.
Data cutoff: 22 September 2023.
Abbreviations: dMMR, DNA mismatch repair deficient; IA2, second interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

Table 14: KM analysis of TTD of dostarlimab in the dostarlimab arm, IA1 (dMMR/MSI-H population)

Month	N at risk	N events (cumulative)	N events	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Month	N at risk	N events (cumulative)	N events	P(event)	S(t)
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: REQ0381_T_01_11_KM_TTD_IA1_DOST.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; TTD, time-to-treatment discontinuation.

Table 15: KM analysis of TTD of dostarlimab in the placebo arm, IA1 (dMMR/MSI-H population)

Month	N at risk	N events (cumulative)	N events	P(event)	S(t)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: REQ0381_T_01_12_KM_TTD_IA1_PL.
Data cutoff: 28 September 2022.
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; TTD, time-to-treatment discontinuation.

Table 16: Median duration of follow up for KM Analysis (dMMR/MSI-H population)

KM Analysis	Median duration of follow-up Weeks (95%CI)	
	Dostarlimab arm	Placebo arm
IA1 OS	[redacted]	[redacted]
IA2 OS	[redacted]	[redacted]
IA1 PFS per investigator assessment	[redacted]	[redacted]
IA1 PFS (BICR)	[redacted]	[redacted]
IA2 PFS2	[redacted]	[redacted]
IA1 TTD	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; dMMR, DNA mismatch repair deficient; IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; NR, not reported; OS, overall survival; PFS, progression-free survival; PFS2 progression-free survival 2; TTD, time-to-treatment discontinuation.

A9. Please present PFS, OS, TTD and PFS2 Kaplan-Meier plots from RUBY-1 separately for people with and without recurrent disease. Please also provide the OS data as per the above table separately for people with or without recurrent disease.

Due to time constraints and data availability, the Kaplan Meier data which splits the cause of censoring events by censored due to the data cut and censored due to other reasons are not available for this subgroup analysis.

The KM plots stratified by disease status: patients with recurrent disease and patients without recurrent disease for;

- PFS (Figure 9 and Figure 10),
- OS (Figure 11 and Figure 12),
- TTD (Figure 13 and Figure 14),
- and PFS2 (Figure 15 and Figure 16)

from RUBY-1 have been provided in the figures below. The company notes running these analyses produces smaller patient numbers as each is a subgroup of the dMMR/MSI-H subgroup. These results should be interpreted with caution, given that the study was not powered to detect a treatment difference in these subgroups.

As expected, a smaller separation between the KM curves is observed for the primary advanced disease cohort relative to the recurrent disease cohort given their relatively better prognosis. Notably a similar plateau in PFS is observed in the dostarlimab arm in both the recurrent and primary advanced cohorts. In fact, across each of the efficacy outcomes the dostarlimab arm produces similar event-free survival estimates between recurrent and primary advanced cohorts. This is in contrast with the placebo arm where the event rate is higher for the Recurrent cohort, reflecting their poorer prognosis.

Figure 9: KM analysis of PFS, recurrent disease IA1 (dMMR/MSI-H population)

Source: REQ0381_F_05_01_KM_PFS_REC
Data cutoff: 28 September 2022
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Figure 10: KM analysis of PFS, without recurrent disease IA1 (dMMR/MSI-H population)

Source: REQ0381_F_05_01_KM_PFS_REC
Data cutoff: 28 September 2022
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival.

Figure 11: KM analysis of OS, recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_02_KM_OS_REC
Data cutoff: 22 September 2023
Abbreviations: CI, confidence interval; dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; NE, not estimable; MSI-H, microsatellite instability-high; OS, overall survival.

Figure 12: KM analysis of OS, without recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_02_KM_OS_REC
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; OS, overall survival.

Figure 13: KM analysis of TTD, recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_04_KM_TTD_REC
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; TTD, time to treatment discontinuation.

Figure 14: KM analysis of TTD, without recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_04_KM_TTD_REC
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; TTD, time to treatment discontinuation.

Figure 15: KM analysis of PFS2, recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_03_KM_PFS2_REC
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

Figure 16: KM analysis of PFS2, without recurrent disease IA2 (dMMR/MSI-H population)

Source: REQ0381_F_05_03_KM_PFS2_REC
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair-deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS2, progression-free survival 2.

A10. Please provide updated results from IA2 for best overall response, DOR for all responders, and DOR for complete responders. Please provide the Kaplan Meier data for duration of Complete Response among those with a best response of Complete Response with events being loss of Complete response, and parallel data for Partial Response among those with a best response of Partial Response (4 tables) in the same format, as previous questions preferably for IA2 but if this is not possible for IA1.

Due to time constraints and data availability, the Kaplan Meier data which splits the cause of censoring events by censored due to the data cut and censored due to other reasons are not available for this subgroup analysis.

Duration of response (DOR) was not analysed as part of IA2; therefore, no updated data on DOR is available. Below is a summary of the response data collected during IA1 split by complete responders and partial responders.

In the RUBY-1 trial, at IA1, tumour response by investigator assessment for patients with evaluable disease at baseline showed that nearly [redacted] of dMMR/MSI-H patients treated with dostarlimab in combination carboplatin paclitaxel (CP) achieved a complete response (CR), compared with approximately [redacted] patients [redacted] receiving CP alone.

The results indicate that patients achieving a CR demonstrated highly durable and prolonged durations of response. The KM plot and risk table illustrating the DOR for patients achieving CR in the dMMR/MSI-H population, as assessed by investigator assessment, are presented in Figure 17 and Table 17.

Figure 17: KM curves of DOR for patients with CR – RECIST v.1.1 based on investigator assessment IA1 (dMMR/MSI-H population)

Source: SSDR103710_f_km_dor_inv.rtf
Data cutoff: 28 September 2022
Abbreviations: CR, complete response; dMMR, DNA mismatch repair deficient; DOR, duration of response; KM, Kaplan-Meier; MSI-H, microsatellite instability-high

Table 5: Summary of KM Analysis of DOR for patients with CR - RECIST v1.1 based on investigator assessment and primary censoring (dMMR/MSI-H population)

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number of patients with CR		
n	15	12
DOR		
Status n (%)		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for DOR (months)		
Quartile (95% CI)		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
Duration ≥ 6 months, n (%)	[redacted]	[redacted]
Duration ≥ 12 months, n (%)	[redacted]	[redacted]
Probability of DOR (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

Source: SSDR103710_t_km_dor_inv.rtf
Data cutoff: 28 September 2022
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; CR, complete response; dMMR, DNA

mismatch repair deficient; DOR, duration of response; KM, Kaplan-Meier; MSI-H. microsatellite instability-high; NE, not estimable

Rates of patients achieving a partial response (PR) were similar between arms, [redacted] for the dostarlimab arm and [redacted] in the CP arm. However, the KM plots and risk table illustrated in Figure 18 and Table 19 demonstrate that the durability of partial response (PR) is longer for patients in the dostarlimab arm, with [redacted] of the partial responders maintaining their response for more than 12 months. In comparison, just [redacted] of the partial responders in the CP arm maintained their response for more than 12 months.

Figure 18: KM curves of DOR for patients with PR – RECIST v.1.1 based on investigator assessment (dMMR/MSI-H population)

Source: REQ0381_F_06_06_KM_DOR_INV
Data cutoff: 28 September 2022
Abbreviations: dMMR, DNA mismatch repair deficient; DOR, duration of response; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PR, partial response.

Table 6: Summary of KM Analysis of DOR for patients with PR - RECIST v1.1 based on investigator assessment and primary censoring (dMMR/MSI-H population)

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number of patients with CR		
n	[redacted]	[redacted]
DOR		
Status n (%)		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Estimates for DOR (months)		
Quartile (95% CI)		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
Duration ≥ 6 months, n (%)	[redacted]	[redacted]
Duration ≥ 12 months, n (%)	[redacted]	[redacted]
Probability of DOR (95% CI)		
Month 6	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

Source: REQ0381_t_06_05_km_dor_INC
Data cutoff: 28 September 2022
Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; dMMR, DNA mismatch repair deficient; DOR, duration of response; KM, Kaplan-Meier; MSI-H. microsatellite instability-high; NE, not estimable; PR, partial response.

A11. Please provide a summary of the most recent data from GARNET for best overall response, DOR for all responders, and DOR of CR for complete responders

The most recent data from the GARNET trial in patients with dMMR/MSI-H endometrial cancer comes from Oaknin et al. 2023 based on a third interim analysis (IA3) of the data and is summarised below (1):

- Overall response rate (ORR): the ORR per RECIST v1.1 criteria was 45.5% (n=64/143 [95% CI: 37.1%, 54.0%]). This included 23 patients (16.1%) with confirmed CR and 42 patients (29.4%) with confirmed PR.

- DOR for all responders: among all responders (CR or PR), the median DOR was not reached in the dMMR/MSI-H population (median follow-up 27.6 months), with a probability of maintaining response at 24 months at 83.7% (95% CI 70.8-91.2), indicating a sustained clinical benefit.

These data from the GARNET trial demonstrate a meaningful and durable clinical response, particularly among complete and partial responders, supporting the treatment's efficacy in the dMMR/MSI-H endometrial cancer population.

A12. The economic model appears to include updated TTD data (IA2). If available the TTD (IA2) carboplatin + paclitaxel (2 tables) and the TTD (IA2)

dostarlimab for the dostarlimab arm (1 table) in the same format as that requested under the previous question.

Due to time constraints and data availability, the Kaplan Meier data which splits the cause of censoring events by censored due to the data cut and censored due to other reasons are not available for this subgroup analysis.

For clarity, the economic model does not include any TTD data related to the IA2 data cut. The model did include placeholders for IA2 data, which were left over from the global CEM in case of further data being collected. However, at the time of Company submission, no additional TTD data was available as part of IA2. Since Company submission, analysis of TTD data for IA2 has been conducted. The TTD KM data for dostarlimab is provided in Table 20. This analysis was run only for the safety analysis set (N=117) as one patient did not receive any dostarlimab. The exclusion of a single patient from the safety analysis population is a small deviation from the original IA1 TTD data included in the model. However, since this patient did not receive any treatment and was not captured within the efficacy data, the impact on the TTD results is negligible.

The results beyond the three-year timepoint should be interpreted with caution, with only approximately [redacted]% of patients still at risk at month 36, making the Kaplan-Meier (KM) data unreliable. Additionally, although the KM data indicates a small proportion of patients remain on treatment at 3 years, just [redacted] of the [redacted] doses administered ([redacted]%) were given after 3 years, demonstrating that any impact of doses observed beyond the stopping rule in RUBY-1 on costs and efficacy will be minimal.

Table 7: Dostarlimab TTD KM data, IA2 (dMMR/MSI-H population)

Month	Number at risk	Number of events (cumulative)	Number of events per month	Probability (event)	Survival (t)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]					

Source: REQ0381_T_01_13_KM_TTD_IA2_DOST
Data cutoff: 22 September 2023.
Abbreviations: IA2, second interim analysis; KM, Kaplan-Meier.

As patients in the RUBY-1 trial only received carboplatin + paclitaxel for the first 18 weeks of the trial, completion rates data was used to inform this in the model, not the placebo TTD. For completeness, the placebo TTD from IA2 has been provided in Table 21.

Table 8: Placebo TTD KM data, IA2 (dMMR/MSI-H population)

Month	Number at risk	Number of events (cumulative)	Number of events per month	Probability (event)	Survival (t)
[redacted]					

Source: REQ0381_T_01_14_KM_TTD_IA2_PL
Data cutoff: 22 September 2023.
Abbreviations: IA2, second interim analysis; KM, Kaplan-Meier.

A13. Please add to Table 7 information with disease status at baseline split by ECOG 0 at baseline and ECOG 1 at baseline.

Due to timing constraints, it has not been possible to describe disease status at baseline by ECOG score.

Table 7 in Document B for this submission reports prognostic stratification factors of the RUBY trial however ECOG performance status has not been identified as a prognostic factor.

A14. Please provide a breakdown of disease stage at trial baseline for people with recurrent disease.

Patients with recurrent endometrial cancer were not re-staged upon recurrence (2, 3). Details as to the type of recurrence (be it local, regional, distant or oligometastatic recurrence) were not recorded (2). Inclusion into RUBY was for those patients where the clinician deemed the patient to be low potential for cure by radiation therapy or surgery alone or in combination with chemotherapy (2). Consequently, no data is available on the breakdown of disease stage at trial baseline for people with recurrent disease.

A15. For years 1 (i.e. the year from baseline), 2 and 3 please tabulate the numbers of patients remaining on dostarlimab at the start of year, the numbers discontinuing dostarlimab and the reasons for these discontinuations for the IA2 data cut (3 tables). If this data is not available for the IA2 data cut please provide it for the IA1 data cut.

Please see below the breakdown of discontinuations as requested presented in Table 22.

Table 9: Reasons for dostarlimab discontinuation in years 1–3, IA2 (dMMR/MSI-H population)

Variable	Year 1	Year 2	Year 3
Dostarlimab arm n = 53			
Time Period	0-1 year	1-2 year	2+ year
Number of patients alive and remaining on dostarlimab at the start of time period	[redacted]	[redacted]	[redacted]
Number of patients discontinuing Dostarlimab during the time period	[redacted]	[redacted]	[redacted]
Reasons of discontinuing dostarlimab [n(%)]			
AE	[redacted]	[redacted]	[redacted]

Clinical Progression	[redacted]	[redacted]	[redacted]
PD According to RECIST V1.1 criteria per investigator assessment	[redacted]	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Risk to patient, as judged by the investigator, sponsor or both	[redacted]	[redacted]	[redacted]
Severe noncompliance, as judged by the investigator, sponsor, or both	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Confirmed complete response, treated for at least 3 years with study treatment	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]

Source: REQ0381_T_09_01_TRT_FREQ
Data cutoff: 22 September 2023
Abbreviations: dMMR, DNA mismatch repair deficient; MSI-H. microsatellite instability-high; PD, progressed disease.

A16. Please state how many patients continued to receive dostarlimab beyond 3 years for the IA2 data cut, together with the mean number of dostarlimab doses these patients received beyond 3 years. If this data is not available for the IA2 data cut please provide it for the IA1 data cut.

Completion rates for dostarlimab for IA2 are presented in Question B8. The 30th cycle of dostarlimab corresponds to the first administration beyond year 3 post-randomisation. [redacted] patients received treatment beyond 3 years.

Using the IA2 completion rates from question B8, until data cut-off there were [redacted] doses given beyond 3 years, which equates to an average of [redacted] doses per patient.

A17. For the IA2 data cut how many patients with PD received dostarlimab during PD? What was their mean duration of treatment during PD, their mean number of 500mg Q3W administrations during PD and their mean number of 1000mg Q6W administrations during PD? If this is not available for the IA2 data cut please provide it for the IA1 data cut. How were these patients treated in construction of the dostarlimab TTD KM curve? How were these patients treated in the Data Store D56:D61 patient numbers?

KM curves for TTD and PFS for the dostarlimab arm show that the proportion of patients remaining on active therapy never exceed the proportion who are PF (Figure 19). This indicates good adherence to discontinuation upon progression per the trial protocol. This is also consistent with expected clinical practice. It is not

expected that that clinicians would continue to expose a patient to treatment which is failing to suppress tumour growth.

Figure 19: KM analysis of TTD and PFS in the dostarlimab arm (dMMR/MSI-H population)

Data cutoff: 22 September 2023
Abbreviations: CP, carboplatin plus paclitaxel; dMMR, DNA mismatch repair deficient; KM, Kaplan-Meier; MSI-H, microsatellite instability-high; PFS, progression-free survival; TTD, time-to-treatment discontinuation.

A18. Please augment Table 15 of Document B of TA963 with the following duration of response data separately by arm and by best response CR and best response PR (4 tables). If the SAP specifies a window of assessment around the 6 month timepoints, e.g. ±2 weeks, please state what this is. Similarly, please specify any window that has been applied in the response. Again, it would be appreciated if this could be supplied for the IA2 data cut but if this is not possible please supply it for the IA1 data cut.

As outlined in question A10, DOR was not reanalysed as part of IA2, and therefore, no updated data on DOR is available to augment the referred table. The company have provided a detailed analysis of DOR for IA1 separately by complete responders and partial responders as part of question A10 and believe that this is comprehensive assessment of the response rates seen in RUBY-1.

Time to loss of response for CR and loss of response for PR are implicitly captured within the duration of response (DOR) time-to-event outcomes. This is because once a patient loses a complete response they are no longer considered a responder and therefore are considered to have disease progression. This is similarly the case for

patients with a best response of PR. It is therefore not possible to complete the table as requested by the EAG as this classification system is not consistent with how response is considered in practice nor in the RUBY trial: Complete responders do not become recategorized as partial responder upon disease progression, instead this is recorded as a PFS event which is analogous to loss-of-response in the Duration of Response analysis.

The SAP does not specify a window of assessment around the 6-month timepoint.

The definition of best overall response (BOR) used to derive the response end points is included within the sap as follows:

The BOR according to RECIST v1.1 will be assessed based on overall timepoint responses at different evaluation points from the randomization date until documented disease progression, following the rules outlined below:

- CR = at least one determination of CR ≥ 35 days from randomization and before progression
- PR = at least one determination of PR ≥35 days from randomization and before progression (and not qualifying for a CR)
- Stable disease (SD) = at least one SD assessment ≥ 35 days from randomization and before progression • non-CR/non-PD = at least one non-CR/non-PD assessment ≥ 35 days from randomization and before progression
- No disease = at least one determination of No disease ≥ 35 days from randomization and before progression
- Progressed disease (PD) = progression after randomization
- Not evaluable (NE) = all other cases. The 35-day window includes the randomization date.

The hierarchical order to determine the BOR for a patient is: CR>PR>SD> non-CR/non-PD>No disease>PD>Not Evaluable

Only tumour assessments performed before the start of any further anti-cancer treatment and up to the first documented PD will be considered in the assessment of BOR.

A19. Please estimate hazard ratios for OS and PFS for the impact of ECOG 1 vs 0 within RUBY-1, and also estimate the OS hazard ratio of treatment effect by ECOG subgroup (e.g. Figure 8), reporting number of people and events, plus proportions with best response of PR and proportion with best response CR.

The proportion of patients with best response of PR and CR by ECOG status is outlined in Table 23. Notably the ORR as well as the proportion of PR and CR responders is [redacted] in the dostarlimab arm compared with the placebo arm in both the ECOG 0 and ECOG 1 subgroups. This trend in dostarlimab benefits across ECOG subgroups is similarly observed in PFS and OS outcomes as illustrated in Figure 20 and Figure 21, respectively.

Table 10: Proportion of patients with best response CR and PR by ECOG status, IA2 (dMMR/MSI-H population)

Best Overall Response by RECIST v1.1	ECOG Status: 0 (N=67)		ECOG Status: 1 (N=50)	
	Dostarlimab arm (n=28)	Placebo arm (n=39)	Dostarlimab arm (n=24)	Placebo arm (n=26)
CR	[redacted]	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]	[redacted]
ORR n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 20: Forest plot of PFS and 95% CIs by subgroup, IA1 (dMMR-MSI-H population)

Source: REQ0381_F_07_01_PFS_FOREST.rtf.
Data cut-off: 28 September 2022.
Note: HRs presented are from unstratified Cox regression model. HR estimation with 95% CI is displayed as 'Not Applicable' for the subgroup where there are less than five events in a subgroup or there is no event in one treatment arm.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; dMMR, DNA mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression free survival.

Figure 21: Forest plot of OS and 95% CIs by subgroup, IA1 (dMMR-MSI-H population)

REQ0381_F_07_01_OS_FOREST.rtf.
Data cut-off: 22 September 2023.
Note: HRs presented are from unstratified Cox regression model. HR estimation with 95% CI is displayed as 'Not Applicable' for the subgroup where there are less than five events in a subgroup or there is no event in one treatment arm.
*At baseline, as per the electronic case report form.
Abbreviations: CI, confidence interval; dMMR, DNA mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

Section B: Clarification on cost-effectiveness data

B1. Please provide detail on how the mean age from the NCRAS data reported in section B.3.3.1 was calculated, enabling the EAG to reproduce the estimate. The age information available in the NCRAS report does not appear to include the ages of people with recurrent disease. Please explain why the reported mean age disagrees with the mean age reported in section B.2.2.1

In section B.2.2.1, the mean age refers to the population eligible for immune checkpoint inhibitor (ICI) treatment according to the RUBY-1 study's inclusion criteria, termed the "ICI-eligible cohort." Additionally, a more specific subgroup was analysed—those eligible for ICI per RUBY-1 and who received first-line chemotherapy with carboplatin and paclitaxel—referred to as the "ICI-eligible RUBY cohort." This cohort's mean age was used in the scenario analysis in section B.3.3.1. The company acknowledges the inconsistency and clarifies that the ICI-eligible cohort mean age should have been used throughout the document.

The company notes that the age difference is minor, resulting in a minimal impact on the base case ICER: an increase of £[redacted] if [redacted] is used and £[redacted] if [redacted] is used.

The accompanying data tables and figures, which contain median and mean age data by biomarker, have been uploaded to the NICE portal (as per question A5). The calculation of the mean and median age included age at advanced diagnosis or age at recurrence.

B2. Please provide information on how long infusions of dostarlimab typically take to prepare and administer? What does carboplatin and paclitaxel add to this? How does this compare with administration of only carboplatin and paclitaxel?

As per the SmPC, dostarlimab should be administered by intravenous infusion using an intravenous infusion pump over 30 minutes (4, 5).

Paclitaxel is administered by intravenous infusion over 3 hours and Carboplatin is administered by intravenous infusion over 30 minutes (5-7). In addition to the administration of the chemotherapy agents, pre-medication is also recommended 30 minutes prior to paclitaxel infusion (5).

Reconstitution may be performed within either a clinical area or an NHS pharmacy aseptic facility (8). Therefore, the preparation will not be a time-limiting factor and would likely take around 10–15 minutes.

The administration of carboplatin and paclitaxel is time consuming and often requires patients remaining in the treatment chair for many hours. When considering this, the addition of dostarlimab during the combination phase (the first six Q3W cycles) is a small addition to the existing regimen and does not pose a significant increase to the administrative burden.

B3. PRIORITY Please provide separately by arm for the IA2 data cut the number of patients receiving each 2nd line treatment and the mean and median number of treatment cycles and durations completed by the IA2 cutoff including any treatments beyond year 3. For Letrozole and Medroxyprogesterone Acetate rather than the number of treatment cycles please provide the mean duration of treatment by the IA2 cutoff including any treatments beyond year 3, or if possible the mean number of items dispensed. Please provide this separately for those discontinuing from 1st line (2 Tables) and for those progressing (2 Tables). Given the model inputs in Data Store O456:Y457, If possible it would also be appreciated if this could be supplied for the IA1 data cut (2+2 Tables) but this is not necessary unless the data for the IA2 data cut cannot be provided.

The first follow-up anticancer treatment, i.e. second line treatment, received in each arm of the RUBY trial following discontinuation of either dostarlimab or placebo for any reason are presented in Table 24 below. A comparable analysis is presented in Table 25, in respect of patients who discontinued study drug specifically due to disease progression. Both of these analyses are based on the most mature IA2 data cut. Notably, [redacted] and [redacted] of patients who discontinued study drug specifically due to disease progression in the dostarlimab and placebo arms, respectively, went on to receive a second line treatment.

Whilst the initiation of second line treatments was recorded as part of the RUBY trial, the time and reason for discontinuation of these therapies have not been reported. As such it has not been possible to derive mean or median duration-of-treatment, nor number of cycles received. In any case, given the immaturity of PFS2 data (43.2%

maturity) the reporting of average duration of treatments would be skewed towards those discontinuing early and significantly underestimate the true treatment durations at second line.

The method for estimating subsequent treatment cost used in the base-case analysis for this submission however used UK clinical opinion rather than the data from the RUBY-1 trial and is a conservative estimate which underestimates the true cost of subsequent treatment in the comparator arm. Notably, only one subsequent line of therapy is costed within the model as well as an assumption that a proportion of patients do not receive any subsequent therapy. In the trial, as is the case in practice, patients can require third and later lines of therapy. Given the strong PFS2 data indicating higher rates of second progression events in the comparator arm, treatment with CP alone is expected to require more lines of therapy which has not been accounted for in our modelling.

Table 11: Patients discontinuing study drug for any reason and follow-up anti-cancer therapy received, IA2 (dMMR/MSI-H population)

First follow-up anti-cancer treatment received	Patients discontinuing drug	
	Dostarlimab discontinued (n=40)	Placebo discontinued (n=60)
Any follow-up anti-cancer therapy	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Pembrolizumab/Lenvatinib	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]
Retifanlimab/Epacadostat	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
Paclitaxel/Carboplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin	[redacted]	[redacted]
Carboplatin/Vinorelbine	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Epirubicin	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]
Radiation Therapy	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Hormonal Therapy	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Megestrol Acetate	[redacted]	[redacted]
Other	[redacted]	[redacted]
Pemigatinib	[redacted]	[redacted]

Source: Subsequent treatment derivations, REQ0381_T1_02_02_FUACT.rtf

Abbreviations: CP, carboplatin plus paclitaxel; IA2, second interim analysis.

Table 12: Number of patients from IA2 receiving subsequent therapy regimens (discontinuation due to progression)

Subsequent treatment regimen	No. of patients receiving subsequent treatment, N (%)	
	Dostarlimab discontinued (n=15)	Placebo discontinued (n=40)
First follow-up anti-cancer therapy	[redacted]	[redacted]
Immunotherapy		
Pembrolizumab	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]
Retifanlimab + epacadostat	[redacted]	[redacted]
Chemotherapy		
Paclitaxel + carboplatin	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Pegylated liposomal doxorubicin	[redacted]	[redacted]
Carboplatin + vinorelbine	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Eprirubicin	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]
Radiation Therapy		
Radiotherapy	[redacted]	[redacted]
Hormonal Therapy		
Letrozole	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Megestrol acetate	[redacted]	[redacted]
Megestrol acetate + tamoxifen	[redacted]	[redacted]
Other		
Pemigatinib	[redacted]	[redacted]

Source: Subsequent treatment derivations
Data cutoff: 22 September 2023
Abbreviations: CP, carboplatin plus paclitaxel ; IA2, second interim analysis.

B.4 Please provide the following RUBY EQ-5D tariff score data based upon the UK tariff separately by each EQ-5D collection point (CP) and for EoT, separately by arm and by ITT and dMMR/MSI-H (4 tables) for the IA1 data cut or the IA2 data cut if available, specifying which data cut is provided

EQ-5D was not collected and analysed as part of IA2, as such the requested data has been provided for the IA1 data cut.

Table 13: Summary Statistics of EQ-5D Utility Scores by Visit for patients in the dostarlimab arm, IA1 (ITT Population)

	Progression free survival			Progressed		
Collection Point	n reporting	EQ-5D mean	EQ-5D standard deviation	n reporting	EQ-5D mean	EQ-5D standard deviation
Baseline	[redacted]					
Cycle 2 Day 1						
Cycle 3 Day 1						
Cycle 4 Day 1						
Cycle 5 Day 1						
Cycle 6 Day 1						
Cycle 7 Day 1						
Cycle 8 Day 1						
Cycle 9 Day 1						
Cycle 10 Day 1						
Cycle 11 Day 1						
Cycle 12 Day 1						
Cycle 13 Day 1						
Cycle 14 Day 1						
Cycle 15 Day 1						
Cycle 16 Day 1						
Cycle 17 Day 1						
Cycle 18 Day 1						
Cycle 19 Day 1						
Cycle 20 Day 1						
Cycle 21 Day 1						
Cycle 22 Day 1						
Cycle 23 Day 1						
Cycle 24 Day 1						
Cycle 25 Day 1						
Cycle 26 Day 1						
Cycle 27 Day 1						
Cycle 28 Day 1						
End of treatment						
Safety Follow-up						
Survival Follow-up Assessment 1				[redacted]		

Survival Follow-up Assessment 2	[redacted]					
Survival Follow-up Assessment 3	[redacted]					
Survival Follow-up Assessment 4	[redacted]					
Survival Follow-up Assessment 5	[redacted]					
Survival Follow-up Assessment 6	[redacted]					
Survival Follow-up Assessment 7	[redacted]					
Survival Follow-up Assessment 8	[redacted]					

Source: T10_01_ru_uk_stats, T10_02_ru_uk_stat,
Data cutoff: 28 September 2022
Abbreviations: IA1, first interim analysis; ITT, intention to treat

Table 14: Summary Statistics of EQ-5D Utility Scores by Visit for patients in the placebo arm, IA1 (ITT Population)

	Progression free survival			Progressed		
Collection Point	n reporting	EQ-5D mean	EQ-5D standard deviation	n reporting	EQ-5D mean	EQ-5D standard deviation
Baseline	[redacted]					
Cycle 2 Day 1	[redacted]					
Cycle 3 Day 1	[redacted]					
Cycle 4 Day 1	[redacted]					
Cycle 5 Day 1	[redacted]					
Cycle 6 Day 1	[redacted]					
Cycle 7 Day 1	[redacted]					
Cycle 8 Day 1	[redacted]					
Cycle 9 Day 1	[redacted]					
Cycle 10 Day 1	[redacted]					
Cycle 11 Day 1	[redacted]					
Cycle 12 Day 1	[redacted]					
Cycle 13 Day 1	[redacted]					
Cycle 14 Day 1	[redacted]					
Cycle 15 Day 1	[redacted]					
Cycle 16 Day 1	[redacted]					
Cycle 17 Day 1	[redacted]					
Cycle 18 Day 1	[redacted]					
Cycle 19 Day 1	[redacted]					
Cycle 20 Day 1	[redacted]					
Cycle 21 Day 1	[redacted]					
Cycle 22 Day 1	[redacted]					
Cycle 23 Day 1	[redacted]					
Cycle 24 Day 1	[redacted]					
Cycle 25 Day 1	[redacted]					
Cycle 26 Day 1	[redacted]					
Cycle 27 Day 1	[redacted]					
Cycle 28 Day 1	[redacted]					
End of treatment	[redacted]					

Safety Follow-up	[redacted]					
Survival Follow-up Assessment 1	[redacted]					
Survival Follow-up Assessment 2	[redacted]					
Survival Follow-up Assessment 3	[redacted]					
Survival Follow-up Assessment 4	[redacted]					
Survival Follow-up Assessment 5	[redacted]					
Survival Follow-up Assessment 6	[redacted]					
Survival Follow-up Assessment 7	[redacted]					
Survival Follow-up Assessment 8	[redacted]					

Source: T10_01_ru_uk_stats, T10_02_ru_uk_stat,
Data cutoff: 28 September 2022
Abbreviations: IA1, first interim analysis; ITT, intention to treat

Table 15: Summary Statistics of EQ-5D Utility Scores by Visit for patients in the dostarlimab arm, IA1 (dMMR/MSI-H Population)

	Progression free survival			Progressed		
Collection Point	n reporting	EQ-5D mean	EQ-5D standard deviation	n reporting	EQ-5D mean	EQ-5D standard deviation
Baseline	[redacted]					
Cycle 2 Day 1	[redacted]					
Cycle 3 Day 1	[redacted]					
Cycle 4 Day 1	[redacted]					
Cycle 5 Day 1	[redacted]					
Cycle 6 Day 1	[redacted]					
Cycle 7 Day 1	[redacted]					
Cycle 8 Day 1	[redacted]					
Cycle 9 Day 1	[redacted]					
Cycle 10 Day 1	[redacted]					
Cycle 11 Day 1	[redacted]					
Cycle 12 Day 1	[redacted]					
Cycle 13 Day 1	[redacted]					
Cycle 14 Day 1	[redacted]					
Cycle 15 Day 1	[redacted]					
Cycle 16 Day 1	[redacted]					
Cycle 17 Day 1	[redacted]					
Cycle 18 Day 1	[redacted]					
Cycle 19 Day 1	[redacted]					
Cycle 20 Day 1	[redacted]					
Cycle 21 Day 1	[redacted]					
Cycle 22 Day 1	[redacted]					
Cycle 23 Day 1	[redacted]					
Cycle 24 Day 1	[redacted]					
Cycle 25 Day 1	[redacted]					
Cycle 26 Day 1	[redacted]					

Cycle 27 Day 1						
Cycle 28 Day 1						
End of treatment						
Safety Follow-up						
Survival Follow-up Assessment 1						
Survival Follow-up Assessment 2						
Survival Follow-up Assessment 3						
Survival Follow-up Assessment 4						
Survival Follow-up Assessment 5						
Survival Follow-up Assessment 6						
Survival Follow-up Assessment 7						

Source: T10_03_ru_uk_stats, T10_04_ru_uk_stat,
Data cutoff: 28 September 2022
Abbreviations: dMMR, DNA mismatch repair deficient; IA1, first interim analysis; MSI-H, microsatellite instability high.

Table 16: Summary Statistics of EQ-5D Utility Scores by Visit for patients in the placebo arm, IA1 (dMMR/MSI-H Population)

	Progression free survival			Progressed		
Collection Point	**n reporting**	**EQ-5D mean**	**EQ-5D standard deviation**	**n reporting**	**EQ-5D mean**	**EQ-5D standard deviation**
Baseline						
Cycle 2 Day 1						
Cycle 3 Day 1						
Cycle 4 Day 1						
Cycle 5 Day 1						
Cycle 6 Day 1						
Cycle 7 Day 1						
Cycle 8 Day 1						
Cycle 9 Day 1						
Cycle 10 Day 1						
Cycle 11 Day 1						
Cycle 12 Day 1						
Cycle 13 Day 1						
Cycle 14 Day 1						
Cycle 15 Day 1						
Cycle 16 Day 1						
Cycle 17 Day 1						
Cycle 18 Day 1						
Cycle 19 Day 1						
Cycle 20 Day 1						
Cycle 21 Day 1						
Cycle 22 Day 1						
Cycle 23 Day 1						
Cycle 24 Day 1						
Cycle 25 Day 1						

Cycle 26 Day 1						
Cycle 27 Day 1						
Cycle 28 Day 1						
End of treatment						
Safety Follow-up						
Survival Follow-up Assessment 1						
Survival Follow-up Assessment 2						
Survival Follow-up Assessment 3						
Survival Follow-up Assessment 4						
Survival Follow-up Assessment 5						
Survival Follow-up Assessment 6						
Survival Follow-up Assessment 7						

B5. It appears that the SAE quality of life effects for both 1st line and 2nd line are conditioned by the cycle length. In other words, the input values are QoL detriment not QALYs with the implicit assumption that the duration of each SAE is of 1 week duration. Is this the intention and if so what is the justification for it? If this is an error there is no need to submit an amended model and set of results.

The approach to modelling SAE quality of life effects using an implied one-week duration in the model is intentional. Due to a low number of patients experiencing serious adverse events in the RUBY trial, and similar rates of events between the dostarlimab arm and the CP arm, a one-week duration was implied as a simplifying assumption. SAE disutilities were not identified as a key model driver in the one-way sensitivity analysis conducted by the Company, suggesting that it is unlikely to have a significant impact on cost-effectiveness, and hence modelling longer durations would add unnecessary complexity to the model.

B6. Please provide the patient numbers that underlie Data Store O456:Y457 and AK456:AU457. Please also provide the corresponding numbers for those who progress. While the patient numbers will in some instances be small please also provide for the UK subset of patients. The EAG assumes that this data is specific to dMMR/MSI-H patients, but if it is not please provide this.

The RUBY-1 trial contained 4 patients from the UK within the dMMR subgroup, none of whom had gone on to receive a subsequent anticancer therapy as of the most recent IA2 data cut.

In the RUBY IA1 data cut, 15 (28.3%) patients in the dostarlimab arm and 38 (58.5%) patients in the placebo arm received subsequent therapy For the IA2 data cut, 15 (28.3%) patients in the dostarlimab arm and 39 (60.0%) in the placebo arm received subsequent therapy (10). Notably, no new patients in the dostarlimab arm received subsequent therapy between IA1 and IA2, while one additional patient in the placebo arm went on to receive a subsequent therapy (9, 10).

Data Store O456:Y457 in the CEM reflects the proportion of patients who received commonly used anticancer therapies in the RUBY trial, as captured in the IA1 data cut. (9). For the purposes of modelling the IA1 subsequent treatments, the number of

patients who received a subsequent therapy following progression was used to inform the CEM. As reported in Table 24, [redacted] in the dostarlimab arm and [redacted] patients in the placebo arm started subsequent anticancer therapy following a confirmed progression event. To derive subsequent treatments for modelling purposes, only the most frequently used treatments in each drug class available in the NHS were selected. The model inputs along with the corresponding sample sizes are reported in Table 24.

A similar approach was used to inform the cells AK456:AU457 in the CEM. However, as data relating to progression events was not available as part of the IA2 data cut, the sample size in this instance was based on all patients receiving subsequent therapy, not just those after progression. As reported in Table 30, [redacted] patients in the dostarlimab arm and [redacted] patients in placebo arm received any subsequent anticancer therapy regardless of progression. The same methodology was applied, with only the most frequently used treatments in each drug class available in the NHS included for modelling. A full list of therapies received as part of second-line treatments are reported in Table 22 above.

Table 17: Number of patients receiving each subsequent therapy regimen

Subsequent treatment regimen	Proportion of patients receiving subsequent therapy regimen following progression- RUBY IA1, % (N)		Proportion of patients receiving subsequent therapy regimen regardless of progression - RUBY IA2, % (N)	
	Dostarlimab arm ([redacted])	CP arm [redacted]	Dostarlimab arm [redacted]	CP arm [redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Medroxyprogesterone acetate	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Source: Subsequent treatment derivations
Abbreviations: CP, carboplatin plus paclitaxel.

B7. It appears that inputs to Data Store R68:R73, R80:R85, Y68:Y73 and V80:V85 are pooled across the arms. Please provide this data separately by

arm. The EAG assumes that this data is specific to dMMR/MSI-H patients, but if it is not please provide this.

The IA2 completion rates reported were for dMMR/MSI-H patients. Table 31 reports the IA2 completion rates per cycle for carboplatin and paclitaxel, by treatment arm, collected in dMMR/MSI-H patients.

Table 18: IA2 chemotherapy completion rates per cycle

Model cycle	Patients receiving dose of carboplatin n (%)		Patients receiving dose of paclitaxel n (%)	
	Dostarlimab arm (n=53)	CP arm (n=65)	Dostarlimab arm (n=53)	CP arm (n=65)
1	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]

Source : ssdr103971_t2_comp_rate.rtf
Data cutoff : 22 September 2023
Abbreviations: CP, carboplatin plus paclitaxel.

B8. Please provide the equivalent of Data Store M56:M61 for each 1000mg Q6W administration including any that occurred beyond year 3. The EAG assumes that this data is specific to dMMR/MSI-H patients, but if it is not please provide this.

Table 32 reports the IA2 completion rates per cycle for dostarlimab, for each 1000mg Q6W administration, collected in dMMR/MSI-H patients. The first dostarlimab 1000mg dose was given in cycle 7, and cycle 31 is the first cycle beyond the 3-year stopping rule.

Table 19: IA2 completion rates – dostarlimab 1000mg dose (dMMR/MSI-H population)

Cycle	Patients receiving dose of dostarlimab (n)	Patients receiving dose of dostarlimab (%)
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]

Cycle	Patients receiving dose of dostarlimab (n)	Patients receiving dose of dostarlimab (%)
19	[redacted]	[redacted]
20	[redacted]	[redacted]
21	[redacted]	[redacted]
22	[redacted]	[redacted]
23	[redacted]	[redacted]
24	[redacted]	[redacted]
25	[redacted]	[redacted]
26	[redacted]	[redacted]
27	[redacted]	[redacted]
28	[redacted]	[redacted]
29	[redacted]	[redacted]
30	[redacted]	[redacted]
31	[redacted]	[redacted]
32	[redacted]	[redacted]
33	[redacted]	[redacted]
34	[redacted]	[redacted]
35	[redacted]	[redacted]

Abbreviations: IA2, second interim analysis.

B9. Please provide an account of the calculation of the RDI for dostarlimab for weeks 19+, outlining what weeks' data has been used and how this has been pooled. Please also supply the data inputs, preferably for each Q6W week, and each Q3W week should this be within the calculations, prior to any pooling of data.

The value of 97.61% RDI was calculated as per the SAP and is outlined in Table 33. The RDI calculation is based on the number of patients receiving a dose by cycle, by population. It has been sourced from RUBY at Q3W and Q6W intervals and has been calculated using the completion rates This utilised the completion rates that are presented as part of Question B7 and B8.

Table 20: 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)
	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 SAP

Abbreviations: RDI, relative dose intensity; ADI, actual dose intensity.

B10. Please supply the total administered product (in mg) of carboplatin and of paclitaxel separately by arm for the IA2 data cut if possible but for the IA1 data cut if not, specifying which.

The total cumulative dose for carboplatin and paclitaxel was not available as administered product in mg. The CSR contains data on mean cumulative dosing which has been highlighted in Table 34.

Table 21: Mean cumulative dose for carboplatin and paclitaxel, IA2 (dMMR/MSI-H Population)

	Dostarlimab arm (N=52)	CP arm (N=65)
Carboplatin	24.8692 AUC	23.9033 AUC
Paclitaxel	916.5066 mg/m2	919.9113 mg/m2

Source: CSR Table 14.1.1.28 and 14.1.1.30
Abbreviations: AUC, area under the curve; CP, carboplatin plus paclitaxel.

B11. Please confirm that the data of table 13 is specific to dMMR/MSI-H patients, but if it is not please provide this. The EAG considers the BSA as quite high, would value confirmation that it is correct.

The body surface area (BSA) data provided in Table 13 of Document B is specific to dMMR/MSI-H patients and is correctly aligned with the RUBY-1 trial data. The Company consider the BSA value to be suitably reflective of the high rates of obesity in endometrial cancer. Within the UK, 34% of uterine cases are linked to obesity, with several literature reviews highlighting the increased risk associated between obesity and endometrial cancer (11-14).

An alternative method for calculating body surface area (BSA) is the Mosteller method (15), which uses the formula:

$$BSA = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$

Applying this method with the mean height and weight of dMMR/MSI-H patients pooled across arms from the RUBY trial (mean weight of [redacted]kg and mean height of [redacted]m) yields a BSA of [redacted]m^2. This value is higher than the BSA reported using the RUBY trial data directly.

The Mosteller method was also employed in a scenario analysis by the ERG in TA904 (pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer), where a mean weight of 85 kg was used, resulting in a BSA of 1.96 m^2, closely matching the value used in this submission (16). Additionally, mean weight/BSA was not identified as a key model driver in the one-way sensitivity analysis conducted by the Company, suggesting that it is unlikely to have a significant impact on cost-effectiveness.

Section C: Textual clarification and additional points

C1. In Appendix D.1.3.1.2-5, the text repeatedly refers to "unique ITCs". Please confirm whether this should read "unique RCTs", as in D.1.3.1.1.

Apologies, this is a typo. As per D.1.3.1.1, it should read 'unique RCTs'.

C2. There appears to be a small discrepancy between the OS HR of TA963 Document B Table 13 and that of the model for IA1. Please provide an account of this.

The Company acknowledges that in TA963, the OS HR used in the model for IA1 differs from that reported in the clinical section of Document B (Table 13). As discussed in Section B.3.3.4.2 of TA963, the unstratified HR for dostarlimab in combination with CP compared with CP was used in the model ([redacted]; redacted in table 24), as a more conservative approach to modelling the OS of dostarlimab using a HR approach, rather than the stratified OS HR reported in Table 13 (0.30).

C3. The quality of life values of Document B Table 20 differ from those presented in the 14 April 2023 advisory board. Please provide an account of this.

The values presented in both the model and the dossier are accurate and reflect those included in the CSR. However, the values shown at the advisory board for dMMR patients were incorrect, though they are not used in the model. For the all-comers group, the values for PFS presented at the advisory board are correct, but the values for PD contain an error. Specifically, a value of [redacted] was shown for PD, whereas it should have been [redacted]. If [redacted] were applied in the model, the QALYs would increase slightly from [redacted] to [redacted], and the ICER would rise from £[redacted] to

£[redacted]—a minor difference of £[redacted]. Therefore, this discrepancy does not affect the model's assumptions or outcomes.

C4. Please provide a copy of the original model, Document B and its appendices and the responses to the EAG clarification questions from TA963, marked up for confidentiality but not redacted, together with the reference pack (in particular references 3, 4, 5, 102 and 150).

Both references 102 and 150 were submitted as part of ID6426. The Original CEM, Document B and appendices, reference pack and responses to EAG clarification questions from TA963 have been provided alongside this response document. Notable changes to the model base case from the original model have been highlighted in Table 35.

Table 22: Notable Base case settings updated since original model

Data		Original model	Updated model	Reason for change
Clinical data	OS curves – data source	RUBY OS from IA1 data used.	RUBY OS from IA2 data used.	Updated data available from the RUBY trial, to mitigate uncertainty in estimates raised by the committee in TA963.
	OS curves - approach	• Piecewise approach assumed for CP, utilising the KM followed by a log-logistic extrapolation. • KM followed by HR vs CP assumed for dostarlimab	• Log-logistic distribution assumed for both dostarlimab, and CP • Landmark estimates of OS validated by clinicians at a July 2024 advisory board	Full parametric extrapolation of OS curves used, in line with EAG preferred approach in TA963
	AE incidence	Grade 3+ TEAEs in >5% patients in either arm modelled (IA1)	Grade 3+ TEAEs in >2% patients and occurring more frequently in dostarlimab arm modelled (IA2)	In line with EAG preferred approach in TA963, and using updated data from the RUBY trial
	Subsequent treatment duration	Pembrolizumab and lenvatinib duration of treatment: 10.7 months	Pembrolizumab and lenvatinib duration of treatment: 6.6 months	The median PFS of 10.7 months for dMMR/MSI-H patients in TA904 was used in the original model. This was updated to 6.6 months (the MMRp/MSS equivalent value) to provide a conservative proxy estimate and reflect the possibility of median treatment duration for this combination being lower than median PFS (given that median TTD is not reported in TA904). This value increases the incremental costs associated with dostarlimab compared to the 10.7 months value.
	Subsequent treatment proportions	UK expert opinion	HCP feedback with CDF therapies excluded and proportions reweighted	In line with clinical opinion to the company. Since TA963, Pembrolizumab

			RUBY IA2 data included as option	monotherapy has become available, this has been accounted for in updated estimates.
Utility data	AE disutility	-	Disutility values added for additional AEs	
Cost data	Administration costs, Resource use costs, AE costs	Sourced from NHS reference costs 2020/21	Sourced from NHS reference costs 2021/22	More recently available NHS cost data
	RDI	100% compliance assumed	97.6% RDI from trial	RDI was not calculated in the IA1 CSR and so an assumption of 100% compliance was made. RDI was calculated in the IA2 CSR as highlighted in Question B9.
	Acquisition costs (Primary and subsequent therapy)	Cost of treatments sourced from BNF 2023	Cost of treatments sourced from BNF 2024	More recently available cost data

Abbreviations: AE, adverse event; BNF, British National Formulary; CDF, Cancer Drugs Fund; CP, carboplatin plus paclitaxel; CSR, clinical study report; dMMR, DNA mismatch repair deficient; EAG, external assessment group; HCP, Health Care Professional; HR, hazard ratio; IA1, first interim analysis; IA2, second interim analysis; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; TEAE, treatment-emergent adverse events; TTD, time-to-treatment discontinuation; UK, United Kingdom.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Endometrial cancer with high microsatellite instability or mismatch repair deficiency (MA review of TA963) [ID6426]

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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].

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Peaches Womb Cancer Trust
3. Job title or position	Policy and advocacy lead (voluntary)
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 manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	None

If so, please state the name of manufacturer, amount, and purpose of funding.	
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 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 with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) or unspecified molecular subtype. • 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 of a patient expert (Hannah) who has lived experience of MSI-H/dMMR endometrial cancer, which was treated with a PD-1 inhibitor immunotherapy – along with updated statement to reflect her experiences after completing 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 in the technology under appraisal here. 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 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 one's 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 crying 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 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 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, change in bladder and bowel habit 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."* **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/ gatherings due to tiredness, access to the toilet 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 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 your loved one and less time for yourself, and physically due to the additional activities on top of your 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.

> *"It 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 an unmet need for patients with this condition:** **Unmet need for equal access to effective treatments for women with advanced or recurrent endometrial cancer** Many 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 had 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 these patients, with the standard of care being "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 endometrial cancer hope for living with no, or well-managed disease, for longer. **Lack of effective first-line treatments through the NHS routes causes uncertainty and inequity in access.** Access to the technology for patients with MSI-H/dMMR endometrial cancer through the Cancer Drugs Fund is not a long-term solution and creates uncertainty about treatment withdrawal. Additionally, access is limited to specific individuals, which excludes some patients. Accessing treatment this way, or through special license, can lead to delays in obtaining necessary care. One patient, speaking about her deceased mother, said: *"[My mother's] cancer was aggressive and oestrogen sensitive. There is a lot of paperwork and red tape to get funding; patients and their families don't have time to wait for approvals. It needs to be available and ready."* **Limited access to immunotherapy on the NHS.** Current access to immunotherapy for patients with dMMR endometrial cancer, such as pembrolizumab combined with lenvatinib or pembrolizumab as a monotherapy, is only available as a second-line treatment. Patients have clearly articulated the need for earlier access to these innovative and effective treatment options. 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 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, 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 primary 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.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Potential role of new treatment:** **1. Earlier access to more effective treatments for patients with MSI-H/dMMR endometrial cancer:** Patients with MSI-H/dMMR disease would benefit from receiving effective treatments earlier in their treatment pathway. Patients with stage 3 MSI-H/dMMR endometrial cancer would benefit from a first-line treatment that may reduce the risk of recurrence. *"[I want] the cancer to be gone and the risk of recurrence to be hugely, (ideally completely), eliminated."* This offers longer overall survival, and the potential for access to a curative treatment that prevents recurrence or progression. For patients with MSI-H/dMMR stage 4 or recurrent disease, access to the technology on the NHS would mean:

- **Extended progression-free survival:** Offers hope for achieving 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.

2. **Impact on treatment pathway and independence**
   Gaining access to more effective treatments earlier in the treatment pathway could lead to:
   a. **Better symptom control:** Fewer debilitating symptoms in the long term.
   b. **Longer remission or stable disease:** Patients desire treatments that keep them in remission or maintain stable disease for extended periods, which allows them to retain independence longer and live life as fully as possible.

3. **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.

4. **Hope through immunotherapy**
   Access to immunotherapies offers hope for patients facing an advanced 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:

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 MSI-H/dMMR subtype, having being 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 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 in the first-line setting, 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 how she has experienced worse fatigue than when her primary tumour was treated *"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 life 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 an immunotherapy 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.	While the technology is expected to benefit individuals with primary advanced or recurrent MSI-H/dMMR endometrial cancer, the relatively larger group of patients with MSS/pMMR endometrial cancer would not benefit if the technology were recommended for use by the NHS as a result of this appraisal.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None identified

Other issues	
13. Are there any other issues that you would like the committee to consider?	None identified

Key messages

15. 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 primary advanced or recurrent endometrial cancer.

2. There is a need for permanent and wider access to dostarlimab through the NHS which would provide assurance of ongoing, reliable and equitable access to treatment

3. People 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.

4. People 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 endometrial cancer feel frustrated and abandoned due to the lack of effective first-line treatments, especially when compared to other cancers with multiple available lines of treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

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 **Tuesday 11 February 2025.** 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 primary advanced or recurrent endometrial cancer with MSI-H or dMMR 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,UK
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 primary advanced or recurrent endometrial cancer with MSI-H or dMMR? ☒ A specialist in the clinical evidence base for primary advanced or recurrent endometrial cancer with MSI-H or dMMR 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 primary advanced or recurrent endometrial cancer with MSI-H or dMMR? (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 however.
10. In your view, is there an unmet need for patients and healthcare professionals in primary advanced or recurrent endometrial cancer with MSI-H or dMMR?	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).
11. How is primary advanced or recurrent endometrial cancer with MSI-H or dMMR 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	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 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,

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	generally with a progestagen can be effective alternative treatment approach to chemotherapy. The treatment pathway is well-defined and the guidelines referred to above would be followed in all centres treating endometrial cancer. 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-deficient disease, this would most likely be single agent dostarlimab or pembrolizumab. 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 recommend the use of immune checkpoint inhibitors with carboplatin-paclitaxel in the first-line setting for the patient group included in this TA. This TA would allow dostarlimab to continue to be given as part of first-line treatment with chemotherapy as recommended in TA 963.
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 where the initial efficacy evaluation for PFS was planned to occur in the MMR-deficient subgroup. 24% of trial participants had MMR-deficient disease. In this 118 patient subgroup, after a median follow-up of 24.8 months, the rate of 24 month PFS was 61.4% in the dostarlimab-containing arm compared to 15.7% in the placebo arm (HR 0.28 if favour of dostarlimab p<0.001). Overall survival (OS) at 24 months was also significantly higher in the dostarlimab arm (83% vs 59%; HR 0.30 in favour of dostarlimab) at simultaneous interim analysis with 26% data maturity. 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. OS in the MMR-deficient subgroup was a prespecified exploratory analysis. Data maturity for this analysis had increased to 40%. 54% on patients who received placebo has died compared to 23% of those who received dostarlimab. Median OS was 31.4 months in the placebo group and had not been reached in those receiving dostarlimab and their risk of death was significantly lower (HR 0.32 95% CIs 0.17-0.63 p=0.0002). 3 year OS was 78% (dostarlimab) vs 46% (placebo).

	This improvement was seen despite 42% of participants in the placebo arm receiving immunotherapy after disease progression (compared to 15% receiving dostarlimab) indicating the importance of using immunotherapy in the first-line setting. The flat tails of the Kaplan-Meier PFS and OS curves in the dostarlimab arms and duration of response data for dostarlimab should be noted indicating the durable benefit from immunotherapy treatment in this patient group when compared to chemotherapy alone. Patient-reported outcomes in the MMRd subgroup have recently been published (Valabrega et al Int J Gynecol Cancer 2025). These were assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Endometrial Cancer Module and were prespecified secondary endpoints. Meaningful differences (least-squares mean [standard error]) favoring the dostarlimab arm compared to placebo were reported for change from baseline to end of treatment for QoL (14.7 [5.45]; p=0.01), role function (12.7 [5.92]); p=0.03), emotional function (14.3 [4.92]; p<0.01), social function (13.5 [5.43]; p=0.01), and fatigue (-13.3 [5.84]; p=0.03). A further exploratory analysis presented at the European Society of Gynaecological Oncology Congress last year (Boere et al 2024) showed that in this MMRd subgroup, patients receiving dostarlimab maintained their quality of life for longer than those receiving placebo (HR 0.27 favouring dostarlimab for time to first permanent deterioration on global QoL). These analyses demonstrate that patients with advanced/recurrent MMRd endometrial cancer who receive dostarlimab compared to placebo, in additional to substantially longer OS, experience a better health-related quality of life and maintain this for longer.

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-deficient advanced/recurrent endometrial cancer. This is the molecularly-defined subgroup that is most likely to benefit from immune checkpoint inhibitors.
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 to select patients eligible for dostarlimab 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	Yes. This is the first novel biomarker-directed therapy to be licensed as part of the first-line treatment of advanced/recurrent endometrial cancer.

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 substantial improvements in both PFS and OS seen in the RUBY trial and the durable responses seen with first line dostarlimab are a step-change in the treatment of MMR-deficient advanced/recurrent endometrial cancer and offer women with this condition the potential for long-lasting control of their disease, better QoL and extended survival which is not achievable with current treatment options. The movement of immunotherapy into the first-line setting will open this treatment option up to larger numbers of potentially eligible patients who may not be fit enough to receive subsequent second-line therapy.
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 incidence of ≥G3 adverse events considered related to dostarlimab/placebo was higher in the dostarlimab arm (33.2% vs 19.5% with placebo). However treatment discontinuation due to a presumed immune-related event was low in both arms(7.9% dostarlimab vs 3.7% 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. Importantly the patient-related outcome data for the RUBY trial reported to date shows no negative impact of dostarlimab on HRQoL during the chemotherapy phase (Fig S6 Mirza et al 2023) and subsequent improved HRQoL in those patient receiving dostarlimab (Valerenga et al Int J Gynecol Cancer 2025; Boere et al ESGO 2024).
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?	Yes

• 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?	
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. All have shown large clinically significant improvements in PFS associated with immunotherapy in the subgroup of patients with MMR-deficient disease; Pembrolizumab- NRG GY018 trial (Eskander et al NEJM 2023)- 225 MMRd cases. HR 0.30 12month PFS Pembro 74%, placebo 38%. Atezolizumab-AtTEnd trial (Colombo et al Lancet Oncol 2024). 125 MMRd cases. HR 0.36 median PFS; Atezo- not reached Placebo 6.9months Durvalumab- DUO-E (Westin et al J Clin Oncol 2024). MMRd- HR 0.42 median PFS durvalumab-not reached placebo 7.0months. 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. The primary efficacy results from the KEYNOTE B21 trial evaluating the addition of pembrolizumab vs placebo to adjuvant carboplatin-paclitaxel +/- radiotherapy in newly diagnosed high-risk endometrial cancer (defined as Stage I/II non-endometrioid histology or endometrioid with TP53 abnormality; Stage III or I Stage I/II non-endometrioid histology or endometrioid with TP53 abnormality; Stage III or IVa) with no residual disease after curative intent surgery have also been published recently (Van Gorp et al Ann Oncol 2024; Slomovitz et al J Clin Oncol 2025). 26% of the 1095 participants had MMRd endometrial cancer. In

	this subgroup a clinically significant 12% improvement in 2-year Disease-Free Survival was reported with the addition of pembrolizumab (92% vs 80%; HR 0.31 95% CIs 0.14-0.69). This demonstrates that the addition of immunotherapy to platinum-based chemotherapy is effective in stage III disease (and earlier stages).
22. How do data on real-world experience compare with the trial data?	I am not aware of any published real-world experience of first-line use of immune checkpoint inhibitors in advanced/ recurrent endometrial cancer.
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	Nil specific.

• 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.	

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.
Mismatch-repair deficiency defines an important biological subgroup that makes up 20-25% of endometrial cancer and is associated with distinct clinical behaviour. These tumours can be identified using a routine immunohistochemistry panel on diagnostic biopsy.
Mismatch-repair deficiency identifies tumours that are more likely to respond to immune checkpoint inhibitors, often with durable responses.
In the RUBY trial, the addition of dostarlimab to first-line carboplatin-paclitaxel in the treatment of mismatch-repair deficient advanced/recurrent endometrial cancer increased overall survival at 3 years by 32% compared to placebo.
Dostarlimab treatment has manageable adverse effects and was associated with improved quality-of-life compared to placebo.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

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.

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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 23 January 2025.** 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.

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Part 1: Treating primary advanced or recurrent endometrial cancer with MSI-H or dMMR and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant Clinical 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 primary advanced or recurrent endometrial cancer with MSI-H or dMMR? ☐ A specialist in the clinical evidence base for primary advanced or recurrent endometrial cancer with MSI-H or dMMR 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.	none

8. What is the main aim of treatment for primary advanced or recurrent endometrial cancer with MSI-H or dMMR? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Main aim of treatment is to improve quality of life and control disease (ie tumour shrinkage with subsequent delay in progression of disease, thereby reducing disease burden and symptoms extending survival) Historically these patients are not cured. However, with the use of targeted treatments for isolated recurrence and oligometastatic disease as well as the introduction of immunotherapy in MMR deficient (MMRd) cases there are a proportion of these patients who may be more likely to be 'cured'.
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)	Clinically meaningful improvement in quality of life ie improvement in functional status meaning patients can do what they want to do. Length of extension of survival depends upon the duration of treatment duration and toxicity burden
10. In your view, is there an unmet need for patients and healthcare professionals in primary advanced or recurrent endometrial cancer with MSI-H or dMMR?	Yes, these patients often have extensive symptoms and, depending upon their disease pattern, may be a significant burden on healthcare resources eg with bowel obstruction, fluid accumulation (pleural or ascitic).
11. How is primary advanced or recurrent endometrial cancer with MSI-H or dMMR 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?	Overall the pathway of care is well defined within my practice (which is within England) but across the country I am aware that the pathway of care is not always well defined. In general guidance such as the ESMO/ESP/ESTRO guidance are followed but these are not very specific and other guidelines such as BGCS uterine cancer guidelines have not been updated particularly recently. If patients have disease that is amenable to surgical resection without any anticipated residual they may be operated on. This, however, is not consistent practice across the country and depends upon surgical expertise and experience. This surgery would then be followed by chemotherapy and possibly radiotherapy if disease was pelvic confined and/or nodal confined. If patients have single site of disease they may undergo surgery, radiotherapy or other focal therapy to try to remove or ablate the disease. The TCGA molecular classification should impact the treatment offered. However, even the testing for MMR, p53 and POLE which are all essential to be able to molecularly classify a patient is not consistently carried out across the country.

	MMRd disease is usually treated now with carboplatin paclitaxel and dostarlimab immunotherapy (aka RUBY trial- accessed via CDF) but if they are hormone positive with low grade disease and not very symptomatic, even in the MMRd patients, they may be managed with oral hormonal therapy first due to the limited toxicity this has in comparison with chemotherapy and immunotherapy. Second line therapy in MMRd patients who have not received previous immunotherapy would be single agent immunotherapy. If they have already received immunotherapy we would offer trials or weekly paclitaxel or carbo taxol again if the time interval has been long. As this treatment is already accessed via CDF its approval would not change this pathway but if it was to be not approved then that would remove it from the pathway.
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)	I see this as current standard of care as it is used via CDF funding. It is used in specialist oncology centres only and these centres should already have the necessary training/facilities/support already in place.
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?	The addition of dostarlimab to chemotherapy in this setting (as per RUBY trial) leads to a 72% reduction in risk of progression or death with a 46% increase in progression free survival at 2 years and 25% increase in overall survival. Also, when you review the progression free survival curves these are flat from 1 year onwards suggesting that there is a proportion of patients who experience very long term control with this treatment. From the data and from clinical experience

• Do you expect the technology to increase health-related quality of life more than current care?	this treatment as a single agent is very well tolerated and does not limit quality of life significantly in the majority of patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This addition of immunotherapy to chemotherapy is far more effective in the MMRd population compared to MMRp with a flat survival curve beyond 12 months and it may possibly be leading to very prolonged disease control (?cure) for 30-40% of patients. Hence this approval is being sought for MMRd patients only. We do not have any further biomarker that could predict the ~40% of patients who do exceptionally well because of immunotherapy within the MMRd population.
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)	Already implemented due to CDF funding Compared to chemotherapy alone which is the alternative standard of care it is more burdensome to add immunotherapy due to longer duration of treatment, need to monitor hormone bloods tests, need to perform imaging every 9-12 weeks and increased burden on clinic appointments as well as chemotherapy suite.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Due to the duration of treatment being 3 years patients do have imaging every 9-12 weeks which they probably would not be having otherwise but this is already happening due to access to this via CDF
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	No

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
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?	Absolutely. This treatment is a game changer for MMRd endometrial cancer and really is a step change in the treatment and potential survival in this cohort.
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?	There is a significant risk of toxicity with this treatment but it does appear to all be manageable and as centres/clinicians are becoming more confident with management of immunotherapy toxicity this is not impacting quality of life for patients detrimentally.
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 the clinical trials reflect UK practice
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?	Seems comparable

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.	No specific inequalities to consider within this.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The aim of treatment is generally to improve quality of life and survival where possible, but the introduction of immunotherapy for MMRd disease is potentially improving long term survival to the point of potential cure in a significant proportion of patients

The RUBY data shows the addition of dostarlimab to chemotherapy in this setting improves progression free and overall survival to very significant levels (72% reduction in risk of progression/death).

In general, clinicians should be now familiar and comfortable managing patients on immunotherapy and their toxicities.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.

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Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with primary advanced or recurrent endometrial cancer with MSI-H or dMMR or caring for a patient with primary advanced or recurrent endometrial cancer with MSI-H or dMMR. 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.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** 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.

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Patient expert statement

Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID6426]

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Part 1: Living with this condition or caring for a patient with primary advanced or recurrent endometrial cancer with MSI-H or dMMR

Table 1 About you, primary advanced or recurrent endometrial cancer with MSI-H or dMMR, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☒ A patient with primary advanced or recurrent endometrial cancer with MSI-H or dMMR? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with primary advanced or recurrent endometrial cancer with MSI-H or dMMR? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Peaches Womb Cancer Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with primary advanced or recurrent endometrial cancer with MSI-H or dMMR? **If you are a carer (for someone with primary advanced or recurrent endometrial cancer with MSI-H or dMMR) please share your experience of caring for them**	I was originally diagnosed with stage 1, grade 1 endometrial cancer in February 2023 during fertility (IVF) treatment. Following 5 months of conservative treatment of my cancer with a Mirena coil, I was recommended to proceed with a full hysterectomy in October 2022 following evidence of disease progression. The biopsy following surgery indicated that my cancer had progressed to stage 4 cancer – although all active cancer was removed during surgery (along with all my pelvic lymph nodes). Following surgery, I had chemo-radiation for 5 weeks (with cisplatin), and then had 4 chemotherapy sessions (paclitaxel and carboplatin) with dostarlimab included from the second chemotherapy session. Since finishing my chemotherapy (in May 2024), I have proceeded with standalone dostarlimab every 6 weeks and I have been advised I will be on that for a 3 years in total. Physically, I noticed absolutely no additional side effects from taking dostarlimab once it was added to my treatment protocol during my second chemotherapy. Since being on it as a standalone treatment, I observe very few side effects from it (other than my long term side effects from radiotherapy / surgical menopause). I notice some increased fatigue and some changes in bowel movements for 48 hours afterwards, but no medication is required for this.

	I have had a clear CT scan since my surgery, and I'm currently having a scan every 4 months. I am in total remission.
7a. What do you think of the current treatments and care available for primary advanced or recurrent endometrial cancer with MSI-H or dMMR on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Without this immunotherapy, I would have been incredibly concerned about the available treatment for me. After radiotherapy and chemotherapy, I was advised that I could only be on an aromatase inhibitor (anastrozole). That did not feel sufficient to me for my staging and having Lynch. My oncologist did not think that Dostarlimab was available for me when my initial treatment protocol was drawn up and my staging was subject to some discussion at the MDT. There was substantial uncertainty about whether I would be eligible for dostarlimab due to the nature of the licensing at the time – I had private health insurance so the request was made to BUPA (rather than the cancer drugs fund) who reviewed the evidence and decided to fund for 3 years. My oncologist advised me that if I was in the NHS I would have unlikely been able to approved for treatment through the cancer drugs fund (as he knew of previous patients in my position where this had not happened). Without this immunotherapy, I would have been incredibly concerned about the risk of recurrence and I had been advised that while radiotherapy was very effective, standalone chemotherapy was not for me. However being on dostarlimab as a first line treatment, rather than only being considered for it if I had a recurrence, has been absolutely vital to me getting my life back to "normal". From a psychological perspective, I can draw confidence from the fact that I am on treatment at a time when this is most likely to come back. And from a physical perspective the side effects for the immunotherapy seem to pale in comparison to experiences with aromatase inhibitors.

8. If there are disadvantages for patients of current NHS treatments for primary advanced or recurrent endometrial cancer with MSI-H or dMMR (for example, how they are given or taken, side effects of treatment, and any others) please describe these	For me, chemotherapy was incredibly tough to deal with but I observed no additional side effects with the immunotherapy. Other than the additional time in clinic (up to an hour), when you are already there for 8 hours in a day it makes little practical difference. For my standalone treatment for dostarlimab, I take no additional medication other than what I might take for side effects as a result of radiotherapy / medical menopause. I am even back to playing sport two days after treatment, and I'm back at work the very next day.
9a. If there are advantages of dostarlimab with carboplatin and paclitaxel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does dostarlimab with carboplatin and paclitaxel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I did not work during my cancer treatment (I went back to work 6 months after I completed chemotherapy). Taking it with paciltacel and carboplatin, I had all the same side effects someone having these drugs would have: extreme nausea, fatigue, very low neutrophils etc and took a combination of steroids and anti-emetics. However, with just standalone immunotherapy, my life has gone back to normal. I take the time off work for treatment, but other than that I am exercising, working and socialising as normal. I have been back at work for 4 months and I have taken on a promotion – even a day of work wasn't possible when I was on chemotherapy, so to be able to take a step forward at work is the confidence I can draw given I'm still on treatment and the minimal side effects I experience from treatment. While I continue to look over my shoulder that the cancer that might come back – and the cancer that might be around the corner (given I have lynch) - I believe that this immunotherapy is the reason why I'm heathy and cancer free right now.
10. If there are disadvantages of dostarlimab with carboplatin and paclitaxel over current treatments on the NHS please describe these.	Only the emotional toll of being back in clinic every 6 weeks for treatment. But every day I would take that over being back on cancer treatment for a recurrence.

For example, are there any risks with dostarlimab with carboplatin and paclitaxel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from dostarlimab with carboplatin and paclitaxel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I cannot comment on this point comprehensively. As someone with Lynch Syndrome, I am aware that I was lucky enough to receive treatment. Those with pMMR tumours still face having to wait for progression to receive treatment and face fewer treatment options. I think anyone with a womb cancer diagnosis who is MMR deficient, regardless of their staging, should benefit from this drug. It is a low toxicity, minimal side effect drug and having it as a first line treatment for lynch patients could be invaluable. I would also like to highlight that this drug has been truly life changing for me and my quality of life and life expectancy has been transformed as a result. The reason that I wanted to take part in the NICE appraisal is because I feel that people with advanced endometrial cancer deserve access to treatment options that enable them to live longer and fuller lives and even thrive with a cancer diagnosis. I would like to see this option offered to as many people as possible.
12. Are there any potential equality issues that should be taken into account when considering primary advanced or recurrent endometrial cancer with MSI-H or dMMR and dostarlimab with carboplatin and paclitaxel? Please explain if you think any groups of people with this condition are particularly disadvantage 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.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. Dostarlimab has been lifechanging for me in terms of quality of life and impact of my survival. I currently have no evidence of disease, and it has been a crucial part of me getting back to “normal”
2. I experienced no additional side effects with taking immunotherapy, above and beyond those people experience from being on chemotherapy. Other than the additional time spent in clinic, the inclusion of immunotherapy has made very little physical difference to me but it has been immeasurable in terms of the hope it has offered me.
3. Physically and psychologically, my outlook would be very different if I had only received doslarlimab for a recurrence. It means I’ve been given a chance to be cured first time around, rather than simply accessing it if it came back.
4. My experience of existing treatments (chemotherapy and radiotherapy) have been that they have a significant impact on quality of life and are a ‘belts and braces’ treatment which are physically and psychologically difficult to manage. They also offer limited hope for the future as standalone treatments.
5. People with advanced, recurrent or metastatic endometrial cancer diagnosis deserve to have the very best possible first line treatment, rather than only accessing treatment if their cancer comes back In my experience, dostarlimab is a much kinder treatment, with fewer debilitating side effects, which has enabled me to thrive and live my life fully.

Thank you for your time.

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External Assessment Group's report

Title: *Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (MA review of TA963): EAG Report*

Produced by	*Warwick Evidence*
Authors	*Ewen Cummins, Health Economist, McMDC Ltd* *Emma Loveman, Systematic Review Consultant, Effective Evidence* *Shivashri Chockalingam, Research Fellow, University of Warwick* *Anna Brown, Information Specialist, University of Warwick* *Jill Colquitt, Systematic Review Consultant, Effective Evidence* *Sarah Kitson, Clinical Lecturer and Honorary Consultant Gynae-oncologist, University of Manchester* *Rhona Johnston, Computer Programmer, McMDC Ltd* *Daniel Gallacher, Assistant Professor, University of Warwick*
Correspondence to	*Dr Daniel Gallacher: d.gallacher@warwick.ac.uk*
Date completed	*05/12/2024*

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None

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors
All authors read and accepted the final report. DG compiled the report and reviewed the statistical analysis in the clinical and cost-effectiveness sections. EC reviewed the economics of the submission, revised the company model and provided the cost effectiveness estimates. EL, SC and JC reviewed the clinical evidence. AB reviewed the company's literature searches. SK and MP provided expert advice to the team.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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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 for the appraisal of dostarlimab plus carboplatin and paclitaxel (CP) for primary advanced or recurrent high microsatellite instability or mismatch repair deficient endometrial cancer. This is a managed access review of TA963 and consists of updated follow-up from interim analysis two (IA2) of RUBY-1 for three outcomes (PFS, PFS2 and OS). The cut-off for IA2 was 22 September 2023, representing an additional year of follow-up compared to IA1 (28 September 2022) which was appraised before entering managed access. This summary also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 0.1 provides an overview of the key issues. Section 0.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 0.3 to 0.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (Section 1).

All issues identified represent the EAG's view, not the opinion of NICE.

0.1 *Overview of the EAG's key issues*

The EAG considers that the key issues raised in TA963 are not resolved by this updated analysis and remain areas of uncertainty and concern.

Table 1: Summary of key issues

ID6426	Summary of issue	Report sections
1	Limitations of RUBY-1 trial and most recent data-cut	2.2
2	Modelling of progression-free survival	3.2.6.1
3	Modelling of overall survival	3.2.6.2
4	Modelling of time to treatment discontinuation	3.2.6.3, 3.2.6.4, 5.3.3
5	Modelling of subsequent therapies received	3.2.9.4

0.2 *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:

- Increasing the time spent in progression-free survival health state, and also overall survival

Overall, the technology is modelled to affect costs by:

- Having a different price to the comparator treatments
- Changing eligibility for and take up of subsequent therapies, and hence their associated costs

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit
- Time to treatment discontinuation for dostarlimab+CP

0.3 *The decision problem: summary of the EAG's key issues*

The EAG did not identify any issues relating to the decision problem.

0.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1: Limitations of the RUBY-1 trial and most recent data-cut

Report section	2.2
Description of issue and why the EAG has identified it as important	Concerns remain about the reliability of information coming from RUBY-1. The small sample size and misclassification of disease type confounding the randomisation process, along with the low average age of the trial population compared to expected real-world use. The limited follow-up means the benefits of subsequent immunotherapy in the CP arm are unlikely to be captured. There were additional concerns about the subsequent treatments received following dostarlimab+CP in RUBY-1 (see Key Issue 5). The current follow-up ends at roughly the same time treatment with dostarlimab ends meaning there is insufficient evidence to inform treatment efficacy beyond this point. No new data on quality of life or duration of response has been provided.
What alternative approach has the EAG suggested?	The EAG has amended the starting age in the economic model, but is unable to meaningfully explore the impact of these other generalisability concerns.
What is the expected effect on the cost-effectiveness estimates?	The impact of these concerns cannot be estimated beyond acknowledging the high degree of uncertainty. The EAG anticipates that the RUBY-1 trial is likely to overestimate the benefit of dostarlimab+CP due to the impact of subsequent therapies. Increasing the starting age of the model decreases the cost-effectiveness of dostarlimab.
What additional evidence or analyses might help to resolve this key issue?	Longer trial follow-up would inform on duration of response beyond the time on treatment, and reporting on quality of life and response outcomes. Real-world follow-up may provide a better source of efficacy estimates over the RUBY-1 trial.

0.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 2: Modelling of progression-free survival

Report section	3.2.6.1
Description of issue and why the EAG has identified it as important	The company's modelling of PFS is based on old data and does not capture the increased hazard rate observed at the end of follow-up.
What alternative approach has the EAG suggested?	The EAG uses models fitted to updated follow-up, and applies treatment effect waning from 36 months, across a 2 year duration. This sets the hazard rates to be equal in both arms from 5 years based on what was observed in RUBY-1 and the rationale that people remaining free of progression on CP will be unlikely to have a higher risk of disease progression beyond this point.
What is the expected effect on the cost-effectiveness estimates?	This has a small effect on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up from RUBY-1 would inform the long-term PFS for both arms.

Issue 3: Modelling of overall survival

Report section	3.2.6.2
Description of issue and why the EAG has identified it as important	The company's modelling of OS is unsupported by the clinical evidence.
What alternative approach has the EAG suggested?	The EAG applies treatment effect waning from 36 months, across a 2 year duration. This sets the hazard rates to be equal in both arms from 5 years, based on the assumption that people alive at this point will have had to respond positively to a previous therapy, and their subsequent prognosis is independent of what initial therapy they received. Other waning scenarios are explored, plus using exponential distributions that are most consistent with observed data.
What is the expected effect on the cost-effectiveness estimates?	This has a large effect on the ICER, roughly doubling the company base case ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up from RUBY-1 would inform the long-term OS for both arms. Real-world data may help demonstrate the generalisability of RUBY-1 data to NHS care

Issue 4: Modelling of time to treatment discontinuation for dostarlimab+CP

Report section	3.2.6.3, 3.2.6.4, 5.3.3
Description of issue and why the EAG has identified it as important	The company's modelling of time to treatment discontinuation shows a large separation between PFS and TTD for dostarlimab+CP due to differing censoring rules. In effect this assumes that people withdrawing from dostarlimab treatment sustain the benefits of the treatment without incurring the costs. The EAG notes that within the trial, almost all people receiving dostarlimab and remaining free of progression also remain on treatment.
What alternative approach has the EAG suggested?	The EAG implement an approach based on the ratio of the numbers at risk in the TTD and PFS outcomes, and applies this to the PFS extrapolation, avoiding a large separation of these outcomes in the model.
What is the expected effect on the cost-effectiveness estimates?	This has a reasonably large effect on the ICER, increasing the company base case ICER by 25%
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up from RUBY-1 would inform the long-term OS for both arms.

Issue 5: Modelling of subsequent therapies received

Report section	3.2.9.4
Description of issue and why the EAG has identified it as important	The company's modelling of the distribution of subsequent therapies is based on clinical expert opinion and is inconsistent with the underlying clinical evidence from RUBY-1. This is an inconsistency between the clinical evidence and cost-effectiveness modelling which introduces bias in favour of dostarlimab, since the benefits of subsequent immunotherapies are modelled but not costed.
What alternative approach has the EAG suggested?	The EAG applies the distribution of subsequent treatments based on RUBY-1.
What is the expected effect on the cost-effectiveness estimates?	This has a moderate effect on the ICER, increasing the company base case ICER by around 10%.
What additional evidence or analyses might help to resolve this key issue?	Data on duration of 2nd line treatment in RUBY-1 from those with a PFS2 event.

0.6 *Other key issues: summary of the EAG's view*

The EAG did not identify any other key issues.

0.7 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG makes a number of changes to the company base case, the main ones being, with their impact shown in Table 2:

- Correcting some elements of the model structure and applying the publicly available CMU EMIT drug prices rather than BNF list prices.
- Applying EAG estimated PFS curves [redacted].
- Applying treatment waning from the end of the third year, over two years.
- For the dostarlimab+CP arm estimating the proportion of patients who have not progressed that will be treated with dostarlimab based upon the patient numbers who had not progressed and the patient numbers that received treatment.
- A baseline age of 67.1 years.

Table 2: EAG deterministic base case summary

	Section	Δ Cost	Δ QALY	ICER
Company BC	4.1	[redacted]	[redacted]	[redacted]
EAG01: EAG corrections	4.5.1	[redacted]	[redacted]	[redacted]
EAG02: EAG PFS params	3.2.6.1	[redacted]	[redacted]	[redacted]
EAG03: Waning	5.1.2	[redacted]	[redacted]	[redacted]
EAG04: Baseline age 67.1 yrs	5.1.3	[redacted]	[redacted]	[redacted]
EAG05: DOST % PFS treated	5.3.3	[redacted]	[redacted]	[redacted]
EAG06: DOST week 157	5.3.4	[redacted]	[redacted]	[redacted]
EAG07: RUBY IA2 2nd line	5.1.4	[redacted]	[redacted]	[redacted]
EAG08: 2nd line % PFS2 treated	5.3.8	[redacted]	[redacted]	[redacted]
EAG09: EAG admin costs	5.3.6	[redacted]	[redacted]	[redacted]

These result in the following deterministic cost effectiveness estimates.

Table 3: EAG deterministic base case summary

	Dostarlimab	Placebo	Net
Total QALYs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

Probabilistic modelling results in a similar central cost effectiveness estimate.

The EAG provides a number of one-way sensitivity analyses:

- SA01: Treatment effect waning from the end of years 4 and 5 over 2 years.
- SA02: Exponential curves rather than log-logistic curves for overall survival, with treatment waning from years 3, 4 and 5 over 2 years.
- SA03: Sampling baseline age.
- SA04: Company experts' 2nd line treatment balance rather than that of the key trial.
- SA05: Subgroup specific quality of life data from the key trial rather than data from the whole trial population.
- SA06: An alternative source of ongoing resource use supplied by the company, also exploring no additional cost for blood pressure and heart monitoring within this.
- SA07: A duration of 2nd line dostarlimab of [redacted] months rather than the [redacted] months of the base case.
- SA08: Halving and doubling 2nd line treatment costs

Table 4: EAG Scenario Analyses

	Δ Cost	Δ QALY	ICER
EAG Base case	[redacted]	[redacted]	[redacted]
SA01a: Waning end of year 4	[redacted]	[redacted]	[redacted]
SA01b: Waning end of year 5	[redacted]	[redacted]	[redacted]
SA02a: Exponential OS curves	[redacted]	[redacted]	[redacted]
SA02b: SA02a + waning end of year 4	[redacted]	[redacted]	[redacted]
SA02c: SA02a + waning end of year 5	[redacted]	[redacted]	[redacted]
SA03: Sampling baseline age	[redacted]	[redacted]	[redacted]
SA04: Company experts' 2nd line	[redacted]	[redacted]	[redacted]
SA05: RUBY-1 dMMR/MSI-H QoL	[redacted]	[redacted]	[redacted]
SA06a: GARNET ongoing resource use	[redacted]	[redacted]	[redacted]
SA06b: SA06a + £0 for Heart/BP	[redacted]	[redacted]	[redacted]
SA07: 2nd line dostarlimab [redacted] months	[redacted]	[redacted]	[redacted]
SA08a: Halving 2nd line costs	[redacted]	[redacted]	[redacted]
SA08b: Doubling 2nd line costs	[redacted]	[redacted]	[redacted]
SA09: Dostarlimab genetic test costs	[redacted]	[redacted]	[redacted]

Results are sensitive to all the elements explored by the EAG with the exception of SA05 and whether all patients' or the target subgroups' quality of life values are used.

Sampling age instead of using the mean as in SA03 is not particularly influential.

All of the other elements explored by the EAG are model drivers.

External Assessment Group Report

Abbreviations

AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
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
CSR	Clinical study report
DCR	Disease control rate
dMMR	Mismatch repair deficient
DOR	Duration of response
EAG	External assessment group
EAM	Early access to medicine
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FIGO	International Federation of Gynaecological and Obstetrics
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
IA1	First interim analysis
IA2	Second interim analysis
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
ITT	Intention-to-treat
KM	Kaplan-Meier
LTFU	Lost to follow-up
LY	Life year
MAA	Managed access agreement
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
NSMP	No 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
PFS	Progression-free survival
PFS2	Progression-free survival 2
PH	Proportional hazards
POLE	polymerase epsilon
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
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
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
WTP	Willingness to pay

1 INTRODUCTION AND BACKGROUND

1.1 *Introduction*

1.1.1 Remit of this appraisal

To appraise the clinical and cost effectiveness of dostarlimab with carboplatin and paclitaxel (dostarlimab+CP) for treating primary advanced or recurrent endometrial cancer with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

1.1.2 Condition, epidemiology, symptoms and humanistic burden

Endometrial cancer originates in the endometrium, the lining of the uterus. It is the most common type of uterine cancer; the terms endometrial cancer and uterine cancer are often used synonymously.[1] Approximately 20% of endometrial cancers are not diagnosed at an early stage but are at an advanced stage at diagnosis where the disease has spread beyond the uterus.[1, 2] Diagnosis is typically staged with the International Federation of Gynaecology and Obstetrics (FIGO) staging system;[3] advanced stage endometrial cancer is classed as primary Stage III or Stage IV.

The company reports that there are around 9,800 cases of endometrial cancer diagnosed in the UK each year, with around a quarter of these being primary advanced or recurrent disease.[4] Recurrent disease can be experienced by people who were diagnosed at any stage of disease, and is defined as a malignancy that cannot be detected after primary treatment but is radiologically or histologically detected at a later point in time.[5]

Molecular classification is also important in the diagnosis of endometrial cancer as this guides management of the disease.[6] The CS focus is on those with the molecular classification of MSI-H or dMMR (collectively referred to as dMMR/MSI-H) endometrial cancer; which accounts for around 25-30% of endometrial cancers.[7] Further description can be found in CS sections B.1.3.1 and B.1.3.2. The company's description of the condition and epidemiology appropriately reflect the citations reported and internationally recognised approaches.[3, 8]

CS section B.1.3.3 describes the burden of endometrial cancer. The description of the clinical and humanistic burden of primary advanced or recurrent endometrial cancer appears to appropriately reflect the experiences of people with endometrial

cancer. Endometrial cancer can have an effect on an individual's quality of life from difficulties in undertaking daily activities, physical symptoms and psychological impacts.[9, 10]

1.1.3 Current Treatment Pathway

The CS describes the current clinical pathway for people with advanced or recurrent endometrial cancer in section B.1.3.4 and in CS Figure 2. First line treatment for advanced or recurrent endometrial cancer includes platinum-containing chemotherapy (PCC) with carboplatin and paclitaxel.[11] The EAG clinical advisers confirm this is standard first line treatment. The EAG discussed issues with the treatment pathway as described in CS Figure 2 in the TA963 EAG report[12] as follows:

- *People with advanced endometrial cancer (stage III or IV) are presented as one in the lower part of CS Figure 2 with 'surgery may be considered' and that 'neoadjuvant/adjuvant radiotherapy, chemotherapy, or hormone therapy can also be received'. EAG clinical advice is that most people with primary stage III endometrial cancer will have surgery +/- neoadjuvant/adjuvant treatment. These people would then be monitored and first line treatment considered subsequently. People with stage IV endometrial cancer are less likely to receive surgery but it would be considered, and in some cases neoadjuvant chemotherapy would be given followed by scanning to check if a tumour has responded enough to become operable.*
- *Neoadjuvant and adjuvant chemotherapy, if used, is typically platinum containing chemotherapy (PCC), usually carboplatin with paclitaxel, and if first line chemotherapy is then required this is often used again. It is therefore difficult to define where first line PCC therapy commences to appropriately represent the pathway for all people with advanced endometrial cancer.*

The EAG considers these aspects to remain relevant.

As shown in CS Figure 2, dMMR/MSI-H patients with disease progression after first line treatment can currently be managed with dostarlimab monotherapy (via the Cancer Drugs Fund, CDF) or pembrolizumab monotherapy.

1.1.4 Dostarlimab

Dostarlimab is described in CS Table 2. A summary of the mechanism of action of dostarlimab is presented as: *Dostarlimab is a humanised monoclonal antibody of the immunoglobulin G4 (IgG4) isotype that binds to programmed death 1 (PD-1) receptors. The interaction of PD1 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, programmed death-ligand 1 and 2 (PD-L1 and PD-L2), potentiating T-cell responses, including anti-tumour immune-responses (GSK Summary of product characteristics).*[13]

Dostarlimab is indicated in combination with PCC for the treatment of dMMR/MSI-H primary advanced or recurrent endometrial cancer, in those who are candidates for systemic therapy. Since April 2024, dostarlimab with PCC is recommended by NICE with managed access under the CDF as an option for treating primary advanced or recurrent endometrial cancer with dMMR/MSI-H in adults who are candidates for systemic therapy.

1.1.5 Proposed placement of dostarlimab in treatment pathway

The CS describes the positioning of dostarlimab in Section B.1.3.4.4. Dostarlimab is positioned as an addition to first line treatment with PCC (carboplatin and paclitaxel), the established standard of care (SoC). The company makes the case that the combination of dostarlimab with current SOC ensures familiarity with efficacy and side effects for clinicians and allows additional impact on survival outcomes. Similarly to the EAG view in the TA963 EAG report,[12] the potential positioning of dostarlimab as an addition to carboplatin and paclitaxel at first line therapy is considered to be appropriate, however, the number of cycles of carboplatin and paclitaxel used in UK practice may differ from the use in the pivotal trial informing the CS (see Section 2.2.1.2.2).

1.2 *Critique of company's definition of decision problem*

The decision problem provided by the company (CS Doc B Section B.1.1) is broadly consistent with the NICE scope with the EAG main concern pertaining to the eligibility of people with Stage III disease who may be eligible for radiotherapy, who

have not been represented in the company submission, but are within the NICE scope.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with primary advanced or recurrent endometrial cancer with microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)	As per Scope	N/A	The EAG agrees that the population is consistent with the NICE scope. The EAG notes that in the previous appraisal decision problem[14] the CS decision problem focused on people with endometrial cancer who were candidates for systemic therapy. This is not reported to be the focus in the present decision problem, however, the EAG notes that the evidence is from the same pivotal trial. *The population in the CS was focused on those who had a low potential for cure by radiotherapy or surgery alone or in combination, in line with the evidence from the RUBY-1 trial. The EAG notes this may not fully reflect the anticipated NICE scoped population, in particular*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				with regards to people with stage III advanced EC.
Intervention	Dostarlimab with platinum-containing chemotherapy	As per scope	NA	The EAG agrees that the intervention is consistent with the NICE final scope.
Comparators	Platinum-based doublet chemotherapy	Platinum containing chemotherapy, Carboplatin and paclitaxel	N/A	The comparator used by the company, carboplatin + paclitaxel in combination is consistent with the NICE final scoped comparator of platinum-based doublet chemotherapy. EAG clinical advisers confirm that this is the most appropriate comparator for use in the UK.
Outcomes	The outcome measures to be considered include: • Progression-free survival • Time to second objective disease progression • Overall survival • Response rates	As per scope, with the addition of progression free survival 2 (PFS2)	PFS2 is an additional secondary efficacy outcome evaluated in the RUBY-1 trial.	The EAG agrees that the outcomes presented by the company are in line with the NICE final scope. As stated in the previous EAG report the outcomes reported are from an ongoing trial and as such are from an interim analysis. Results therefore may be subject to change as the trial progresses.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Duration of response • Adverse effects of treatment • Health-related quality-of-life.			
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial	As per scope	N/A	The model and analyses provided by the company adheres to the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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.	Dostarlimab has already received marketing authorisation from the MHRA (2nd October 2023) for the indication covered by this submission.	N/A	The EAG does not have any concerns.

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

CS Appendix D reports a systematic literature review (SLR) to identify randomised controlled trials (RCTs) on the efficacy and safety of treatments for primary advanced or recurrent endometrial cancer. Searches were originally undertaken in November 2021 and updated on 22 February 2023 for the previous NICE appraisal of dostarlimab+CP for this indication (TA963).[14] Three additional updates have been run since the previous submission, the most recent being on 16 May 2024.

2.1.1 Search strategies

2.1.2 CS Appendix D.1.1 describes the literature search sources and strategies, and the company's response to clarification question A7 further explains the process of updating the searches using date limits in MEDLINE, Embase and Cochrane databases. A good, appropriate range of sources were searched, including bibliographic databases, conference proceedings, HTA agencies' websites and the ClinicalTrials.gov trials register, although full details (search terms or browsing strategies) of the conference, website and trials register searches are not reported. The sources searched and the search terms used have not been changed since the submission for NICE TA963.[14] The searches combine terms for population (recurrent or advanced endometrial cancer) with a study type filter for randomised controlled trials, so could retrieve studies of any treatment, including dostarlimab with chemotherapy and relevant comparators. A few potentially useful subject headings are missing from the search (for example MesH 'Recurrence' and Emtree 'Recurrent disease' and 'Terminal cancer'), and the SIGN filters for RCTs are used, which are not the most comprehensive available.[15] Additionally, the searches of Cochrane databases (Appendix D.1.1.4.3 / Clarification response A7, Table 4) exclude trial registry and conference abstract records and limit to randomised controlled trials; actions which seem unnecessarily restrictive as registry and conference records are included from other sources, and Cochrane CENTRAL is a database of controlled trials only. However, as per the EAG's assessment of the company's searches for TA963,[12] the searches are likely to have retrieved everything of relevance to the decision problem. SLR Methods

Selection of clinical evidence for the company's SLR is described in CS Appendix D.1.2. As noted in TA963, initial eligibility criteria were sufficiently detailed (CS Appendix Tables 5 and 6), but these were not aligned with the decision problem. Additional steps regarding eligibility were undertaken but were not clearly defined.

CS Appendix D.1.3 describes the number of studies identified in the original SLR and four update searches. Updates 1 to 4 report the number of 'unique ICTs' identified; at clarification this was confirmed to be a typographical error, and the CS intended to state 'unique RCTs'.

The results of the original SLR searches and Update 1 were described in TA963. In the present CS, a PRISMA flow diagram (CS Appendix Figure 1) is presented for Update 4 only. The flow of studies identified at Updates 2 and 3, including number of full texts excluded at the first stage and reasons for exclusion, is not reported. CS Appendix Table 9 lists studies excluded at the additional step only (Original SLR: 55 studies, Update 1: 21 studies, Update 2: 12 studies, Update 3: 6 studies, Update 4: 9 studies). The EAG has checked the excluded studies list and notes three records linked to RUBY-1 were excluded for the reason 'duplicate'. The EAG can confirm they contain no new data. No other RCTs of dostarlimab were identified in the excluded studies list.

CS Appendix Table 8 lists the 60 unique trials identified by the original SLR and all updates. Studies from the update searches are highlighted in green, including those from Update 1 reported in TA963. Six additional unique studies (42 additional publications) were included in the present SLR. Sixteen of the additional publications identified in the update searches were further publications of RUBY-1. No other RCTs of dostarlimab were included. The SLR was unlikely to have excluded any relevant studies.

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The evidence for the clinical effectiveness of dostarlimab+CP is from RUBY-1 (NCT03981796), an international multi-centre, double-blind, placebo controlled Phase III randomised controlled trial (RCT). The trial is described in full in CS section B.2.2 and TA963 EAG report section 2.2[12] and summarised below.

2.2.1 Trial overview

The study comprised a 16-week period of dostarlimab+CP or placebo+CP followed by an extended period of up to 3 years of dostarlimab monotherapy or placebo.

The population in RUBY-1 is women with primary advanced or recurrent EC not amenable to curative therapy by radiotherapy or surgery. The population relevant to this appraisal is the subgroup of RUBY-1 with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

The previous appraisal (TA963) considered data from the first interim analysis, data-cut 28 September 2022, with a median duration of follow-up 24.79 months. For the second (current) interim analysis (IA2), data-cut 22 September 2023, the median follow-up is 36.6 months. IA2 was a pre-planned interim analysis for overall survival in the overall (ITT) population (clarification response A2).

The EAG notes that the IA2 data-cut was more than one year ago. CS section B.2.11 states that no additional interim data cuts are expected and that the study is expected to complete in Q3 2026.

Table 6 provides a summary of the RUBY-1 trial methodology and cross-reference to the relevant sections in the CS where more detail can be found; further description is provided below.

Table 6: Summary of RUBY-1 methodology

Method step	Summary details	Section(s) of CS of relevance
Method of randomisation	Randomisation was performed in a blinded manner using an interactive Web response system, stratification factors were MMR/MSI status, prior external pelvic radiotherapy status and disease status	CS Appendix D, Table 10
Eligibility criteria	Female ≥18 years Histologically or cytologically proven EC with advanced or recurrent disease Adequate tumour tissue sample for MMR/MSI status testing Primary stage III or stage IV disease or first recurrent EC with a low potential for cure	CS Section B.2.2
Trial drugs by period of study	Dostarlimab or placebo in combination with CP for 6 cycles followed by dostarlimab or placebo for up to 3 years	CS Section B.2.3.3

Primary endpoints of relevance to the decision problem	Progression free survival Overall survival	CS Section B.2.3.4 CS Table 3
Key secondary endpoints of relevance to the decision problem	Objective response rate (ORR) Duration of response (DOR) HRQoL Adverse events	CS Section B.2.3.4 CS Table 3
Statistical analysis	A hierarchical testing strategy was used. Time-to-event analyses were performed using Kaplan-Meier (KM) methods with 2-sided 95% confidence intervals where appropriate. Cox regression models were used to estimate the hazard ratios.	CS Section B.2.4, CS Appendix N.1.

2.2.1.1 Eligibility

The CS reports the key eligibility criteria for the RUBY-1 trial in CS Table 3 and CS Section B.2.2. In RUBY-1 eligible participants were adult females with primary advanced (FIGO stage III or IV) or recurrent EC that was not amenable to curative therapy by radiotherapy or surgery. No further definition of how the low potential for cure was confirmed is reported in RUBY-1, the CS or the CSR. The EAG discussed this issue in TA963,[12] noting that some patients with stage III disease are amenable to cure. In the dMMR population, the proportion with stage III disease was approximately 20% but not enough detail of these people was presented in the CS to explore if they would be surgically treated in the real world.

People with recurrent EC were eligible if they had previously received neoadjuvant/adjuvant systemic anticancer therapy and had a recurrence or progressive disease after at least 6 months after completing treatment (first recurrence only). The EAG clinical expert confirmed that this is considered usual practice in the real-world setting. The EAG notes that CS Figure 3 suggests that only people with stage I/II are considered to become eligible as 'recurrent', however this is not in line with the eligibility criteria for RUBY-1 (CS Table 3), see Section 1.1.3 for further discussion.

In TA963, the CS decision problem focused on people with EC who were candidates for systemic therapy. The EAG noted that there were no specific eligibility criteria in the RUBY-1 trial relating to candidacy for treatment, and the CS and CSR did not report how this was established. However, candidacy for systemic therapy is not specified in the decision problem of the current appraisal (CS Table 1). The EAG notes that people could be included if they had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and have adequate organ function. People were also excluded if they had a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy (see RUBY-1 protocol, provided with the CS and cited in CS Doc B as '[GSK Data on file] Ruby Clinical Study Protocol 4010-03-001 Version 4.0. Dec 2022. Mar 2022')).

2.2.1.2 Interventions

2.2.1.2.1 Dostarlimab

The CS describes the administration of dostarlimab in section CS B.2.3.3 and CS Figure 4. Dostarlimab 500mg IV (or placebo) was administered every three weeks (Q3W) for six cycles (Cycles 1-6), then at 1000 mg every six weeks (Q6W) for all cycles thereafter (Cycle 7 onwards).

2.2.1.2.2 Cycles of carboplatin and paclitaxel

In the first 16 weeks of RUBY-1 participants received dostarlimab in addition to what the company state is the most common regimen of standard of care (CS B.1), combination carboplatin and paclitaxel. Clinical advice to the EAG confirms that carboplatin with paclitaxel is the most commonly used treatment for EC. In the RUBY-1 trial participants received six cycles of carboplatin and paclitaxel in both treatment arms with response monitored after three treatment cycles. The EAG clinical adviser confirmed that in the real world the number of cycles of carboplatin and paclitaxel can vary by patient and that six cycles is not a fixed quantity, for example a person may be given just three cycles and then have ongoing surveillance for toxicity or response.

CS Table 19 reports the proportions of completion rates for carboplatin and paclitaxel across each cycle, the weighted percentage of completion for both carboplatin and paclitaxel in RUBY-1 were: [redacted]. In the CSR for the dMMR/MSI-H population the [redacted] which may not be reflective of typical practice in the real world, see further discussion on generalisability (section 2.5.2). Section 2.2.2.5.1 describes additional information on delays and discontinuations of treatments.

2.2.1.2.3 Subsequent Treatments

Following the 16-week period of dostarlimab+CP versus placebo+CP, participants were followed up to 3 years during a dostarlimab monotherapy versus placebo period (CS Figure 4). In TA963,[12] the EAG requested summary information on subsequent treatments received by the dMMR/MSI-H subgroup of RUBY-1. Data were provided in TA963[12] clarification response A9 but were incomplete due to limited duration of follow-up. Data on subsequent anti-cancer therapies from IA2 are presented in section 2.2.1.2.3

2.2.1.3 Risk of Bias of RUBY-1

The company assessed the ROB of RUBY-1 using the checklist provided in the NICE STA user guide for company evidence submissions[16] (CS Appendix D.3). The company rated the trial as having a low risk of bias. In TA963,[12] the EAG considered that the overall risk of bias assessed using Cochrane ROB2 in RUBY-1 was low, although noted an imbalance in numbers between arms of the pre-specified, stratified dMMR/MSI-H subgroup (dostarlimab+CP n=53 vs placebo+CP n=65, total n=118). This was because there were two different classifications of MMR/MSI status due to it being captured at two timepoints (see CS Doc B.2.4.1.1).

Classification based on the source verified value of MMR/MSI status collected in the electronic case report form (eCRF), which reflects the actual MMR/MSI status, was chosen for the prespecified primary analysis to reduce the impact of misclassification on the dMMR/MSI-H population. Sensitivity analysis was undertaken based on MMR/MSI classification entered for randomisation. Further details were found in CSR IA1 p55:

[redacted] The EAG also noted differences in some potential prognostic factors at baseline between arms in the pre-specified subgroup based on source verified data; the impact of these differences is unclear (section 2.2.2.1).

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2.2.2 Trial Results

2.2.2.1 Baseline characteristics

There were a total of 494 participants in the ITT (overall) population and 118 participants in the pre-specified dMMR/MSI-H subgroup based on source verified data, of whom 53 were randomised to dostarlimab+CP and 65 to the comparator arm. The study recruited from 164 sites from 19 countries globally, five of the sites were from the UK although only three recruited participants (TA963 clarification response A14), two of whom were in the dMMR/MSI-H subgroup relevant to this appraisal.

Baseline characteristics for the dMMR/MSI-H subgroup and the ITT population by study arms are provided in Table 7. There is no change in baseline characteristics from TA963. As noted in the EAG risk of bias assessment for RUBY-1 there were some slight imbalances in the subgroup arms. It is possible that these are due to the small sample size and/or misclassification of disease type confounding the randomisation process. CS section B.2.3.5 acknowledges that BMI is higher in the placebo arm, although states that additional analysis conducted by the company in TA963 found that the difference did not affect the hazard ratio. The company also notes that the proportion with ECOG PS 1 is higher in the dostarlimab+CP arm. The

EAG requested data on disease status at baseline split by ECOG 0 at baseline and ECOG 1 at baseline, however the company were unable to provide this due to time constraints (clarification A13). A breakdown of disease stage at trial baseline for people with recurrent disease was also requested by the EAG, but the company explained that these data were not available (clarification A14).

In addition, EAG considers that the proportion aged ≥65 years appears higher in the placebo arm (see Table 7 for details of baseline characteristics). The impact of these differences is unclear, however it is possible that any difference in outcomes observed for this subgroup might be influenced by this imbalance in baseline characteristics. The EAG also notes that almost [redacted] of the relevant subgroup of RUBY-1 had non-evaluable disease at baseline. The EAG discusses the generalisability of the RUBY-1 trial population in Section 2.5.2.

Table 7: Baseline characteristics for RUBY-1

Characteristic	dMMR/MSI-H dostarlimab + CP subgroup (N=53)	dMMR/MSI-H CP + placebo subgroup (N=65)	ITT population dostarlimab + CP (N=245)	ITT population CP + placebo (N=249)
Race, n (%)				
White	44 (83.0)	56 (86.2)	189 (77.1)	191 (76.7)
Black or African American	4 (7.5)	6 (9.2)	28 (11.4)	31 (12.4)
Asian	2 (3.8)	0	7 (2.9)	8 (3.2)
American Indian or Alaska Native	0	1 (1.5)	1 (0.4)	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (1.9)	0	1 (0.4)	0
Unknown	1 (1.9)	1 (1.5)	19 (7.8)	18 (7.2)
Not Reported	1 (1.9)	1 (1.5)		
Age (years)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median	61.0	66.0	64	65
Q1, Q3	[redacted]	[redacted]	NR	NR

Min, Max	45, 81	39, 85	41, 81	28, 85
Age Group, n (%)				
19-64	30 (56.6)	30 (46.2)	NR	NR
>=65	23 (43.4)	35 (53.8)	118 (48.2)	135 (54.2)
BMI (kg/m^2)				
Mean (SD)	[redacted]	[redacted]	NR	NR
Median	30.55	35.50	30.8	32.8
Q1, Q3	[redacted]	[redacted]	NR	NR
Min, Max	20.1, 54.4	17.9, 58.1	17.6, 60.6	17.7, 68.0
ECOG Performance Status, n (%)				
0	28 (53.8)	39/65 (60.0)	145/241 (60.2)	160/246 (65.0)
1	24 (46.2)	26/65 (40.0)	96/241 (39.8)	86/246 (35.0)
Disease status				
Primary stage III	10 (18.9)	14 (21.5)	45 (18.4)	47 (18.9)
Primary stage IV	16 (30.2)	19 (29.2)	83 (33.9)	83 (33.3)
Recurrent	27 (50.9)	32 (49.2)	117 (47.8)	119 (47.8)
MMR/MSI status				
dMMR/MSI-H	53 (100.0)	65 (100.0)	53 (21.6)	65 (26.1)
MMRp/MSS	0	0	192 (78.4)	184 (73.9)
Previous external pelvic radiotherapy				
Yes	8 (15.1)	13 (20.0)	41 (16.7)	45 (18.1)
No	45 (84.9)	52 (80.0)	204 (83.3)	204 (81.9)
FIGO stage at initial diagnosis				
Stage I	18 (34.0)	22 (33.8)	65 (26.5)	71 (28.5)
Stage II	3 (5.7)	5 (7.7)	13 (5.3)	13 (5.2)
Stage III	14 (26.4)	20 (30.8)	75 (30.6)	65 (26.1)
Stage IV	14 (26.4)	15 (23.1)	72 (29.4)	84 (33.7)
Unknown	4 (7.5)	3 (4.6)	20 (8.2)	16 (6.4)
Disease at baseline				
No disease	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Tables 5 to 7 and RUBY-1 publication[17] Table 1
Abbreviations: BMI: body mass index; CP: carboplatin/paclitaxel; dMMR: DNA mismatch repair deficient; ECOG: Eastern Cooperative Oncology Group; MSI-H: microsatellite instability-high; MSS: microsatellite stable; MMRp: DNA mismatch repair proficient; SD: standard deviation

2.2.2.2 Prior anti-cancer treatments

Prior anti-cancer treatments received by participants in RUBY-1 are presented in Table 8. Around [redacted] of the dMMR/MSI-H subgroup received prior anti-cancer treatment, the most common treatment was paclitaxel-carboplatin (dostarlimab+CP [redacted]; placebo+CP [redacted]. Around [redacted] of participants had previous radiotherapy and around [redacted] had previous anti-cancer surgery. The CSR does not describe whether treatments were adjuvant or neoadjuvant, and data were not presented according to disease status (i.e. recurrent, primary stage III or primary stage IV).

Table 8: Prior anticancer treatment

	dMMR/MSI-H dostarlimab + CP subgroup (N=53)	dMMR/MSI-H CP + placebo subgroup (N=65)	ITT population dostarlimab + CP (N=245)	ITT population CP + placebo (N=249)
Any prior anticancer treatment	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel - carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxyprogesterone	[redacted]	[redacted]	[redacted]	[redacted]
Ifosfamide	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]

Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Previous Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Anti-cancer surgery	[redacted]	[redacted]	[redacted]	[redacted]

Source: IA1 CSR.

2.2.2.3 Subsequent Treatments

Subsequent anti-cancer therapies received during RUBY-1 are summarised in Table 9. Fewer patients received subsequent cancer therapy in the dostarlimab+CP arm (28.3%) than in the placebo+CP arm (60.0%). Of the different type of therapies available, the difference between arms was greatest for immunotherapies (dostarlimab+CP: 15.1%; placebo+CP: 41.5%). The types of treatments received also differed between the arms. Further treatments most commonly used in the dostarlimab+CP arm were pembrolizumab monotherapy, pembrolizumab+lenvatinib, doxorubicin, [redacted]. Further treatments most commonly used in the placebo+CP arm were pembrolizumab monotherapy, [redacted]. As noted by the EAG in TA963[12] there were instances of treatment with an additional immunotherapy in the dostarlimab+CP arm but the impact of this treatment on the results is unclear and this would not be reflected in the current UK treatment pathway. The EAG also noted that the timing and duration of treatment with each of these subsequent treatments is currently not reported. The mean time from the last dose of study treatment to the start of subsequent anti-cancer treatment was [redacted] [dostarlimab+CP: [redacted] days (SD [redacted]) placebo+CP: 83.1 days (SD [redacted])].

CS section B.3.5.5 and CS Table 28 report subsequent anti-cancer therapies costed in the economic model post progression. These differ to those costed in TA963 due to changes in the treatment landscape and include carboplatin with paclitaxel, pembrolizumab monotherapy, doxorubicin, bevacizumab, pembrolizumab with lenvatinib, and letrozole (see Section 3.2.9.4). The company states in CS section B.3.5.5 that the subsequent treatment pathway for NHS patients who progress following treatment with CP now better resembles that of the RUBY-1 trial. A direct comparison of these numbers in Table 9 is not recommended due to how the model

applies the costs of subsequent therapy. However, there is one important difference between the proportions of treatments in RUBY-1 and those costed in the model. The EAG's understanding is that patients are unlikely to be eligible for subsequent immunotherapy in the NHS, but notes that some patients did receive immunotherapy after discontinuing dostarlimab+CP, potentially biasing the RUBY-1 clinical results in favour of dostarlimab+CP.

The company's base case does not included treatments currently available via the CDF (dostarlimab in previously treated patients), but a scenario was conducted using data on subsequent treatments from RUBY-1 IA2, which includes dostarlimab as an option for patients who have not received prior immunotherapy treatment.

Table 9: Summary of the most commonly reported follow-up anti-cancer therapies in the dMMR/MSI-H population

Subsequent treatment	RUBY-1 Dostarlimab + CP (N=53)	RUBY-1 Placebo + CP (N=65)	Company expert opinion: Dostarlimab + CP	Company expert opinion: CP
Any follow-up anti-cancer therapy	15 (28.3%)	39 (60.0%)		
Any immunotherapy	8 (15.1%)	27 (41.5%)		
Pembrolizumab	4 (7.5%)	21 (32.3%)	0%	42.6%
Pembrolizumab/ Lenvatinib	3 (5.7%)	2 (3.1%)	0%	[redacted]
Dostarlimab	0	3 (4.6%)		
Any chemotherapy	[redacted]	[redacted]		
Doxorubicin	[redacted]	[redacted]	19.6%	6.2%
Paclitaxel/ carboplatin	[redacted]	[redacted]	35.1%	13.1%
Any hormonal therapy	[redacted]	[redacted]		
Letrozole	[redacted]	[redacted]	5.2%	3.8%
Megestrol acetate	[redacted]	[redacted]		
Medroxyprogesterone acetate	[redacted]	[redacted]	5.2%	3.8%
Any radiation Therapy	[redacted]	[redacted]		

Radiotherapy	[redacted]	[redacted]	14.1%	10.0%

Source: IA2 CSR; CS Table 28; Powell et al, 2024[18]

2.2.2.4 Treatment Efficacy

In this new submission, updated results from IA2 of RUBY-1 were only available for some outcomes: Overall Survival and PFS2. OS is defined as the time from randomisation until death, whilst PFS2 is defined as the time from randomisation until disease progression on first subsequent therapy following the study intervention. At the clarification stage, [redacted].

For ease of comparison the EAG has combined recreated data from each data-cut for these two outcomes into single Kaplan-Meier plots (Figure 1 and Figure 2), and presented an overview of their relative effect estimates in Table 10. The data from IA2 appears consistent with the previous data-cut, with dostarlimab demonstrating a benefit for OS and PFS2, with the estimated hazard ratios remaining similar with a wide 95% confidence interval.

Table 10: Comparison of outcomes across RUBY-1 IA1 and IA2

	Dostarlimab+CP vs CP IA1	Dostarlimab+CP vs CP IA2
Median OS, months (95% CI)	[redacted] vs [redacted]	[redacted] vs [redacted]
OS Hazard Ratio (95% CI)	0.30 (0.13, 0.70)	0.32 (0.166, 0.629)
Median PFS2, months (95% CI)	NR (NA, NA) vs [redacted]	[redacted] vs 21.6 [redacted]
PFS2 Hazard Ratio (95% CI)	0.37 (0.19, 0.73)	0.33 (0.175, 0.627)
PFS Investigator Hazard Ratio (95% CI)	0.28 (0.16, 0.50)	[redacted]

NA = not available, NR = not reached

2.2.2.4.1 Overall Survival

For OS, the EAG considers that neither arm of RUBY-1 demonstrates a plateau (Figure 1), and that the limitations of the IA1 data still apply, namely that the follow-up from IA2 remains immature from a small sample size and is insufficient to inform

long-term extrapolations. The confidence intervals remain wide, and data remains ill-suited for extrapolation.

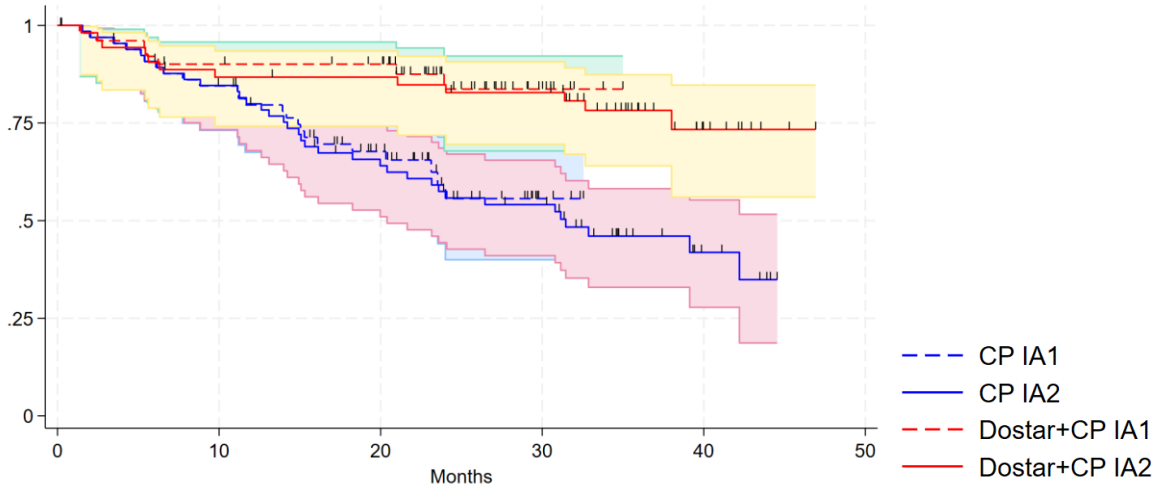

Figure 1: Kaplan-Meier plot of overall survival from IA1 and IA2 of RUBY-1.

2.2.2.4.2 PFS2

For PFS2, the Kaplan-Meier plot shows a potential plateau for dostarlimab+CP, however the extent of the censoring makes this highly uncertain (Figure 2).

Figure 2: Kaplan Meier plot of PFS2 from IA1 and IA2 of RUBY-1.

2.2.2.4.3 Progression-Free Survival

[redacted]

The EAG is unclear why data for the response related outcomes have not been included in IA2. These were requested during the clarification stage (Question A10) but were not provided.

Figure 3: Progression-free survival from RUBY-1 interim analyses 1 and 2.

2.2.2.4.4 Additional RUBY-1 analyses

Time to treatment discontinuation

In their response to clarification question A12, the company presented updated information on time to treatment discontinuation (TTD), capturing the time spent on the randomly allocated trial therapies.

The EAG notes that for CP, that PFS falls below TTD, whilst for dostarlimab+CP, TTD falls below PFS. The disagreement between these outcomes is due to a difference in the censoring rules. For PFS, someone discontinuing therapy or withdrawing is censored whilst this counts as a TTD event.

Figure 4: [redacted]

PFS2

The EAG also requested analyses of the PFS2 outcome, but only for those who had received a subsequent therapy (Figure 5). Whilst the groups are not balanced, it gives a better representation of the efficacy of the subsequent therapies received. [redacted].

Figure 5: PFS2 for people who received subsequent therapies (taken from Figure 4 of company clarification responses)

For completion, results for analyses that have not been updated since the IA1 are presented in Table 11. Whilst response rates were similar across arms, the duration of response was typically longer for dostarlimab+CP. The main PFS outcome was similar to the PFS by blinded independent central review (BICR). The EAG note that the PFS estimate from scenarios using IA1 which classified as PFS events deaths previously censored at most recent assessment and discontinuations or starting a new therapy did differ slightly from the main analysis.

Table 11: Summary of key results from IA1 of RUBY-1

	Dostarlimab+CP (N=53)	**CP (N=65)**
PFS BICR Hazard Ratio (95% CI)	0.29	
PFS Hazard Ratio Scenario including new treatment, discontinuation and death as PFS events (95% CI)		
PFS Hazard Ratio Scenario as above, using randomised dMMR/MSI-H status (95% CI)		

Disease Control Rate	[redacted]	[redacted]
Objective Response Rate	78%	69%
Median Duration of Response (95% CI)	Not Reached (10.1, NR)	5.4 (3.9, 8.1)
Complete Responders: Number of PFS events Median DOR (months)	n=15 [redacted]	n=12 [redacted]
Partial Responders Number of PFS events Median DOR (months)	n=23 [redacted]	n=28 [redacted]

In summary, dostarlimab+CP shows a clear benefit over CP across the main clinical outcomes of PFS, PFS2, and OS.

2.2.2.4.5 Quality of Life

No new quality of life data were included in IA2. The protocol gave no indication that data collection would stop after IA1, and the EAG is unclear whether further data exists.

In TA963 the only QoL information that was provided was for the EORTC QLQ C-30 global score specific for the dMMR/MSI-H population of RUBY-1. This information suggested there could be a small benefit of QoL for dostarlimab+CP which may have occurred for reasons such as better disease control, differences in baseline characteristics or by chance.

As mentioned in the EAG report in TA963, there are limitations for the health-related quality of life outcomes.[12] These are: the high drop-out on both arms, that dostarlimab+CP patients do not appear to have any worsening in QoL despite receiving 6 cycles of chemotherapy plus additional dostarlimab therapy compared to the CP arm, and that equivalent information for other QoL outcomes has not been presented.

The quality-of-life information used in the company base case come from RUBY-1 IA1 and are likely subject to these same limitations.

2.2.2.5 Adverse Events

2.2.2.5.1 Treatment Exposure and Interruption to Treatment

Duration on treatment and interruption to treatment is summarised in Table 12. Results are similar between IA1 and IA2; the key differences are that more participants have had more than three years of treatment, therefore the upper limit of the range of treatment has increased. The proportion of people with infusion delays lasting at least 3 days has also [redacted] between IA1 an IA2, this is discussed below.

Duration of treatment and proportion of people with at least 54 weeks, 102 weeks and 156 weeks of study treatment is [redacted] in the dostarlimab+CP arm. At IA2 only [redacted] participants in the dMMR/MSI-H subgroup ([redacted] in the overall population) have received more than 3 years of treatment (compared with [redacted] in the dMMR/MSI-H subgroup and [redacted] in the overall population at IA1), see Table 12 for details per study arm. At IA1, median [redacted] treatment duration of dostarlimab/placebo appeared longer in the dostarlimab+CP arm compared with the placebo+CP arm, although the ranges were similar. This [redacted] at IA2.

The median number of actual dosing cycles was [redacted] in the dostarlimab+CP arm in the overall population ([redacted] in dMMR/MSI-H) and [redacted] in the placebo plus carboplatin-paclitaxel arm ([redacted] in dMMR/MSI-H). CSR Table 7 also reports relative dose intensity (not reproduced here).

Infusion delays (not clearly stated in the CS but assumed to be of any drug component) lasting at least 3 days were [redacted] in the dostarlimab+CP arm, with [redacted] incident of delay being the most common. The number of people with infusion delays lasting at least 3 days [redacted] between IA1 and IA2; the [redacted] appears to be slightly greater in the dostarlimab+CP arm of the dMMR/MSI-H subgroup ([redacted]), but this could be a spurious observation as numbers are small. Infusion delays were due to adverse events in around [redacted] (other reasons not defined). In the dMMR/MSI-H population, the proportion of participants who at had at least 4 incidents of infusion interruption was [redacted] versus [redacted] in the dostarlimab+CP and placebo+CP arms, respectively. The EAG notes the proportion with zero incidents was [redacted] in the placebo+ CP arm: [redacted] versus [redacted], respectively.

The EAG asked the company how many patients with progressive disease received dostarlimab during progressive disease and for details of the treatment (clarification A17). The company said that KM curves for time to treatment discontinuation (TTD) and progression free survival (PFS) for the dostarlimab arm show that the proportion of patients remaining on active therapy never exceed the proportion who are progression free, which indicates good adherence to discontinuation upon progression per the trial protocol. However, the company did not provide the numbers or details of treatment requested.

Table 12: Treatment exposure and interruption to treatment

	dMMR/MSI-H subgroup		Overall population	
	Dostarlimab + CP (N=52)	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Duration of dostarlimab/placebo weeks, median (range); mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of study treatment, > 54 weeks N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of study treatment, 102 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Duration of study treatment, 156 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Infusion delays lasting >3 days	[redacted]	[redacted]	[redacted]	[redacted]
Number of infusion delays lasting > 3 days				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for infusion delays more than 3 days (proportion of events): adverse event	[redacted]	[redacted]	[redacted]	[redacted]

Source: September 2023 data cut CSR, sections 5.5.1 and 5.5.2 and Tables 14.1.1.24 and 14.1.1.27.
[a]Response to clarification A16 states [redacted].

Treatment Emergent Adverse Events

Adverse events from RUBY-1 are detailed in CS Section B.2.10 and CS Appendix F. The EAG has presented key data and provides a comparison of the IA2 with IA1. Summaries of adverse events are provided both for the dMMR/MSI-H subgroup, and the overall population owing to the larger sample size. The safety population of RUBY-1 is based on all participants who received at least one dose of study treatment; in the dostarlimab+CP arm of the dMMR/MSI-H subgroup the safety population included 52 participants.

Table 13 provides a summary of treatment-emergent adverse events (TEAEs) for both the dMMR/MSI-H subgroup and the overall trial population. The CS states that in the dMMR/MSI-H subgroup, participants in the dostarlimab+CP arm experienced over 10% higher incidence of Grade ≥3 TEAEs related to any treatment and TEAEs requiring infusion interruption compared with the placebo+CP arm. The EAG notes that rates of any Grade ≥3 TEAEs were also close to [redacted] in the dostarlimab+CP group compared with the placebo+CP group. As reported by the CS, immune-related TEAEs and treatment-related immune TEAEs were substantially more frequent [redacted] in the dostarlimab+CP arm than the placebo+CP arm. There were two TEAEs leading to death reported in the dostarlimab+CP group. The EAG highlights that TEAEs leading to infusion interruption were higher in the dostarlimab+CP arm [redacted] compared to the placebo arm [redacted]. In the dMMR/MSI-H subgroup, the rates of TEAEs were similar between IA1 and IA2, with the most notable difference in the dostarlimab+CP arm being an increase in any serious adverse event to [redacted] from [redacted]

Table 13: Overview of treatment emergent adverse events

	dMMR/MSI-H subgroup		Overall population	
Adverse event category	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostar +CP (N=241)**	**Placebo + CP (N=246)**
Any TEAE	52 (100%)	65 (100%)	241 (100%)	246 (100%)
Any Grade ≥3 TEAEs	39 (75.0%)	43 (66.2%)	174 (72.2%)	148 (60.2%)

Any TEAE with outcome of death[a]	2 (3.8%)	0	5 (2.1%)	0
Any serious adverse event	17 (32.7%)	21 (32.3%)	96 (39.8%)	69 (28.0%)
Any TEAEs leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to infusion interruption	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to infusion delay	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to dose reduction	11 (21.2%)	18 (27.7%)	68 (28.2%)	68 (27.6%)
Any immune-related TEAEs	39 (75.0%)	26 (40.0%)	141 (58.5%)	91 (37.0%)
Any infusion-related reactions	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related Grade ≥3 TEAE	[redacted]	[redacted]	NR	NR

Source: CS Table 10; CS Appendix Table 3, Table 13; CSR Table 15; Powell et al, 2024;[18, 19] Auranen et al, 2024[20] (any immune related TEAEs)

[a] assessed by the investigator to be not related to carboplatin or paclitaxel, and only related to dostarlimab or placebo (CS Appendix Table 71)

2.2.2.5.2 Grade ≥ 3 Treatment Emergent Adverse Events

In the dMMR/MSI-H population, rates of Grade ≥ 3 anaemia, decreased neutrophil count and decreased white blood cell count (Table 14) were higher in the placebo+CP arm than in the dostarlimab+CP arm; these differences are unexplained and may be due to the small numbers. Grade ≥3 neutropenia rates were higher in the dostarlimab+CP arm than the placebo+CP arm. No other differences were observed across arms and there were no differences observed compared to IA1. Grade ≥3 TEAEs occurring in at least 2% of patients in the overall population and

with higher proportions in the dostarlimab+CP arm were included in the company's economic model and are presented in Table 14 below. There were no notable differences to report compared to IA1. As reported in the CS, during the dostarlimab monotherapy phase (after cycle 7), a decrease in any Grade ≥3 TEAEs was observed in the dostarlimab+CP arm ([redacted] versus [redacted]).

Table 14: Summary of Grade ≥3 TEAEs in RUBY-1 IA2

	dMMR/MSI-H subgroup		Overall population	
Adverse event category	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
TEAEs Grade ≥3 occurring in ≥2% of patients in the overall population (used in the CS economic model)				
Anaemia	8 (15.4%)	14 (21.5%)	36 (14.9%)	41 (16.7%)
Neutropenia	9 (17.3%)	8 (12.3%)	23 (9.5%)	23 (9.3%)
Neutrophil count decreased	4 (7.7%)	12 (18.5%)	20 (8.3%)	34 (13.8%)
Hypertension	5 (9.6%)	4 (6.2%)	17 (7.1%)	8 (3.3%)
White blood cell count decreased	2 (3.8%)	8 (12.3%)	16 (6.6%)	13 (5.3%)
Hypokalemia	3 (5.8%)	4 (6.2%)	[redacted]	[redacted]
Pulmonary embolism	2 (3.8%)	4 (6.2%)	14 (5.8%)[a]	12 (4.9%)
Lymphocyte count decreased	3 (5.8%)	6 (9.2%)	13 (5.4%)	18 (7.3%)
Lipase increased	3 (5.8%)	0	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	3 (5.8%)	2 (3.1%)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	0	4 (6.2%)	[redacted]	[redacted]

Rash	3 (5.8%)	0	[redacted]	[redacted]

From CS Appendix Tables 8, 9, 12; CSR Table 19; Powell et al, 2024[18]
[a]Data as reported in CS Table 27, CSR and Powell et al, 2024[18, 19]

2.2.2.5.1 Deaths and Serious Adverse Events

At IA2, there were no additional TEAEs leading to death in either the dMMR/MSI-H group or the overall group (Table 13), details are reported in the previous EAG report.[12]

A summary of serious adverse events is provided in Table 15. As noted above, in the dMMR/MSI-H group, the incidence of any serious TEAE was higher in the dostarlimab+CP than the previous data-cut, [redacted]. Specific types of serious TEAEs occurring in at least 1% of either group can be seen in Table 15 below. None were observed to differ from IA1, however, there were a number of additional specific types of serious TEAEs with an incidence greater than 1% in this data cut than previously owing to the longer follow-up (indicated in the Table 15). As highlighted in the previous EAG report, [redacted] was more frequently observed in the dostarlimab+CP arm of both the dMMR/MSI-H subgroup and the overall population. The CS reports that the most frequently reported serious TEAEs in the dMMR/MSI-H group with higher incidence in the placebo+CP arm compared to the dostarlimab+CP arm included urinary tract infection, anaemia, asthenia, pulmonary embolism and colitis. However, the EAG notes the incidence of specific events remains low across the overall population.

Table 15: **Serious TEAEs occurring in ≥1% of either group**

	dMMR/MSI-H subgroup		**Overall population**	
Adverse event category	**Dostarlimab + CP**	**Placebo + CP**	**Dostarlimab + CP**	**Placebo + CP**
	(N=52)	**(N=65)**	**(N=241)**	**(N=246)**
Any serious TEAEs	[redacted]	[redacted]	96 (39.8%)	69 (28.0%)
Sepsis	[redacted]	[redacted]	8 (3.3%)	1 (0.4%)
Pulmonary embolism	[redacted]	[redacted]	8 (3.3%)	5 (2.0%)

Pyrexia	[redacted]	[redacted]	7 (2.9%)	2 (0.8%)
Dyspnoea	[redacted]	[redacted]	5 (2.1%)	1 (0.4%)
Muscular weakness	[redacted]	[redacted]	5 (2.1%)	1 (0.4%)
Anaemia	[redacted]	[redacted]	3 (1.2%)	6 (2.4%)
Asthenia	[redacted]	[redacted]	2 (0.8%)	6 (2.4%)
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Colitis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain[a]	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory distress syndrome[a]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation[a]	[redacted]	[redacted]	[redacted]	[redacted]
Balance disorder[a]	[redacted]	[redacted]	[redacted]	[redacted]
Cancer pain[a]	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Cerebrovascular accident[a]	[redacted]	[redacted]	[redacted]	[redacted]
Coccydynia[a]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration[a]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gastric ulcer[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal haemorrhage[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal pain[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal stoma complication[a]	[redacted]	[redacted]	[redacted]	[redacted]
Hydronephrosis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia[a]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia[a]	[redacted]	[redacted]	[redacted]	[redacted]
Hypovoalaemic shock[a]	[redacted]	[redacted]	[redacted]	[redacted]
Ileus[a]	[redacted]	[redacted]	[redacted]	[redacted]
Infected lymphocele[a]	[redacted]	[redacted]	[redacted]	[redacted]
Infection[a]	[redacted]	[redacted]	[redacted]	[redacted]

Intestinal perforation[a]	[redacted]	[redacted]	[redacted]	[redacted]
Keratitis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased[a]	[redacted]	[redacted]	[redacted]	[redacted]
Migraine[a]	[redacted]	[redacted]	[redacted]	[redacted]
Myelodysplastic syndrome[a]	[redacted]	[redacted]	[redacted]	[redacted]
Myelosuppression[a]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia[a]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenic sepsis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Pain[a]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Peritonitis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Polymyalgia rheumatica[a]	[redacted]	[redacted]	[redacted]	[redacted]
Small intestinal obstruction[a]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal claudication[a]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope[a]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia[a]	[redacted]	[redacted]	[redacted]	[redacted]
Type 1 diabetes mellitus[a]	[redacted]	[redacted]	[redacted]	[redacted]
Urosepsis[a]	[redacted]	[redacted]	[redacted]	[redacted]
Wound infection[a]	[redacted]	[redacted]	[redacted]	[redacted]

From CS Appendix F Table 14; CSR Table 25 and 14.3.1.12; Powell et al, 2024[18]
[a]Not reported in IA1

2.2.2.5.2 Dostarlimab-or Placebo related treatment emergent adverse events

The incidence of TEAEs of any grade (Table 16), attributed solely to dostarlimab or placebo (excluding those related to carboplatin or paclitaxel), was [redacted] in patients receiving dostarlimab+CP compared to those receiving placebo+CP. This trend was observed both in the dMMR/MSI-H subgroup and in the overall study population. This increase was primarily attributed to a higher incidence of gastrointestinal disorders, rash, and hypothyroidism among participants in the dostarlimab+CP treatment arm, particularly in the dMMR/MSI-H subgroup. The EAG highlights that in the dMMR/MSI-H subgroup, the proportion of any dostarlimab treatment related TEAEs has increased to [redacted] compared to IA1 [redacted] The rates of specific treatment related TEAEs are generally consistent with IA1, with the exception of arthralgia which is higher [redacted] than previously [redacted]. There are minimal

differences in the proportion of adverse events compared to the previous data-cut in the overall population.

Table 16: **Treatment-related adverse events related to dostarlimab or placebo only (occurring in >8% of either arm)**

	dMMR/MSI-H subgroup		Overall population	
Adverse event category N (%)	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Appendix F Table 7, CSR Table 22

2.2.2.5.3 Immune-related TEAEs

Immune-related adverse events (irAEs) of Grade ≥2 observed in the overall population only are summarized in Table 17.

Arthralgia was the most frequently reported irAE in both treatment arms, occurring in 14.9% of patients in the dostarlimab+CP group and 13% in the placebo+CP group. Hypothyroidism was the most common irAE specifically related to dostarlimab, with an incidence of 12%. The incidence of any irAES related to dostarlimab has increased compared to the previous data-cut (was 38.2% now 40.7%). There were

only minimal differences compared to IA1in other event categories. The EAG also compared the differences of irAE in the dMMR/MSI-H subgroup, presented in CS Appendix F Tables 16 and 17, with the previous data cut (not presented here). There were notable differences in any dostarlimab-related irAEs (now [redacted], was [redacted]); any non-hypersensitivity dostarlimab-related (now [redacted], was [redacted]); immune-mediated musculoskeletal dostarlimab-related (now [redacted], was [redacted]) and arthralgia dostarlimab-related events (now [redacted], was [redacted].

Overall, the adverse events observed in Ruby-1 were similar to those reported in IA1.

Table 17: **Immune-related TEAEs (defined as Grade ≥2) in the overall population**

	Dostarlimab + CP (N=241)		**Placebo + CP (N=246)**	
	All events	**Dostarlimab-related**	**All events**	**Placebo-related**
Any immune-related AE	**141 (58.5%)**	**98 (40.7%)**	**91 (37.0%)**	**40 (16.3%)**
Arthralgia	36 (14.9%)	16 (6.6%)	32 (13.0%)	16 (6.5%)
Infusion-related reaction	31 (12.9%)	4 (1.7%)	30 (12.2%)	0
Hypothyroidism	29 (12.0%)	29 (12.0%)	8 (3.3%)	7 (2.8%)
Hypersensitivity/ Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Rash	22 (9.1%)	17 (7.1%)	6 (2.4%)	5 (2.0%)
Rash maculo-papular	17 (7.1%)	12 (5.0%)	0	0
Pruritus	16 (6.6%)	8 (3.3%)	4 (1.6%)	3 (1.2%)
ALT increased	15 (6.2%)	15 (6.2%)	4 (1.6%)	3 (1.2%)
AST increased	12 (5.0%)	10 (4.1%)	3 (1.2%)	2 (0.8%)
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR Table 39; Powell et al, 2024;[18] Auranen et al, 2024[20]

2.3 *Real World Evidence*

In section B.2.2.1 the CS reports details of a UK real-world evidence (RWE) study conducted using the National Cancer Registration and Analysis Service (NCRAS); results of this study were provided in TA963 to provide context to the results of the RUBY-1 trial, but data were not available for the dMMR/MSI-H subgroup. An update of the study was conducted to identify patients who were tested for MMR status between 2019 and 2021, and this was included in the current submission.

The NCRAS study defines several different cohorts or subgroups of women diagnosed with advanced/recurrent EC (n=[redacted] in the overall cohort between 2013 and 2021). Data stratified according to biomarker status (dMMR, MMRp or not tested) were reported for the following two subgroups:

- ICI eligible 1L: described as the subgroup of patients akin to the RUBY-1 trial cohort who received a first line systemic anticancer treatment (2019-2021 [redacted]). Of these patients, [redacted] were *not* tested for biomarker status.
- ICI eligible 1L CP: described as the subgroup of patients akin to the RUBY-1 trial cohort who received first line systemic anticancer treatment alone (i.e. not in combination with radiotherapy), and the first line treatment was CP (2019-2021 [redacted]). Of these patients, [redacted] were *not* tested for biomarker status.

In section B.2.2.1, the CS reports that the dMMR/MSI-H subgroup [redacted] of the NCRAS study had a mean age of [redacted] at advanced diagnosis or recurrence and [redacted] were white, similar to the mean age of the relevant subgroup from RUBY-1 ([redacted] years). The EAG notes that this mean age value is for the ICI eligible 1L cohort. However, in section B.3.3.1, the CS reports a mean age of [redacted] years using the NCRAS data, and uses this value as the starting age in scenario analysis in the economic model. The EAG notes that this is the mean age for the ICI eligible 1L CP cohort ([redacted]) who have been filtered using RUBY-1 trial inclusion criteria, and therefore may not be representative of the UK NHS population. The EAG has several concerns regarding the cohorts selected by the company and notes their [redacted] sample size, which is due to a [redacted] of exclusions. Data were not available for the [redacted] of patients diagnosed between 2013 and 2018 when MMR status was not available on the NCRAS database. The NCRAS data show that some people in the UK have radiotherapy at first line or other types of chemotherapy at first line (some of which were used in RUBY-1), but these patients are excluded

from the company's selected cohort. In addition, different sequences and combinations of systemic anticancer therapy and radiation therapy were used in the RWE to define sequences of treatment/line of therapies, and this led to the subsequent exclusion of some patients from the company's selected cohorts. Furthermore, a [redacted] proportion of the selected cohorts diagnosed from 2019 onwards were not tested for biomarker status. From the NCRAS report tables provided to the EAG at clarification (clarification question A5), the EAG notes that mean age in the 'not tested' groups was [redacted] than the dMMR subgroup at [redacted] years for the ICI eligible 1L cohort and [redacted] years for the ICI eligible 1L C-P cohort; these values are [redacted] to the TA963 committee's preferred starting age of 67 as reported by a UK collaborative trial[21] reported in the original EAG report,[12] and used in TA904.[22]

The representativeness of the cohorts selected by the company in relation to current patients who might require the intervention in the UK is therefore uncertain. The EAG preference for the starting age in the model is discussed in Section 5.1.3.
[redacted]The company also mention the average age of the people who have receive dostarlimab through early access to medications scheme (EAMS).[23] Whilst the mean age is [redacted], the EAG is concerned at the small number of patients contributing information means this estimate is uncertain (advanced = [redacted], recurrent = [redacted]). The EAG experts mentioned that limited access to the treatment may have limited the uptake of dostarlimab, meaning this group is not representative of the wider dMMR/MSI-H population with advanced or recurrent disease.

2.4 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

No indirect comparison was performed by the company.

2.5 *Additional work on clinical effectiveness undertaken by the EAG*

2.5.1 Updated searches

The company conducted the latest update of their literature searches on 16 May 2024. The EAG updated these by running searches in Medline, Embase and the

Cochrane Library for RCTs of dostarlimab. The company's search strings for advanced endometrial cancer were used, with terms added for dostarlimab, the Cochrane search filter for RCTs (which is more sensitive than that used by the company), and limited to articles published in 2024. Full details of the EAG search can be found in Appendix 8.1. A total of 35 hits were identified after de-duplication and were independently screened by two reviewers. Six records were identified as relevant for the assessment of clinical effectiveness, one of which was already identified by the CS.[24] All five new records were additional publications of RUBY-1, reporting adverse events (2 conference abstracts),[20, 25] overall survival analysis (2 conference abstracts),[18, 26] and patient-reported outcomes (1 full text).[27] The EAG has checked the data in these publications against data provided in the CS but no additional data were reported.

2.5.2 One additional ongoing study was identified. The DOMENICA trial is comparing CP chemotherapy with dostarlimab monotherapy in advanced or recurrent endometrial cancer with dMMR, at first line. The trial intention to publish is December 2030. [28, 29]

[redacted]Generalisability

In TA963,[12] the EAG noted a number of issues that remain relevant to the current appraisal around the generalisability of the RUBY-1 trial to NHS care, which the EAG consider still apply:

- The EAG is uncertain that the dMMR / MSI-H population in the RUBY-1 trial is representative of the population in England and Wales who would be eligible for first line treatment for advanced or recurrent EC. RUBY-1 was a multinational study with only two UK participants in the dMMR/MSI-H group.
- The EAG considers that there are likely to be several differences between the RUBY-1 trial population and the relevant population in the UK. For instance, the mean age of participants in the UK independent of MMR status is higher than the RUBY-1 trial population (Section 2.3).
- EC is associated with obesity and commonly people with BMI significantly greater than the mean BMI in the trial are seen in the UK. This factor can limit treatment options as many will have significant co-morbidities.

- Patients with an ECOG score of 2 or higher would be provided with treatment in the UK, whereas RUBY-1 excluded these patients (which is common in clinical trials). In addition, a proportion of patients in the RUBY-1 trial did not have evaluable (or measurable) disease (Section 2.2.2.1), but in the UK only those with evaluable disease would be treated.
- There may also be differences in treatments between those in RUBY-1 and in UK clinical practice. Radiotherapy is used to treat stage III patients in the UK (Section 2.3), but this varies in other countries. The number of cycles of CP used in RUBY-1 is likely to be higher than used in UK clinical practice (Section 2.2.1.2.2), and the subsequent anti-cancer treatments are also likely to be different (Section 2.2.2.3).

2.6 *Conclusions of the clinical effectiveness section*

Overall, the EAG considers the same limitations apply to the evidence as were raised in TA963, and that the evidence provided more closely resembles a technology entering rather than emerging from managed access. Uncertainty and potential for bias remain due to the limited follow-up, small sample sizes and misclassification of patients during the randomisation of RUBY-1. The subsequent therapies used and their impact on the effectiveness data, along with the presence of patients without evaluable disease are further causes for concern. Whilst the EAG accepts that dostarlimab+CP provides clear benefit to patients over CP, the magnitude of the benefit and generalisability of the evidence to NHS patients remains uncertain.

3 COST EFFECTIVENESS

3.1 *EAG comment on company's review of cost-effectiveness evidence*

CS Appendices G, H and I provide details of SLRs to identify cost-effectiveness studies, health-related quality of life (HRQoL) and cost and healthcare resource use studies for patients with primary advanced or recurrent endometrial cancer. Searches were originally undertaken in November 2021 and updated on 22 February 2023 for the previous NICE appraisal of dostarlimab+CP for this indication (TA963).[14] Two further updates were run on 26 October 2023 and 16 May 2024.

3.1.1 Search strategies

CS Appendices G.1.1, H.1.1 and I.1.1 describe the literature search sources and strategies. A good, appropriate range of sources were searched for all three SLRs, including bibliographic databases, conference proceedings and HTA agencies' websites, although full details (search terms or browsing strategies) of the conference and website searches are not reported. The sources searched and the search terms used have not changed since the submission for NICE TA963.[14] The searches combine terms for population (recurrent or advanced endometrial cancer) with study type filters for cost-effectiveness, HRQoL and costs/resource use studies. As reported in the EAG's assessment of the company's searches for TA963, the search filters used for cost-effectiveness and HRQoL studies are quite narrow, but additional searches by the EAG at that time did not retrieve any further relevant studies.[12]

3.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

3.2.1 NICE reference case checklist

Table 18: NICE reference case checklist

Element	Reference case	EAG comment
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Yes.
Perspective on costs	NHS and PSS	Yes.

Element	Reference case	EAG comment
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. The time horizon is to when the patient is aged 100 years.
Synthesis of evidence on health effects	Based on systematic review	Clinical effects are taken from the RUBY-1 dMMR/MSI-H subgroup. Quality of life values are taken from the RUBY-1 ITT population. Values for the RUBY-1 dMMR/MSI-H subgroup are also presented.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.

Element	Reference case	EAG comment
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes. Costs are inflated to 2023 prices.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company reuses its TA963 model, revising some model inputs to reflect the IA2 data cut, most notably the overall survival (OS) data.

The model is a partitioned survival model with health states of progression free survival (PFS) and progressed disease (PD). It models the clinical and cost outcomes of dostarlimab+CP against placebo+CP. It uses data from the RUBY-1 dMMR/MSI-H subgroup for the main clinical effect estimates.

The model has a weekly cycle. The company base case applies the RUBY-1 baseline mean age of [redacted] years and has a time horizon to age 100 years.

For the company base case OS curves derived from the RUBY-1 IA2 data cut are estimated independently for the dostarlimab+CP arm and for the placebo+CP arm. The company base case applies the log-logistic curves with no treatment waning. When extrapolation of the log-logistic curves suggests a lower mortality risk than general female population mortality the model switches to general female population mortality.

PFS is similarly derived from parameterised curves independently estimated for the dostarlimab+CP arm and the placebo+CP arm, but these are from the RUBY-1 IA1 data cut. The company base case applies flexible splines for PFS. When the PFS curve cuts the OS curve the company assumes that PFS then follows the OS curve.

The proportion of patients with PD is the residual of OS minus PFS, this falling to zero when the PFS curve cuts the OS curve.

Quality of life values in the company base case for PFS of [redacted] and for PD of [redacted] are taken from the means of the RUBY-1 EQ-5D data of the ITT patient group. The means of the dMMR/MSI-H subgroup are [redacted] and [redacted]. The PFS and PD quality of life values are modelled to decline with age using standard UK sources.

In line with the SmPC dostarlimab is assumed to have a maximum treatment duration of 3 years. The proportion of patients receiving dostarlimab and its administration cost are based upon four main sources, all being based upon the IA1 data cut:

1. For the first 18 weeks cycle specific proportions of patients receiving dostarlimab+CP are taken from the RUBY-1 trial.
2. From week 19 the proportion receiving treatment is based upon the RUBY-1 Kaplan Meier (KM) time to treatment discontinuation (TTD) curve for dostarlimab, this data extending to 146 weeks.
3. For the short period after 146 weeks a Weibull fitted to the TTD data is applied. The model has the facility to apply parameterised curves rather than the TTD KM curve from an earlier point, including from baseline.
4. From week 19 a relative dose intensity (RDI) of [redacted] is applied.

The cost of 1st line carboplatin and paclitaxel are based upon RUBY-1 dosing data pooled across the arms and assuming a 100% RDI.

Patients who are modelled as progressing from PFS to PD incur the costs of a 2nd line treatment basket, the balance between treatments being based upon company expert opinion. Treatment costs per patient progressed are £4,951 for the dostarlimab+CP arm and £46,055 for the placebo+CP arm. The difference is due to it being assumed there is no 2nd line pembrolizumab in the dostarlimab arm, while there is substantial use of 2nd line pembrolizumab in the placebo arm. 2nd line costs result in large cost offsets for the company base case and are key model drivers.

Ongoing monitoring costs are based upon company expert opinion, differentiated by arm, by PFS and PD and by pre 18 weeks and from week 19.

SAEs are included in the model but have little effect upon net QALYs or net costs.

The details of the model structure and inputs are provided in sections 3.2.3 to 3.2.9. Most readers may wish to skip forward to the company cost effectiveness results of section 4.

3.2.3 Population

The baseline characteristics are an age of [redacted] years based upon RUBY-1, a weight of [redacted] kg and a body surface area (BSA) of [redacted] m^2.

3.2.4 Interventions and comparators

The company compares two treatment sequences.

- Dostarlimab+CP arm: 1st line dostarlimab in conjunction with carboplatin and paclitaxel followed by a basket of 2nd line treatments for those who progress.
- Placebo+CP arm: 1st line carboplatin and paclitaxel followed by a basket of 2nd line treatments for those who progress.

The 2nd line treatment baskets differ by arm, the balance of treatments within them being based upon company expert opinion. The key difference is the proportion of patients who progress that receive 2nd line pembrolizumab; 0% in the dostarlimab arm and 47% in the placebo arm.

3.2.5 Perspective, time horizon and discounting

The time horizon is set to when the patient is aged 100 years. The perspective and discounting are as per the NICE reference case.

The model includes the facility to include societal costs.

3.2.6 Treatment effectiveness and extrapolation

3.2.6.1 Progression-free survival

The company's modelling uses data from IA1 for PFS, [redacted]

[redacted]

Figure 6: PFS hazard rate from IA1 [redacted] of RUBY-1

3.2.6.1.1 Progression-Free Survival - CP

For the CP arm of RUBY-1, the EAG, company and committee all accepted the 2 knot odds spline model in TA963, which the company has maintained in the current submission.

The EAG remain content with this choice of model [redacted]. The difference is shown in Figure 7.

Figure 7: Impact of fitted 2-knot odds model to [redacted] IA1 (blue) for CP arm of RUBY-1.

3.2.6.1.2 Progression-Free Survival - Dostarlimab+CP

For PFS of dostarlimab+CP, the company preferred a 1 knot odds spline model in TA963 fitted to data from IA1, which the company maintains in this current submission. The EAG shows the impact of using the same model fitted to [redacted] and notes that [redacted]. The EAG was previously concerned about the lack of justification for a sustained long-term difference in hazard rates for PFS, where the people remaining event free after a number of years are likely to have equal prognosis regardless of which previous treatment they have received.

Previously, the EAG modelled an equal PFS hazard rate from roughly 5 years, where the hazard rates for the EAG preferred models crossed, to prevent a higher hazard rate for dostarlimab+CP. This could be considered a conservative assumption as there is a hypothetical risk of the hazard rate of dostarlimab+CP increasing above that of CP. The EAG's clinical expert stated it was possible that as dostarlimab therapy is stopped at 3 years, responders to dostarlimab+CP who have

sustained a response up to this point may then lose their response when stopping therapy, whilst the CP arm have no change to their care at this time.

The EAG considers this hypothesis to be potentially supported by the results from the NRG-GY018 trial investigating pembrolizumab+CP for advanced endometrial cancer where there is a late PFS event in the dMMR subgroup of the pembrolizumab+CP arm.[30]

[redacted]

[redacted]

Figure 8: [redacted]

[redacted]

The current EAG preference is to set the hazard rate for the PFS of dostarlimab+CP to tend towards that of CP from 3 years, being equal from 5 years (Figure 10). The EAG considers this approach [redacted] and supported by clinical rationale.

[redacted] The choice of flexible parametric model is fairly inconsequential, as all with 1 knot or more have a very similar visual fit to the data, and so the EAG maintains the use of the 1 knot odds model for simplicity.

The EAG also considers scenarios where the hazard rate for PFS is set equal from 5 years, and from 3 and 5 years where it becomes equal over a period of 2 years. The impact of this change on its own is relatively minor, due to PFS being constrained by the OS extrapolations.

Figure 9: Long term PFS Hazard Rates using the company's preferred models for CP (blue) and dostarlimab+CP (red) from RUBY-1 IA2.

Figure 10: Hazard rates from EAG base case assumption.

3.2.6.2 Overall survival

Previously, the company extrapolated overall survival data for CP via a piecewise approach where they used the Kaplan-Meier estimator for the duration of observed follow-up and then going beyond this using the hazard rate of a parametric model fitted to the data. For dostarlimab+CP in TA963, the company applied a hazard ratio estimated using data from RUBY-1 and applying this to the extrapolation for CP beyond the observed follow-up period.

In this current submission, using OS data from IA2, the company has switched to using standard parametric extrapolations without using the Kaplan-Meier estimates for both CP and dostarlimab, and no longer uses a hazard ratio. The information criteria of these are presented in Table 19, with the exponentials having the lowest AIC and BIC.

Table 19: OS parameterised curves information criteria

	EXP	WEIB	GOMP	LOGL	LOGN	GGAM	GAMM
Dostarlimab							

AIC	[redacted]						
BIC	[redacted]						
Placebo	[redacted]						
AIC	[redacted]						
BIC	[redacted]						

Exp: exponential, WEIB: Weibull, GOMP: Gompertz, LOGL: log logistic, LOGN: log normal, GGAM: generalised gamma, GAMM: gamma.

For dostarlimab+CP, all curves have a similar visual fit, as is common with such immature data (CS Doc B Figure 16). The company eliminates the exponential based upon the RUBY-1 data showing the hazard falling to week 50 then being broadly flat to week 150: Document B, Figure 14, page 66. Of the remaining curves it notes that the log-normal and log-logistic have the lowest information criteria, choosing the log-logistic due to it being a slightly more conservative extrapolation. For dostarlimab excluding the exponential model results in all the remaining AIC being within 1 point of each other, with the exception of the generalised gamma which is 1.3 above the log-normal though only 0.7 above the log-logistic. Similarly, all the BIC are within 1 point of each other with the exception of the generalised gamma. Figure 11 shows the differing predictions made by each parametric model.

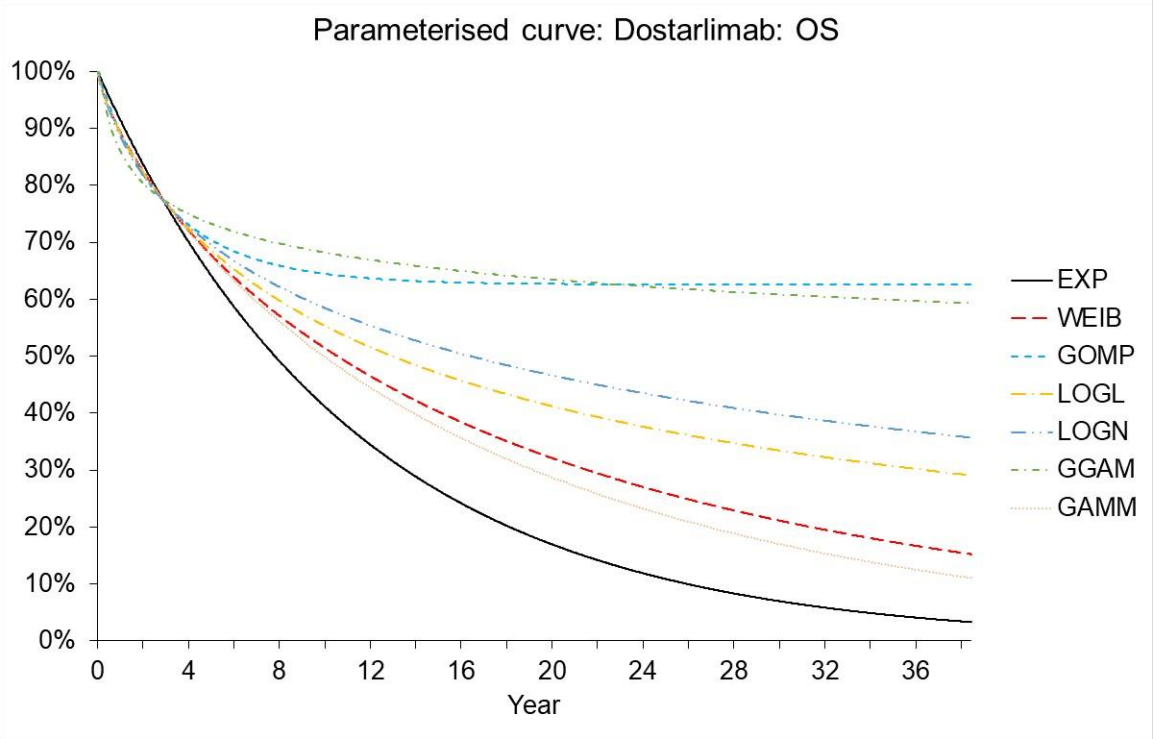

Figure 11: Overall survival parameterised curves: Dostarlimab

For the log-logistic model, the probability of dying becomes less than that of the female general population at 14.7 years when 47.4% of dostarlimab patients are modelled as surviving (Figure 12). These patients are subsequently extrapolated using the female general population probabilities of dying.

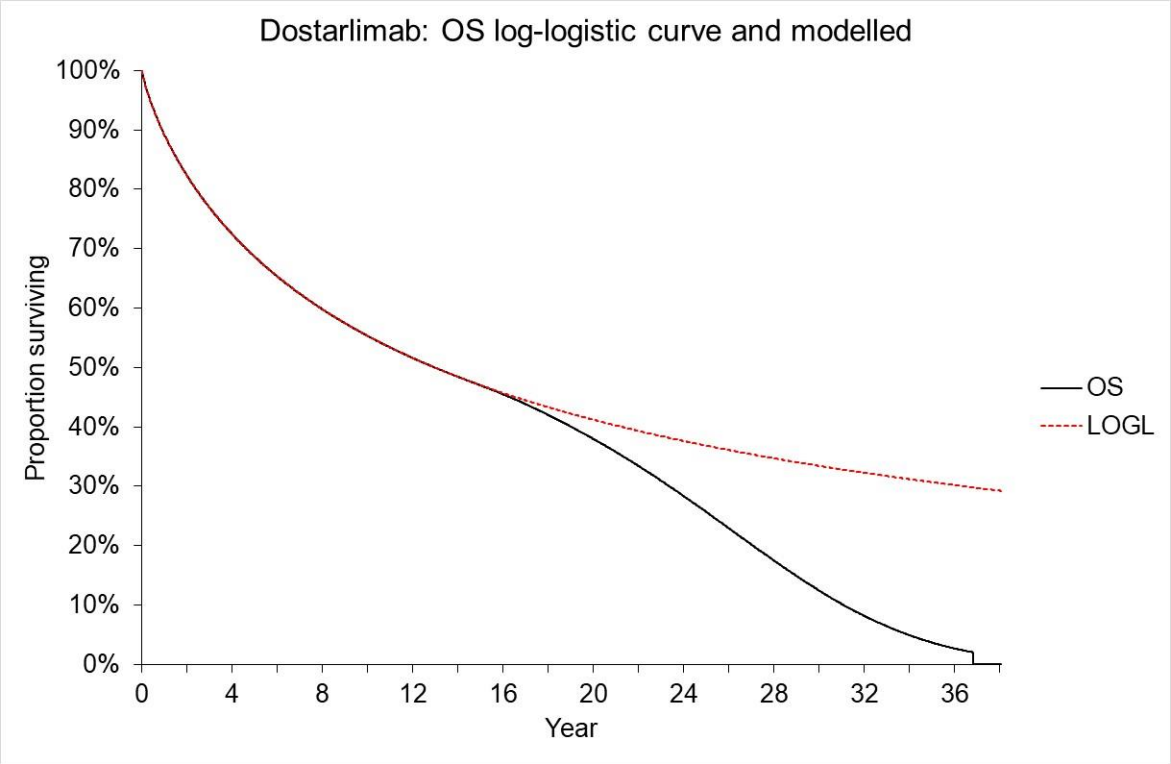

Figure 12: OS log-logistic curve and general mortality: Dostarlimab

Based upon the mean of company experts' opinions the company also selects the log-logistic for the placebo arm, which along with the log-normal provide the highest estimates of overall survival.

Table 20: Mean company experts' estimates for placebo OS versus curves

Year	Experts	EXP	WEIB	GOMP	LOGL	LOGN	GGAM	GAMM
5	21%	27%	22%	22%	27%	29%	28%	23%
10	9%	7%	3%	1%	12%	13%	11%	4%
15	5%	2%	0%	0%	7%	7%	5%	1%
20	4%	1%	0%	0%	5%	5%	3%	0%
Exp: exponential, WEIB: Weibull, GOMP: Gompertz, LOGL: log logistic, LOGN: log normal, GGAM: generalised gamma, GAMM: gamma.								

The EAG is concerned that the company's approach may fail to capture the benefit of subsequent immunotherapies received by patients initially receiving CP which is unlikely to be observed in the follow-up provided, and was raised by committee during TA963. The EAG is unable to explore this area of uncertainty and maintains the log-logistic extrapolation for CP in the EAG base case.

In Figure 13, the hazard rates for OS are shown for both arms, which can be compared with the hazard rates of the company's preferred extrapolations in Figure 14. The EAG considers that the hazard rate for both arms could be considered to be constant, and that the exponential model best represents the observed data. Note that the scale of the hazard plots for OS is much smaller than for PFS, suggesting there is very minimal change in either hazard rate over time.

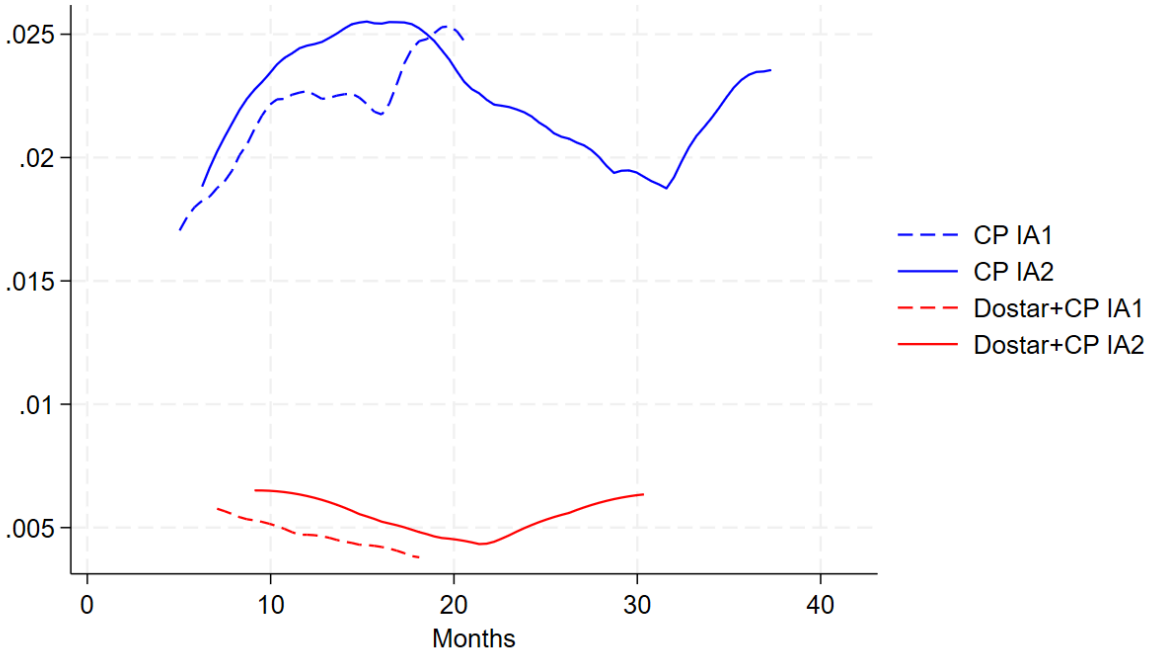

Figure 13: Smoothed hazard rates for OS from RUBY-1

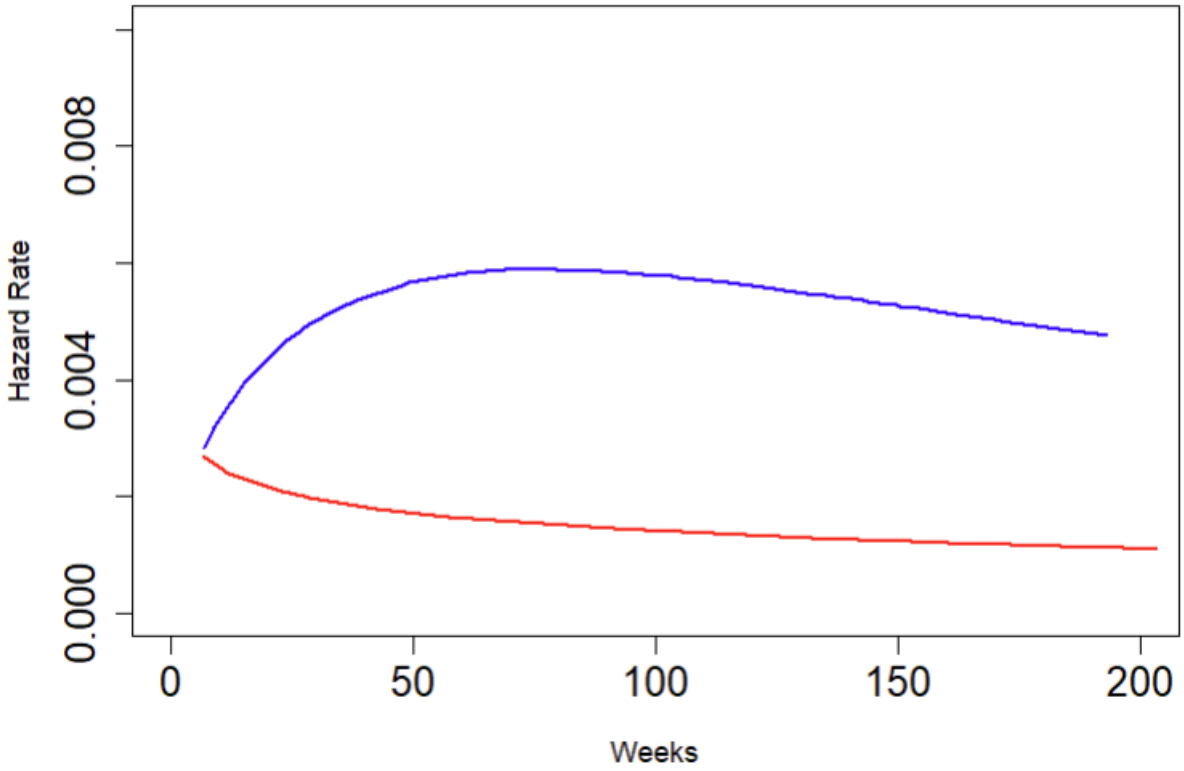

Figure 14: Overall Survival hazard rates from company's preferred log-logistic models fitted to IA2 data (blue = CP, red = dostarlimab+CP).

Examination of the company's economic model shows that the hazard rates converge at 21 years but only because background mortality is applied to the dostarlimab+CP hazard rate.

This is inconsistent with comments from the EAG clinical experts who stated that patient outcomes beyond 5 years were likely to be independent of which initial treatment was received. The EAG understands that patients surviving this long would have had a good response to a previous treatment, and there is no reason why mortality rates would differ beyond this point given the availability of subsequent immunotherapies to patients in the CP. The company's approach does not account for the impact of finishing treatment with dostarlimab, which is capped at 3 years, after which the EAG anticipates a more rapid convergence of the hazard rates than at 21 years.

Returning to the company's dostarlimab+CP OS extrapolation, the EAG is concerned by the reliance on background mortality, where almost 50% of people on dostarlimab remain alive. These people could be considered cured, as their mortality rate is no different to the UK general population. EAG expert opinion suggest cure rates for

dostarlimab might optimistically be up to around two thirds of the [redacted]% maintaining a complete response during RUBY-1 or around [redacted]%, though notes that some will argue that a cure might be possible among all those maintaining a complete response during RUBY.

As mentioned earlier, the behaviour of the hazards suggest the exponential may be most appropriate for OS extrapolation. EAG expert opinion suggests that at 5 years 40% of dostarlimab patients may remain alive, with this falling to perhaps around 30% at 10 years. The exponentials may therefore slightly underestimate long term overall survival for dostarlimab, given Figure 11. Given EAG expert opinion about possible cure rates the log-logistic with treatment effect waning at cessation of treatment may be more reasonable.

The proportion of baseline patients "cured" by dostarlimab+CP in terms of not progressing and coming to have the same mortality risk as the general population is presented in Table 21. Note that this applies the EAG preferred baseline age of 67.1 years briefly revised in section 5.1.3 below and [redacted].

Table 21: Modelled dostarlimab+CP 'cure' proportions using log-logistic OS

Waning	Waning Duration	Proportion Cured	Alive at age 77 (10 years)
None	[redacted]	[redacted]	[redacted]
After 3 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
After 4 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
After 5 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

The EAG explores the impact of these models on the cost-effectiveness results, and represents the EAG preferred models in Figure 15. For the EAG base-case, the EAG applies a convergence of hazard rates (waning) from 3 years, over a two year period, being equal at 5 years consistent with the EAG modelling for PFS.

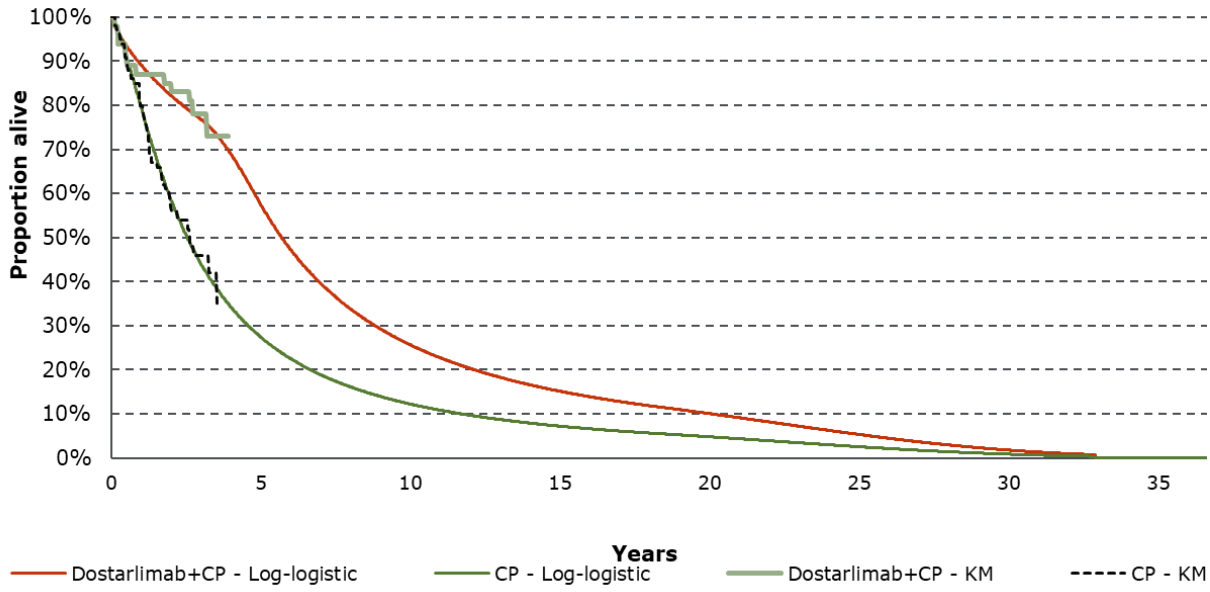

Figure 15: Log-logistic extrapolations of RUBY-1 IA2 OS, with waning applied for dostarlimab

Additionally, the EAG explores using an exponential model to extrapolate OS data for both arms. This choice of model is supported by the observed hazard rate in the available follow-up, and the small amount of data available, meaning more complex models are not advised.[31] The exponential model is the best statistical fit for dostarlimab+CP according to both AIC and BIC, and the best for CP for BIC.

The EAG acknowledges that the long-term estimates for both arms using the exponential model could be considered pessimistic, but as the data remains immature, a conservative extrapolation may be preferred by committee.

However, the EAG considers that the log-logistic model with waning applied aligns more closely with the estimates of the EAG's clinical experts (Table 22).

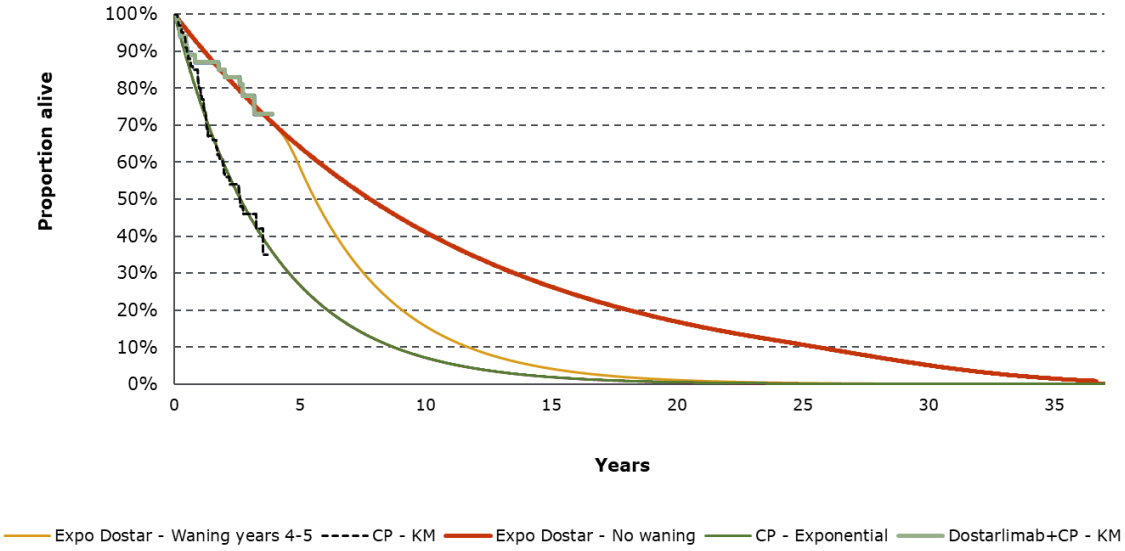

Figure 16: Exponential extrapolations of RUBY-1 IA2 OS

Table 22: Comparison of long-term OS predictions and extrapolations for dostarlimab

Time	EAG Expert Estimates	Log-logistic	Log-logistic 4-5 year waning	Exponential	Exponential 4-5 year waning
5 years	40%-60%	68.5%	62.9%	64.0%	58.4%
10 years	20%-30%	55.2%	28.0%	41.0%	15.6%
15 years	18%-20%	46.9%	16.5%	26.3%	4.2%
20 years	15%-20%	37.8%	11.2%	16.8%	1.1%

A summary of company and EAG preferences to modelling of PFS and OS is shown in Table 23.

Table 23:Overview of PFS and OS modelling preferences

	Company Base Case	EAG Base Case
PFS CP	2-knot odd spline extrapolation of RUBY-1 dMMR subgroup IA1	2-knot odd spline extrapolation of RUBY-1 dMMR subgroup [redacted]

PFS Dostar+CP	1-knot odd spline extrapolation of RUBY-1 dMMR subgroup IA1	1-knot odd spline extrapolation of RUBY-1 dMMR subgroup [redacted], then equal hazard rate to CP from 3 years
OS CP	Log-logistic extrapolation of RUBY-1 dMMR subgroup IA2	Log-logistic extrapolation of RUBY-1 dMMR subgroup IA2
OS Dostar + CP	Log-logistic extrapolation of RUBY-1 dMMR subgroup IA2	Log-logistic extrapolation of RUBY-1 dMMR subgroup IA2 with hazards becoming equal across years 4 - 5.

3.2.6.3 Time-to-discontinuation of dostarlimab

The dostarlimab+CP time to treatment discontinuation (TTD) is handled differently to OS and PFS. The company fits the usual set of parameterised curves (Figure 17). The information criteria for the parameterised curves fitted to TTD are shown in Table 24.

Figure 17: IA1: Parameterised curves: Dostarlimab: TTD

Table 24: Dostarlimab+CP TTD parameterised curves information criteria

	EXP	WEIB	GOMP	LOGL	LOGN	GGAM	GAMM
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exp: exponential, WEIB: Weibull, GOMP: Gompertz, LOGL: log logistic, LOGN: log normal, GGAM: generalised gamma, GAMM: gamma.							

But in contrast to the modelling of PFS the parameterised curves are largely unused, the modelling of the dostarlimab+CP TTD consisting of three portions:

- Weeks 1 to 16: Applying the proportion of patients who received treatment with dostarlimab based upon IA1 data.
- Week 16 to week 145: Applying the TTD Kaplan Meier IA1 curve.
- Week 146 to week 150: Extrapolating by applying the probability of treatment cessation from a parameterised curve fitted to the TTD KM IA1 curve, the base case applying the Weibull. For the company base case this only applies to the last Q6W dostarlimab treatment so the choice of curve has little bearing upon costs.

- In line with the SmPC it is assumed that dostarlimab treatment is withdrawn at the end of year 3.

At baseline [redacted] of dostarlimab+CP PFS patients are modelled as receiving dostarlimab treatment. This steadily [redacted] until by the end of the third year [redacted] of those remaining in PFS are modelled as being treated with dostarlimab as shown in Figure 18.

Figure 18: Relationship between PFS and TTD: Dostarlimab

3.2.6.4 Time-to-discontinuation of CP

The numbers receiving CP treatment from baseline to week 16 are pooled across the dostarlimab arm and the placebo arm and applied.

The company provides the arm specific TTD KM curves and arm specific parameterised curves fitted to this data but neither are applied in the company base case. The relationship between PFS and TTD from IA1 of RUBY-1 is shown in Figure 19, treatment with carboplatin and paclitaxel only extending to a maximum of 18 weeks.

Figure 19: Relationship between PFS and TTD from RUBY-1 IA1: Carboplatin and paclitaxel

3.2.7 Adverse events

The company applies estimates for a range of adverse events based upon those which were experienced by at least 2% in the ITT population and the IA2 data cut, as tabulated in Table 27 on page 88 of CS Document B.

Costs are taken from a range of NHS reference costs, with quality of life decrements being taken from the literature. For the calculation of the QALY losses all adverse events are assumed to last one week. This results in total costs of £670 in the dostarlimab arm, £600 in the placebo arm and a net effect of £70. The estimated effects upon QALYs are insignificant.

For the adverse events of 2nd line treatments a range of values are taken from the literature. These have little effect upon results and are not further explored by the EAG.

3.2.8 Health related quality of life

The quality of life values for the PFS health state and PD health state are taken from RUBY-1 EQ-5D, the company presenting mean (SE) values for the ITT population and the dMMR/MSI-H population of Table 25. The company chooses the ITT values due to them being from a larger data set, which also have a higher value for PFS and a larger difference between PFS and PD.

Table 25: Company quality of life values

	dMMR/MSI-H Mean (SE)	ITT Mean (SE)	Difference: ITT – dMMR/MSI-H
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
PFS - PD	[redacted]	[redacted]	[redacted]

3.2.9 Resources and costs

All costs are inflated to 2023 prices.

3.2.9.1 Diagnostic costs

The company base case does not include test costs.

The model contains the facility to include immunohistochemistry test costs of £237 based upon Snowsill et al,[32] and assuming a prevalence in the tested population of 23% based upon the NICE DG42 resource impact report for testing for Lynch syndrome in people with endometrial cancer. If included this increases costs in the dostarlimab arm by £1,051.

3.2.9.2 1st line drug and administration costs

Carboplatin dosing is based upon the area under the plasma concentration time curve 5mg per mg/ml/min (Table 26). Given a glomerular filtration rate of 63.91 mL/min/1.73m^2 the company infers a required dose of 445mg so applies the cost of the 450mg vial.

Paclitaxel is dosed at 175mg per m^2 body surface area (BSA). Given a BSA of [redacted] m^2 this results in a dose of [redacted] mg and a requirement for four 100mg vials.

The administration cost of carboplatin plus paclitaxel is taken from NHS reference cost SB13Z: More Complex Parenteral Chemotherapy, First Attendance.

Table 26: 1st line drug and administration costs: placebo arm: 3 weekly

	mg	Cost	Dose	Req.	Vials	Cost
Carboplatin	450	£169	5	445	1	£169
Paclitaxel	100	£200	275	343	4	£801
Admin						£364
Total						£1,334

The dosing for dostarlimab for the first 18 weeks is 500mg every three weeks in conjunction with carboplatin and paclitaxel (Table 27). Dostarlimab with carboplatin and paclitaxel is assumed to have the same administration cost as carboplatin and paclitaxel.

The dosing for dostarlimab from week 19 is 1,000mg every 6 weeks. Administration costs are less and are based upon NHS reference cost SB12Z: Simple Parenteral Chemotherapy, First Attendance.

Table 27: 1st line drug and administration costs: dostarlimab arm

	mg	Cost	Dose	Req.	Vials	Cost
Weeks 1 to 18: 3 weekly						
Dostarlimab	500	[redacted]	500	500	1	[redacted]
Carb+Pacl						£970
Admin						£364
Total						[redacted]
From week 19: 6 weekly						
Dostarlimab	500	[redacted]	1,000	1,000	2	[redacted]
RDI adjusted						£4,885
Admin						£295
Total						[redacted]

Note that Table 27 is not strictly correct to sum the dostarlimab cost with the carboplatin and paclitaxel cost during weeks 1 to 18 due to differing proportions receiving these in the dostarlimab+CP arm.

3.2.9.3 Relative dose intensity (RDI) for dostarlimab

From week 19 onwards a relative dose intensity, RDI, of [redacted] is applied to the proportion of patients modelled as receiving dostarlimab. The company states that this is defined in the statistical analysis plan (SAP). Unfortunately, the EAG has not been able to find this within the SAP despite free text searches.

The RDI appears to be the ratio of the total product administered from week 19 divided by that which would have been administered if dosing had been 1,000mg every 6 weeks for the duration of therapy. The [redacted] RDI is a simple average across patients, and not weighted by duration of treatment.

3.2.9.4 2nd line drug and administration costs

2nd line drug costs per treatment cycle, not per model cycle, are as presented in Table 28, with administration costs being either SB13Z or SB12Z. 2nd line carboplatin plus paclitaxel is assumed to incur two SB13Z administration costs so a total of £728. Doxorubicin is dosed based upon the mean BSA of [redacted], with bevacizumab dosed based upon the mean weight of [redacted].

Table 28: 2nd line drug and administration costs: per treatment cycle

	mg	Cost	Dose	Req.	Units	Cost
Carboplatin	600	£233	5	445	1	£233
Paclitaxel	100	£200	175	343	4	£801
Admin						£728
Total						£1,762
Pembrol.	100	£2,630	400	400	4	£10,520
Admin						£295
Total						£10,815
Doxorubicin	50	£712	70	137	3	£2,137
Admin						£295
Total						£2,432

Bevacizumab Admin	400	£810	15	£1,337	4	£3,240 £295
Total						£3,535
Pembrol. Lenvatinib Admin	100 300	£2,630 £1,437	200 10 b.d.	200 20 * 21	2 1.4	£5,260 £2,012 £295
Total						£7,567

Letrozole and medroxyprogesterone acetate do not have treatment cycles but are rather daily treatments. Letrozole is £1.20 for a 28 tablet pack resulting in a monthly cost of £1.30, while medroxyprogesterone acetate is £59 for a pack of 30 resulting in a monthly cost of £59.53.

The mean duration of treatment and number of cycles are presented in Table 29 based upon the cycle length in weeks. The mean durations of treatment are taken from a number of papers in the literature. Radiotherapy is also added with a cost of £3,338, based upon that used in TA779. When coupled with the company expert opinion it results in the average total cost by arm.

Table 29: 2nd line drug and administration costs: total cost

	£/Cyc.	Cyc.Len	Mths	Cycles	Cost	DOST	PLAC
Carb+Pacl	£1,762	3	3.2	4.64	£8,171	[redacted]	[redacted]
Pembro.	£10,815	6	12.2	8.84	£95,618	[redacted]	[redacted]
Doxo.	£2,432	3	2.1	3.04	£7,403	[redacted]	[redacted]
Beva.	£3,535	3	4.2	6.04	£21,364	[redacted]	[redacted]
Pemb+L	£7,567	3	6.6	9.57	£72,383	[redacted]	[redacted]
Letrozole	£1.30	n.a.	3.2	3.2	£4	[redacted]	[redacted]
Med.Acet.	£59.53	n.a.	3.2	3.2	£190	[redacted]	[redacted]
Radio.					£3,338	[redacted]	[redacted]
None					..	[redacted]	[redacted]
Total						[redacted]	[redacted]

Carb+Pacl: carboplatin plus paclitaxel, Pembro. : pembrolizumab, Doxo.: doxorubicin, Beva.: bevacizumab, Pemb+L: pembrolizumab plus lenvatinib, Med.Acet.: medroxyprogesterone acetate, Radio.: radiotherapy

There is a large discrepancy in 2nd line therapy cost. In the dostarlimab+CP arm those progressing incur a 2nd line therapy cost of [redacted], while in the placebo arm those progressing incur a 2nd line therapy cost of [redacted]. The difference between these costs is mainly due to [redacted] who progress in the dostarlimab+CP arm receiving 2nd line pembrolizumab, but [redacted] who progress in the placebo arm receiving 2nd line pembrolizumab.

3.2.9.5 Ongoing resource use

Ongoing resource use is based upon expert opinion (Table 30). This is differentiated by weeks 1 to 18 and from week 19 and by whether the patient is in PFS or PD. It is also differentiated by arm for those in PFS from week 19, those in the placebo arm requiring fewer OP visits, CT scans and blood counts. This is coupled with a variety of unit costs, which are largely taken from NHS reference costs, though unit costs of primary care are taken from the PSSRU Unit Costs and Health and Social Care. The model contains a placeholder for blood pressure and heart rate monitoring but no resource use is specified here.

Table 30: Company ongoing quarterly resource use: Expert opinion

	Weeks 1 - 18		Weeks 19+			
	PFS	PD	DOST PFS	PLAC PFS	PD	Cost
OP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194
CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139
Blood count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3
BP and Heart	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222
Specialist nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59
GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47
Quarterly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Weekly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

3.2.9.6 End of life costs

An end of life cost of £8,105 is taken from Guest et al,[33] which inflated to 2023 prices increases to £8,717.

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

There are commercial agreements in place for pembrolizumab and lenvatinib. The results of this section only include the patient access scheme (PAS) discount for dostarlimab. Other treatments are costed using list prices as per Table 26, Table 27 and Table 28 above. A confidential cPAS appendix that applies the other price discounts has been supplied[1].

4.2 *Company's sensitivity analyses*

Undiscounted survival estimates are presented in Table 31, with discounted QALYs being presented in Table 32.

Table 31: Company base case undiscounted survival in years

	Dostarlimab	Placebo	Net
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 32: Company base case discounted QALYs

	Dostarlimab	Placebo	Net
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

[1] The EAG revised model has the cPAS prices redacted but retains the cPAS functionality that is used by the EAG to generate the cPAS appendix. The EAG urges the company to check this implementation.

The disaggregate costs of the company base case are presented in Table 33.

Table 33: Company base case disaggregate costs

	Dostarlimab	Placebo	Net
Test costs	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]
Carboplatin + Paclitaxel	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
Total 1st line costs[2]	[redacted]	[redacted]	[redacted]
2nd line treatments	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]
Total health state costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

This results in the net effects and cost effectiveness estimate of Table 34.

Table 34: Company base case disaggregate costs

	Dostarlimab	Placebo	Net
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

The probabilistic modelling estimates a central cost effectiveness of [redacted] per QALY and a probability of dostarlimab+CP being the most cost-effective treatment of [redacted] at willingness to pay values of £20,000, £30,000 and £50,000 per QALY. Figure 20 presents the company base case cost effectiveness acceptability curve (CEAC).

[2] The total 1st line costs and health state costs are taken from the company model, the disaggregate costs within these from the EAG model rebuild due to the company model not costs disaggregated to this level.

Figure 20: Company base case CEAC

4.3 *Company subgroup analysis*

No subgroup analyses are presented due to the dMMR/MSI-H already being a pre-specified subgroup of RUBY-1 and patient numbers being small.

4.4 *Company scenario analyses*

The company provides a range of one-way sensitivity analyses and scenario analyses. For the parameters of the OS log-logistic curves the company applies the lower and upper limits of the confidence intervals as outlined in Table 35.

Table 35: Company OS log-logistic curve parameters

	Dostarlimab+CP arm			Placebo arm		
	Mean	Low C.I.	Upper C.I.	Mean	Low C.I.	Upper C.I.
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These result in the results within Table 36.

Table 36: Company one-way sensitivity analyses

	Original	Lower	ICER	Upper	ICER
Base case	..	..	[redacted]	..	[redacted]
DOST: OS Log-L params	Mean	Low C.I.	[redacted]	Upper C.I.	[redacted]
Cost pemb. tx	£95,618	£61,879	[redacted]	£136,581	[redacted]
DOST: Dost. % wk 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PLAC: 2nd line pemb. %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DOST: PFS OP wk 19+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OP unit cost	£194	£125	[redacted]	£277	[redacted]
PLAC: OS Log-L params	Mean	Low C.I.	[redacted]	Upper C.I.	[redacted]
PLAC: 2nd line no tx	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DOST: PFS CT wk 19+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DOST: £ admin wk 19+	£295	£191	[redacted]	£421	[redacted]

Cost pemb. Tx: Total cost for 2nd line pembrolizumab, Dost. % wk 16: % receiving dostarlimab week 16, PFS CT wk 19+: proportion getting CT scan from week 19

The company scenario analyses are presented in Table 37. Due to the EAG cPAS appendix that incorporates the confidential price discounts of other treatments, the EAG does not present the company scenarios for discounts on the price of lenvatinib and pembrolizumab.

Table 37: Company scenario analyses

	Original	Scenario	Net Cost	Net QALY	ICER
Base case	..	..	[redacted]	[redacted]	[redacted]
Baseline age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	1.5%	[redacted]	[redacted]	[redacted]
2nd line treatments	Experts	RUBY	[redacted]	[redacted]	[redacted]
DOST OS curve	Log-L	G.Gam	[redacted]	[redacted]	[redacted]
DOST OS curve	Log-L	Weibull	[redacted]	[redacted]	[redacted]
OS curves	Indep.	HR	[redacted]	[redacted]	[redacted]
Waning	None	8 to 10 yr	[redacted]	[redacted]	[redacted]

G.Gam: Generalised gamma, Indep: independent, HR: Hazard ratio applied to placebo curve

4.5 *Model validation and face validity check*

4.5.1 EAG cross check model rebuild

The EAG has fully rebuilt the deterministic economic model for the company base case. When applying the company base case inputs and assumptions the resulting net gain, net cost and ICER of 4.418 QALYs, [redacted] and [redacted] per QALY are very close to the 4.418 QALYs, [redacted] and [redacted] per QALY of the company base case.

There are some minor errors in the company model structure and inputs. BNF list prices have also typically been used rather than the publicly available CMU eMIT prices where available.

- There is a referencing error in the OS hazard ratios. This does not affect the company base case.
- The cost of the fourth carboplatin and paclitaxel administration is not included in the dostarlimab+CP arm.
- The quality of life values applied for SAEs due to Model Parameters cells L337:L341 not being zero.
- A price indexing error in the cost of 2nd line radiotherapy.
- The company applies BNF costs of £20,20, £56.92, £168.85 and £232.54 for 50mg, 150mg, 450mg and 600mg of carboplatin, rather than the eMIT costs of £9.28, £20.22, £48.09 and £71.44.
- The company applies a BNF cost of £200.35 for 100mg of paclitaxel albumin. EAG expert opinion suggests that the CMU eMIT cost of £9.13 for 100mg standard paclitaxel should be applied, this being in line with the NICE price checker.
- The NICE price checker suggests that rather than the company BNF cost of £712.49 for 50mg pegolated doxorubicin the eMIT cost of £495.98 for 50mg pegolated doxorubicin should be applied, EAG expert opinion agreeing that

pegolated doxorubicin is appropriate rather than standard doxorubicin at an eMIT cost of £12.15 for 50mg.

4.5.2 Validation

As reviewed in greater detail in section 5.1.2 below, the company base case estimates that 60% of those in the dostarlimab arm are "cured" in the sense of never progressing. If those "cured" are also required to have general population mortality risks the proportion "cured" is around 50%.

EAG expert opinion suggests that "cure" is typically not used when treating advanced or recurrent endometrial cancer, but that some or all of those with a complete response could maintain this response. EAG expert opinion notes the absence of much evidence for the period beyond 3 years when dostarlimab treatment is withdrawn.

The proportions with a best response of complete response at IA1 in RUBY-1 were [redacted] in the dostarlimab arm and [redacted] in the placebo arm. At IA1 complete response was retained by [redacted] in the dostarlimab arm. EAG expert opinion is that it might optimistically be assumed that two thirds of these or around [redacted] might be "cured" by dostarlimab.

EAG expert opinion also notes that those with a partial response are likely to experience disease recurrence, but that ongoing dostarlimab use may help postpone this for the duration of dostarlimab use.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL CRITIQUE AND ANALYSES

5.1 *EAG critique of clinical elements of the company model*

5.1.1 Model structure

The EAG has two concerns about the company model structure.

- It does not model patients discontinuing dostarlimab for reasons other than progression. The EAG thinks that the underlying assumption is in effect that

those discontinuing dostarlimab for reasons other than progression have the same risks of progression as those remaining on dostarlimab but with none of the costs of dostarlimab. This causes the PFS curve and the TTD curve to diverge. During RUBY-1 the treatment rates of those in PFS was quite high. For instance, for the RUBY-1 IA1 data cut at week 99 of the [redacted] patients in PFS all [redacted] or 100%[3] remained on treatment. The company base case assumes that at week 99 only 74% of those in PFS remain on treatment. This issue is addressed in greater detail in section 5.3.3 below.

- It exhibits some non-linearity in age. This could argue for an individual patient model structure. At clarification the company supplied the histogram of age at baseline for the RUBY-1 dMMR/MSI-H population, banded into 6 year ranges. Applying the RUBY-1 age histogram results in an ICER of [redacted], or around 4% worse than the company base case. The EAG will provide a scenario analysis that samples age. It can be argued that the base case should adopt this approach.

5.1.2 The modelled proportion of patients cured by dostarlimab

The results of the survival modelling suggest that some people could be considered 'cured', though this depends on your definition of cure. For example, this could be when there is no probability of moving from the PFS health state into the PD health state. Alternatively, it could be taken to be when there is no probability of moving from the PFS health state into the PD health state and the probability of dying from PFS is no worse than that of the general public.

The trial data defines progression as either moving into progressive disease or dying. Figure 21 presents the modelled weekly probabilities of (1) moving from PFS into PD for the dostarlimab arm, (2) dying from PFS and (3) the general female population probability of death.

[3] Assuming that there were no PD patients being treated at this point.

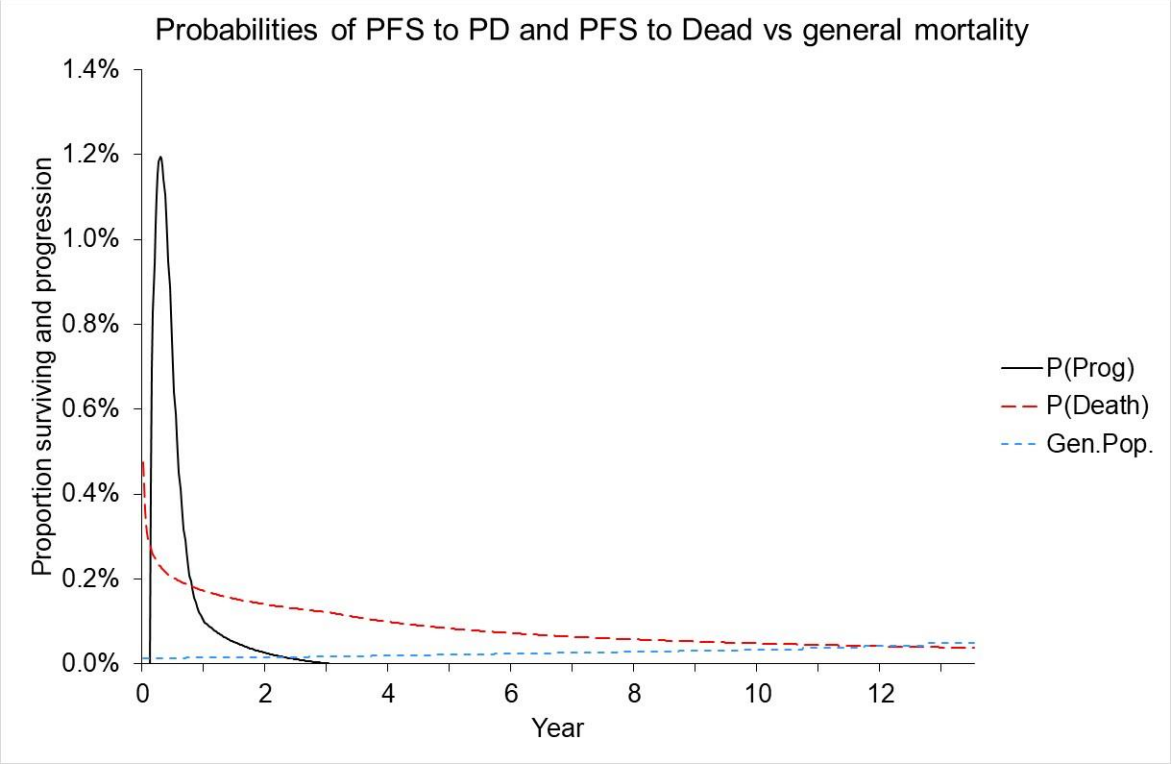

Figure 21: Probabilities of moving from PFS to PD and of moving from PFS to death set against general population mortality: dostarlimab+CP arm.

Figure 21 shows that within the dostarlimab+CP arm for the company base case, by year 3.1 there is no probability of moving into progressive disease and so no probability of incurring the costs of 2nd line treatment and the lower quality of life of progressive disease. This applies when 56.9% of patients in the dostarlimab+CP arm are modelled as being in PFS.

The PFS mortality[4] remains above that of the general population until year 11.7 when the proportion of the original population who are modelled as still surviving and remaining in PFS is 41.9%.

This figure needs to be adjusted for general population mortality; i.e. given a baseline age of [redacted] years, after 11.7 years general mortality means that [redacted]% of the general population remain alive. If the 41.9% who remain in PFS at 11.7 years are deemed to have been cured, the proportion of the baseline population that would

[4] Calculated as the probability of moving out of PFS minus the probability of progressing into PD

need to have been cured within around 6 months of baseline and so only subject to general population mortality is 41.9% / [redacted]% = [redacted]%.

Which figure should be viewed as the modelled cure rate for dostarlimab+CP is a matter for debate.

- 56.9% at year 3.1, or 58.3% of baseline when adjusted for general mortality
- 41.9% at year 11.7, or 48.5% of baseline when adjusted for general mortality

The EAG has some sympathy with the 58.3% at year 3.1 due to the model assuming that from this point forwards no patients in the dostarlimab arm move into progressive disease, meaning that none incur the costs or quality of life detriments associated with PD. This might best be described as all surviving patients being in indefinite remission or cured. But there are arguments in favour of the other proportion which suggests around 50% of the baseline population being cured.

These “cure” rates can be compared to the RUBY-1 IA1 proportions of those with a best response of complete response and those with a best response of partial response. Table 38 provides this for the subset of those with evaluable disease at baseline.

Table 38: IA1: Best response of Complete Response and Partial Response

Best response	Complete Response		Partial Response	
	Dostar	Placebo	Dostar	Placebo
N	53	65	53	65
N with eval. dis.	49	58	49	58
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Note that in Table 38 the percentages of those with a best response of partial response do not tally with the patient numbers, the latter suggesting percentages of [redacted] for the dostarlimab+CP arm and [redacted] in the placebo arm. The EAG may have misinterpreted the figures supplied in response to clarification question A10, the denominator may differ for partial response for some reason or there may be a company error.

For the IA1 data cut, in the dostarlimab arm only [redacted] patient(s) with complete response lost response status by month 24 with a Kaplan Meier S(t) of [redacted], suggesting an IA1

retention of complete response as a proportion of all patients at baseline at month 24 of [redacted] for the dostarlimab+CP arm. But only [redacted] of the original [redacted] dostarlimab arm patients with complete response remained at risk at 24 months due to the limited follow up of IA1, with [redacted] remaining at risk by month 30.

The above is complicated by the company response to Factual Accuracy Check (FAC) possibly suggesting that loss of a best response of complete response was only recorded if the patient progressed. It is unclear to the EAG if this means that those with a best response of complete response with subsequent disease recurrence but a superior disease state to their baseline disease state would not be classed as having lost complete response. It is possible that fewer than the [redacted] patients with evaluable disease at baseline and a best response of complete response had no evidence of disease recurrence at IA1.

During FAC the company highlighted pembrolizumab data which suggested that some patients retain partial response and stable disease into the medium term. The EAG does not dispute this but it does not address the question to hand. Do those with partial response have no probability of progression and no elevated mortality risk compared to the general population? And similarly do those with stable disease have no probability of progression and no elevated mortality risk compared to the general population?

The proportion retaining complete response at 24 months is around half the proportion that are modelled as being cured. The EAG thinks that maintenance of complete response is a necessary condition for being cured, in the sense of never progressing and having the same mortality risk as the female general population.

It can be noted in passing that retention of response among those with a best response of complete response was much lower in the placebo arm, with [redacted] of the [redacted] placebo arm patients losing their response.

If available IA2 data for loss of complete response could provide more confidence in the estimates of duration of response, at least for the period patients remain on dostarlimab treatment. But only a few more patients losing complete response by the IA2 data cut would significantly reduce the proportion of patients retaining complete response. It may be possible for the company to clarify this during FAC.

The proportion of those with a best response of partial response was virtually the same in both arms. Loss of partial response was slower in the dostarlimab arm. By month 24, [redacted] patients had been recorded as losing partial response with a Kaplan Meier S(t) of [redacted], though only [redacted] patients at risk remained at this point. But this compares favourably with [redacted] loss of partial response events among the [redacted] with a best response of partial response having been recorded in the placebo arm and few if any retaining partial response after 24 months.

This is consistent with EAG expert opinion that suggests for those with partial response dostarlimab treatment may delay progression while patients remain on treatment, and perhaps even beyond the 3 year point when dostarlimab treatment is withdrawn. But EAG expert opinion is that it will not prevent progression among those with a best response of only partial response once treatment is withdrawn and that there will be convergence with the placebo arm over time. Again, assessment of this as in all the clinical variables is hampered by there being little data about what happens to patients when dostarlimab is withdrawn at 3 years.

EAG expert opinion suggest ‘cure’ rates for dostarlimab might optimistically be up to around two thirds of the [redacted] maintaining a complete response during RUBY-1 or around [redacted], though notes that some will argue that a ‘cure’ might be possible among all those maintaining a complete response during RUBY-1.

As reviewed in section 3.2.6.2 the behaviour of the hazards suggests that the exponential may be most appropriate for OS extrapolation. EAG expert opinion suggests that at 5 years 40% of dostarlimab patients may remain alive, with this falling to perhaps around 30% at 10 years. The exponentials may therefore slightly underestimate long term overall survival for dostarlimab, given Figure 11. Given EAG expert opinion about possible cure rates the log-logistic with treatment effect waning at cessation of treatment may be more reasonable.

The proportion of baseline patients “cured” by dostarlimab in terms of never progressing and having the same mortality risk as the general population is presented in Table 39 below. Note that this applies the EAG preferred baseline age of 67.1 years as briefly reviewed in section 5.1.3 below [redacted] in order to permit consideration in the context of the EAG revised base case.

The scenarios with OS waning also wane PFS on the same basis.

Table 39: Modelled "cure" proportion for log-logistic OS with waning

Waning	Waning duration	Proportion cured	Alive at age 77
None	[redacted]	[redacted]	[redacted]
After 3 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
After 4 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
After 5 years	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Given EAG expert opinion, the EAG exploratory base case applies the log-logistic with waning from the end of year 3 over a 2-year period. This results in the following curves.

Figure 22: EAG revised base case OS and PFS curves

The EAG provides scenarios of waning after 4 years and after 5 years, each with 2 years waning duration. The EAG also provides scenarios that apply the OS exponentials, with no waning and with waning from year 3 over 2 years.

5.1.3 Mean baseline age

The EAG report for the previous assessment preferred a mean age of 67.1 years based upon Pennington et al,[21] rather than the [redacted] years taken from RUBY-1. The EAG noted that though the sample size was small at N=39, Pennington et al. was the most relevant population to England and Wales, was supported by expert opinion and reflected the preferences of Committee during TA904. Table 16 of the EAG report for TA963 also outlines a number of alternative sources which are aligned with the EAG preference

As reviewed in greater detail in section 2.3, the EAG retains its preference and will apply the 67.1 years in its exploratory base case.

5.1.4 2nd line treatments: RUBY-1 versus the NHS

Whether NHS patients will be eligible for 2nd line pembrolizumab, or pembrolizumab + lenvatinib, after having had dostarlimab is uncertain. The EAG has not been able to find anything that definitively states that patients cannot have pembrolizumab after dostarlimab within the NHS.

During Factual Accuracy Check the company cites NHSE guidance for pembrolizumab stating eligibility criteria that "*the patient has not received any prior antibody treatment which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) unless the patient has received pembrolizumab via the MSD company early access scheme and all other treatment criteria on this form are fulfilled".*

When assessing the likelihood of treatment with pembrolizumab there may be a need to distinguish between:

- those who have had something close to 3 years treatment with dostarlimab and progress after the 3 year point,

- those who stopped dostarlimab treatment due to progression after a reasonable duration of dostarlimab,
- those who stopped dostarlimab treatment due to progression after a short duration of dostarlimab treatment, and,
- those who stopped dostarlimab treatment for reasons other than progression after a short duration of dostarlimab treatment.

Only those who are modelled to have progressed incur the costs of 2nd line treatments. This may not have been the case during RUBY. Some dostarlimab patients may have discontinued dostarlimab for reasons other than progression, possibly relatively early in their treatment, and it may be these patients who tended to receive subsequent pembrolizumab. This may be an additional argument to that of section 5.3.3 below for explicitly modelling those who discontinue from dostarlimab for reasons other than progression.

What is clear is that during RUBY-1 there was a significant proportion of patients in the dostarlimab arm which clinicians thought would benefit from subsequent treatment with pembrolizumab, and that the clinical effectiveness estimates incorporate the benefits of this subsequent treatment with pembrolizumab.

The EAG did not ask about it at clarification but enumeration of the detail of the dostarlimab patients who received subsequent pembrolizumab or pembrolizumab + lenvatinib in terms of when, why and after how many administrations they ceased dostarlimab treatment could help this discussion.

Might some NHS patients who have only had a few administrations of dostarlimab and who do not get on with it be switched to pembrolizumab, or to pembrolizumab + lenvatinib as may well have happened during RUBY?

The previous EAG report noted the divergence of views between the company experts, raising uncertainty about the probable balance between subsequent treatments. Current EAG expert opinion is also quite divided about the balance between subsequent treatments. One suggests differing proportions but that some patients would receive pembrolizumab after dostarlimab, the other that the same proportions would apply in both arms and that none would get pembrolizumab.

Table 40: Balance between 2nd line treatments

	Company Experts		RUBY-1 IA2	
	DOST	PLAC	DOST	PLAC
Dost.	[redacted]	[redacted]	[redacted]	[redacted]
Carb+Pacl	[redacted]	[redacted]	[redacted]	[redacted]
Pembro.	[redacted]	[redacted]	[redacted]	[redacted]
Doxo.	[redacted]	[redacted]	[redacted]	[redacted]
Beva.	[redacted]	[redacted]	[redacted]	[redacted]
Pemb+L	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Med.Acet.	[redacted]	[redacted]	[redacted]	[redacted]
Radio.	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]

Dost: Dostarlimab, Carb+Pacl: carboplatin plus paclitaxel, Pembro. : pembrolizumab, Doxo.: doxorubicin, Beva.: bevacizumab, Pemb+L: pembrolizumab plus lenvatinib, Med.Acet.: medroxyprogesterone acetate, Radio.: radiotherapy

Due to:

- The benefits of subsequent treatments being reflected in the clinical effectiveness estimates for dostarlimab, and
- Those in RUBY-1 who received pembrolizumab after having had at least some dostarlimab possibly also reflecting what may occur in the NHS for some patients such as those with only a short duration of dostarlimab treatment,

the EAG base case will apply the RUBY-1 proportions for subsequent treatments in its exploratory base case. It will supply a scenario analysis of the mean of the company experts' responses. This scenario analysis does not revise the clinical effectiveness estimates so does not reflect the probable clinical effectiveness of the assumed treatment sequences.

5.2 *EAG critique of the handling of quality of life within the model*

5.2.1 RUBY-1 quality of life data: dMMR/MSI-H vs ITT

The EAG views the quality of life data as a clinical input. Due to the clinical data being from the RUBY-1 dMMR/MSI-H subgroup the EAG thinks that the natural default is to apply the RUBY-1 dMMR/MSI-H subgroup quality of life data[5].

The previous assessment explored this but with the EAG applying the RUBY-1 ITT quality of life data in its base case. The FAD does not appear to mention the issue, suggesting that it may not have been much considered by Committee.

For consistency the EAG will retain the RUBY-1 ITT quality of life data in its base case, but has considerable sympathy with the view that all clinical data, including quality of life data, should come from the RUBY-1 dMMR/MSI-H subgroup. It has relatively little effect upon the cost effectiveness estimate.

5.3 *EAG critique of the handling of costs within the model*

5.3.1 Test costs

The SmPC states under posology and method of administration that "*Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS*".

During Factual Accuracy Check the company notes that the diagnostic guidance DG42 recommends all endometrial patients undergo MMR testing and subsequent genetic counselling.

The EAG provides a scenario analysis which includes the company estimates for test costs in the dostarlimab+CP arm.

5.3.2 TTD Dostarlimab+CP KM curve versus parameterised curves

For dostarlimab+CP the company base case applies the numbers receiving treatment for the first 18 weeks followed by the TTD Kaplan Meier curve, with a very

[5] The EAG requested additional EQ-5D data at clarification. The data supplied by the company had considerable numbers of patients reporting EQ-5D for progressed disease at baseline. The EAG is unable to take this data any further. There may be a misinterpretation on the part of the company or the EAG in terms of the question and the data supplied.

short section of the Weibull curve being appended to this from week 155. This is in contrast to the modelling of PFS which applies a smooth parameterised curve from baseline.

There is no obvious justification for the difference in approach between the modelling of the TTD curve to the 3 year point and the modelling of the PFS curve to the 3 year point. Kaplan Maier curves can be viewed as over fitting the data and this is a common reason for smoothing them out with parameterised curves. Applying the Weibull TTD curve from baseline slightly worsens the company base case ICER from £[redacted] to [redacted] per QALY.

The EAG agrees with parameterising the PFS curve rather than using the Kaplan Meier plot to 3 years. The EAG thinks that if it is appropriate to apply a TTD curve estimated independently from the PFS curve this should also apply to the TTD curve. Whether it is appropriate to apply a TTD curve estimated independently from the PFS curve is the subject of the next section.

5.3.3 Proportion of patients in PFS receiving dostarlimab

As outlined above in Figure 18 of Section 3.2.6.3, the proportion of patients in PFS who are modelled as incurring the cost of dostarlimab declines over the first three years of the model until by the end of the third year only 66% of those in PFS and so eligible for dostarlimab treatment are modelled as incurring the cost of dostarlimab.

EAG expert opinion is that they would seek to continue to treat those doing well on dostarlimab up to the 3 years permitted by the SmPC. The EAG notes that there is a treatment burden but that after the initial 18 weeks infusions are only once every 6 weeks, though patient monitoring is staggered between infusions and also every 6 weeks.

It can be noted that the Kaplan Meier S(t) curves for PFS and TTD show the same pattern as the modelled curves of the company base case, the ratio between these as measured by the right hand axis of Figure 23 falling over time until at around 3 years it has fallen to about 66%.

Figure 23: IA1: Dostarlimab: Kaplan Meier TTD S(t) and PFS S(t) and the ratio between these

But the reason for the separation between the PFS Kaplan Meier S(t) curve and the TTD Kaplan Meier S(t) curve arises in part due to the different handling of those censored due to being lost to follow-up and so having ceased treatment. At clarification the company supplied the IA1 PFS Kaplan Meier data grouped by 2-month ranges, splitting those who were censored into those who were lost to follow-up and those who were still being followed up but were censored due to the data cut. The company also supplied the equivalent IA1 TTD Kaplan Meier data but without the censoring split, which the EAG assumes is due to all those who were lost to follow up being treated as an event in the TTD curve rather than as censoring as in the PFS curve.

Table 41: PFS and TTD Kaplan Meier patient numbers

	PFS				TTD		
Month	N	Event	LTFU	Data Cut	N	Event	Data Cut
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LTFU: Lost to follow-up (censored for reasons other than data-cut)

The patient numbers are not perfectly aligned between PFS and TTD, but apart from the steps at 4 and 20 months they are closely aligned[6].

The broad assumption underlying the construction of the PFS KM curve is that both those censored due to being lost to follow-up (LTFU) and those censored due to the data cut have the same risk of progression as the patients remaining in PFS and followed up beyond the point of their censoring, despite the former having ceased treatment. But patients who are LTFU are treated as events within the construction of the TTD KM curve. The two curves are constructed on different bases and in the opinion of the EAG are not directly comparable. The same number, [redacted], are censored

[6] During Factual Accuracy Check the company noted that PFS censoring for reasons other the end of trial could be classed as different types of events, such as adverse events or lost to follow-up. For current purposes the EAG groups these as lost to follow up as the distinctions do not matter. This means that LTFU in this report does not correspond with LTFU as defined within the RUBY SAP and the CSR.

due to the data cut but it is assumed that there are only [redacted] progression events compared to [redacted] discontinuation events.

The EAG thinks that there is an argument for explicit modelling of those discontinuing dostarlimab for reasons other than progression. This would require additional clinical data and reasonably considerable model revision so the EAG cannot undertake this.

There is an alternative argument to retain the company model structure but analyse the PFS data and OS data with different assumptions about those who are LTFU, not treating this as uninformative censoring but making alternative assumptions such as them having the same risks of events as those in the placebo arm. In other words, LTFU is informative censoring in terms of the risk of future progression. The EAG cannot undertake this due to it not having full access to the trial data.

The simpler alternative to the above two approaches is to examine how many patients were in PFS and how many of these patients remained on treatment.

The number in RUBY-1 who remained in PFS and the number who remained on treatment is plotted in Figure 24, this also presenting the ratio between the two measured against the right hand axis[7].

Figure 24: IA1: Dostarlimab: Patients on treatment, patients in PFS and the ratio between these

[7] There is a brief period at around week 135 when the ratio is [redacted], though patient numbers are small.

The number of patients in PFS and the number remaining on treatment moves in virtual lockstep. For instance, for IA1 of RUBY-1 at week 99 there were [redacted] patients remaining in PFS. At week 99 all [redacted] of these patients were still being treated with dostarlimab[8]. But based upon the IA1 data cut the company base case assumes that at week 99 only [redacted] of those in PFS are still being treated with dostarlimab. The EAG thinks that this is unreasonable.

The ratio between those receiving treatment and those in PFS rises above 100% towards the end of the curves, possibly due to patients catching up on previous treatment holidays or delays. The absolute patient numbers are small, but this may have a bearing upon the assumed RDI of 97.6% as briefly reviewed in section 5.3.5 below.

[redacted]

[redacted]

[8] Assuming that none of the 16 patients being treated had progressive disease.

[redacted]25[redacted]

[redacted]

[redacted]

[redacted]26[redacted]

[redacted]

The EAG exploratory base case will apply [redacted] of the number remaining on treatment to the number remaining in PFS to determine the proportion of those in PFS who incur the costs of dostarlimab during each treatment cycle.

5.3.4 Treatment with dostarlimab to 3 years

The SmPC specifies that treatment with dostarlimab "*should continue until disease progression or unacceptable toxicity, or for a duration of up to 3 years*". The company model assumes a maximum treatment duration of 156 weeks. This does not include the treatment at the start of week 157 which is within the 3 year window.

At clarification the company stated that "*cycle 31 is the first cycle beyond the 3-year stopping rule*" this being at week 163 in the model.

The EAG will include dostarlimab treatment at the start of week 157.

5.3.5 Treatment with dostarlimab beyond 3 years and RDI

At clarification the company provided additional data on the number of patients receiving dostarlimab during each treatment cycle, including those receiving treatment beyond the 3 year point.

For the IA2 data cut there were [redacted] patients remaining on dostarlimab treatment at month 34, this declining by around [redacted] to [redacted] patients at month 36, this then further gradually declining to none by month [redacted]. Among these [redacted] patients there were an additional [redacted] dostarlimab treatments administered after 3 years. The company states that since the [redacted] administrations after year 3 are only [redacted] of the total [redacted] dostarlimab administrations, the effect of this upon costs will be minimal. The EAG thinks that this cannot be concluded due to the small number of patients followed up to the 3 year point and beyond under IA2. Subsequent data cuts will follow more patients to the 3 year point and beyond. If [redacted] of patients reaching the 3 year point continue to receive dostarlimab with an average of [redacted] more dostarlimab treatments the additional costs would be substantial.

This will interact with the [redacted] RDI. The EAG thinks that even if it were appropriate to apply an RDI due to the [redacted] RDI being a simple average across patients the EAG thinks that it may be biased to apply this within the model structure. It is possible that a less than 100% RDI tended to occur among those doing badly on dostarlimab who are also more likely to be those with a short treatment duration. Applying the [redacted] RDI to all patients over the 3 year maximum treatment duration may be biased.

The IA2 estimate of [redacted] of dostarlimab administrations occurring after 3 years should also be read alongside the company RDI estimate of [redacted].

This also needs to be viewed alongside the Kaplan Meier data of Figure 24 of the previous section that shows that towards the end of the 3 years more patients receive dostarlimab than are in PFS. The reasons for this are not known but the EAG thinks that this may suggest some ongoing treatment, possibly due to patients having missed or delayed some previous treatments due to treatment holidays.

Whatever the reason, the EAG thinks that the most reasonable modelling approach, given the application of the N receiving treatment to N in PFS ratio outlined in the previous section, is to assume an RDI of 100% for those receiving treatment.

There remains an argument for modelling some additional treatments beyond 3 years. The EAG has not explored this.

5.3.6 Administration costs

The company base case applies a cost of £364 per administration during the first 18 weeks when dostarlimab is used in conjunction with carboplatin and paclitaxel, based upon the NHS reference cost SB13Z for more complex chemotherapy. This reduces to £295 after 18 weeks when carboplatin and paclitaxel is no longer being administered, based upon NHS reference cost SB12Z for simple parenteral chemotherapy. This fall in the administration cost is reasonable given the additional time required for the carboplatin and paclitaxel during the first 18 weeks.

The same cost of £364 per administration during the first 18 weeks is applied in the placebo arm. This fails to take into account the shorter infusion time in the placebo arm due to it not involving the preparation time and half hour infusion of dostarlimab.

There will be some bias over the first 6 administrations but the dostarlimab infusion of 30 minutes is considerably shorter than the 3 hours for paclitaxel and 30 minutes for carboplatin. Even allowing for the same reduction in cost of around £70 per administration, which strikes the EAG as unreasonably large, would only affect net costs by around £400. Given total net costs this is insignificant and the EAG does not pursue it further.

The EAG has not been able to validate the company costs. NHS 2022-23 reference costs suggest that the majority of chemotherapy administrations are day cases, but with a significant proportion being handled as outpatients. Ignoring inpatient administrations, the EAG derives weighted average costs of £459 and £393 for SB13Z and SB12Z respectively, though it can be noted that 30% of chemotherapy administrations in SB12Z through to SB15Z are classified as SB15Z: deliver subsequent elements of a chemotherapy cycle at an average cost of £374.

The EAG will apply the £459 and £393 costs in its revised base case.

5.3.7 Ongoing resource use: Previous TA963 company expert opinion

The company estimates for ongoing resource use based upon company expert opinion differ quite markedly from an alternative set of company inputs within the model. The EAG reproduces Table 30 below in Table 42 to ease comparison with

the alternative inputs. During Factual Accuracy Check the company states that this data was "*derived using the opinion of several HCPs via independent survey and considered to be a robust source of evidence*". They are presented in Table 43.

Table 42: Company ongoing quarterly resource use: Expert opinion (duplicate of Table 30)

	Weeks 1 - 18		Weeks 19+			
	PFS	PD	DOST PFS	PLAC PFS	PD	Cost
OP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194
CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139
Blood count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3
BP and Heart	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222
Specialist nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59
GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47
Quarterly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Weekly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 43: Company ongoing quarterly resource use: TA963 expert opinion

	Weeks 1 - 18		Weeks 19+			
	PFS	PD	DOST PFS	PLAC PFS	PD	Cost
OP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£194
CT scan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139
Blood count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3
BP and Heart	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£222
Specialist nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59
GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47
Quarterly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Weekly cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

It can be noted that these costs are in addition to the direct drug administration costs, both 1st and 2nd line, and are also in addition to the end of life costs.

The main differences between the two sources are the ongoing outpatient visits and blood pressure and heart monitoring visits while in PFS. There are additional specialist nurse visits for those in PD, though again this needs to be read alongside the end of life costs that are applied. The main effect is to increase the resource use among those surviving meaning that the additional survival from dostarlimab comes at a higher cost.

EAG expert opinion suggests that the TA963 resource use may be more representative of the NHS. It is also unclear why the company felt the need to gather additional expert opinion subsequent to that gathered under TA963. Within this data the EAG questions whether an additional £222 would be required for blood pressure and heart rate monitoring given that they occur with the same frequency as OP visits.

The EAG will explore the company TA963 expert opinion resource use estimates, and also within this setting the cost of blood pressure and heart monitoring to £0.

5.3.8 Costs of 2nd line treatments

The costs of each 2nd line treatment during RUBY are determined by the assumed duration of subsequent therapy, the proportion assumed to remain on treatment during this subsequent therapy and the RDI. The EAG has reviewed the durations of the 2nd line treatments and their alignment with the relevant papers.

The company derives a mean duration of 2nd line dostarlimab of [redacted] months from the GARNET trial as reported by Oaknin et al.[34] For the subset of 72 patients (67%) with a minimum follow-up of at least 14 months the median PFS was [redacted] months. The company assumes that this [redacted] months PFS among the 67% with at least 14 months follow up applies to the 33% with less than 14 months follow up. It is unclear how patients who discontinued prior to 14 months were handled. At the extreme they could imply a PFS of [redacted] months, though this is to assume that all would progress quickly.

In contrast to the costing of 1st line treatments, the company also assumes that among those receiving a 2nd line treatment 100% are treated at each administration with a 100% RDI. The EAG thinks that in the absence of other data it is more reasonable to apply the 1st line proportion of PFS being treated as a proxy for what is

likely with 2nd line treatments. For the EAG revised base case the [redacted]

The company approach is reasonable if there is no other relevant data, but RUBY-1 provides IA2 PFS2 data. The EAG base case applies the RUBY-1 IA2 balance between 2nd line treatments. It is possible that RUBY-1 IA2 data could also supply data on the durations of 2nd line treatments which would be directly relevant to the patient group under consideration.

The company was asked to supply the durations and mean number of cycles of 2nd line treatments during RUBY-1. It states that "*Whilst the initiation of second line treatments was recorded as part of the RUBY trial, the time and reason for discontinuation of these therapies have not been reported. As such it has not been possible to derive mean or median duration-of-treatment, nor number of cycles received. In any case, given the immaturity of PFS2 data (43.2% maturity) the reporting of average duration of treatments would be skewed towards those discontinuing early and significantly underestimate the true treatment durations at second line.*"

The company cites a 43% maturity for PFS2 data, but clarification data shows [redacted] PFS2 events among the 65 patients in the placebo arm with an additional 3 patients being lost to follow up. So [redacted] of the 65 patients in the placebo arm have complete PFS2 data. If no PFS2 2nd line treatment duration or PFS2 duration data is available from RUBY-1 IA2 the company approach is broadly reasonable. But RUBY-1 is the obvious starting point and PFS2 data for the placebo arm appears reasonably complete. There is no obvious reason not to present the 2nd line treatment durations by arm for those having had a PFS2 event.

During Factual Accuracy Check the company states that duration of 2nd line treatments was not presented as this data was not available. It might still be useful as a 2nd best alternative to present the durations of PFS2 by treatment received as this might help place an upper bound on the assumed durations of PFS2 treatments or at a minimum place given them some context.

The EAG base case will apply the 90% on treatment to PFS ratio for 2nd line treatments. A scenario of only [redacted] months duration of treatment for 2nd line

dostarlimab will be presented. The EAG will supply scenarios that arbitrarily halve and double the costs of 2nd line treatments.

5.4 *Exploratory and sensitivity analyses undertaken by the EAG*

The sections which follow apply the dostarlimab PAS. The relevant publicly available prices for the other treatments are applied within EAG revision EAG01 in section 5.4.1 and are applied throughout sections 5.4.2 and 5.4.3. The EAG supplies a cPAS appendix that applies the confidential discounts for the other treatments.

5.4.1 EAG model revisions

The EAG makes the following changes to the company base case.

- EAG01: Correcting the model structure and model input errors, largely revising drug costs from BNF list price to CMU EMIT, identified in section 4.5.1.
- EAG02: EAG PFS curve parameters [redacted]
- EAG03: Treatment waning from the end of year 3 over 2 years.
- EAG04: Baseline age 67.1 years
- EAG05: Dostarlimab PFS proportion treated being the RUBY-1 [redacted], coupled with an RDI of 100%
- EAG06: Including week 157 dostarlimab
- EAG07: RUBY-1 IA2 2nd line treatment proportions
- EAG08: 2nd line proportion treated of 90% of those in PFS2
- EAD09: EAG SB12Z and SB13Z administration costs

Note that the corrections of EAG01 affect the costs of 2nd line treatments. The revision of the balance of these under EAG08 does not reflect the application of CMU EMIT costs.

Table 44: EAG changes: pairwise cost effectiveness estimates vs placebo

	Section	Δ Cost	Δ QALY	ICER
Company BC	4.1	[redacted]	[redacted]	[redacted]
EAG01: EAG corrections	4.5.1	[redacted]	[redacted]	[redacted]

EAG02: EAG PFS params	3.2.6.1	[redacted]	[redacted]	[redacted]
EAG03: Waning	5.1.2	[redacted]	[redacted]	[redacted]
EAG04: Baseline age 67.1 yrs	5.1.3	[redacted]	[redacted]	[redacted]
EAG05: DOST % PFS treated	5.3.3	[redacted]	[redacted]	[redacted]
EAG06: DOST week 157	5.3.4	[redacted]	[redacted]	[redacted]
EAG07: RUBY IA2 2nd line	5.1.4	[redacted]	[redacted]	[redacted]
EAG08: 2nd line PFS2 treated	5.3.8	[redacted]	[redacted]	[redacted]
EAG09: EAG admin costs	5.3.6	[redacted]	[redacted]	[redacted]
EAG BC: EAG01 to EAG09	..	[redacted]	[redacted]	[redacted]

5.4.2 EAG revised base case

The EAG changes result in the undiscounted survival estimates of Table 45 and discounted QALYs of Table 46.

Table 45: EAG base case undiscounted survival in years

	Dostarlimab	Placebo	Net
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 46: EAG base case discounted QALYs

	Dostarlimab	Placebo	Net
PFS	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

The disaggregate costs of the EAG base case are presented in Table 47.

Table 47: EAG base case disaggregate costs

	Dostarlimab	Placebo	Net
Test costs	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]

Carboplatin + Paclitaxel Administration SAEs	[redacted]	[redacted]	[redacted]
Total 1st line costs	[redacted]	[redacted]	[redacted]
2nd line treatments	[redacted]	[redacted]	[redacted]
PFS PD End of life	[redacted]	[redacted]	[redacted]
Total health state costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

This results in the net effects and cost effectiveness estimate of Table 48 .

Table 48: EAG base case summary

	Dostarlimab	Placebo	Net
Total QALYs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

The probabilistic modelling estimates a central cost effectiveness of [redacted] per QALY and a probability of dostarlimab+CP being the most cost-effective treatment of [redacted] at willingness to pay values of £20,000, £30,000 and £50,000 per QALY. Figure 20 presents the company base case cost effectiveness acceptability curve (CEAC).

Figure 27: EAG base case CEAC

5.4.3 EAG scenario analyses

The EAG presents the following scenario analyses.

- SA01: Treatment effect waning from the end of years 4 and 5 over 2 years.
- SA02: Exponential curves for overall survival, with treatment waning from years 3, 4 and 5 over 2 years.
- SA03: Sampling baseline age.
- SA04: Company experts 2nd line treatment balance.
- SA05: RUBY-1 dMMR/MSI-H specific quality of life data.
- SA06: Applying the company TA963 expert opinion estimates of ongoing resource use, also exploring a £0 cost for blood pressure and heart monitoring within this.
- SA07: Duration of 2nd line dostarlimab of [redacted] months.
- SA08: Halving and doubling 2nd line treatment costs
- SA09: Genetic test costs for dostarlimab

Table 49: EAG Scenario Analyses

	Δ Cost	Δ QALY	ICER
EAG Base case	[redacted]	[redacted]	[redacted]
SA01a: Waning end of year 4	[redacted]	[redacted]	[redacted]
SA01b: Waning end of year 5	[redacted]	[redacted]	[redacted]
SA02a: Exponential OS curves	[redacted]	[redacted]	[redacted]
SA02b: SA02a + waning end of year 4	[redacted]	[redacted]	[redacted]
SA02c: SA02a + waning end of year 5	[redacted]	[redacted]	[redacted]
SA03: Sampling baseline age	[redacted]	[redacted]	[redacted]
SA04: Company experts' 2nd line	[redacted]	[redacted]	[redacted]
SA05: RUBY dMMR/MSI-H QoL	[redacted]	[redacted]	[redacted]
SA06a: TA963 ongoing resource use	[redacted]	[redacted]	[redacted]
SA06b: SA06a + £0 for Heart/BP	[redacted]	[redacted]	[redacted]
SA07: 2nd line dostarlimab [redacted] months	[redacted]	[redacted]	[redacted]
SA08a: Halving 2nd line costs	[redacted]	[redacted]	[redacted]
SA08b: Doubling 2nd line costs	[redacted]	[redacted]	[redacted]
SA09: Dostarlimab test costs	[redacted]	[redacted]	[redacted]

Results are sensitive to all the elements explored by the EAG with the exception of SA05 and whether the ITT or the subgroup specific RUBY-1 quality of life values are used.

Sampling age instead of using the mean as in SA03 is not particularly influential.

All of the other elements explored by the EAG are model drivers.

5.5 *Conclusions of the cost effectiveness section*

Considerable uncertainty remains in the cost-effectiveness analyses, owing to the small sample size and limited follow-up of the pivotal trial. The sensitivity analyses of Table 49 identify the key model drivers that the EAG thinks warrant attention, the most influential of which is the long-term survival extrapolation of dostarlimab+CP. Without additional data from extended follow-up these are largely matters of judgement.

The EAG report sent to the company for Factual Accuracy Check (FAC) highlighted a number of uncertainties that it might be possible for the company to clarify. The company responses have been worked into this report, the EAG also noting the following.

- Section 5.1.2: The proportion retaining complete response is key to the assessment of the possible "cure" rate for dostarlimab. Only IA1 data is currently available to the EAG. If there is bias it is likely to be in one direction since with a longer data cut it seems unlikely more will attain complete response, only that some may lose it. Duration of complete response data from IA2 could increase the confidence in this estimate. The company notes in response to clarification A10 that duration of response was not analysed as part of IA2. This may be complicated by the next bullet point.
- Section 5.1.2: Within the response to clarification question A10 is loss of response for those with a best response of complete response (A) loss of complete response or (B) loss of both complete response and partial response? During FAC the company response appears to suggest that the loss of a best response of complete response required disease progression. The EAG interpretation of this is that a patient with a given disease state at baseline who had a best response of complete response who subsequently had some recurrence of evaluable disease but still remained superior to their baseline health state would not be classed as having lost complete response. But this depends upon what a progression event was defined as among those with a best response of complete response. This may mean that in the dostarlimab arm among the [redacted] patients with a best response of complete response more than the [redacted] patient(s) who subsequently progressed may have had disease recurrence. The [redacted] rate of retention of complete response among those with evaluable disease at baseline in the dostarlimab arm may be an upper bound to the proportion retaining complete response into the medium and long term.
- Section 5.1.4: For those receiving 2nd line treatments IPD enumeration of their durations of 1st line treatment split by arm, reason for discontinuation of 1st line treatment and subsequent 2nd line treatment would aid an assessment of

why patients received e.g. 2nd line pembrolizumab and whether this might reflect probable NHS practice.

- Section 5.3.3: Of the [redacted] in Table 41 who were lost to follow-up for PFS the number who were assessed for response, the number whose best response was complete response and the number whose best response was partial response. During FAC the company note that within the timelines it was not possible to ascertain this. The company also stresses that among these patients there may not have been any responses and these patients' best responses may have been stable disease. The EAG thinks that this underlines that PFS censoring for reasons other than data cut may not have been uninformative in terms of the probability of progression among those censored for PFS, particularly in the light of them apparently also discontinuing dostarlimab treatment.
- Section 5.3.8: 2nd line duration of treatments and number of treatment cycles are critical to the estimation of 2nd line treatment costs, so are model drivers. PFS2 data for the placebo arm appears reasonably complete. The EAG thinks that RUBY-1 2nd line treatment durations and numbers of treatment cycles split by arm limited to patients with a PFS2 event could reduce the uncertainty around the 2nd line treatment costs. If this is not available a 2nd best could be durations of PFS2 split by 2nd line treatment received in order to place the assumed 2nd line treatment durations in context. The RUBY-1 data split by arm is the obvious starting point for estimating 2nd line treatment costs.

6 SEVERITY MODIFIERS

[redacted]The company estimates a [redacted] QALY shortfall compared to the general population so concludes that no adjustments to the modelled QALYs should be made.

The EAG notes that its preferred baseline age of 67.1 years is likely to reduce the QALY shortfall to below the company estimate.

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8 Appendices

8.1 *Additional Searches undertaken by EAG*

Update of the company's searches for the clinical effectiveness SLR:

Ovid MEDLINE(R) ALL <1946 to October 11, 2024>
Date searched: 14/10/24

1 exp endometrial neoplasms/ or ((endometrial or endometrium or uterine or uterus) adj3 (cancer$ or neoplasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab. 68292
2 exp Neoplasm Metastasis/ or (recurrent or recurrence or relaps$ or advanced or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage iii$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab. 2578190
3 (dostarlimab or jemperli or TSR-042).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 159
4 1 and 2 and 3 79
5 exp randomized controlled trial/ 624813
6 controlled clinical trial.pt. 95619
7 randomized.ab. 664025
8 placebo.ab. 252583
9 drug therapy.fs. 2743326
10 randomly.ab. 444002
11 trial.ab. 718905
12 groups.ab. 2747763

13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 [Cochrane highly sensitive search strategy for RCTs, Sensitivity-maximizing version (2023 revision), as found here: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts] 6093318

14 4 and 13 61

15 limit 14 to yr="2024 -Current" 19

Embase <1974 to 2024 October 11>

Date searched: 14/10/24

1 exp endometrium cancer/ or ((endometrial or endometrium or uterine or uterus) adj3 (cancer$ or neoplasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tumour$)).ti,ab. 108307

2 exp Metastasis/ or (advanced or recurrent or recurrence or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage iii$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab. 3465051

3 (dostarlimab or jemperli* or TSR-042).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 927

4 1 and 2 and 3 271

5 exp randomized controlled trial/ 850626

6 controlled clinical trial/ 474142

7 random$.ti,ab. 2131466

8 randomization/ 100238

9 intermethod comparison/ 309051

10 placebo.ti,ab.384846

11 (compare or compared or comparison).ti,ab. 8166037

12 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 3234672

13 (open adj label).ti,ab. 119497

14 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 288219

15 double blind procedure/ 224800

16 parallel group$1.ti,ab. 34485

17 (crossover or cross over).ti,ab. 130958

18 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 444673

19 (assigned or allocated).ti,ab. 525985

20 (controlled adj7 (study or design or trial)).ti,ab. 486496

21 (volunteer or volunteers).ti,ab. 293286

22 human experiment/ 673058

23 trial.ti. 439871

24 or/5-23 10803353

25 ((random$ adj sampl$ adj7 "cross section$") or questionnaire$1 or survey$ or database$1).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 1953826

26 cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical trial/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) 413743

27 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 22965

28 systematic review.ti,ab. not (trial or study).ti. 376341

29 (nonrandom$ not random$).ti,ab. 19893

30 "random field$".ti,ab. 3123

31 (random cluster adj3 sampl$).ti,ab. 1688

32 (review.ab. and review.pt.) not trial.ti. 1240397

33 "we searched".ab. and (review.ti. or review.pt.) 55304

34 "update review".ab. 147

35 (databases adj4 searched).ab. 72089

36 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1271764

37 animal experiment/ not (human experiment/ or human/) 2676180

38 or/25-37 6242281

39 24 not 38 [Cochrane Embase RCT filter 2023 revision as found at https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts/embase-rct-filter] 8900161

40 4 and 39 110

41 limit 40 to yr="2024 -Current" 23

Cochrane CENTRAL (via Cochrane Library, Wiley)

https://www.cochranelibrary.com/advanced-search/search-manager

Date searched: 14/10/24

ID Search Hits

#1 MeSH descriptor: [Endometrial Neoplasms] explode all trees 1232

#2 (endometrial or endometrium or uterine or uterus) NEAR/3 (cancer* or neoplasm* or hyperplas* or malignan* or carcinoma* or sarcoma* or adenocarcinoma* or tumor* or tumour*) 10361

#3 #1 OR #2 10422

#4 MeSH descriptor: [Neoplasm Metastasis] explode all trees 7638

#5 recurrent or recurrence or relaps* or advanced or metastas* or metastat* or "end-stage" or "late-stage" or terminal or (stage NEXT 3*) or (stage NEXT iii*) or "stage three" or (stage NEXT 4*) or "stage iv" or "stage four" 257985

#6 #4 or #5 258109

#7 dostarlimab or jemperli or "TSR-042" 127

#8 #3 AND #6 AND #7 with Publication Year from 2024 to 2024, in Trials 10

8.2 *Details of technology price sources used in EAG cPAS appendix.*

Name	**Source**

Pembrolizumab (with lenvatinib) (TA904)	Commercial Access Agreement (TA904)
Pembrolizumab (TA914)	Commercial Access Agreement (TA914)
Doxorubicin	eMIT (October 2024)
Bevacizumab	MPSC (formerly CMU)
Lenvatinib	PAS (commercial pricing list)
Letrozole	eMIT (October 2024)
Medroxyprogesterone acetate	BNF
Dostarlimab	PAS (commercial pricing list)
Carboplatin	eMIT (October 2024)
Paclitaxel	eMIT (October 2024)

The cPAS appendix contains the EAG and company base case analyses, and the EAG scenarios S01-S08.

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (MA review of TA963) [ID6426]

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 Monday 16th December** 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 [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Contents

Issue 1 Modelling of Time to Treatment Discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The EAG have repeated on a number of occasions that a notable amount of patients were 'lost-to-follow-up' resulting in a significant discrepancy between the modelled TTD and PFS curves, limiting the interpretability of the clinical evidence. This is incorrect.	Table 41: The term 'LTFU' be replaced with a more accurate description of the [redacted] censored for reasons other than being event-free at the time of the data-cut Section 5.3.3: The entire section should be amended to refer to subjects censored prior to the data cut rather than being described as lost to follow-up (LTFU). Other similar phrases within this section should be adapted accordingly. Section 5.3.3 following Table 41: GSK suggest the EAG withdraw or amend this due to the misrepresentation of those labelled 'LTFU' by the EAG.	The EAG proposes that there are a significant number of patients being LTFU yet recorded as 'events' when deriving TTD, despite LTFU being potentially uninformative. In addition, the EAG points to those labelled as 'LTFU' in the report as being censored in the PFS analysis. The impact of this is a supposed unwarranted divergence of TTD and PFS curves in the model which impacts the ICER significantly. This is inaccurate. Only [redacted] of the [redacted] discontinuations in the trial were recorded as 'loss-to-follow-up' ([redacted]). The most common reasons for discontinuation were disease progression, followed by AEs, followed by patients	The EAG does not consider this a factual error. The EAG remains concerned about the possibility of informative PFS censoring given that some people censored for reasons other than data-cut (labelled LTFU) for PFS have stopped treatment, whilst those remaining in the trial continue to receive treatment. The EAG has added a clarifying footnote in Section 5.3.3, and to Table 41.

		reaching the 3-year treatment cap	
Page 113 The EAG have queried of the [redacted] patients marked as "LTFU" in Table 41, it would be helpful to understand whether the patients had a best response was complete response and the number whose best response was partial response.		It is not possible to ascertain within the timelines provided the depth of response, if any, of the [redacted] subjects identified in table 41. These 11 patients represent a subset of patients identified as progression free but were censored prior to the data-cut being made. However, GSK would like to remind the EAG that not all patients marked as 'progression-free' obtained a response. Any patient with no evaluable disease at baseline and those whose best response is 'stable disease' may be progression free without being categorise as either a complete or partial responder.	The EAG has added a summary of the company text by way of further clarification to Section 5.5. This is the key point: How many of those marked as LTFU had a response since those who remained progression free when LTFU may not have had a response. This may have a bearing upon their probability of progression given their cessation of treatment on or around the point they were LTFU for PFS.

Page 100 The EAG have inaccurately stated that the TTD when, accounting for those labelled as 'LTFU', is unchanged between IA1 (presented and discussed) and IA2 (not presented nor discussed). This does not appear to be the case.	Section 5.3.3 from Figure 24 onwards: Following discussion of IA1 data, the report states: "A similar pattern occurs with the IA2 data cut" GSK suggest this be amended to reflect a diverging pattern indicated by the more mature IA2 data. In addition, given the clarification offered by GSK within this section regarding the patients labelled as 'LTFU', GSK suggests the EAG clarify some of the limitations of this abstract methodological approach i.e. it assumes the observed TTD is inappropriate, it does not take into account the timing occurring of events and therefore rates, doesn't reflect discontinuations for reasons other than progression, etc.	The EAG have proposed to disregard the observed TTD from the RUBY trial and instead derive a TTD-PFS relationship based on absolute patient number at milestone timepoints. The EAG have incorrectly stated that the pattern observed in the PFS-TTD trend is unchanged between IA1 and IA2, however the IA2 data indicates an increasing number of off-treatment patients as a proportion of PFS at milestone timepoints. Notwithstanding the omission of the more mature dataset resulting in a pattern of divergence, GSK do not believe this is a suitably robust method of inferring TTD.	The EAG does not state that TTD is unchanged between IA1 and IA2. It states that "A similar pattern occurs with the IA2 data". The EAG has added another figure to the IA2 data to Section 5.3.3.
Page 92 and 113 The EAG state:	The Company would like to clarify that patients do not move from complete response to partial response when response is lost. Any progression event	This addresses the clarification requested by the EAG.	There remains some ambiguity.

Page 92 – *"For the duration of response among those with a best response of complete response the EAG asked the company to provide data for the duration of complete response. The EAG thinks that this is what was provided at clarification but it is unclear whether loss of response among those with a best response of complete response was loss of complete response or loss of both complete and partial response. The EAG would be grateful if the company could confirm this during FAC as it is critical to assessing the loss of response data that was supplied at clarification"* Page 113 – "*Within the response to clarification question A10 is loss of response for those with a best response of complete response (A) loss of complete response or (B)*	is categorised as loss of response, loss of response does not follow a categorical scale.		The EAG interpretation of the company response is that (1) it means that the events were not merely loss of response events but were progression events and (2) this means that among those with a best response of complete response their disease may have recurred to some extent but not to the extent of having been categorised as having progressed. The EAG has added additional text to sections 5.1.2 and 5.5 reflecting the above.

loss of both complete response and partial response? If the latter, what number of those with a best response of complete response lost complete response status?"			
Page 89, Section 5.1.1 The EAG states that the company '*does not model patients discontinuing dostarlimab for reasons other than progression'* This is inaccurate as the company uses all-cause discontinuation to inform the TTD curve included within the model.	Remove this sentence.	Over 50% of patients discontinue dostarlimab for reasons other than progression (e.g. adverse events) which is reflected in the fact the TTD curve sits below the PFS curve.	No factual error. No response required. See response to first issue above.

Abbreviations: CS, company submission; dMMR, mismatch repair deficient; EAG, external assessment group; LTFU lost to follow up, TTD; time to treatment discontinuation

Issue 2 Modelling of Progression-free survival

Descri	Description of proposed amendment	Justification for amendment	EAG Response
Page 62 The EAG have included hazard rates that do not	GSK request the EAG replace or supplement the figure with the corresponding IA1 graphs submitted by GSK (Appendix O, Supplementary Material to B.3). The EAG should clarify why Figure 6 appears to omit the 'CP IA1' curve and why the	The graph is not adequately labelled and so it is unclear how robust the presented evidence is. It diverges from the corresponding IA1 graph submitted in the CS which was derived from patient-level data which has not been provided to the EAG. The evidence submitted by GSK should be included for completeness.	The line has not been omitted, [redacted]. The graph is as produced by the statistical software. [redacted]

reflect those presented in the CS which are derived using patient-level data.	CP curves are truncated at ~X=19. The X-axis should be labelled to display which time units are being used.		The EAG has updated the plot to indicate the time axis.
Page 64 The EAG state: "*The current EAG preference is to set the hazard rate for the PFS of*	GSK request the EAG amend the following statement to [redacted], and to reflect the clinical evidence which supports the long-term durable effect of immunotherapies following discontinuation: *The EAG considers this approach* [redacted] *and supported by clinical rationale*	In the RUBY-1 trial, a clinically meaningful, statistically significant and sustained PFS benefit was observed for the dostarlimab + CP arm compared with CP at the IA1 data cut-off (as presented in the original company submission). [redacted] demonstrated that this significant and sustained benefit persists, with clear separation between the curves being maintained for up to three years and potentially beyond, which is supported by the [redacted] and the calculated PFS	Not a factual error. The company is confusing absolute loss of efficacy of immunotherapy with a change in relative efficacy to CP in people who have responded well to CP. The company's response is incorrect to refer to the numbers at risk after the events have occurred as these would not affect the accuracy of earlier estimates.

dostarlimab+CP to tend towards that of CP from 3 years, being equal from 5 years (Figure 10 of EAG report). The EAG considers this approach consistent with the observed data and support	Please amend this sentence to: "*The EAG considers this approach consistent with the clinical opinion provided to the EAG*"	probability remaining constant from 18 months onwards. [redacted], however, there are significant potential issues in the assertion or implication that these two events demonstrate a clear trend from three years onwards. Firstly, from month 12 to month 42 (a two-and-a-half-year period) just three PFS events were observed, demonstrating there is a marked reduction in the risk of progression or death beyond 12 months. Secondly, at the point at which the two events occurred, the numbers at risk for PFS dropped from 11/53 (20.8%) to 4/53 (7.5%), meaning the data beyond the three-year timepoint are less reliable should be interpreted with caution, and as a result are unable demonstrate a clear trend in the hazard. Additionally, the sustained PFS benefit that is observed for dostarlimab is also observed in longer-term data from other immunotherapy treatments in second-line dMMR/MSI-H EC. Clinical rationale does not support the cessation of an immunotherapy treatment	

ed by clinical rationale” However, this is not supported by the RUBY-1 trial, the peer review publication and longer-term data from similar therapies in second-line dMMR/MSI-H EC.		effect immediately upon discontinuation. The company sought expert opinion from 5 clinicians to help choose the most appropriate curve that matched experts estimate (presented in CS Appendix O). It is therefore not correct to say that the idea posed by the EAG is well supported by clinical rationale and is instead only supported by the EAGs clinical experts. The amendment is therefore required to distinguish the data and expert opinion for which the EAG’s preference in approach can be considered consistent with.	

Abbreviations: CP, carboplatin plus paclitaxel; CQ, clarification question; dMMR, mismatch repair deficient; EAG, external assessment group; EC, endometrial cancer; IA2, second interim analysis; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2.

Issue 3 Modelling of Overall Survival

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 69 and 93: The EAG state: Page 69 – "*In Figure 13, the hazard rates for OS are shown for both arms, which can be compared with the hazard rates of the company's preferred extrapolations in Figure 14. The EAG considers that the hazard rate for both arms could be considered to be constant and that the exponential model best represents the observed data*" Page 93 – "*As reviewed in section 3.2.6.2 the behaviour of the hazards suggests that the exponential may be most*	Please amend the following sentences to: Page 69 – "*In Figure 13, the EAG reconstructed smoothed hazard rates for OS are shown for both arms, which are at odds with ~~can be compared with~~ the hazard rates presented by the company in the CS using patient level data and depicted in figure X. ~~of the company's preferred extrapolations in Figure 14. The EAG considers that the hazard rate for both arms could be considered to be constant and that the exponential model best represents the observed data~~*" Page 93 – "*In section 3.2.6.2, the EAG reconstructed smoothed hazard rates for OS are shown for both arms and the exponential model was chosen by the EAG"*	Given a hazard rate plot was provided in the company submission (Figure 14, CS Doc B), which was generated using patient-level data, the company believe that this plot should be presented in place of, or alongside the figure presented in the EAG report. This is because the Figure in the company submission will have greater accuracy given it has been derived directly from the patient-level data, and also because it provides a clearer view of any inflection points in the hazards and at which timepoints these occur. This latter point is critical, as changes observed towards the end of the Kaplan-Meier data are often a product of	Not a factual error. The EAG considers the two hazard plots to be equally reliable given the small numbers of patients in the study meaning the recreated dataset had a very high level of accuracy.

appropriate for OS extrapolation" However, the provided hazard rate plot for OS is at odds with that presented by the company (Figure 14 in the CS) which was produced using patient level data as opposed to reconstructed KM data. The two hazard rate graphs also show different things as Figure 13 shows the 'Smoothed hazards'. The displayed graph also does not appear to show a 'constant' hazard rate given the turning points observed in both the dostarlimab in combination with CP, and CP curves. This is therefore not suggestive of an exponential model.		low numbers at risk towards the end of the follow-up period rather than representing a true trend. The smoothed plot alone may give the impression any changes in the hazards across both arms occur at a much earlier timepoint than the data truly demonstrates.	
Page 70 The EAG state: *"This is inconsistent with comments from the EAG*	Please amend this sentence to: *"This is inconsistent with comments from the EAG clinical experts who stated that patient outcomes beyond 5 years were likely to be independent of*	The company believe this amendment more accurately reflects what the data and the plurality of expert opinion has suggested about the long-	The EAG has made minor amendments to this text.

clinical experts who stated that patient outcomes beyond 5 years were likely to be independent of which initial treatment was received. Patients surviving this long would have had a good response to a previous treatment, there is no reason why mortality, and rates would differ beyond this point given the availability of immunotherapies to both arms" However, not all patients in the CP arm are expected to receive immunotherapy at subsequent lines (as shown by the subsequent treatments as supported by UK clinical experts and presented in the CS). Immunotherapies have also been shown to have long term efficacy benefits years after stopping treatment (6, 7). Therefore, the statement that there is "*no reason why mortality would differ*"	*which initial treatment was received. The EAG consider that patients surviving this long would likely have had a good response to a previous treatment, ~~there is no reason why mortality~~, and consider that mortality rates would be less likely to differ beyond this point given the availability of subsequent immunotherapies to some patients in the CP arm"*	term mortality. It also reflects that not all patients in the CP arm would be treated with immunotherapies following primary treatment. Furthermore, during the original appraisal for dostarlimab, the company sought expert opinion from 5 clinicians to help choose the most appropriate curve that matched experts estimate (presented in original CS TA963 Document B). The statement made by the EAG does not reflect the plurality of expert opinion and instead only recognizes the opinion sought by the EAG.	

beyond 5 years is an inaccuracy.			
Page 70 The EAG state: *"The company's approach does not account for the impact of finishing treatment with dostarlimab, which is capped at 3 years, after which the EAG anticipates a more rapid convergence of the hazard rates than at 21 years."* The selection of independent curves which result in a gradual convergence implicitly capture the impact beyond treatment with dostarlimab.	Please amend this sentence to: The company's approach ~~does not~~ implicitly account~~s~~ for the impact of finishing treatment with dostarlimab which is capped at 3 years, however the~~, after which the~~ EAG anticipates a more rapid convergence of the hazard rates than at 21 years."	Given the outcomes of patients who have discontinued dostarlimab are captured in the observed IA2 data, the extrapolations do capture any change in the observed hazards post-discontinuation as demonstrated in the company submission for ID6426 (CS, Document B, Section B.3.3.2.2, Figure 14)	Not a factual error. The company has not applied any adjustment to the extrapolations to account for fact that dostarlimab treatment is stopped at the same time that trial follow-up ends.
Page 72 The EAG state: "*The EAG acknowledges that the long-term estimates for both arms using the*	The Company would like to clarify that whilst the log-logistic model with waning does produce results that are more closely aligned with EAG clinical opinion, the 15 and 20-year OS estimates remain significantly below	This clarifies that both the exponential and log-logistic distributions provide estimates of long-term OS that are below those	Not a factual error.

exponential model could be considered pessimistic, but as the data remains immature, a conservative extrapolation may be preferred by committee. *However, the EAG considers that the log-logistic model with waning applied aligns more closely with the estimates of the EAG's clinical experts (Table 22)"*	those predicted by EAG clinical opinion. The sentence could be amended to say: "*The EAG acknowledges that the long-term estimates for both arms using the exponential model and log-logistic could be considered pessimistic, but as the data remains immature, a conservative extrapolation may be preferred by committee.* *The EAG considers that the log-logistic model with waning applied aligns more closely with the estimates of the EAG's clinical experts (Table 22)"*	estimated by the EAG's clinical experts.	

Abbreviations: CDF, Cancer Drugs Fund; CS, company submission; dMMR, mismatch repair deficient; EAG, external assessment group; MSI-H, microsatellite instability-high.

Issue 4 Further Clarifications on Cost-effectiveness Modelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The EAG have suggested that sustained, long term remission is only possible in a subset of patients recorded as achieving a complete response. This is not correct.	Section 5.1.2 following table 38: GSK request that this section be revised to account for the potential for patients other than CR patients (i.e. PR, CR, NED) to achieve long-term remission with anti-PD1 immunotherapies.	It is inaccurate to conclude that long-term remission is only possible amongst those with a complete response. This does not take into account the mechanism of action of immunotherapies, which are not directly cytotoxic or cytostatic, or the external evidence on this topic. It has been demonstrated that patients with partial response and even stable disease can sustain long-term remission in susceptible tumour types at follow-ups out to 10 years (6). This is similarly reflected in second-line dMMR tumours, including dMMR EC, where a notably higher proportion of patients achieve PFS and OS plateaus (~30% and ~40%, respectively) compared with the small proportion achieving a best response of CR (14.7%).	The EAG does not conclude this. The EAG only concludes, based upon expert opinion, that a “cure” in terms of having no probability of progression and no elevation of mortality risk compared to the general population is typically not talked of at this stage of endometrial cancer and to the extent it occurs would probably be restricted to some or all of those with a best response of complete response. This is further complicated by the EAG interpretation of the company response to Issue 1 Pages 92

		(7) In EC, it has been acknowledged by a previous NICE committee that this is durable out to at least 6 years in this more heavily pre-treated population	and 113 about retention of complete response and measured loss of complete response apparently being progression. The EAG has added a clarifying paragraph to Section 5.1.2.
Page 89 The EAG have misdescribed the modelling assumptions of the company CEM. The modelling approach is accepted as a Partition Survival Model (PSM), however the EAG are inappropriately deriving explicit transition probabilities from a calculation designed to conservatively estimate subsequent treatment costs.	Section 5.1.2 GSK suggest the following sections based on the EAG's derived 'cure' should be removed: • *Figure 21 presents the modelled weekly probabilities of (1) moving from PFS into PD for the dostarlimab arm, (2) dying from PFS and (3) the general female population probability of death.* • *for the company base case, by year 3.1 there is no probability of moving into progressive disease and so no probability of incurring the costs of 2nd line treatment and the lower quality of life of progressive disease* • *The PFS mortality remains above that of the general population until year 11.7 when the proportion of the*	As the CEM is structured as a PSM, for the purpose of informing health-state occupancy explicit transition probabilities to and from each health state are not required, nor have they been derived from trial data. However, for the purposes of estimating subsequent treatment costs for those entering the PD state from PF, a simplifying assumption is made to approximate the proportion of PFS events are Death and which are Progression *. The EAG incorrectly infers that	No factual error. No response required. As the company suggests, it does derive some transition probabilities when estimating subsequent treatment costs. There are also extensive explicit transition probabilities within the model: e.g. Extrapolations worksheet columns A, J, M, P, Y AB, AD, AG, AI, AS, AV. Admittedly these columns are

	original population who are modelled as still surviving and remaining in PFS is 41.9%. • *The EAG has some sympathy with the 58.3% at year 3.1 due to the model assuming that from this point forwards no patients in the dostarlimab arm move into progressive disease, meaning that none incur the costs or quality of life detriments associated with PD. This might best be described as all surviving patients being in indefinite remission or cured* • *The proportion of baseline patients "cured" by dostarlimab in terms of never progressing and having the same mortality risk as the general population is presented in Table 39 below.* • *Table 39* The remainder of Section 5.1.2 up to Table 38 should be revised to account for the model not explicitly modelling survival from between PF and PD or Death states.	these transitions are informing mortality in the PSM. As per conventional PSM methodology, occupancy of the PF state at each time is driven by the PFS curve, Death by the OS curve, and PD disease by the difference between PF and Death at each time point. The lower HRQoL associated with PD is captured by PSM methods. The 'Cure' proportions described by the EAG, derived from subsequent treatment costs, are inappropriate and not relevant when attempting to estimate those with the most durable response to treatment. *The CEM calculation to estimate subsequent treatment costs assumes deaths from PF and PD are proportional to the occupancy of the PF and PD states, respectively. Subsequent treatment costs are then assigned to the ΔPFS *not* dying and therefore progressing. This is conservative, resulting in	hazards but they are adjusted to supply transition probabilities. It is the Extrapolations worksheet column A transition probabilities that the EAG is primarily referring to when it talks of the proportion being "cured" within the model.

		underestimating subsequent treatment costs, as clinical expectation is that most deaths would occur from the PD state, as confirmed by the trial data.	
Page 98 The EAG state: Page 98 – *"The EAG base case includes the company estimates for test costs in the dostarlimab+CP arm."* This assumes that only patients who would be considered to have dostarlimab are given a dMMR test which is not in line with clinical practice which mandates that all EC patients should be tested.	Please remove this assumption from the EAG base case as it incorrectly suggests that the introduction of dostarlimab would lead to MMR testing costs.	MMR testing is a cost that applies to the whole EC population regardless of treatment. This misrepresents the widespread availability of dMMR testing in England and Wales, highlighted in the original company submission and TA779 (8, 10). This was confirmed during consultations with NHS England and is recommended in the NICE diagnostics guidance (DG42) that all EC patients undergo MMR testing and subsequent genetic counselling if necessary (11).	The EAG has removed test costs from its base case and supplies this as a scenario analysis SA09, amending the text in Section 5.3.1.
Page 80 The EAG state: Page 80 –*"The EAG does not know whether the [redacted]% RDI is a simple average across patients, or was*	The Company would like to clarify that the RDI is calculated using a simple average across patients and therefore, this can be reflected in the wording.	Clarification as requested by the EAG. The company would like to highlight that including an RDI within the model helps to accurately reflect the actual	The EAG has revised Section 3.2.9.3, added additional text in Section 5.3.5.

weighted by duration of treatment. It might help Committee if this was clarified by the company during the factual accuracy check of this appraisal"		amount of dostarlimab administered in practice. Administrations may need to be spaced out or paused on occasions, for example when adverse events occur and need to resolve before continuing treatment.	
Page 87 The EAG state: Page 87 – *"There is a referencing error in the OS hazard ratios. This does not affect the company base case."*	The company would like to note that there is also an error in the implementation of the EAG's correction to the company error.	Incorrect EAG formula: The company agree that there was an error in the model, when 'observed hazard after observed period' is selected in cell D53 of clinical inputs sheet, then the hazard from median follow up was selected instead. However, there is also an error in the EAG implementation of the correction to this error, as in 'Data store' cell I462, the formula references when parameter 'OS_HR_param_dost' = 3, when in fact there is no option for that parameter to have a value of 3. However, this is not affecting the base case.	The EAG accepts this. As it does not affect any of the presented analyses the EAG has not yet addressed this in the modelling.

Page 106: The EAG have incorrectly stated that the document *GSK 20230426_HCRU Output Data* was collected during the phase 1 GARNET single arm trial.	Please withdraw this sentence.	This statement is incorrect. This data was collected during the original appraisal of dostarlimab in combination with CP (TA963) and presented during the original submission. The HCRU frequencies were derived using the opinion of several HCPs via independent survey and considered to be a robust source of evidence. This source has been provided along with this FAC document.	The EAG has revised Section 5.3.7 and the wording of SA06 accordingly.
Page 106 The EAG states: *"The costs of 2nd line treatments are driven by the assumed duration of PFS2, the proportion in PFS2 remaining on treatment and the RDI"* However, PFS2 data is not used in the company model, neither is RDI for 2nd line treatments.	Please amend this sentence to: *"The costs of each 2nd line treatments are driven by the assumed duration of subsequent therapy, the EAG explore RDI for 2nd line treatments separately. This was also a driver of costs "*	This amendment clarifies that PFS2 is not used in the cost-effectiveness model and that RDI is only considered implicitly by EAG scenario analysis	The EAG has amended the initial paragraph of section 5.2.8, with an additional minor amendment to the third paragraph of 5.2.8.

Page 107 The EAG states: "*The company cites a 43% maturity for PFS2 data, but clarification data shows 47 PFS2 events among the 65 patients in the placebo arm with it being likely that there are a number of additional patients who are lost to follow up within this, suggesting a high completion rate for PFS2 in the placebo arm*" The EAG is inferring that the majority of no-events are LTFU, which is not accurate.	Please amend this sentence to: "*The company cites a 43% maturity for PFS2 data, but clarification data shows 47 PFS2 events among the 65 patients in the placebo arm ~~with it being likely that there are a number of additional patients who are lost to follow up within this, suggesting a high completion rate for PFS2 in the placebo arm~~*"	Only 3 patients in the placebo arm and 25 patients in the dostarlimab arm were LTFU (CSR Table 3).	The EAG has added the additional data to its report and considers that the additional 3 patients LTFU means that in the placebo arm [redacted] out of 65 patients suggests that this PFS2 data is really quite complete.
Page 107 The EAG states: "*There is no obvious reason not to present the 2nd line treatment durations by arm for those having had a PFS2 event"* However, as stated in the text, *"Whilst the initiation of*	Please amend this sentence to: "*The 2nd line treatment durations by arm for those having had a PFS2 event was not presented as this data was not available from the RUBY trial"*	This amendment clarifies that this data was not available from the RUBY-1 trial	The EAG added text to this effect but considers that PFS2 duration data split by PFS2 treatment would still have been useful, possibly placing an upper bound on the

second line treatments was recorded as part of the RUBY trial, the time and reason for discontinuation of these therapies have not been reported". Therefore, it was not possible to present this information			PFS2 treatment durations.
Page 113 The EAG state: "*IA2 retention of complete response data could significantly increase the confidence in this estimate. The company notes in response to clarification A10 that duration of response was not analysed as part of IA2, but this does not necessarily mean that the data required for this are not available to be analysed*"	The Company would like to mention that despite duration of response not being analysed as part of IA2, the single incremental PFS event between IA1 and IA2 suggests that duration of response would be expected to remain durable in IA2	This is a clarification of the duration of response for IA2	No factual error, no response required.

Abbreviations: CSR, clinical study report; CP, carboplatin plus paclitaxel; CS, company submission; dMMR, mismatch repair deficient; EAG, external assessment group; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; PFS, progression-free survival; RCT, randomised controlled trial; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TTD, time-to-treatment discontinuation.

Issue 5 Baseline Age

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 95, Section 5.1.3 In this section the EAG only reference two sources for the mean baseline age, saying they prefer the data from the Pennington et al. study over RUBY-1, but there is no reference made to the fact that new evidence have been provided in the submission that were made available since the original submission.	The company request the following addition is made to this section: *"The company noted in their submission that in the time since the original submission several sources of RWE have been collected that indicate the mean patient age in practice may align more closely with the RUBY-1 trial than the Pennington et al. indicates. This includes RWE using NCRAS data as well as RWE collected from the early access to medicines scheme (EAMS) for dostarlimab, which reported patients mean age of [redacted] years and [redacted] years, respectively."*	Failing to reference these additional data sources in this section that have been made available since the original appraisal may give the false impression that the choice of evidence sources remains the same as it was back when the committee made their original decision regarding their preferred base-case assumptions.	Not a factual inaccuracy, the EAG report on p95 refers to Section 2.3 where the choice of source is discussed in more detail.
Page 54 The EAG state that one of their key concerns with using data on baseline age from the Early Access to Medications Scheme was the limited sample size of patients introducing	The company request the removal of the sentence: *"Whilst the mean age is [redacted], the EAG is concerned at the small number of patients contributing information means this estimate is uncertain (advanced = [redacted], recurrent = [redacted])."*	The statement presents the EAMS data as more uncertain than the EAG's preferred assumption on the grounds of sample size when the sample size is larger than that of the Pennington publication	Not a factual inaccuracy. The EAG's preferred age was accepted previously by committee, and there is insufficient information to persuade the EAG to deviate.

uncertainty, despite the fact that their preferred source (Pennington et al.) included fewer patients			

Abbreviations: EAG; evidence assessment group, EAMS; Early access to medicines scheme, NCRAS; National Cancer Registration and Analysis Service, RWE; real-world evidence,

Issue 6 Limitations of RUBY-1 trial and most recent data-cut

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 27, Table 6 In the 3rd row after the heading row, in column 2 – "*Eligibility criteria*", the EAG does not include that patients must have an ECOG performance status of 0 or 1. This should be added to the list.	Please amend the list to include: "An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1"	The amendment is necessary to accurately reflect the full eligibility criteria, which specify that patients must have an ECOG performance status of 0 or 1.	Not a factual inaccuracy, this is a summary and the ECOG status criteria are discussed within the narrative of the section that follows 2.2.1.1.
Page 35 The EAG state: "*The EAG also noted that the timing and duration of treatment with each of these*	The company request the addition of the sentence: *"The EAG requested during clarification for the company to provide duration of subsequent treatments. The company clarified that this data was not*	This amendment now accurately reports the company's inability to report this data due to trial design.	Not a factual error.

subsequent treatments is currently not reported." However, timing and duration of treatment are not possible to collect because they were not included as outcomes in the trial design, and reporting the actual mean time-on-treatment would require 100% data maturity.	*accurately captured within the RUBY-1 trial as it was not a designated trial outcome and involved only a small number of patients who had received a subsequent line of therapy."*		
Page 38 The EAG state: "*For PFS2, the Kaplan-Meier plot shows a potential plateau for dostarlimab+CP, however the extent of the censoring makes this highly uncertain (Figure 2)*." However, given the 67% reduction in the risk of death or progression following the first subsequent anticancer therapy (HR: 0.33; 95% CI: 0.175, 0.627), the potential plateau observed in the Kaplan-Meier plot for PFS2	Please amend the sentence to: "*For PFS2, the Kaplan-Meier plot shows a potential plateau for dostarlimab+CP, however, there may be some uncertainty due to censoring (Figure 2).*"	The substantial reduction in risk demonstrates that the observed plateau reflects sustained efficacy, with the treatment potentially offering long-term benefits beyond initial progression. This trend is further validated by the durable PFS benefit at first-line. Therefore, the language should reflect this.	Not a factual error.

with dostarlimab+CP is promising (3, 4).			
Page 40 The EAG state: "*Whilst the groups are not balanced, it gives a better representation of the efficacy of the subsequent therapies received.*" However, it is not accurate to claim that this provides a better representation of efficacy, given the unbalanced groups, smaller sample sizes, and the bias introduced by the post-randomisation event, which occurs at different rates across the arms.	Please remove: "~~*Whilst the groups are not balanced, it gives a better representation of the efficacy of the subsequent therapies received*~~.""	The amendment highlights key issues—unbalanced groups, smaller sample sizes, and post-randomisation bias—which impact the validity of claiming a better representation of efficacy.	Not a factual error. To infer anything on the efficacy of subsequent therapies, it is logical to focus on people who receive subsequent therapies, rather than pool them with people who did not receive them.
Page 41, Table 11 A footnote should be added to the table for clarity, specifying that the PFS hazard ratios in rows 2 and 3 (following the heading row) relate to sensitivity analysis	Please amend to add the following footnote to both rows: *This data corresponds to sensitivity analysis 2, which assumes that all discontinuations and new treatments are considered PFS events	This amendment adds further clarity on how these PFS hazard ratios were generated.	This information has been expanded, but is already included in the table.

2, which assumes that all discontinuations and new treatments are considered PFS events.			

Abbreviations: CSR, clinical study report; CP, carboplatin plus paclitaxel; CS, company submission; dMMR, mismatch repair deficient; EAG, external assessment group; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; PFS, progression-free survival; RCT, randomised controlled trial; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TTD, time-to-treatment discontinuation.

Issue 7 Modelling of subsequent therapies received

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 106 The EAG's assertion that the costs of second-line treatments are driven by the assumed duration of PFS2 is incorrect, as PFS2 is not utilised within the economic model.	Remove the wording that 2nd line treatment costs are driven by PFS2 and amend with: In the company base case, costs of 2nd line treatments are informed by HCP expert opinion for the distribution of treatments and relevant literature to inform cycle length. The EAG have explored scenarios using the RUBY-1 trial data that include the distribution of 2L treatments being informed by those patients in the trial who progressed and received any follow-up anti-cancer therapy (FUACT).	The wording used is an inaccurate way to describe how 2L treatments are informed in the model and misrepresents the company's position on this parameter.	See EAG response to Issue 4 Page 107 above.

Page 81 The EAG state: *"Radiotherapy is also added with a cost of £3,338, though the source of this cost is not provided"* going on to request the source.	The company would like to clarify that the Radiotherapy cost is sourced from TA779 (Table 80: PSA inputs and distributions) and inflated to the most recent cost year using the PSSRU inflation indices (10)	This source utilises an agreed upon cost value for radiotherapy in this patient population and line of therapy and was considered appropriate for use in TA779.	The EAG has amended Section 3.2.9.4 accordingly.
Page 95 The EAG states: *"Whether NHS patients will be eligible for 2nd line pembrolizumab, or pembrolizumab + lenvatinib, after having had dostarlimab is uncertain"* However, the Company would like to highlight that, as per the NHS England national cancer drugs fund list, a typical condition for immunotherapy usage is that patients have not received any prior treatment	The company consider the following sentence to be a more accurate portrayal given the evidence provided: *"NHS patients are not expected to be eligible for 2nd line pembrolizumab, or pembrolizumab + lenvatinib, after having had dostarlimab given NHS England guidelines"*	The amendment echoes guidelines from NHS England on conditions of immunotherapy treatment, for example one of the eligibility criteria for pembrolizumab is *'the patient has not received any prior antibody treatment which targets PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) unless the patient has received pembrolizumab via the MSD company early access scheme and all other treatment criteria on this form are fulfilled'* (11).	The EAG has added the additional NHSE text in section 5.1.4 to reflect the points made by the company.

with anti PD-1, anti PD-L2 etc. treatments (9).			
Page 107 The EAG states that the company assumes 100% of those in PFS2 are treated which is not an accurate representation of the company base case.	Request that the EAG clarify that the assumption that 100% of patients being treated at 2L is only accurate when using the RUBY-1 trial data to inform subsequent treatments. The company did not submit this as its base case, and this has been proposed by the EAG only.	The company base case is based on clinical expert feedback and explicitly accounts for patients who have no subsequent treatment (20.5% in the dostarlimab arm and 14.9% in the CP arm) and so does not assume 100% of patients are treated at 2L. The EAG has disregarded the most suitable source of data provided by the company which includes elements to reduce the risk of overestimating 2L treatment distribution by including a 'No further Treatment' option.	The EAG has amended this to better reflect the company approach.

Abbreviations: CSR, clinical study report; CP, carboplatin plus paclitaxel; CS, company submission; dMMR, mismatch repair deficient; EAG, external assessment group; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; PFS, progression-free survival; RCT, randomised controlled trial; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TTD, time-to-treatment discontinuation.

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 21, Table 5 In the 5th column of the 1st row after the heading row, the EAG state: "*As mentioned in the EAG report from TA963:[12] the population in the CS was focused on those who had a low potential for cure by radiotherapy or chemotherapy in line with the evidence from the RUBY-1 trial.*" This misrepresents the RUBY-1 trial population, which consisted of patients with a low potential for cure by radiation therapy or surgery alone or in combination.	Please amend the sentence to: "~~*As mentioned in the EAG report from TA963:[12]*~~ *The population in the CS was focused on those who had a low potential for cure by radiotherapy or surgery alone or in combination, in line with the evidence from the RUBY-1 trial.*"	Clarification of the population included within the CS and the RUBY-1 trial.	The text has been amended.
Page 26 The EAG state:	Please amend the sentence to:	The amendment ensures the EAG accurately reflects that the RUBY-1 trial was	The text has been amended.

"*The evidence for the clinical effectiveness of dostarlimab+CP is from RUBY-1 (NCT03981796), an international multi-centre, double-blind, Phase III randomised controlled trial (RCT).*" This does not mention that the RUBY-1 trial was also placebo-controlled	"*The evidence for the clinical effectiveness of dostarlimab+CP is from RUBY-1 (NCT03981796), an international multi-centre, double-blind, placebo-controlled Phase III randomised controlled trial (RCT).*"	placebo-controlled, which is an important aspect of the study design.	
Page 26 The EAG cross-reference to Appendix D does not match the statement: "CS Appendix D.1.3.1 describes the number of studies identified in the original SLR and four update searches." It would be more accurate to refer to D1.3.	Please amend: *"D.1.3.1"* to *"D.1.3"*	Cross-reference to Appendix D amended for accuracy.	The text has been amended.
Pages 27, 29, 30, 75 and 76 The EAG states:	Please amend the sentences to: Page 27 - "*The study comprised an 18-week period of dostarlimab+CP or placebo+CP followed by an extended*	The amendments correct the EAG's statements to accurately reflect that the initial combination treatment	Not a factual error, to the EAG's understanding since administration occurs in

Page 27 - "*The study comprised a 16-week period of dostarlimab+CP or placebo+CP followed by an extended period of up to 3 years of dostarlimab monotherapy or placebo.*" Page 29 - "*In the first 16 weeks of RUBY-1 participants received dostarlimab in addition to what the company state is the most common regimen of standard of care (CS B.1), combination carboplatin and paclitaxel.*" Page 30 - "*Following the 16-week period of dostarlimab+CP versus placebo+CP, participants were followed up to 3 years during a dostarlimab monotherapy versus placebo period (CS Figure 4).*" Page 75 - "*•Weeks 1 to 16 : Applying the proportion of patients who received*	*period of up to 3 years of dostarlimab monotherapy or placebo.*" Page 29 – ""*In the first 18 weeks of RUBY-1 participants received dostarlimab in addition to what the company state is the most common regimen of standard of care (CS B.1), combination carboplatin and paclitaxel"* Page 30 – "*Following the 18 -week period of dostarlimab+CP versus placebo+CP, participants were followed up to 3 years during a dostarlimab monotherapy versus placebo period (CS Figure 4).*" Page 75 – "*•Weeks 1 to 18: Applying the proportion of patients who received treatment with dostarlimab based upon IA1 data.* *•Week 19 to week 145: Applying the TTD Kaplan Meier IA1 curve"* Page 76 – *"The numbers receiving CP treatment from baseline to week 18 are pooled across the dostarlimab arm and the placebo arm and applied"*	period was 18 weeks, based on treatment given every 3 weeks for 6 cycles, not 16 weeks.	the first week of the cycle. The EAG thinks that the proportions data only applies to weeks 1 to 16 as per Data Store D56:D61. The EAG also notes that KM Data AH33:AH34 = [redacted] and that this is aligned with the data in Trace (Dostarlimab + CP) BP27.

treatment with dostarlimab based upon IA1 data. *•Week 16 to week 145: Applying the TTD Kaplan Meier IA1 curve"* Page 76 – *"The numbers receiving CP treatment from baseline to week 16 are pooled across the dostarlimab arm and the placebo arm and applied"* However, patients in the trial received either dostarlimab in combination with CP, or CP alone every 3 weeks for 6 cycles, meaning the initial combination treatment period was 18 weeks, not 16 weeks.			
Page 27 The EAG state: "*The population in RUBY-1 is women with primary*	Please amend the sentence to: *"The population in RUBY-1 consists of women with primary Stage III or IV EC or first recurrent EC, with a low potential for curative therapy by*	The amendment accurately reflects the RUBY-1 trial population.	Not a factual error

advanced or recurrent EC not amenable to curative therapy by radiotherapy or surgery" However, this description does not fully capture the trial population, which consists of female patients with primary Stage III or IV endometrial cancer or first recurrent endometrial cancer, with a low potential for cure by radiation therapy or surgery alone or in combination.	*radiotherapy or surgery alone or in combination."*		
Page 31 The EAG refer to the incorrect page number in the CSR: "*Further details were found in CSR IA1 p54:"* The correct page number in the CSR is Page 55.	Please amend: "*p54*" to "*p55*"	CSR page number amended for accuracy.	The text has been amended.
Page 34 The EAG state:	Please amend the sentence to: *"Around xxx of the dMMR/MSI-H subgroup received prior anti-cancer*	This amendment more accurately reflects the prior	Not a factual error as this refers to both arms.

"*Around [redacted] of the dMMR/MSI-H subgroup received prior anti-cancer treatment, the most common treatment was paclitaxel-carboplatin (dostarlimab+CP [redacted]; placebo+CP [redacted].*" However, in accordance with Table 8 of the EAG report, as well as the above statement, [redacted]% of patients in the dostarlimab arm received prior anticancer treatment. Therefore, the statement should be amended to around 13%.	*treatment, the most common treatment was paclitaxel-carboplatin (dostarlimab+CP [redacted]; placebo+CP [redacted].*"	anticancer treatment data for the dMMR/MSI-H population.	
Page 32 The EAG state: "*A breakdown of disease stage at trial baseline for people with recurrent disease was also requested by the EAG, but the company explained that these data were not available.*"	Please amend the sentence to: "*A breakdown of disease stage at trial baseline for people with recurrent disease was also requested by the EAG, but the company explained that these data were not available. The company further clarified in CQ response A14 that patients with recurrent endometrial cancer were not re-staged upon recurrence; instead, staging at diagnosis was applied."*	The amendment reflects the company's clarification that staging at diagnosis was used for recurrent endometrial cancer, as patients were not re-staged at recurrence, in line with trial protocol and standard clinical practice.	Not a factual error.

However, it was clarified in response to EAG clarification questions that patients with recurrent endometrial cancer were not re-staged upon recurrence; instead, staging at diagnosis was applied (1, 2) (CQ response A14).			
Page 45 The EAG state: "*The CS states that in the dMMR/MSI-H subgroup, participants in the dostarlimab+CP arm experienced over 10% higher incidence of Grade ≥3 treatment-related TEAEs and TEAEs requiring infusion interruption compared with the placebo+CP arm*." On page 45 of the CS, it is stated that: "*Incidences of participants experiencing Grade ≥3 TEAEs related to any treatment, and TEAEs*	Please amend the sentence to: "*The CS states that in the dMMR/MSI-H subgroup, participants in the dostarlimab+CP arm experienced over 10% higher incidence of Grade ≥3 ~~treatment-related~~ TEAEs related to any treatment, and TEAEs requiring infusion interruption compared with the placebo+CP arm*."	This amendment accurately reflects the CS.	The text has been amended.

leading to infusion interruption were >10% higher in the dostarlimab arm compared with the placebo arm." The EAG statement is misleading and should be updated to accurately reflect the CS.			
Page 53 The EAG state: "*The EAG notes that this is the mean age for the ICI eligible 1L CP cohort ([redacted]) who have been matched to RUBY-1 trial inclusion criteria, and therefore may not be representative of the UK NHS population*." However, the ICI-eligible 1L CP cohort was not formally matched to the RUBY-1 trial inclusion criteria; instead, the cohort was filtered based on the RUBY-1 criteria. It is therefore inaccurate to say that the cohorts have been	Please amend the sentence to: "*The EAG notes that this is the mean age for the ICI eligible 1L CP cohort ([redacted]) ~~who~~ have been filtered using RUBY-1 trial inclusion criteria. ~~and therefore may not be representative of the UK NHS population~~*."	This amendment accurately reflects the methodology used to generate the ICI-eligible 1L CP cohort, which was filtered based on the RUBY-1 criteria rather than being formally matched. Additionally, it incorporates the clinical expert opinion that the RUBY-1 trial is representative of UK clinical practice (5).	An amendment has been made but the EAG does not fully accept the point raised by the company.

matched. Furthermore, expert clinical opinion suggests that the RUBY-1 trial is representative of UK clinical practice (5).			
Page 61 and 82 The EAG state: Page 61 – *"The 2nd line treatment baskets differ by arm, the balance of treatments within them being based upon company expert opinion. The key difference is the proportion of patients who progress that receive 2nd line pembrolizumab; 0% in the dostarlimab arm and 47% in the placebo arm"* Page 82 – "*The difference between these costs is mainly due to 0% who progress in the dostarlimab+CP arm receiving 2nd line pembrolizumab, but 47% who progress in the*	Please amend this sentence to: Page 61 – *"The 2nd line treatment baskets differ by arm, the balance of treatments within them being based upon company expert opinion. The key difference is the proportion of patients who progress that receive 2nd line pembrolizumab; 0% in the dostarlimab arm and 42.6% in the CP arm"* Page 82 – "*The difference between these costs is mainly due to 0% who progress in the dostarlimab+CP arm receiving 2nd line pembrolizumab, but 42.6% who progress in the CP arm receiving 2nd line pembrolizumab"*	This amendment aligns this value with the correct value presented in the CS.	No factual error. This includes those receiving pembrolizumab monotherapy and pembrolizumab + lenvatinib.

placebo arm receiving 2nd line pembrolizumab" However, the proportion of patients in the CP arm that receive pembrolizumab in CP arm is 42.6% based on UK clinical expert opinion.			

Abbreviations: CS, company submission; CSR, clinical study report; EAG, external assessment group; IA1, first interim analysis; SLR, systematic literature review.

Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Page 37 "*At the clarification stage, PFS output was also provided from IA2*."	Not in public domain	Please mark "[redacted]." as CiC.	Highlighting has been added.
Page 39 "*For PFS, the Kaplan-Meier estimates are similar to the previous data-cut (**Error! Reference source not found.**). For CP, there are* [redacted] *new events and the only*	PFS data was exclusively provided to the EAG and is not in the	Please mark "[redacted] ***Error! Reference source not found.*** [redacted]"	Highlighting has been added.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
change for IA2 is [redacted]. For dostarlimab+CP, the EAG estimates there is extended follow-up for [redacted]. The company reports that [redacted]. The EAG is unclear about the circumstances around this case. The EAG notes that [redacted].”	public domain.	[redacted]*.”* as CiC.	
Page 45/46, Table 13	dMMR/MSI-H subgroup data are not in	Please mark all dMMR/MSI-H subgroup data in Table 13 as CiC.	The EAG understands that the data that are not marked CiC

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
	public domain.		are available in Powell 2024, EAG reference 19, as indicated in a footnote to table 13.
Page 47, Table 14	dMMR/MSI-H subgroup data are not in public domain.	Please mark all dMMR/MSI-H subgroup data in Table 13 as CiC.	The data that are not marked CiC are available in Powell 2024, EAG reference 19, as indicated in a footnote to table 14.
Pages 61, 62, 63 and 79	Information relating to PFS collected at	Please mark all sentences and figure headings referring to IA2 PFS as CiC: Page 61 - "*The company's modelling uses data from IA1 for PFS* [redacted]	[redacted]

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
	IA2 is not in the public domain and therefore us considered to be CiC.	[redacted] Page 62 - "[redacted]." Page 62 - "[redacted]" Page 62 - "[redacted]." Page 63 - "[redacted]*1*." Page 63 - "[redacted] ***Error! Reference source not found.*** [redacted]."	[redacted]

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
		Page 71 – "[redacted]."	
Page 71 Table 21	In reference to Table 21, the EAG state: "*Note that this applies the EAG preferred baseline age of 67.1 years briefly revised in section 5.1.3 below and the EAG IA2 PFS curves.*" Therefore, if the table	Please mark all information that was generated using IA2 PFS data as CIC.	Highlighting has been added.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
	is generated using IA2 PFS data, it should all be CiC.		
Page 76 "*At baseline 98% of dostarlimab+CP PFS patients are modelled as receiving dostarlimab treatment. This steadily declines until by the end of the third year 66% of those remaining in PFS are modelled as being treated with dostarlimab as shown in* ***Error! Reference source not found.***".	The EAG has marked Figure 18 as CiC. The information describing Figure 18 is therefore considered to be CiC.	Please mark the following CiC. "*At baseline* [redacted] *of dostarlimab+CP PFS patients are modelled as receiving dostarlimab treatment. This steadily* [redacted] *until by the end of the third year* [redacted] *of those remaining in PFS are modelled as being treated with dostarlimab as shown in* ***Error! Reference source not found.***".	Highlighting has been added.
Page 79 Table 27 drug costs for dostarlimab	Not in public domain, marked CiC in CS.	Please mark the four instances in which the dostarlimab discounted price is mentioned as CiC.	Highlighting has been added. 6 Instances including totals.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Pages 83 and 84 Table 32	Information in the total QALYs row should be CiC.	Please mark “[redacted]”, “[redacted]” and “[redacted]” as CiC.	Highlighting has been added.
Page 90 Figure 21	It is not clear whether this figure contains IA2 PFS data. If so, please mark as CiC.	Please mark Figure 21 as CiC if produced using IA2 PFS data.	This does not [redacted], so no CiC marking is needed.
Page 106 “*The company derives a mean duration of 2nd line dostarlimab of 12.2 months*”	12.2 months has been marked CiC in the model and CS.	Please mark the following CiC. “*The company derives a mean duration of 2nd line dostarlimab of [redacted] months*”.	Highlighting has been added.

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3. 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.
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10. 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: November 2024). 2022.

11. National Cancer Durgs Find List. Availble at https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ (accessed on November 2024) 2024