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 [ID3986]

Committee Papers

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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 [ID3968]

Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from GlaxoSmithKline:
   a. Summary of Information for Patients (SIP)
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Peaches Womb Cancer Trust
4. **External Assessment Report** prepared by Warwick Evidence
5. **External Assessment Report – factual accuracy check**
6. **Expert personal perspectives** from:
   a. Andrew Clamp, Consultant in Medical Oncology – clinical expert, nominated by GSK
   b. Laura Tookman, Consultant Medical Oncologist – clinical expert, nominated by GSK
   c. Helen White, Trustee and Peaches Patient Voices Lead – patient expert, nominated by Peaches Womb Cancer Trust
   d. Susan Woodburn – patient expert, nominated by Peaches Womb Cancer Trust
7. **Managed access feasibility statement**

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 ID3968

Document B

Company evidence submission

18 July 2023

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ID3968 Dostarlimab with carboplatin and paclitaxel company evidence submission Document B v1.0 18Jul2023 redacted AIC_CIC.docx	**v1.0**	**Yes**	**18 July 2023**

Contents

Tables and figures

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

B1.1 Decision problem

The decision problem addressed in this submission is presented in Table 1.

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

Table 1: Decision problem

	Final NICE scope issued by NICE	Decision problem addressed in submission	Rationale if different from the final NICE scope
Population	People with primary advanced or recurrent endometrial cancer	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.	Population updated to align with regulatory approach and anticipated license indication (Table 2).
Intervention	Dostarlimab with platinum-containing chemotherapy	As per scope	N/A
Comparator(s)	• Platinum-based doublet chemotherapy For people who had neoadjuvant or adjuvant platinum-based doublet chemotherapy: • Pembrolizumab plus lenvatinib*	Platinum containing chemotherapy – Carboplatin and paclitaxel	The company acknowledges that there is a potential overlap, for a small number of patients who had neoadjuvant or adjuvant platinum-based doublet chemotherapy, between the pembrolizumab plus lenvatinib recommended population (TA904) and the dostarlimab in combination with platinum containing population. However, there are a few limitations when conducting any economic analysis within this patient cohort: Within the dMMR/MSI-H cohort of the RUBY-1 trial data, very low numbers of patients received prior platinum

			containing doublet chemotherapy, in the dostarlimab group [redacted] and in the carboplatin-paclitaxel group [redacted] Any further subgroup analysis of RUBY based on these patient numbers would be highly uncertain and unfeasible. There is no published evidence that the company is aware of from the KEYNOTE-775 trial (pivotal trail investigating pembrolizumab plus lenvatinib in this setting) regarding dMMR/MSI-H patients who specifically received prior platinum-doublet chemotherapy. The manuscript for the KEYNOTE-775 trial notes the proportion of patients who had previously received systemic treatment only as neoadjuvant or adjuvant therapy, though this is broader than prior platinum doublet chemotherapy noted in the scope.[1] No outcomes or baseline characteristics are published for this cohort. In addition, there is no information available within published TA904 committee papers.[2]
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rates • Duration of response	As per scope, with the addition of disease control rate (DCR) and time to second objective disease progression (PFS2)	DCR and PFS2 are two additional secondary efficacy outcomes evaluated in the RUBY trial.

	• Adverse effects of treatment • Health-related quality-of-life.		
Economic analysis	As per NICE Base Case	As per scope	N/A
Subgroups to be considered	Local versus metastatic recurrence • People who had primary debulking surgery vs people who have not	The company do not believe that additional economic analysis in these subgroups will aid decision making or reduce uncertainty within this appraisal. Any further subgroups within the dMMR/MSI-H subgroup will have small sample size which will not provide meaningful analysis.	**Local versus metastatic recurrence**: Within the clinical study report recurrence was captured as a 'yes/no' variable and therefore the type and/or location of recurrence is not readily available. Within the dMMR/MSI-H RUBY trial population, n=27 (50.9%) in the dostarlimab group and n=32 (49.2%) patients in the carboplatin-paclitaxel group had recurrent disease. Recurrent disease status was analysed as a pre-defined subgroup for PFS IA and OS within the dMMR/MSI-H subgroup, with a HR of [redacted] for PFS IA and a HR of [redacted] for OS. Based on the efficacy demonstrated across the entire recurrent cohort, the company do not believe that further subgroup analysis within this subgroup will aid decision making and reduce uncertainty.

			People who had primary debulking surgery vs people who have not: Within the clinical study report prior anti-cancer surgery for endometrial cancer is captured as a 'yes/no' variable and therefore the type and/or outcome of surgery is not readily available. The trial protocol did not outline any specific inclusion or exclusion criteria related to surgery, patients were eligible for inclusion regardless of the type of surgical intervention or lack thereof. The trial was not designed to evaluate outcomes dependent on surgical intervention and therefore the company believe that presenting data for the subgroup is not informative. Within the dMMR/MSI-H RUBY trial population, most patients, [redacted] in the dostarlimab group and [redacted] in the carboplatin-paclitaxel group, had prior anti-cancer surgery for endometrial cancer. Furthermore, across three clinical advisory boards relating to this trial and this appraisal, people who have had primary debulking surgery versus people who have not, was not raised by any of the clinical experts as a subgroup of clinical importance.[3–5]

*Note: Pembrolizumab with lenvatinib was subject to an ongoing appraisal at the time of the decision problem meeting, and achieved recommendation by NICE in June 2023.[2]
Abbreviations: DCR – disease control rate; dMMR – DNA mismatch repair; DNA – deoxyribonucleic acid; IA – Investigator assessed; ITT – intent to treat; 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.

B1.2 Description of the technology being evaluated

Table 2 provides a summary of dostarlimab in combination with platinum-containing chemotherapy (PCC) for the treatment of 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.

The draft Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2: The technology being evaluated (dostarlimab in combination with PCC)

UK approved name and brand name	Dostarlimab (Jemperli®, GSK) in combination with platinum containing chemotherapy (PCC)
Mechanism of action	Dostarlimab is a humanised monoclonal antibody of the IgG4 isotype that binds to programmed death 1 (PD-1) receptors and blocks the interactions of binding with its ligands - programmed death-ligand 1 and 2 (PD-L1 and PD-L2). The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including antitumour immune-responses, through blockade of PD-1 binding to PD-L1 and PD-L2.[6]
Marketing authorisation/CE mark status	[redacted]
Indications and any restriction(s) as described in the SmPC	The proposed indication: *Dostarlimab 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 (EC) and who are candidates for systemic therapy.* Other existing indications include: Dostarlimab is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[6]
Method of administration and dosage	Dostarlimab dosage: Dostarlimab 500 mg IV every 3 weeks for 6 cycles followed by 1000 mg every 6 weeks for all cycles thereafter. Administration of dostarlimab should continue according to the recommended schedule until disease progression or unacceptable toxicity, or for a duration of up to 3 years. PCC dosage: When dostarlimab is administered in combination with PCC, healthcare professionals are advised to consult the Summary of Product Characteristics (SmPC) of the combination product(s) for further information on administration, safety aspects, and pharmaceutical particulars. The dosage regimen for dostarlimab in combination with PCC is presented in Table 3 below.

Table 3: Dose regimen for dostarlimab in combination with 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 prior to PCC on the same day.

Additional tests/ investigations

The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as IHC, PCR or NGS. NICE diagnostics guidance DG42 supports testing all patients with endometrial cancer for dMMR/MSI-H.[7]

List price and average cost of a course of treatment

The list price of dostarlimab is £5,887.33 per 500 mg vial.[8]
The list price of carboplatin is £168.85 per 450 mg vial.[9]
The list price of paclitaxel is £87.50 per 100 mg vial.[10]
Carboplatin and paclitaxel are administered every three weeks 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 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 (every 3 weeks) are shown in the table below:

	Dostarlimab	Carboplatin and Paclitaxel
Cycle (week)	Acquisition cost per treatment cycle (£)	
Up to cycle 18	[redacted]	518.85
Cycle 19+	[redacted]	0.00

Patient access scheme (if applicable)

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.

Abbreviations: dMMR – DNA mismatch repair deficient; FDA – Food and Drug Administration; GSK – GlaxoSmithKline; IHC – Immunohistochemistry; MHRA – Medicines and Healthcare products Regulatory Agency; 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; POP – Participating Orbis Partner; sBLA – supplemental Biologics Licence Application; UK – United Kingdom.

B1.3 Health condition and position of the technology in the treatment pathway

Overview of endometrial cancer epidemiology, and burden

- Dostarlimab in combination with PCC is anticipated to be licensed for treatment of patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer who are candidates for systemic therapy.
- The eligible patient population equates to approximately 500 patients a year in the UK (see Section B1.3.4), reflecting a well-defined proportion of the total endometrial cancer population.
- Patients with primary advanced or recurrent endometrial cancer experience poor survival outcomes, with 48% of patients diagnosed with stage III endometrial cancer surviving longer than one year, dropping to just 15% of stage IV patients.[11] Recurrent disease is difficult to treat, with only 20% patients surviving longer than five years.[12,13]

Current clinical pathway of care and unmet need

- Current clinical practice for treatment of primary advanced or recurrent endometrial cancer uses PCC as the SoC, with the most common regimen being carboplatin plus paclitaxel given every 3 weeks for six cycles.
- There has been no innovation in the primary advanced or recurrent endometrial cancer treatment paradigm since 2012.[14–17] Moving IO therapies earlier in the treatment pathway would improve chances of patients getting access to innovative therapies earlier and improve patient outcomes.[18–20]
- Primary advanced or recurrent endometrial cancer is associated with a range of severe symptoms such as vaginal bleeding, persistent pelvic pain and unintended weight loss, leading to severe impact on HRQoL.[21]

Dostarlimab in combination with PCC

- Dostarlimab is a novel IO therapy and in combination with PCC represents a significant step-change for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer over PCC alone.
- PFS: Treatment with dostarlimab in combination with CP provided a statistically significant and clinically meaningful, sustained benefit in PFS compared with placebo in combination with CP; HR of 0.28 (95% CI 0.16-0.50; p-value 0.0001) with an estimated probability of PFS at 24 months of 61.4% compared with 15.7%, respectively.
- OS: At 24.8 months median follow-up, dostarlimab in combination with CP was associated with a 24-month OS of 83.3%, and a considerable, clinically meaningful reduction in the risk of death compared with placebo in combination with CP at 58.7%; HR of 0.30 (95% CI 0.13-0.70; nominal p-value [redacted]).
- Dostarlimab in combination with CP demonstrated an acceptable safety profile and clinically similar HRQoL outcomes compared with placebo in combination with CP.
- Dostarlimab in combination with PCC represents a critical addition to the treatment pathway for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer who will otherwise have an extremely bleak prognosis with limited life expectancy, significant impacts on HRQoL and almost no hope of receiving an effective treatment.

B1.3.1 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 most (~96%) uterine cancers are endometrial cancer.[22] However, other types of uterine cancer are clinically distinct and are treated differently to endometrial cancer.[17]

There are two main types of cancer of the uterus:

- Endometrial carcinomas (Type I and II) which start in the endometrium, and accounts for approximately 96% of uterine cancers.[23]
- Uterine sarcomas which start in the myometrium or supportive connective tissue of the uterus.

Endometrial cancer has historically been classified into the following two tumour types.

- Type 1 tumours: Type I endometrial cancer comprises oestrogen-dependent endometrioid adenocarcinomas. These tumours represent most endometrial cancers, are generally less aggressive and are often cured by surgery.[24]
- Type 2 tumours: Type 2 endometrial cancer includes oestrogen independent non-endometroid subtypes such as serous, clear cell, undifferentiated carcinomas as well as carcinosarcoma. These subtypes are less common and more aggressive with poorer prognosis than Type I endometrial cancer, with higher rates of recurrence.[24,25,26]

Molecular subgroups of endometrial cancer are discussed in more detail in Section B1.3.3 below.

B1.3.2 Clinical presentation and diagnosis

Primary advanced or recurrent endometrial cancer is associated with a range of debilitating symptoms, affecting physical functioning and health-related quality-of-life (HRQoL).[26–28] The main symptoms include 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.[29] One patient describing that her body "felt like a ton of bricks".[29] Additional symptoms can include pain in the lower back or pelvic region, blood in the urine,[27] the presence of a mass in the lower abdomen or unintentional weight loss.[30] Patients complain of abdominal distension, early satiety, change in bowel or bladder function, and pain during intercourse.[26] Patient testimonials further speak to the debilitating nature of the disease, limiting a patient's ability to carry out everyday activities and impacting confidence and self-esteem.[29,31] HRQoL is impacted by the symptoms of endometrial cancer which include menopausal-like symptoms, impaired sexual function, anxiety/depression, and lasting adverse effects associated with chemotherapy.[26,32,33]

The diagnosis of endometrial cancer is based on clinical examinations to assess the tumour location, volume and spread, radiological examinations of the uterus, and histopathological examinations using a biopsy to determine the histological type and grade.[17] For recurrent endometrial cancer patients, biopsies can be taken to test for molecular subtypes of endometrial cancer if prior testing for molecular markers had not been conducted.[7,34]

B1.3.3 Disease severity

Endometrial cancer is a heterogenous disease, which can range from a treatable and largely curative diagnosis, to an aggressive and life limiting diagnosis. Stage at diagnosis, grade of tumour, histology of tumours and molecular classification of tumours are all factors which contribute to the severity of endometrial cancer. Disease severity is important in the context of this decision problem, to understand the treatment pathways, the unmet need, and the RUBY clinical trial results.

B1.3.3.1 Stage at diagnosis

Upon diagnosis, endometrial cancer is generally surgically staged according to the 2009 FIGO system[17,35] (see Appendix N Table 49). The FIGO staging system is based on the spread of the tumour from its initial location in the endometrium to other tissues or organs. Stages I, III and IV also have subcategories. Most patients with endometrial cancer (approximately 80%) are symptomatic and diagnosed at an early-stage, with a smaller number (approximately 20%) diagnosed with advanced stage III and IV, at which point the disease has spread beyond the uterus.[23,36,37]

B1.3.3.2 Grade of tumour

Endometrioid endometrial tumours may be graded according to the FIGO grading system. The higher the grade of the tumour, the more poorly differentiated and the greater the likelihood that endometrial cancer will metastasise.[38]

- Grade 1: Tumour has ≤5% solid non-squamous growth
- Grade 2: Tumour has between 6% and 50% solid non-squamous growth
- Grade 3: Tumour has >50% solid non-squamous growth (and any non-endometroid tumour)

B1.3.3.3 Tumour histology

There are a multitude of histologies that comprise endometrial cancer, as shown in Table 4.

Table 4: Common endometrial cancer histologies[39,40]

Histology	Characteristics
Endometrioid adenocarcinoma	Well-differentiated tumours; the most common type of endometrial cancer, accounting for 75% of cases; commonly detected early and have a high cure rate
Serous adenocarcinoma	A poorly differentiated tumour accounting for 5%–10% of cases characterised by aggressive growth and poor prognosis
Clear cell adenocarcinoma	Comprises 3%–6% of endometrial cancers and progresses rapidly
Carcinosarcoma	A high-grade tumour accounting for approximately 1%–5% of endometrial cancers characterised by poor prognosis
Other	Additional histologies are rare but may include mucinous adenocarcinoma and squamous cell carcinoma

B1.3.3.4 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 (Table 5).[41,42] The integration of molecular classification with clinicopathological data helps establish subgroups with significant prognostic differences and varying relative risks of recurrence (see Appendix N Table 50).[43] UK clinical feedback was that molecular classifications are now increasingly used, as treatments are tailored according to molecular features and to better represent the disease heterogeneity within endometrial cancer.[3]

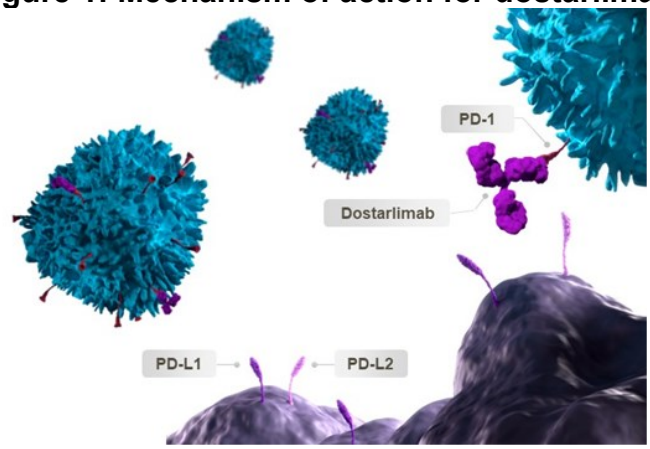
Table 5: Endometrial cancer molecular subgroups

	POLE-mutant	**dMMR/MSI**	**No specific molecular profile (NSMP)**	**TP53-mutant**
Description [17,44]	Ultramutated with pathogenic variations in the exonuclease domain of DNA POLE-ultramutated	Hypermutated, with MSI due to dMMR proteins	Genomically relatively stable, MMR-proficient, with moderate number of mutations	Somatic copy number-low with TP53 mutations
Prevalence in TCGA cohort, %	5-15	25-30	30-40	5-15

Abbreviations: dMMR – dysfunctional mismatch repair; MMR – mismatch repair; MSI – microsatellite instability; POLE – polymerase epsilon; TCGA – The Cancer Genome Atlas.

dMMR/MSI-H is a molecular biomarker indicating the presence of a defective DNA repair process and represents a subgroup where programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibition with immune-oncology therapy is most effective.[45] The mechanism of action for dostarlimab, which targets the PD-1/PD-L1 interaction, is shown in Figure 1.

Figure 1: Mechanism of action for dostarlimab[46]



Abbreviations: PD-1 – programmed death receptor-1; PD-L1 – programmed death ligand-1.

The DNA mismatch repair (MMR) system is a mechanism utilised to restore DNA integrity after mismatch errors have occurred.[47,48] Microsatellites are short tandem repeats of DNA sequences. Micro satellite instability high (MSI-H) describes a condition of genetic hypermutability characterised by changes within microsatellites, short tandem repeats of DNA sequences.[47,49,50]

These two characteristics are intertwined: a dMMR tumour accumulates thousands of mutations particularly clustered in microsatellites resulting in MSI therefore, MSI-H is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR system.[47,49,50] dMMR endometrial cancer can be associated with a higher recurrence rate, a higher rate of distant recurrences and Lynch syndrome, a germline mutation that increases the risk of other cancers, particularly endometrial and colorectal cancer.[7,51]

Endometrial cancer is reported to have the highest incidence of dMMR/MSI-H across all solid tumours, with 20-30% of endometrial cancer cases classified as dMMR/MSI-H.[7,47,52,53] As part of NICE diagnostics guidance DG42, all patients with endometrial cancer are now tested for dMMR/MSI-H at diagnosis. Testing for dMMR/MSI-H uses immunohistochemistry (IHC), which is an inexpensive technique used routinely to test for other cancers. [7]

dMMR/MSI-H endometrial cancer is highly immunogenic and exhibits more tumour-specific neoantigens. This results in increased T-cells (including tumour infiltrating lymphocytes and compensatory upregulation of immune checkpoints).[45] Tumours

with dMMR are more likely to respond to PD-1 blockade and thus anti-PD-1 therapies such as dostarlimab. PD-1 and its known ligands, PD-L1 and PD-L2, are part of a signaling system which negatively regulates T-cells.[54] By inhibiting the binding of PD-1 to PD-L1 and PD-L2, the PD-1 signaling pathway and subsequent immune system evasion by the tumour can be blocked. This increases the anti-tumour immune response and cancer cell death.[55] The combination of increased T cell expression coupled with PD-1/PD-L1 expression, makes dMMR/MSI-H endometrial cancer an effective target for dostarlimab.

B1.3.3.5 Advanced stage and recurrent endometrial cancer

Advanced stage disease refers to patients who present with primary stage III or stage IV cancer who have not undergone complete surgical resection and have at least some residual tumour.[42]

Irrespective of stage at diagnosis, patients with endometrial cancer can experience disease recurrence, defined as disease that cannot be detected after primary treatment, but then is radiologically or histologically detected again at a later point in time.[56]

Patients with advanced or recurrent disease have poorer outcomes than those diagnosed with primary local disease, and these patients have a different treatment intent. These patients are treated with a low potential for cure by radiotherapy, surgery or, a combination of both.[4]

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.[57,58] The RUBY trial inclusion criteria required patients to be diagnosed with primary advanced stage III or stage IV (see Appendix N Table 49) disease or first recurrent endometrial cancer. Further details of RUBY inclusion criteria are outlined in Section B2.3.1.3.

B1.3.4 Epidemiology

In the UK, there are approximately 9,700 cases of endometrial cancer diagnosed annually, making it the fourth most common cancer amongst women and the most common gynaecological cancer.[22]

Incidence of the disease is increased with age;[23] in the UK between 2017 and 2019, 52% of all endometrial cancer deaths were in females aged 75 and over.[22] High body mass index is a common risk factor for endometrial cancer, with 34% of uterine cancer cases in the UK attributable to obesity.[59] Hormonal risk factors that increase the likelihood of endometrial cancer are associated with prolonged or unopposed exposure to oestrogen.[41,60]

Of the 8,048 cases of endometrial cancer diagnosed annually in the England, approximately 2,300 patients are diagnosed with primary advanced or recurrent endometrial disease. Approximately 500 of these annual incidence patients will experience dMMR/MSI-H endometrial cancer and receive frontline treatment and are therefore the relevant patient population for this appraisal decision problem. Full details of the eligible patient population size are outlined in the budget impact analysis document.

B1.4 Prognosis and current NHS care pathway for the management of endometrial cancer

Endometrial cancer mortality rates have increased by approximately 24% in females in the UK from 2017-2019.[22] Ethnicity is a factor in endometrial cancer survival outcomes. When studies balance access to healthcare and histological type, the mortality rate of non-Hispanic black women has been shown to be higher than Caucasian women.[61] In the UK, endometrial cancer survival outcomes have been shown to be 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 increased risk and a 53% increased risk of cancer specific death respectively, compared with the least deprived women.[62]

The key clinical guidelines available for the management of endometrial cancer, include the British Gynaecological Cancer Society (BGCS), the ESMO, and the ESGO/ESTRO and the ESP.[16,41] There are no recent published NICE guidelines for endometrial cancer outside of laparoscopic hysterectomy.[65]

Treatment depends on several factors including location of disease or presence of regional or distant metastasis, suitability for surgery, and the patient's desire for fertility-sparing clinical management.[41,64,66] Initial management typically involves surgical treatment and is dependent on the stage of the disease at diagnosis (Figure 2).[16,41] The RUBY trial was designed to investigate the addition of immunotherapy to standard of care (SoC) chemotherapy for patients with primary advanced or recurrent endometrial cancer where systemic therapy would be indicated.[18]

B1.4.1.1 Chemotherapy (PCC)

Current clinical guidelines regarding the use of chemotherapy in primary advanced and recurrent endometrial cancer are based on the Phase III trial GOG0209 (NCT00063999). The study established SoC treatment for primary advanced or recurrent endometrial cancer as platinum-containing doublet chemotherapy (carboplatin plus paclitaxel [CP]). This treatment is associated with a 50-60% response rate followed by a modest disease-free interval with recurrence anticipated.[14] In the pivotal study which established this SoC, median progression-free survival (PFS) was 13.2 months, and the OS was 37 months for patients receiving CP.[14] This trial had a much broader inclusion criteria compared to RUBY (outlined in Section B2.3.1.3), including patients with lower risk, fully resected stage III disease. Importantly, when restricting to patients with stage III and IV measurable disease and recurrent cancer only (n=400), outcomes are much poorer, with a decreased median OS of 20.4 months.[14] A UK study, in a cohort akin to the RUBY trial treated with CP, highlighted poor survival outcomes for patients, with a median OS from first-line treatment of 17.2 months, dropping to just 8.9 months at second line treatment (see Section B2.2.1).[67]

CP treatment may not be suitable for all patients due to comorbidities, patient choice, performance status and treatment burden. In these circumstances, where it is not appropriate to receive doublet chemotherapy, carboplatin monotherapy or hormone

therapy might be a preferrable and less burdensome option.[3] Hormone therapy is considered a primary therapy for patients with stage III or IV disease, who are not suitable for surgery, and have either widespread recurrent disease, or recurrence as asymptomatic lung metastases. It is worth noting that SoC and treatment pathways are consistent regardless of mutation status (dMMR vs. mismatch repair-proficient (MMRp)).[5,16] Current treatment options show similar outcomes regardless of mutation status.[68–71]

B1.4.1.2 Radiation therapy

Radiation therapy may be administered as a single fraction or as a course of fractionated treatments. Within the primary advanced or recurrent endometrial cancer setting, radiation therapy is frequently used alone in the palliative setting for patients with symptomatic pelvic disease that is inoperable, or for patients who are not fit for surgery and who may have bleeding.[5] Whilst this offers some symptom alleviation, the level of unmet medical need in this patient population remains high. Radiation therapy is also used after surgery in combination with chemotherapy for patients with salvageable recurrent disease or stage III disease. In these patients the combination of radiation therapy with chemotherapy is used with curative intent.[4,5,41,72] Within the RUBY protocol, participants were required to have endometrial cancer with a low potential for cure by radiation therapy, or surgery alone, or in combination. There was restricted use of radiation therapy in the RUBY trial, as the trial was designed to investigate the addition of immunotherapy to SoC chemotherapy, which is not recommended in combination with radiation therapy in the relevant patient population.

B1.4.1.3 Subsequent therapy

Durable response to treatment of primary advanced and recurrent endometrial cancer is of key clinical importance as patients who have relapsed disease post PCC experience shockingly poor health outcomes. Recent UK RWE found that median OS following treatment with chemotherapy in the post PCC setting was only 10.3 months.[73]

Innovative treatment options have recently been made available for patients who experience disease relapse post PCC. Dostarlimab is recommended for a relapsed

endometrial cancer dMMR/MSI-H population via the Cancer Drugs Fund (CDF), and pembrolizumab with lenvatinib is recommended for all previously treated endometrial cancer patients.[2,74] However, in recent UK RWE less than one-third of patients received a subsequent treatment beyond primary treatment, illustrating the importance of having innovative primary treatment options as early as possible in the pathway.[73]

B1.4.2 Burden of endometrial cancer

B1.4.2.1 Clinical and humanistic burden

Endometrial cancer is associated with significant mortality in the UK. There are 2,500 uterine cancer deaths in the UK every year, which equates to approximately 7 patient deaths every day.[22] Patients diagnosed with primary advanced or recurrent endometrial cancer have a particularly poor prognosis and experience a high mortality rate, as outlined in Section B1.4.2.2

Primary advanced or recurrent endometrial cancer is associated with a range of symptoms, as outlined in section B1.3.2. Surgical removal of the uterus and associated impacted tissues can damage sex organs and impair sexual function, with one study reporting that 68.6% of patients experienced sexual dysfunction following treatment for their disease.[75] Post-surgery patients can experience pain during intercourse, have impaired physical functioning, impaired mobility and experience a deficit in usual daily activities.

Patients experience increased anxiety, depression, and psychological problems due to the disease, with one patient describing her anger at her inability to have a family “Why can’t I have a family what did I do to deserve it?”.[76]

Ahead of even beginning treatment patients speak about feeling psychologically unprepared for the rigorous regimen that they are about to embark on.[77] It is important to note the demographic of patients diagnosed with primary advanced or recurrent endometrial cancer, which is largely women in their 60s. These patients are often active in the workforce in addition to 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 subsequent impact on

their finances, their inability to engage in everyday activities alongside the emotional burden that the disease and treatment have on their family and friends.[31]

The use of doublet chemotherapy in this setting is long-standing. There are well established management guidelines and protocols to address the AEs associated with CP. Patients are monitored during treatment and checked regularly at their appointments to highlight any adverse treatments and treat early, minimising side effects.[78]

Once treatment has been completed patients report concerns about the key survivorship issues that still linger. Patients speak about 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.[77]

B1.4.2.2 Unmet need

Advanced stages of endometrial cancer and endometrial cancer with non-endometroid histology are known to be associated with worse prognosis. Approximately 99% of endometrial cancer patients will survive for one year or more when diagnosed at the earliest stage (FIGO stage I) which decreases to 47% of patients when diagnosed at the most advanced stage (FIGO stage IV).[11] More than 92% of people diagnosed with stage I endometrial cancer will survive for five years or more, compared with 15% of people diagnosed at stage IV.[22]

Recurrent endometrial cancer is regarded as an incurable disease, with limited disease-free durations following early stage treatment.[79] When patients have recurrent disease, their prognosis worsens with only approximately 20% of patients surviving for five years.[12,80,81] A European study showed approximately 17% of endometrial cancer patients experienced recurrence, with median survival after recurrence being 23 months.[82]

Since the introduction of CP, there have been no therapeutic advancements, thus there is a need to prevent or delay recurrence and prolong survival in the primary setting. IO therapies have been available for primary treatment of other advanced cancers for several years. The lack of treatments with durable efficacy for patients

with primary advanced or recurrent endometrial cancer was described by a patient advocate - “there are simply no alternatives for these women and their outlook is bleak.” Being left in a “no choice situation” is detrimental to patient’s psychological wellbeing, leaving patients in critical need of new treatment options.[74] Currently in the UK, only patients with relapsed advanced or recurrent endometrial cancer patients have access to immunotherapies.

Previous retrospective endometrial cancer studies have shown that the longer time to recurrence is an independent predictor of prolonged survival after recurrence.[83,84] Bringing innovative therapies into earlier treatment settings in other cancer histologies, such as pembrolizumab for treating advanced melanoma patients in the first-line setting, and olaparib as a first-line maintenance therapy for ovarian cancer patients with *BRCA 1/2* mutation, has resulted in a greater proportion of patients being offered the treatment, and a statistically significant increase in the proportion of patients exhibiting progression-free intervals.[85–87]

By introducing effective treatments in the primary advanced endometrial cancer treatment paradigm, more patients are likely to experience long-term survival, prolonging the relapsed free interval between first- and second-line therapy. Furthermore, there is a need to address an inequality in access to innovative therapies in endometrial cancer compared with other cancer types such as melanoma, ovarian and breast cancer.

B1.4.2.3 Rationale for combining dostarlimab with platinum-containing chemotherapy (PCC)

There is accumulating evidence that, in addition to direct cytostatic and cytotoxic effects, the mechanism of action of conventional chemotherapies may involve activation of tumour-targeted immune responses, including increasing the immunogenicity of cancer cells and reducing immunosuppression of tumours.[88–93]

As endometrial cancer cells overexpress PD-1 (in 75% of cases) and PD-L1 (in 25%-100% of cases),[94] immune checkpoint inhibitors targeting this pathway could be utilised in combination with chemotherapy to improve durability of anti-tumour immune response.

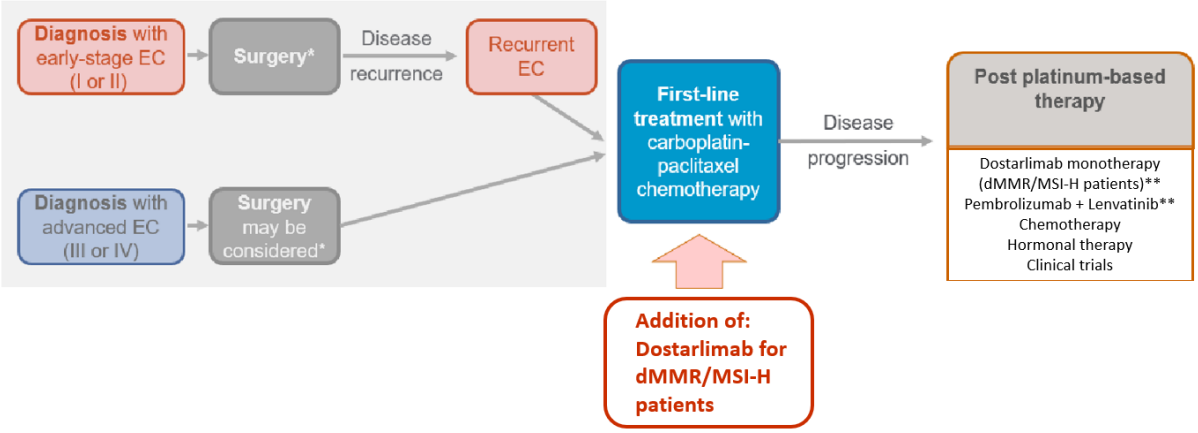
Furthermore, the combination of chemotherapy with immunotherapy has, in other tumours, shown lower instance of the clinical phenomenon “hyperprogression” than that observed with exposure to immunotherapy alone.[95] For patients with primary advanced or recurrent disease the rapid onset of action associated with PCC is beneficial.

B1.4.2.4 Positioning of dostarlimab in combination with PCC in the management of endometrial cancer

Current clinical practice for advanced or recurrent dMMR/MSI-H endometrial cancer is outlined in Figure 2. As dostarlimab is expected to be positioned in addition to current SoC, CP, there would not be any disruptions to the treatment pathway during the combination phase. Dostarlimab monotherapy continuation would be an addition to the treatment pathway. The monotherapy maintenance phase involves six weekly administrations of a 30-minute infusion, until disease progression, toxicity or a maximum of three years. Patient advocates have noted that “dostarlimab has an advantage of being a 30-minute infusion; this has considerable benefits to patients where time is critical to them.” In addition, the extended interaction with the NHS and health care professionals may help reduce patients’ anxiety levels surrounding the potential for a relapse of their disease.

As an addition onto 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. The inclusion of an immunotherapy in the primary setting would have a subsequent impact on the usage of PD-L1 inhibitors at second line.

Figure 2: Current treatment pathway of primary advanced or recurrent EC



*At any stage, patients may also receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery. **As per pivotal trial inclusion/exclusion criteria, anti-PD-L1 not used in post platinum setting if treated with anti-PDL-1 in the first-line.[19,96]

Abbreviations: ACM – appraisal committee meeting; dMMR – DNA mismatch repair deficient; EC – endometrial cancer; MSI-H – microsatellite instability high.

B1.5 Equality considerations

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. 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.[97] 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 endometrial cancer patients of different ethnicities or experiencing different levels of socio-economic deprivation.[22,59] 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

Summary of clinical effectiveness evidence

- RUBY-1 trial (NCT03981796): a Phase 3, randomised, double-blind, multicentre study, provides direct head-to-head evidence for dostarlimab in combination with CP versus placebo in combination with CP in patients with primary advanced (stage III or IV) or recurrent endometrial cancer.
- A clinical SLR did not identify additional trials relevant to the assessment of the efficacy and safety of dostarlimab in combination with PCC.

The RUBY-1 trial

- ITT population, N=494 patients, dMMR/MSI-H population N=118 patients
- The primary endpoints were PFS (investigator assessment per RECIST v1.1) and OS, while secondary endpoints include ORR, PFS (BICR) DOR, DCR, PROs, PFS2 and safety.
- Primary and secondary endpoints were investigated in both the ITT and dMMR/MSI-H population, although OS is not a primary endpoint for the dMMR/MSI-H population (prespecified subgroup analysis).
- The dMMR/MSI-H population only is discussed in this dossier to align with the decision problem population.

PFS and OS for dMMR/MSI-H primary advanced or recurrent patients

PFS Primary Endpoint:

- Dostarlimab in combination with CP improved IA PFS compared with placebo in combination with CP with a HR of 0.28 (95% CI 0.16, 0.50, p<0.0001).
- The probability of PFS at 12 and 24 months was [redacted] and 61.4% for the dostarlimab in combination with CP arm compared with [redacted] and 15.7% in the placebo plus CP arm.

OS (prespecified subgroup analysis, dMMR/MSI-H population):

- Dostarlimab in combination with CP demonstrated a favourable trend in OS compared to placebo in combination with CP (HR of 0.30; 95% CI 0.13,0.70; nominal p-value=[redacted]) (26% maturity).
- The probability of survival at 12 and 24 months was [redacted] and 83.3% for the dostarlimab in combination with CP arm compared with [redacted] and 58.7% in the placebo in combination with CP arm.

ORR and DOR for dMMR/MSI-H primary advanced or recurrent patients

- The ORR rates were 77.6% in the dostarlimab in combination with CP arm versus 69.0% in the placebo in combination with CP arm.
- Dostarlimab in combination with CP delivered more durable responses in comparison to placebo in combination with CP, where the median DOR was not reached compared with 5.4 months (95% CI: 3.9, 8.1) in the respective arms.

HRQoL, safety and tolerability in dMMR/MSI-H primary advanced or recurrent patients

- Clinically similar HRQoL outcomes were seen between patients receiving dostarlimab in combination with CP as compared to those receiving placebo in combination with CP.
- Severe and serious AEs, AEs leading to discontinuation, and irAEs were higher in the dostarlimab arm of the study which is to be expected since dostarlimab treatment continued after the initial six cycles of carboplatin-paclitaxel.
- Immune-related AEs were higher in participants treated with dostarlimab in combination with CP versus placebo in combination with CP. However, most immune-related AEs were not severe or serious in nature and did not lead to treatment discontinuation or death.
- The safety profile for dostarlimab in combination with CP was consistent with the known safety profiles of the individual agents. The regimen was tolerable and toxicities manageable.

Conclusion

- RUBY-1 provides robust outcomes in prolonging PFS and OS, with manageable toxicities. Dostarlimab in combination with PCC would fulfil a high unmet need for the dMMR/MSI-H primary advanced or recurrent endometrial cancer population where novel treatment options are lacking, with existing therapy conferring modest but often short-lived benefits.

B2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted on 10 November 2021 (with a refresh on 22 February 2023) to identify randomised clinical trials (RCT) evidence reporting on the efficacy and safety of dostarlimab in combination with platinum-containing chemotherapy (PCC) 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.

B2.2 List of relevant clinical effectiveness evidence

As per Section B1.4, CP is the SoC treatment option in the primary advanced or recurrent endometrial cancer population. Nine trials were identified to have investigated CP in this population. These trials are summarised in Appendix D. However, none of the identified trials provided direct head-to-head RCT evidence of dostarlimab in combination with CP compared with CP relevant to the decision problem or evidence of CP specific to a dMMR/MSI-H 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 is based on this study. Table 6 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 6: Clinical effectiveness evidence

Study	RUBY (ClinicalTrials.gov number: NCT03981796)
Study design	A multicentre, randomised, double blinded, placebo-controlled Phase 3 study
Location	US, UK, Belarus, Belgium, Canada, Czechia, Denmark, Finland, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Sweden, Turkey, Ukraine
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. (Intention to treat [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	RUBY is the pivotal trial for dostarlimab in combination with CP for the treatment of primary advanced or recurrent endometrial cancer. RUBY included all randomised patients into the ITT and dMMR/MSI-H populations, with all analyses of efficacy endpoints performed on dMMR/MSI-H and MMRp/MSS subsets of the ITT analysis set. The dMMR/MSI-H population is the only relevant population for the decision problem, and therefore, this is the only population deemed relevant for the economic model.
Eligibility criteria	A summary of inclusion and exclusion criteria are provided below with further details in Section B2.3.1.3. Full details of the eligibility criteria are presented within the study protocol.[18] 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 on 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. • Until progression of disease or unacceptable toxicity, up to a maximum of 3 years
Primary outcomes (including scoring methods and timings of assessments)	A summary of outcomes is provided below with full details in the CSR.[98] Outcomes that have been highlighted in bold are included in the economic model. • **Progression-free survival (PFS) by investigator assessment (IA PFS)** • **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)	A summary of outcomes is provided below with full details in the CSR.[98] Outcomes that have been highlighted in bold are included in the economic model.
	• 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)
	  ○ **European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L)[mapped to EQ-5D-3L]**
	  ○ European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (C30 [Core; QLQ-C30])
	  ○ Endometrial Cancer Module [QLQ-EN24])
	• Progression-free survival 2 (PFS2)
	• **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	• Exploratory subgroup analyses on the primary endpoints (IA PFS and OS) were performed on the dMMR/MSI-H population to explore the homogeneity of the treatment effect across relevant participant subsets:

	○ Age (< 65 years or ≥ 65 years) ○ Race (white or other) ○ Region (North America or Europe or Western Europe or Eastern Europe) ○ Histology (endometrioid carcinoma or other) ○ Disease status at baseline (recurrent, primary stage III, or primary stage IV), according to the eCRF (source verified classification) ○ Prior external pelvic radiotherapy (yes or no), according to the eCRF (source verified classification) ○ Subjects 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/paclitaxel; 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; IA ‒ investigator assessed; ITT – intention to treat; IV – intravenous; MMRp – mismatch repair proficient; MSI-H – microsatellite instability-high; MSS – microsatellite stable; ORR – objective response rate; OS – overall survival; PCC – platinum-based chemotherapy; PD-1 – programmed cell death protein 1; PD-L1 – programmed cell death-ligand 1; PD-L2 – programmed cell death-ligand 2; PFS – progression-free survival; 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.

B2.2.1 UK RWE

A RWE study was conducted using the National Cancer Registration and Analysis Service (NCRAS) data for diagnosis between 2013 and 2019.[73] The analysis studied patient characteristics, treatment pathways and health outcomes in real-world English patients with primary advanced or recurrent endometrial cancer. The study demonstrated that almost 8 in 10 (77.8%) of the patients who received first line systemic treatment for advanced or recurrent endometrial cancer (n=2,345) were treated with CP. The results provide an insight into the poor prognosis for patients in the UK. The full report of this NCRAS RWE study is included in Appendix L.

B2.3 Summary of methodology of the relevant clinical effectiveness evidence

B2.3.1 Summary of study methodology

B2.3.1.1 Study design

RUBY is a phase 3, randomised, double-blind, multicentre study. Part 1 of the study (RUBY-1) aims to evaluate the efficacy and safety of treatment with dostarlimab in combination with CP followed by dostarlimab versus treatment with placebo in combination with CP followed by placebo in patients with primary advanced or

recurrent endometrial cancer. Part 2 of the study aims to evaluate the efficacy and safety of treatment with dostarlimab in combination with CP followed by dostarlimab plus niraparib versus treatment with placebo in combination with CP followed by placebo in patients with primary advanced or recurrent endometrial cancer. Currently, only RUBY-1 results are available, specifically the dMMR/MSI-H population of RUBY-1 is relevant to the decision problem and this submission.

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:

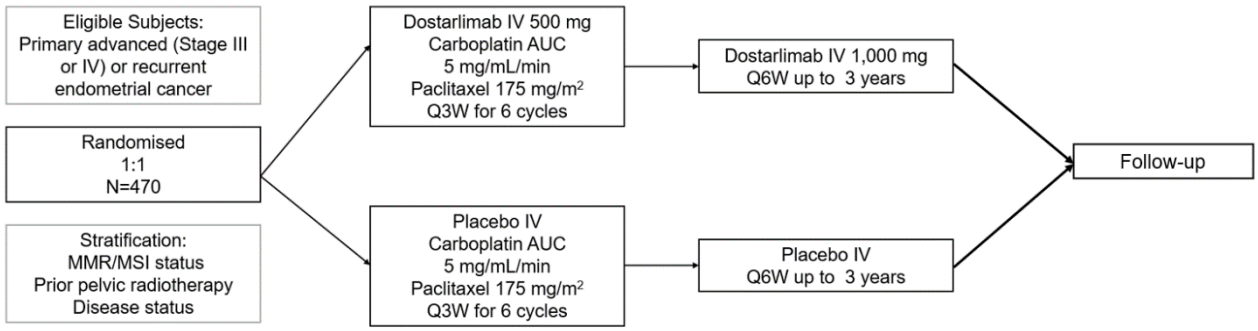
- Intervention arm: Patients received dostarlimab 500 mg intravenous (IV) in combination with CP followed by dostarlimab monotherapy 1,000 mg IV.
- Comparator arm: Patients received placebo IV in combination with CP followed by placebo IV.

Subjects were stratified by MMR and MSI status as dMMR/MSI-H or MMR-proficient (MMRp)/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. Analyses of primary and secondary endpoints were carried out on the ITT population and the dMMR/MSI-H population.

B2.3.1.2 RUBY-1 design

Figure 3 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 7. Following randomisation, patients in the intervention arm received dostarlimab in combination with CP followed by dostarlimab monotherapy. In the comparator arm, patients received placebo in combination with CP followed by placebo.

Figure 3: RUBY-1 design



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

Patients were allowed to continue dostarlimab treatment for up to 3 years or until progressive disease (PD), unacceptable toxicity, withdrawal of consent, investigator's decision, or death. Continued treatment beyond 3 years could be considered following discussion between the investigator and sponsor. Patients with PD who were clinically stable could continue treatment at the investigator's discretion after discussion with the sponsor, until the investigator determined that the patient was no longer experiencing clinical benefit or until study treatment was no longer tolerated by the patient. Similarly, continued treatment beyond 3 years with placebo could be considered following discussion between the investigator and sponsor.

B2.3.1.3 Inclusion and exclusion criteria

Patients were eligible to be included in RUBY-1, only if all criteria applied. All inclusion criteria are listed in detail in the CSR.[98] Key inclusion criteria are listed below:

1. Female patient is at least 18 years of age, able to understand the study procedures, and agrees to participate in the study by providing written informed consent.

2. Patient has histologically or cytologically proven endometrial cancer with advanced or recurrent disease.

3. Patient must provide adequate tumour tissue sample at screening for MMR/MSI status testing. Note: The quality of the tumour tissue sample must

be confirmed by the central laboratory during screening. Patients should not be randomised without central laboratory confirmation.

4. Patient must have primary stage III or stage IV disease or first recurrent endometrial cancer, with a low potential for cure by radiation therapy or surgery alone or in combination, and meet at least one of the following criteria:

    a. Patient has primary stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumour.[99]

    b. Patient has primary stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥10% carcinosarcoma, clear cell, or serous histology), regardless of presence of evaluable or measurable disease on imaging.

    c. Patient has primary stage IIIC2 or stage IV disease, regardless of presence of evaluable or measurable disease.

    d. Patient has first recurrent disease and is naïve to systemic anticancer therapy.

    e. Patient has received prior neoadjuvant/adjuvant systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment (first recurrence only). Note: Patients with uterine sarcoma are not allowed.

5. Patient has an ECOG performance status of 0 or 1.

Patients satisfying any of the below criteria were not eligible for enrolment in RUBY-1. All exclusion criteria are listed in detail in the CSR.[98] Key exclusion criteria are listed below:

1. Patient has received neoadjuvant/adjuvant systemic anticancer therapy for primary stage III or IV disease and one of the following:

    a. Has not had a recurrence or PD prior to first dose on the study OR

    b. Has had a recurrence or PD within 6 months of completing systemic anticancer therapy treatment prior to first dose on the study. Note: Low-dose cisplatin given as a radiation sensitiser or hormonal therapies do not exclude patients from study participation.

2. Patient has had >1 recurrence of endometrial cancer.

3. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

4. Patient has received prior anticancer therapy (chemotherapy, targeted therapies, hormonal therapy, radiotherapy, or immunotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter. Note: Palliative radiation therapy to a small field of ≥1 week prior to Day 1 of study intervention may be allowed.

5. 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. Nonmelanoma skin cancer is allowed.

6. Patient has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both.

B2.3.1.4 Settings and locations

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

B2.3.1.5 Trial drugs and concomitant medications

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

Any medication that the patient took 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 B2.3.1.3.

B2.3.1.6 Study outcomes

The dual primary objectives of RUBY-1, in the ITT population, were to compare the PFS and OS of patients treated with dostarlimab in combination with CP followed by dostarlimab monotherapy to patients administered placebo in combination with CP followed by placebo, as assessed by the Investigator per RECIST v.1.1. OS was a prespecified subgroup analysis in dMMR/MSI-H population. Secondary objectives included the comparison of PFS based on blinded independent central review (BICR) assessment, objective response rate (ORR), duration of response (DOR), disease control rate (DCR), patient-reported outcomes (PROs), PFS2 and safety and tolerability endpoints between patients of both treatment arms.

Table 7 provides a summary of the primary and secondary objectives for the data cutoff date of 28 September 2022.

Table 7: Primary and secondary objectives of RUBY-1

Objective	Definition	Assessment
Primary objectives		
PFS	The time from the date of randomisation to earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurred first	Based on investigator assessment and performed per RECIST v.1.1
OS*	The time from randomisation to the date of death by any cause	Based on investigator assessment
Secondary objectives		
PFS	The time from the date of randomisation to earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurred first	Based on BICR assessment
ORR	The proportion of subjects with a best overall response of complete response (CR) or partial response (PR)	Based on BICR and investigator assessment
DOR	The time from the first documentation of CR or PR until the time of the first documentation of subsequent PD per RECIST v.1.1 or death by any cause in the absence of PD per RECIST v.1.1, whichever occurs first	Based on BICR and investigator assessment
DCR	The proportion of patients who have achieved a best overall response of CR, PR, stable disease (SD), Non-CR/Non-PD per RECIST v.1.1	Based on BICR and investigator assessment
PROs	Assessment of treatment using European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (C30 [Core; QLQ-C30] and Endometrial Cancer Module [QLQ-EN24])	Not applicable
PFS2	The time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever is earlier	Not applicable
Safety and tolerability		

Safety and tolerability	Adverse event (AE) monitoring, physical examinations, vital sign measurements, ECOG performance status, ECGs, clinical laboratory tests, and recording of concomitant medication usage	Not applicable

Outcomes highlighted in bold are utilised in the economic model. Abbreviations: AE – adverse event; BICR – blinded independent central review; CR – complete response; DCR – disease control rate; DOR – duration of response; ECG – electrocardiogram; ECOG – Eastern Cooperative Oncology Group; EORTC – European Organisation for Research and Treatment of Cancer; EQ-5D-5L – European Quality of Life scale, 5-Dimensions, 5-Levels; OS – overall survival; PD – progressive disease; PFS – progression-free survival; PR – partial response; PROs – patient-reported outcomes; SD – stable disease. *OS was a prespecified subgroup analysis in dMMR/MSI-H population.

B2.3.1.7 Patient demographics and clinical baseline characteristics

Table 8 shows a summary of the demographic baseline characteristics of patients in the dMMR/MSI-H population. In the dMMR/MSI-H population, 53 patients were in the dostarlimab in combination with CP arm while 65 patients were in the placebo in combination with CP arm. Most patients in the dMMR/MSI-H population were white with a median age of 64.0 years (84.7%) and baseline ECOG performance status of 0 (57.3%). The median patient age was 61.0 years in the dostarlimab in combination with CP arm and 66.0 years in the placebo in combination with CP arm. 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 in combination with CP arm compared with the dostarlimab in combination with CP arm ([redacted] and [redacted] kg/m^2 versus [redacted] and [redacted] kg/m^2, respectively). ECOG status was worse in the dostarlimab in combination with CP arm as less patients had a performance status of 0 compared with the placebo in combination with CP arm (53.8% versus 60.0%). In total, 46.2% of patients in the dostarlimab in combination with CP arm and 40.0% of patients in the placebo in combination with CP arm had an ECOG performance status of 1. In general, the patients baseline characteristics between treatment arms were considered well balanced.[5]

Table 8: 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]
Min, Max	45, 81	39, 85
Age Group, n (%)		
19-64	30 (56.6)	30 (46.2)
>=65	23 (43.4)	35 (53.8)
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 Performance Status, n (%)		
0	28 (53.8)	39 (60.0)
1	24 (46.2)	26 (40.0)

Source: CSR Table 14.1.1.15.

Abbreviations: BMI – body mass index; BSA – body surface area; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ECOG – Eastern Cooperative Oncology Group; MSI-H – microsatellite instability-high; SD – standard deviation.

Table 9 shows a summary of the disease history of patients in the dMMR/MSI-H population, while Table 10 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, with 52.8% of dostarlimab in combination with CP treatment arm patients and 53.9% of placebo in combination with CP treatment arm patients having a stage III/IV diagnosis. As expected, the most frequent histology type at diagnosis was endometrioid histology (83.0% of patients in the dostarlimab in combination with CP arm and 86.2% in the placebo in combination with CP arm). This was similar for the most recent histology, with 84.9% and 83.1% of patients in the dostarlimab in combination with CP arm and placebo in combination with CP 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 in combination with CP arm compared with the placebo in combination with CP arm (7.5% versus 1.5%). The most common recent grade of disease was grade 3 for dostarlimab in combination with CP arm patients ([redacted]%) and grade 2 for placebo in combination with CP arm patients ([redacted]%). A slightly greater percentage of dostarlimab in combination with CP arm patients had experienced recurrence compared with placebo in combination with CP arm patients (50.9% versus 49.2%). In general, the patients' disease history between treatment arms were considered well balanced.[5]

Table 9: 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: CSR Table 14.1.1.17

Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; FIGO – Federation of Gynaecology and Obstetrics; MSI-H – microsatellite instability-high.

Table 10: 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	53 (100.0)	65 (100.0)
pMMR/MSS	0	0
Previous external pelvic radiotherapy		
Yes	8 (15.1)	13 (20.0)
No	45 (84.9)	52 (80.0)
Disease status		

Primary stage III	10 (18.9)	14 (21.5)
Primary stage IV	16 (30.2)	19 (29.2)
Recurrent	27 (50.9)	32 (49.2)

Source: CSR Table 14.1.1.10

Abbreviations: CP – carboplatin/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.

B2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

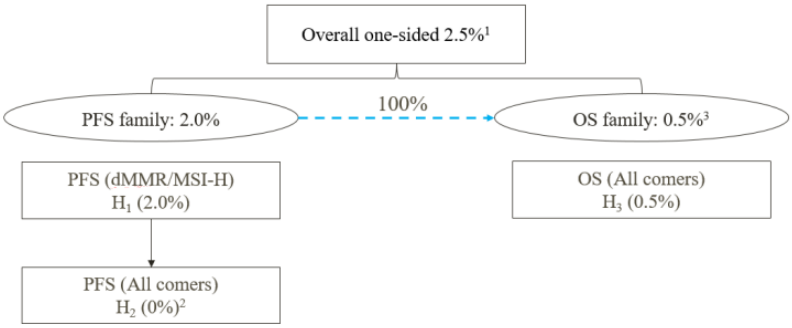
Details of RUBY-1, including a summary of the statistical analyses, are provided in Table 11.

Table 11: Summary of statistical analyses

Study	**RUBY-1 (ClinicalTrials.gov number: NCT03981796)**
Hypothesis objective	RUBY-1 had three null hypotheses: 1. Dostarlimab in combination with CP followed by dostarlimab prolongs PFS (investigator assessment) per RECIST v.1.1 in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo. 2. Dostarlimab in combination with CP followed by dostarlimab prolongs PFS (investigator assessment) per RECIST v.1.1 in patients with primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo in the ITT population. 3. Dostarlimab in combination with CP followed by dostarlimab prolongs OS in patients with primary advanced or recurrent endometrial cancer compared with placebo in combination with CP followed by placebo in the ITT population. A hierarchical testing strategy was used to analyse the primary efficacy outcome of PFS in the dMMR/MSI-H population followed by the overall population.
Statistical analysis	All analyses include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses are performed using Kaplan-Meier (KM) methods. Two-sided 95% confidence intervals are provided, where appropriate. The primary analysis for all efficacy endpoints was based on the dMMR/MSI-H and ITT population. Sensitivity analysis for PFS as assessed by BICR was performed using the dMMR/MSI-H and ITT population. All safety analyses were performed on the safety population. This comprised of all patients who received at least one dose of study intervention (N=487). The safety population included 117 patients who were stratified as dMMR/MSI-H. The ITT analysis population was used to analyse efficacy outcomes and comprised of patients who were randomised regardless of treatment received (N=494). This included 118 patients who were stratified as dMMR/MSI-H. The prespecified dMMR/MSI-H population for efficacy analyses was determined by the source verified value of MMR/MSI status. The number of patients in the dMMR/MSI-H subset of ITT analysis set determined by the source verified value of MMR/MSI status was 53 in the dostarlimab in combination with CP arm and 65 in the placebo in combination with CP arm.

<table>
<tr><th>Study</th><th>RUBY-1 (ClinicalTrials.gov number: NCT03981796)</th></tr>
<tr><td></td><td>For the primary efficacy endpoint parameter, PFS, as determined by the investigator assessment, the distribution was estimated using the KM method, taking the randomisation strata (MMR/MSI status [dMMR/MSI-H or MMRp/MSS], prior external pelvic radiotherapy [yes or no], and disease status [recurrent, primary stage III, or primary stage IV]) into account. The median PFS along with 95% confidence intervals are presented by treatment group. The stratified Cox regression was used to estimate the HR of PFS along with the confidence interval associated with the significance level for hypothesis testing. The censoring rule applied for the primary analysis of PFS is summarised as below.
<table>
<tr><th>Situation</th><th>Primary Analysis</th></tr>
<tr><td>No baseline tumour assessment and no death within 12 weeks</td><td>Censored at randomisation</td></tr>
<tr><td>No baseline tumour assessment and death within 12 weeks</td><td>Progressed at date of death</td></tr>
<tr><td>No PD and no death; new anticancer therapy is not initiated</td><td>Censored at last tumour assessment</td></tr>
<tr><td>No PD and no death; new anticancer therapy is initiated</td><td>Censored at last tumour assessment before new anticancer therapy</td></tr>
<tr><td>PD or death documented after ≥2 missed disease assessments</td><td>Censored at last tumour assessment prior to the ≥2 missed disease assessment</td></tr>
</table>

Graphical approaches were used to provide strong multiplicity control for multiple testing. The family-wise type I error for this study is strongly controlled at 2.5% (one-sided).
Analyses of the secondary efficacy outcomes were based on the ITT and dMMR/MSI-H population. The endpoints included were PFS based on BICR, ORR, DOR based on BICR and investigator assessment, DCR based on BICR and investigator assessment, PROs (EQ-5D-5L EORTC QLQ-C30, and EORTC QLQ-EN24), and PFS2.</td></tr>
<tr><td>Sample size, power calculation</td><td>The sample size calculations for the RUBY trial were driven by the primary efficacy endpoint of PFS (investigator assessed using RECIST v1.1). The following assumptions were made for the sample size calculations:
• dMMR/MSI population (status independent patient population [all-comers]): HR of 0.67, [redacted]
• dMMR/MSI-H population (patient population): HR of 0.50, [redacted]
• Subject distribution by tumour MMR/MSI status: 25% with dMMR/MSI-H and 75% with MMRp/MSS
• 1:1 randomisation
• Alpha = An alpha of 0.02 was initially allocated to hypotheses regarding IA PFS and an alpha level of 0.005 was initially allocated to hypotheses regarding OS. For IA PFS, hypotheses were hierarchically tested in the dMMR–MSI-H population and then in the overall population; OS was tested in the overall population. If the null hypotheses for IA PFS were all rejected, the 0.02 alpha level would be recycled to the hypothesis of OS, which would be tested at a one-sided alpha level of 0.025; otherwise, OS would be tested only at the initially allocated one-sided alpha level of 0.005
• Power = approximately 89% for testing of hypothesis 1 [redacted]
With these assumptions, a total sample size of 470 patients was planned, and approximately 118 patients were expected to be dMMR/MSI-H.</td></tr>
</table>

Study	RUBY-1 (ClinicalTrials.gov number: NCT03981796)
	To maintain the natural distribution of dMMR/MSI-H (25%) and MMRp/MSS (75%) participants in the overall endometrial cancer population in this study, the number of participants enrolled with dMMR/MSI-H or MMRp/MSS endometrial cancer was capped at approximately 120 and 350, respectively. In addition, the total number of patients with carcinosarcoma was capped at 50 (approximately 10%) to prevent overrepresentation of this patient population.
Data management, patient withdrawals	Patients could be discontinued from the study treatment at any time. Specific reasons for discontinuing study treatment include: • AE • Clinical progression • PD according to RECIST v.1.1 criteria per investigator assessment • Risk to subject, as judged by the investigator, sponsor, or both • Severe noncompliance with the protocol, as judged by the investigator, sponsor or both • Subject becomes pregnant • Withdrawal of consent • Lost to follow-up • Death from any cause • Sponsor decision to terminate study
Summary diagram	 1. The alpha level assigned to a subfamily were rolled over only if the hypotheses within the subfamily were all significant based on the weight for re-allocation presented on the dashed lines connecting subfamilies. Within each subfamily, the weights for re-allocation from each hypothesis to the others are represented on the solid lines connecting hypotheses. 2. Hypothesis testing for PFS in all-comers were only performed if null hypothesis of PFS has been rejected in dMMR/MSI-H population. 3. Hypothesis testing for OS started at the time when the hypothesis testing for PFS had completed (i.e., no further hypothesis testing could be performed for PFS), at a re-allocated alpha level (2.5%) if both null hypotheses had been rejected for H1 and H2; otherwise, OS was tested at the initial alpha level (0.5%).

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

Full details on the definition of endpoints are provided in the CSR.[98] 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.[98]

B2.5 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.

B2.6 Clinical effectiveness results of the relevant studies

The following sections present the clinical effectiveness results from the RUBY-1 trial. A descriptive comparison of key outcomes between dostarlimab in combination with CP followed by dostarlimab monotherapy versus treatment with placebo in combination with CP followed by placebo from the first interim analysis is included. The following sections present the clinical effectiveness results for the dMMR/MSI-H population only, as per the decision problem. All results for the ITT population are included in the CSR.[98]

B2.6.1 Duration of follow-up

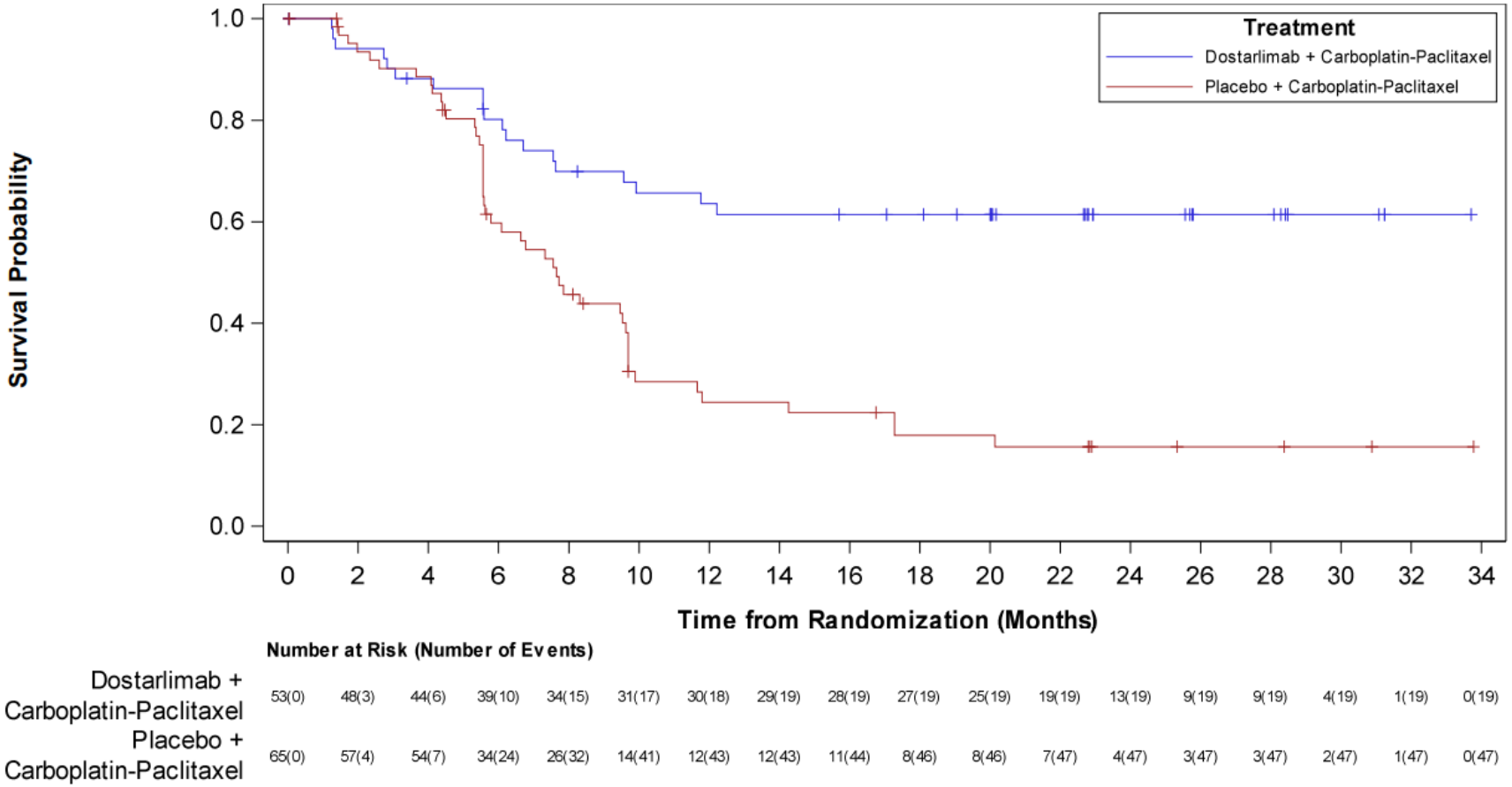
In the dMMR/MSI-H population, the median duration of follow-up was 24.79 months. The median follow-up duration was relatively similar between the dostarlimab in combination with CP treatment arm and placebo in combination with CP treatment arm at [redacted] and [redacted], respectively. The mean follow-up duration in the dMMR/MSI-H population was [redacted], with a mean follow-up duration of [redacted] in the dostarlimab in combination with CP arm and [redacted] in the placebo in combination with CP arm. (Source: CSR Table 14.1.1.34)

B2.6.2 Primary efficacy outcome: Progression-free survival (PFS) (Investigator assessed)

RUBY-1 met its primary endpoint by demonstrating that dostarlimab in combination with CP followed by dostarlimab monotherapy demonstrated a clinically meaningful and statistically significant benefit compared with placebo in combination with CP followed by placebo by prolonging PFS for patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer. Figure 4 shows the KM curves of PFS in the dMMR/MSI-H population. In the dMMR/MSI-H population at the time of data cut-off (56% PFS maturity), dostarlimab in combination with CP reduced the risk of progression or death by 72%, with a HR for progression or death of 0.28 (95% CI

0.16, 0.50, stratified log-rank test p-value <0.0001; median PFS was [redacted] in the dostarlimab in combination with CP arm versus [redacted] in the placebo in combination with CP arm, respectively) (Table 12). The number of PFS events observed in the dostarlimab in combination with CP arm was 19 (35.8%) compared with 47 (72.3%) in the placebo in combination with CP arm. The stopping boundary [redacted] for claiming superiority was crossed. The PFS curves began to separate in favour of the dostarlimab in combination with CP arm at approximately month 6 and continued to diverge over time with a relative plateau of the dostarlimab in combination with CP arm at the 12-month mark. The estimated KM probability of PFS at 24 months were 61.4% (95% CI, 46.3-73.4) in the dostarlimab in combination with CP arm and 15.7% (95% CI, 7.2-27.0) in the placebo in combination with CP arm, representing a nearly four times higher PFS probability with dostarlimab treatment (Table 12).

Figure 4: Kaplan-Meier curves of PFS – RECIST v.1.1 by investigator assessment, Interim Analysis (dMMR/MSI-H patient population)



Source: CSR Figure 15.1.1Data cutoff: 28 September 2022

Abbrevations: dMMR – DNA mismatch repair-deficient; MSI-H – microsatellite instability-high; PFS – progression-free survival.

Table 12: Kaplan-Meier analysis of PFS – RECIST v.1.1 by investigator assessment, Interim Analysis (dMMR/MSI-H patient population)

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
PFS status, n (%)		
Events observed	19 (35.8%)	47 (72.3%)
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	61.4% (46.3%, 73.4%)	15.7% (7.2%, 27.0%)
Hazard ratio (95% CI)	0.28 (0.16, 0.50)	
p-value of 1-sided stratified log-rank test	<0.0001	

Source: CSR Table 14.2.1.1

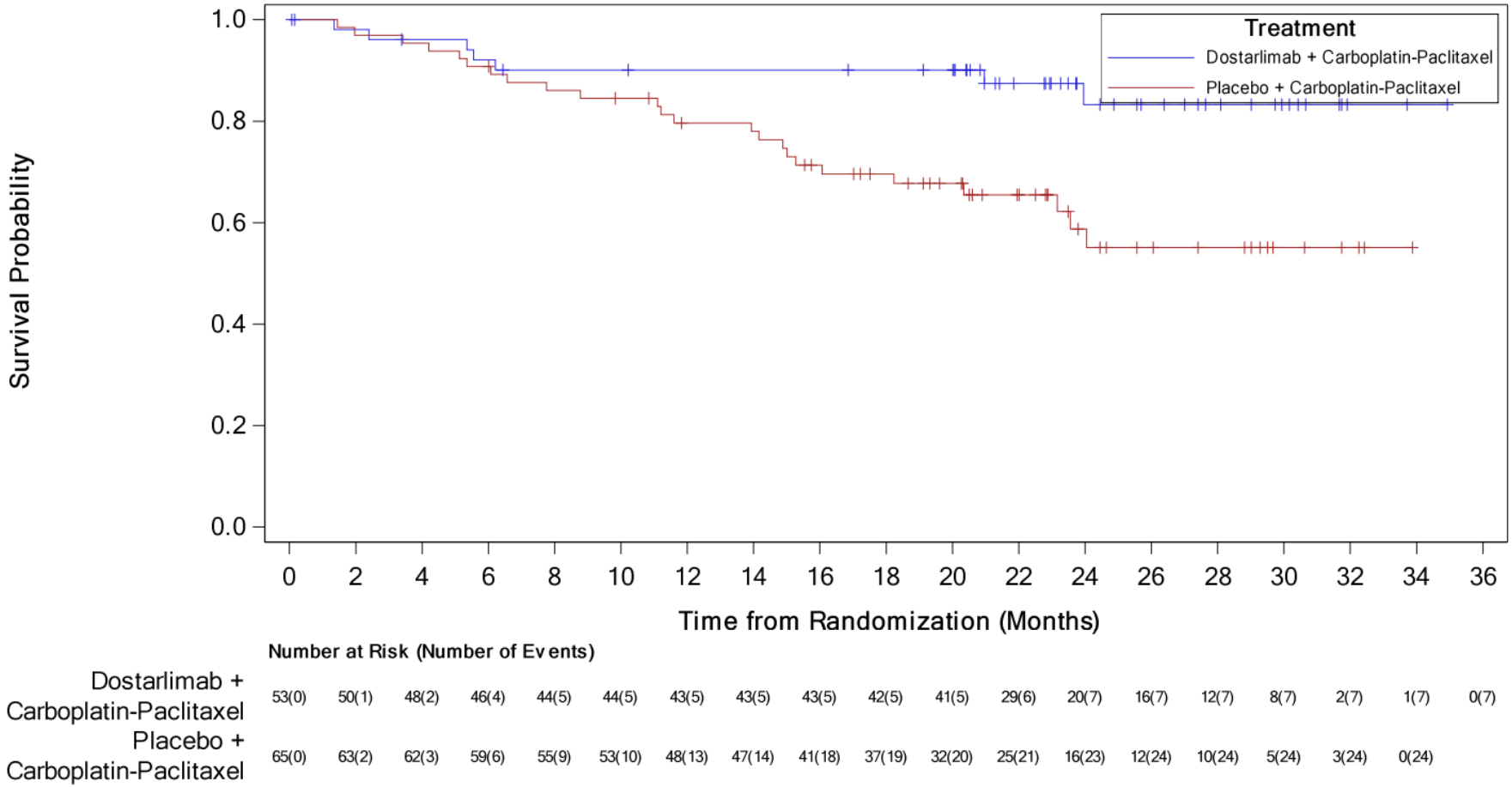
Data cutoff: 28 September 2022

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.

B2.6.3 Prespecified subgroup analysis: Overall survival (OS)

Figure 5 shows the KM analysis of OS in the dMMR/MSI-H patient population. Although OS in the dMMR/MSI-H population is not a primary endpoint, a prespecified subgroup analysis of OS in this population was performed. At 26% OS maturity, there was a considerable, clinically meaningful trend in favour of the dostarlimab in combination with CP arm with a 70% reduction in deaths and a HR of 0.30 (95% CI 0.13-0.70; nominal p-value=[redacted]; median OS not reached for either arm) (Table 13). In the dostarlimab in combination with CP arm, there were seven events (13.2%), whilst in the placebo in combination with CP arm, a total of 24 events (36.9%) were observed. A clear, early and sustained separation of the survival curves began around 6 months, driven by mortality in the placebo in combination with CP arm and a relative plateau in the dostarlimab in combination with CP arm. The KM probability of survival at 24 months was 83.3% (95% CI 66.8-92.0) and 58.7% (95% CI 43.4-71.2) in the dostarlimab in combination with CP and placebo in combination with CP arms, respectively (Table 13).

Figure 5: Kaplan-Meier analysis OS – Interim Analysis (dMMR/MSI-H patient population)



Source: CSR Figure 15.1.8
Data cutoff: 28 September 2022
Abbreviations: dMMR – DNA mismatch repair-deficient; MSI-H – microsatellite instability-high; PFS – progression-free survival.

Table 13: Kaplan-Meier analysis of OS – Interim Analysis (dMMR/MSI-H patient population)

Category subcategory	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%)
Censored	[redacted]	[redacted]
OS (months) Quartile (95% CI)		
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]
OS probability (95% CI)		
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	83.3% (66.8%, 92.0%)	58.7% (43.4%, 71.2%)
Month 30	[redacted]	[redacted]
Hazard ratio (95% CI)	0.30 (0.13, 0.70)	
Nominal p-value of 1-sided stratified log-rank test	[redacted]	

Source: CSR Table 14.2.1.8

Data cutoff: 28 September 2022

Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; NR – not reported; OS – overall survival.

B2.6.4 Secondary efficacy outcomes

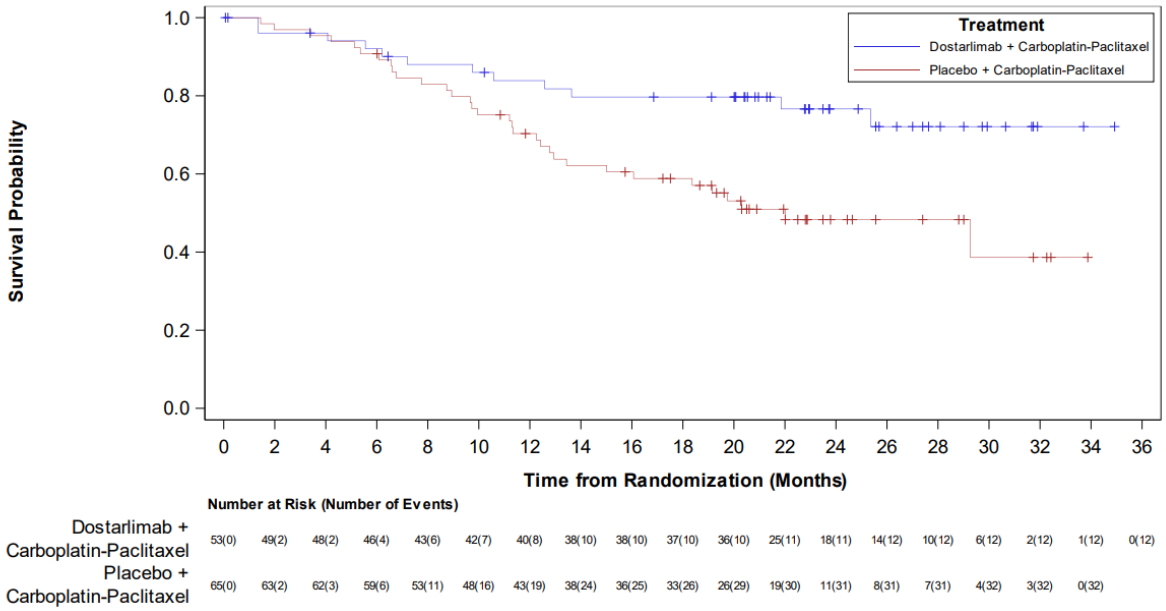
The clinical benefit of adding dostarlimab to CP was consistently observed across all secondary efficacy endpoints in the dMMR/MSI-H population including PFS by BICR, PFS2, ORR, DCR, and DOR.

B2.6.4.1 Progression-free survival 2 (PFS2)

Figure 6 shows the KM curves of PFS2 in the dMMR/MSI-H patient population. At the time of data cut-off, dostarlimab in combination with CP reduced the risk of progression following first subsequent anticancer therapy or death in the dMMR/MSI-H population, by demonstrating a HR of 0.37 (95% CI: 0.19, 0.73) (Table 14). Median PFS2 was [redacted] for patients receiving dostarlimab in combination with CP.

Like the PFS primary analysis, the KM curve of PFS2 showed separation in favour of the dostarlimab in combination with CP treatment arm in the dMMR/MSI-H patient population. The PFS2 results indicated that the benefit of dostarlimab combination therapy extended beyond first progression, leading to long term benefits, and further supports the trend observed for OS.

Figure 6: Kaplan-Meier curves of PFS 2 – Interim Analysis (dMMR/MSI-H patient population)



Source: CSR Figure 15.1.11
Data cutoff: 28 September 2022

Table 14: Summary of Kaplan-Meier of PFS2 – Interim Analysis (dMMR/MSI-H patient population)

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Hazard ratio (95% CI)	0.37 (0.19, 0.73)	
Median PFS2, months (95% CI)	NR	[redacted]
PFS2 Probability at 24 months (95% CI)	[redacted]	[redacted]

Source: CSR Table 14.2.1.39

Data cutoff: 28 September 2022

Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PFS – progression-free survival.

B2.6.4.2 Objective response rate (ORR) and disease control rate (DCR)

ORR and DCR consistently indicated a benefit in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm. ORR by investigator assessment per RECIST v1.1 was higher in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm in the patients with target or non-target lesions at baseline in the dMMR/MSI-H population (77.6% versus 69.0%, respectively) (Table 15). The dMMR/MSI-H population had a higher proportion of CRs and a lower percentage of patients with PD in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm (Table 15). The DCR was very high and was similar in both treatment arms across the dMMR/MSI-H population for patients with evaluable disease at baseline (89.8% versus 87.9%, respectively) (Table 15).

Table 15: Summary of tumour response – RECIST v.1.1. for subjects with evaluable target lesion or non-target lesion at baseline by investigator assessment, Interim Analysis (dMMR/MSI-H patient population)

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Patients with no evaluable disease at baseline, n (%)	4 (7.5%)	7 (10.8)
Patients with evaluable disease at baseline, n	**Dostarlimab in combination with CP (N=49)**	**Placebo in combination with CP (N=58)**
Objective response and disease control rate		
Best response by RECIST v.1.1, n (%)[a]		
CR	15 (30.6%)	12 (20.7%)
PR	23 (46.9%)	28 (48.3%)

SD	6 (12.2%)	10 (17.2%)
PD	2 (4.1%)	4 (6.9%)
Not evaluable	3 (6.1%)	3 (5.2%)
No disease	0	1 (1.7%)
Objective response rate[a]		
n (%)	38 (77.6%)	40 (69.0%)
95% CI	(63.4%, 88.2%)	(55.5%, 80.5%)
Disease control rate[a]		
n/N (%)	44 (89.8%)	51 (87.9%)
95% CI	(77.8%, 96.6%)	(76.7%, 95.0%)

Source: Mirza et al 2022 Table S6 and CSR Table 14.2.1.10.

Data cutoff: 28 September 2022

a. DCR is defined as the percentage of patients with a RECIST v.1.1. CR, PR , SD and No disease, of patients with evaluable disease at baseline.

Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; CR – complete response; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; PD – progressive disease; PR – partial response; SD – stable disease.

B2.6.4.3 Duration of response (DOR)

Within the dMMR/MSI-H patient population, median DOR was not reached in the dostarlimab in combination with CP arm compared with 5.4 months (95% CI: 3.9, 8.1) in the placebo in combination with CP arm (Table 16). The 24-month probability of remaining in response was 62.1% versus 13.2%, respectively. The assessment of DOR by BICR was similar to the investigator assessed DOR (CSR Table 14.2.1.16 and Figure 15.1.10). Insights from an advisory board suggested that in RUBY-1 DOR was highlighted as particularly important outcome for immunotherapy, as responses tend to be durable.[5]

Table 16: Kaplan-Meier analysis of DOR – RECIST v.1.1. based on investigator assessment and primary censoring rule, Interim Analysis (dMMR/MSI-H patient population)

Variable [n (%)]	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number of responders		
n	38	40
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%	NR (10.1, NR)	5.4 (3.9, 8.1)
75%	[redacted]	[redacted]
Duration ≥6 months	[redacted]	[redacted]
Duration ≥12 months	22 (57.9%)	7 (17.5%)
Probability of DOR (95% CI)		
Month 6	76.1%	46.2%
	(59.0%, 86.8%)	(30.2%, 60.7%)
Month 12	62.1%	19.2%
	(44.4%, 75.5%)	(8.6%, 33.1%)
Month 18	[redacted]	[redacted]
	[redacted]	[redacted]
Month 24	62.1%	13.2%
	(44.4%, 75.5%)	(4.6%, 26.3%)

Source: CSR Table 14.2.1.15
Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; DOR – duration of response; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; NR – not reported.

B2.6.4.4 Patient reported outcomes (PROs)

The improved PFS outcomes seen within the dostarlimab in combination with CP arm were not associated with a decrease in patient health related quality of life (HRQoL).

Table 17 shows the summary of changes from baseline in EORTC QLQ-C30 global QoL score in the dMMR/MSI-H patient population, while Table 18 shows the summary of changes from baseline in EQ-5D-5L Visual Analogue Score (VAS). Assessment of QoL measures indicated that dMMR/MSI-H patients in the dostarlimab in combination with CP arm had clinically similar, and numerically improved QoL compared with the placebo in combination with CP arm. There appears to be visual separation in the reported QoL score for global health, physical functioning, and pain, illustrating that patients treated with dostarlimab in combination with CP do not experience any worsening of HRQoL during treatment.

Insights from an advisory board suggested that in RUBY-1 results, there is a clear separation between the reported QoL scores over time as patients treated with dostarlimab in combination with CP have improved disease control.[5] In terms of the absolute difference in score seen at cycle 13, there is an absolute difference of [redacted]

and [redacted] in the mean change from baseline scores across the dostarlimab and placebo treatment arms in the EORTC QLQ-C30 and EQ-5D-5L VAS score, respectively. The results were consistent across all analyses as supported by changes from baseline in EQ-5D-5L VAS score (Figure 8 and Table 18) and EORTC QLQ-C30 (

Figure 7 and Table 17).

Figure 7: Changes from baseline and confidence intervals in EORTC QLQ-C30 global QoL score – Interim Analysis (dMMR/MSI-H patient population)

Source: CSR Figure 15.4.2
Data cutoff: 28 September 2022
Abbreviations: BSLN – baseline; Cx – cycle X; dMMR – DNA mismatch repair deficient; EOT – end of treatment; MSI-H – microsatellite instability-high; QOL – quality of life; SFU – safety follow-up visit; SVFU – survival follow-up visit; WPB – worst post-baseline.

Table 17: Summary of changes from baseline in EORTC QLQ-C30 global QoL score – Interim Analysis (dMMR/MSI-H patient population)

Visit	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Baseline (n)	[redacted]	[redacted]
Mean (SD) baseline score	[redacted]	[redacted]
Status at cycle 7 (n)	[redacted]	[redacted]

Mean (SD) change from baseline to cycle 7	[redacted]	[redacted]
Status at cycle 13 (n)	[redacted]	[redacted]
Mean (SD) change from baseline to cycle 13	[redacted]	[redacted]
End of treatment (n)	[redacted]	[redacted]
Mean (SD) change from baseline to end of treatment	[redacted]	[redacted]

Source: CSR Table 14.4.1.1
Data cutoff: 28 September 2022
Abbreviations: CP- carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; SD – standard deviation.

Figure 8: Changes from baseline and confidence intervals in EQ-5D-5L VAS score – Interim Analysis (dMMR/MSI-H patient population)

Source: CSR Figure 15.4.4
Data cutoff: 28 September 2022
Abbreviations: BSLN – baseline; Cx – cycle X; dMMR – DNA mismatch repair deficient; EOT – end of treatment; MSI-H – microsatellite instability-high; QOL – quality of life; SFU – safety follow-up visit; SVFU – survival follow-up visit; WPB – worst post-baseline.

Table 18: Summary of changes from baseline in EQ-5D-5L Visual Analogue Scores – Interim Analysis (dMMR/MSI-H patient population)

Visit	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
All participants (n)	[redacted]	[redacted]
Mean (SD) baseline score	[redacted]	[redacted]

Status at cycle 7 (n)	[redacted]	[redacted]
Mean (SD) change from baseline to cycle 7	[redacted]	[redacted]
Status at cycle 13 (n)	[redacted]	[redacted]
Mean (SD) change from baseline to cycle 13	[redacted]	[redacted]
End of treatment (n)	[redacted]	[redacted]
Mean (SD) change from baseline to end of treatment	[redacted]	[redacted]

Source: CSR Table 14.4.1.8

Data cutoff: 28 September 2022

Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; SD – standard deviation.

Among patients with dMMR/MSI-H disease who received dostarlimab in combination with CP, numerical improvements from baseline were observed at cycle 7 in the global QoL score, physical functioning, role functioning, pain, and back/pelvis pain. When compared with the improvements in the placebo in combination with CP arm, these improvements were deemed nominally significant. The least squares means (LSM) were 9.4 (SE, 3.72; p = 0.01), 7.5 (SE, 3.61; p = 0.04), 11.7 (SE, 5.23; p = 0.03), –16.8 (SE, 4.78; p = 0.01), and –12.1 (SE, 5.55; p = 0.03), respectively.[100] Additional details for the EORTC scores and scores for physical functioning and pain can be found in Appendix Q.

B2.7 Subgroup and sensitivity analyses

B2.7.1 Subgroup analysis of PFS and OS

To explore the homogeneity of the treatment effect across relevant patient subsets, prespecified subgroup analyses of PFS and OS were performed at the first interim analysis (see Figure 9 and Figure 10). A forest plot of PFS in the dMMR/MSI-H population showed favourable HRs (<1) for all subgroups, although individual subgroups in this population have small numbers of patients.

The inability to detect a treatment difference in PFS in some subgroups including the primary stage III population, should be interpreted with caution and may be attributed to the smaller patient numbers, low data maturity, and the fact that the analysis was not powered to detect treatment differences in any subgroup.[98] An extended follow-up may therefore be required to observe a treatment effect in certain subgroups.

Figure 9: Forest plot of PFS and 95% confidence intervals by subgroup – Interim Analysis (dMMR/MSI-H subgroup)

Source: CSR Figure 15.2.1
Data cutoff: 28 September 2022
Note: HRs presented are from unstratified Cox regression model

A forest plot of OS in the dMMR/MSI-H patient population showed very favourable HRs (<0.5) for almost all subgroups, despite the low number of observed OS events in the individual subgroups (Figure 10). The only exception was for the histology category “other” [redacted]. These results should be interpreted with caution due to the small sample size and the low number of events.

The RUBY-1 trial enrolled a range of histologies including high-risk histological subtypes, such as carcinosarcoma. The ‘other’ category compared in the subgroup analysis in Figure 10 includes patients with carcinosarcoma and mixed carcinosarcoma. There was a greater proportion of patients within these categories in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm [redacted] compared with [redacted], respectively. The heterogenous histologies present in the RUBY-1 patient population, including histologies which typically respond poorly to treatment in clinical practice, was noted as a strength of the trial by UK clinicans.[102] UK clinicians noted that these histologies, though rare, are seen in the endometrial cancer patients they treat.

When compared to the RWE,[73] RUBY-1 included a more severe range of histologies, than that would also be observed in clinical practice (see Section B2.2.1, and Appendix L for details).[18]

Figure 10: Forest plot of OS and 95% confidence intervals by subgroup – Interim Analysis (dMMR-MSI-H patient population)

Source: CSR Figure 15.2.2
Data cutoff: 28 September 2022
Note: HRs presented are from unstratified Cox regression model

Further details of the subgroup analyses of PFS and OS in the ITT population can be seen in the CSR.[98]

B2.7.2 Sensitivity analysis for PFS: PFS (BICR)

Several sensitivity analyses were performed to interrogate the data and evaluate for potential biases. One sensitivity analysis used BICR assessment instead of investigator assessment for PFS (IA PFS). Like the IA PFS primary analysis, the KM curve of PFS BICR showed separation in favour of the dostarlimab in combination with CP. The HR of PFS from sensitivity analysis using BICR assessment for the dMMR/MSI-H patient population was 0.29 [redacted]. The estimated KM probability of PFS BICR at 24 months were [redacted] and [redacted] in the dostarlimab in combination with CP and placebo in combination with CP arms, respectively (Table 17 CSR[98]). Between the dostarlimab in combination with CP arm

and the placebo in combination with CP arms, agreement on the comparison of determination of event/censoring for IA PFS and through BICR was achieved for [redacted] and [redacted] of patients in the dMMR/MSI-H population, respectively. The PFS results as assessed by BICR were consistent with the IA PFS results across all populations, further supporting the robust clinical benefit demonstrated by dostarlimab.

B2.8 Meta-analysis

As outlined in Section B.1, the comparator in scope for this appraisal is CP. RUBY-1 is the only RCT identified evaluating dostarlimab in combination with CP compared to CP in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer, as such no meta-analysis or indirect treatment comparison is required (Section B2.2).

B2.9 Indirect and mixed treatment comparisons

RUBY-1 is a robust RCT, directly comparing dostarlimab in combination with CP and placebo in combination with CP, the comparator of interest outlined in the NICE scope. Furthermore, RUBY-1 provides direct comparative data in a dMMR/MSI-H primary advanced or recurrent endometrial cancer patient population, with patient baseline characteristics broadly aligned between comparator arms. Therefore, an indirect treatment comparison is not considered necessary to provide indirect evidence to support this submission.

B2.10 Adverse reactions

In RUBY-1 trial, the safety profile of dostarlimab was evaluated based on reported AEs, which were captured as a secondary endpoint. This safety data comprises data from an interim analysis of the data from RUBY-1, with a data cut off of 28 September 2022. 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 subjects were enrolled in the dostarlimab in combination with CP arm (52 of these were dMMR/MSI-H). Safety data are presented for the dMMR/MSI-H patient population.

Overall, dostarlimab in combination with CP has an acceptable safety profile with manageable toxicity and a safety profile consistent with the known profiles of the individual agents.

B2.10.1 Treatment exposure

A summary of duration on treatment in the dMMR/MSI-H population is provided in Appendix R, where patients are still on treatment at database lock. The overall median treatment duration as of the data cutoff date was 76.50 weeks for dMMR/MSI-H population patients in the dostarlimab in combination with CP arm and 31.86 weeks for patients in the placebo in combination with CP arm.

As of the data cut-off date, [redacted] of patients in the dostarlimab in combination with CP arm and [redacted] of patients in the placebo in combination with CP arm received >54 weeks (>1 year) of treatment, and [redacted] and [redacted] received >102 weeks (>2 years) of treatment, respectively. No patients have received >156 weeks (>3 years) of treatment in either arm yet due to the limited follow-up time. The proportion of patients who had follow-up at 1 year, 2 years, and 3 years was as follows: [redacted] in the dostarlimab in combination with CP arm vs placebo in combination with CP arm, respectively.

B2.10.2 Interruption of treatment

A summary of dose modifications for dostarlimab in combination with CP and placebo in combination with CP are presented in Appendix R Table 56. Infusion delays lasting >3 days occurred in [redacted] of patients in the dostarlimab in combination with CP arm and in [redacted] of patients in the placebo in combination with CP arm. In the dMMR/MSI-H population, [redacted] of patients who received dostarlimab in combination with CP had greater than or equal to 4 incidents of infusion interruption, compared with [redacted] of patients who received placebo in combination with CP.

B2.10.3 Summary of treatment emergent adverse events (TEAEs)

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 in

combination with CP 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 19, with full details in Appendix R (Table 57). All safety outcomes including Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs were comparable between arms although generally numerically higher in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm.

Table 19: Overall summary of TEAEs – Interim Analysis (dMMR/MSI-H population)

Adverse event category	Dostarlimab + Carboplatin/Paclitaxel (N=52)	Placebo + Carboplatin/Paclitaxel (N=65)	Total (N=117)
Any TEAE	[redacted]	[redacted]	[redacted]
Any Grade ≥3 TEAEs	[redacted]	[redacted]	[redacted]
Any TEAE with outcome of death	[redacted]	[redacted]	[redacted]
Any serious adverse event (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 infusion-related reactions	[redacted]	[redacted]	[redacted]

Source: CSR Table 14.3.1.1

Data cutoff: 28 September 2022

Abbreviations: SAE – serious adverse event; TEAE – treatment emergent adverse event.

B2.10.4 Any grade TEAEs

In the dMMR/MSI-H population, all patients in both treatment arms had at least one TEAE and at least 50% of patients in both treatment arms experienced alopecia and fatigue. The incidence of TEAEs were comparable (≤10% difference) between patients of both treatment arms except for the incidences of rash ([redacted]), hypertension ([redacted]), hypothyroidism ([redacted]), rash maculopapular ([redacted]), and pyrexia ([redacted]) which were higher in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm. Patients in the placebo

in combination with CP arm experienced higher incidences of anaemia ([redacted]), dyspnea ([redacted]), urinary tract infection ([redacted]), neutrophil count decreased ([redacted]), and white blood cell decreased ([redacted]) compared with the dostarlimab in combination with CP arm.

B2.10.5 Any grade treatment-related TEAEs

All patients had at least one TEAE considered to be related to treatment by the investigator. The incidence of treatment-related TEAEs was generally comparable (≤10% differences) between treatment arms. Exceptions include diarrhoea [redacted], rash [redacted] and hypothyroidism [redacted], which were higher in the dostarlimab in combination with CP arm versus the placebo in combination with CP arm, while anaemia [redacted], neutrophil count decreased [redacted] and white blood cell decreased [redacted] were higher in the placebo in combination with CP arm compared with the dostarlimab in combination with CP arm (Appendix R Table 58).

After cycle 7, during the dostarlimab monotherapy phase, a decrease in treatment-related TEAEs is observed in the dostarlimab in combination with CP arm ([redacted] of dostarlimab arm patients), suggesting that CP is driving treatment-related TEAE occurrence (Appendix R Table 59 and Table 60).

B2.10.6 Treatment-related TEAEs related to dostarlimab or placebo

A summary of the TEAEs related to dostarlimab or placebo, as per investigator assessment, in the dMMR/MSI-H population can be found in Appendix R Table 61. Overall, TEAEs considered not related to carboplatin or paclitaxel and related to dostarlimab or placebo only were higher in patients in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm [redacted]. This difference was primarily driven by rash ([redacted] in the dostarlimab in combination with CP arm compared with [redacted] in the placebo in combination with CP arm) and hypothyroidism ([redacted] in the dostarlimab in combination with CP arm compared with [redacted] in the placebo in combination with CP arm) in the system organ class ‘Skin and subcutaneous disorders’, and differences in

the ‘Gastrointestinal disorders’ system organ class ([redacted] in the dostarlimab in combination with CP arm compared with [redacted] in the placebo in combination with CP arm).

B2.10.7 Grade ≥3 TEAEs

A summary of the Grade ≥3 TEAEs in the dMMR/MSI-H population for overall, before cycle 7 and from cycle 7 onwards can be found in Appendix R Table 62 to Table 64. Grade ≥3 TEAEs were comparable (<10% difference) in patients between treatment arms except for neutrophil count decreased which was higher in the placebo in combination with CP arm compared with the dostarlimab in combination with CP arm [redacted] (see Appendix R Table 62). The most frequently reported Grade 4 TEAEs (>2%) in the dostarlimab in combination with CP arm were [redacted]. Grade 5 TEAEs were reported in [redacted] participants, both in the dostarlimab in combination with CP arm and related to study treatment.

From cycle 7, during the dostarlimab monotherapy phase, a decrease in Grade ≥3 TEAEs was observed in the dostarlimab in combination with CP arm ([redacted]) after cycle 7, suggesting that Grade ≥3 TEAEs are much reduced when patients receive dostarlimab monotherapy in comparison to the combination phase (see Appendix R Table 63 and Table 64).

B2.10.8 Grade ≥3 treatment-related TEAEs

A summary of Grade ≥3 treatment-related TEAEs experienced by patients in the dMMR/MSI-H population can be found in Appendix R Table 66. Treatment-related Grade ≥3 TEAEs were comparable (<10% difference) in patients between both treatment arms, with the exception of neutrophil count decreased which was higher in the placebo in combination with CP arm compared with the dostarlimab in combination with CP arm ([redacted]).

In addition to the dMMR/MSI-H population, a summary of Grade ≥3 treatment-related TEAEs in ≥5% of patients in the ITT population is presented in Appendix R Table 65. The incidence was generally comparable (≤5% differences) in patients between treatment arms, with the exception of neutrophil count decreased (13.8% versus

8.3%) which was higher in the placebo in combination with CP arm compared to the dostarlimab in combination with CP arm.

B2.10.9 Deaths and Serious AEs

The most frequent cause of death for participants in RUBY-1 was disease progression, which was more frequently observed in the placebo in combination with CP arm compared to the dostarlimab in combination with CP arm ([redacted]) and lead to an overall higher death rate in the placebo arm ([redacted]). [redacted] patients in the dMMR/MSI-H population had a TEAE leading to death. TEAEs leading to death in the dMMR/MSI-H population were myelosuppression and hypovolemic shock.

A summary of SAEs experienced by patients in the dMMR/MSI-H population is provided in Appendix R Table 67. The overall incidence of patients experiencing SAEs was comparable between the dostarlimab in combination with CP arm and the placebo in combination with CP arm ([redacted] and [redacted]. The most frequently reported SAE (≥2% of patients) which was higher in patients in the dostarlimab in combination with CP arm versus the placebo in combination with CP arm was sepsis ([redacted] versus [redacted]).

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

B2.10.10 Immune related adverse events (irAE)

As dostarlimab is an immune checkpoint inhibitor, irAEs 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, a pre-defined list of terms for the collection of irAEs was provided with the study protocol and irAEs were identified as any Grade ≥ 2 AEs that met the prespecified criteria.

Appendix R Table 68 to Table 70 summarises the most frequent irAEs observed in the trial including those related to dostarlimab and placebo. Not surprisingly, more irAEs were seen in the dostarlimab in combination with CP arm compared to the

placebo in combination with CP arm [redacted] of which [redacted] were dostarlimab related. The most frequently reported dostarlimab or placebo related irAE was hypothyroidism [redacted] in the dostarlimab in combination with CP arm, and hypothyroidism and arthralgia ([redacted] each) in the placebo in combination with CP arm.

B2.11 Ongoing studies

RUBY-1 is an ongoing study with another interim analysis data cut expected in [redacted]. Data is expected to be available in [redacted], with OS being followed up to reach maturity (PFS is final with primary endpoint met).

B2.12 Interpretation of clinical effectiveness and safety evidence

There is a clear unmet need for an innovative treatment option for primary advanced and recurrent endometrial cancer patients to improve outcomes in this setting. There is no current licensed SOC and treatment primarily consists of the PCC doublet of carboplatin and paclitaxel which provides a modest disease-free interval and limited survival benefit.[14,73] Furthermore, achieving a durable response to treatment in this setting is of paramount importance as less than one-third of primary advanced patients who relapse go on to receive further treatment.[73]

The RUBY-1 study met its primary endpoint and demonstrated that dostarlimab in combination with CP achieved statistically significant improvement in IA PFS in dMMR/MSI-H primary advanced or recurrent endometrial cancer patients with a HR of 0.28 (95%CI: 0.16, 0.50, p<0.0001), reducing the risk of progression or death by 72%. The probability of remaining progression free at 24 months was nearly four times higher for patients receiving dostarlimab in combination with CP followed by dostarlimab monotherapy as compared to patients receiving placebo in combination with CP, the rates were 61.4% (95% CI, 46.3 – 73.4) and 15.7% (95% CI, 7.2–27.0), respectively. PFS curves began to separate in favour of the dostarlimab group at approximately month 6 and continued to diverge over time with a relative plateau of the dostarlimab arm at the 12-month mark. The median duration of follow up is over 2 years (min 19.2, max 36.9 months), giving strength to these results.

At 26% OS maturity, a favourable trend in OS was observed in the dMMR/MSI-H patient population (prespecified subgroup analysis) (HR of 0.30; 95% CI: 0.13 – 0.70; nominal stratified log-rank test p-value=[redacted]). A clear, early and sustained separation of the survival curves began around 6 months, driven by mortality in the placebo in combination with CP arm and a relative plateau in the dostarlimab in combination with CP arm, suggesting that these patients are at high risk of poor outcomes and that upfront use of dostarlimab in combination with chemotherapy was leading to a clinically meaningful impact even with low data maturity. At 24 months, seven OS events had occurred in the dostarlimab in combination with CP arm and 23 events in the placebo in combination with CP arm (83.3% overall survival compared to 58.7% overall survival respectively).

The benefit observed in dMMR/MSI-H patients who received with dostarlimab in combination with CP treatment was consistently observed across all secondary efficacy endpoints including PFS2, ORR, DOR and DCR by both BICR and investigator assessment, and in PFS by BICR assessment. Complete responses were observed in 30.6% of dMMR/MSI-H patients treated with dostarlimab in combination with CP, compared with 20.7% of patients receiving placebo in combination with CP. dMMR/MSI-H patients receiving dostarlimab in combination with CP also had a more durable response to treatment as compared to those receiving placebo in combination with CP, with 62.1% versus 13.2% of patients remaining in response at 24 months, respectively. The improved PFS2 observed in the dMMR/MSI-H population indicates that the benefit of dostarlimab combination therapy extended beyond first progression, leading to long term benefits, and further supports the trend observed for OS.

Dostarlimab in combination with CP has an acceptable safety profile in dMMR/MSI-H primary advanced or recurrent endometrial cancer. Severe and serious TEAEs were approximately 10% higher in dMMR/MSI-H patients receiving dostarlimab in combination with CP followed by dostarlimab monotherapy as compared to those receiving placebo in combination with CP followed by placebo. In addition, irAEs were also higher in the dostarlimab arm of the study. This is not entirely unexpected as dostarlimab treatment continued after the initial six cycles of CP. Furthermore,

most irAEs were not severe or serious in nature and did not lead to treatment discontinuation or death.

UK clinical experts noted that alongside the expected irAE profile of the regimen, dostarlimab was well-tolerated and there appeared to be no meaningful additional toxicity from the addition of dostarlimab to PCC.[5]

The improved PFS outcomes seen within the dostarlimab in combination with CP arm were not associated with a decrease in patient HRQoL. Patients treated with dostarlimab in combination with CP had numerically improved QoL outcomes, including improved pain and physical functioning scores, compared with those who received placebo in combination with CP. The clear separation between the reported QoL scores over time are supported by the absolute difference in score seen at cycle 13 across the treatment arms in the EORTC QLQ-C30 and EQ-5D-5L VAS score, respectively.

B2.13 Strengths of the clinical evidence

RUBY-1 is one of the largest studies to report outcomes for an IO treatment in the primary advanced or recurrent endometrial cancer patient population. The double-blind, randomised, placebo-controlled multicentre study involved 494 patients in the ITT population with 118 patients in the dMMR/MSI-H population. The trial was powered to show significance for both ITT and dMMR/MSI-H populations for PFS and provides direct head-to-head evidence for dostarlimab in combination with CP versus CP alone as aligned with the decision problem. The quality assessment (Section B2.5 and Appendix D) identified a low risk of bias in the RUBY-1 trial design (features include being blinded, randomised 1:1, a balanced population at baseline and according to risk, sufficient follow-up time and use of precise measure of outcome [PFS by investigator RECIST v 1.1]). Both primary and secondary outcomes were assessed by the RECIST v 1.1 criteria which is an international standard for the assessment of response in solid tumours.[99] All efficacy data was reviewed in a blinded manner with PFS being assessed by both investigator and BICR to prevent bias. Furthermore, RUBY-1 has been awarded a category 1 status by the National Comprehensive Cancer Network (NCCN) guidelines, showing a high level of evidence and uniform consensus.[103]

The trial included 164 centres worldwide, including five UK sites and enrolled subjects' representative of patients who would receive dostarlimab in combination with PCC in routine clinical practice in the UK. As part of an advisory board, UK clinical experts confirmed the RUBY patient population is broadly representative of those in UK clinical practice, and it is expected that the benefits reported from this trial are likely to be reflected in clinical practice in England and Wales.[5]

PFS is a well-recognised and meaningful outcome to both patients and healthcare providers. The sufficiently powered patient population and the duration of the trial thus far have provided evidence to observe a statistically significant difference between the median PFS with dostarlimab in combination with CP compared with placebo in combination with CP. PFS may also be better at measuring treatment efficacy than OS as it eliminates potential differential bias from subsequent treatments, and is increasingly used as a primary outcome measure.[104,105] The improved PFS2 observed indicates that the benefit of dostarlimab plus CP, followed by dostarlimab, extended beyond first progression even when patients went onto their second systemic treatment regiment, leading to long term benefits. The value of this alternative endpoint has been recognised by the EMA when maintenance or continuous treatment regimens are used.[106] UK clinical experts considered the magnitude of benefit of the regimen in the dMMR/MSI-H population to be impressive and highly compelling, with sufficient data maturity to guide decision making.[5]

From the subgroup analyses conducted, favourable HRs (<1) were observed for all subgroups for PFS, and very favourable HRs (<0.5) for almost all subgroups for OS, although subgroups populations had small numbers of patients. These results could translate to a range of patients with heterogenous disease treated by clinicians in UK practice, inclusive of serous, clear cell and carcinosarcoma histologies that typically respond poorly to treatment.[5]

The breadth of HRQoL outcomes reported to date, including EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-EN24 data, complement the safety profile. These data showed that improvements in PFS due to addition of dostarlimab to SoC were not accompanied by any substantial deterioration in QoL. The positive trend observed in the dostarlimab in combination with CP arm and separation in QoL scores from the

placebo in combination with CP arm was considered by UK clinical experts to be important as this indicated better disease control with dostarlimab.[5] The RUBY-1 trial continues to follow-up patients and further data is being collected, analysed, and published, with the next read out expected in [redacted]. The continued patient follow-up will enhance the maturity and robustness of the long-term data, such as OS (PFS is final with statistical significance met).

B2.14 Limitations of the clinical evidence

While the RUBY-1 study encompasses a broad patient population with primary advanced or recurrent EC, this submission focuses on a smaller subgroup of patients with dMMR/MSI-H tumour status. By focussing on this subgroup, a smaller number of patients are being assessed as part of this submission. Limited conclusions can be drawn where patient numbers are so small and, in some cases, data are still relatively immature. An extended follow-up may therefore be required to observe a treatment effect in certain subgroups.

Most patients enrolled in the RUBY-1 trial were still alive at the time of data cut off for interim analysis 1 and therefore the OS data is only 26% mature in the dMMR/MSI-H population. The dMMR population was only powered for PFS, with OS as a pre-specified exploratory subgroup. However, even at 26% OS maturity, patients who received dostarlimab in combination with CP has a considerable and clinically meaningful trend in OS with a 70% reduction in deaths and a HR of 0.30 as compared to patients who received placebo in combination with CP.

Patients identified in the NCRAS RWE cohort (n=902) had a median age of 67.9 years at diagnosis. This contrasts with the median age of 64.0 years in the RUBY-1 trial cohort dMMR/MSI-H population (61.0 in the dostarlimab in combination with CP arm and 66.0 in the placebo in combination with CP arm). Details of the NCRAS RWE study can be found in Appendix L.

B2.15 Innovation

Dostarlimab given in combination with CP represents a step-change in the management of dMMR/MSI-H primary advanced and recurrent EC patients who are candidates for systemic therapy. Currently, the primary advanced and recurrent

endometrial cancer patient population experiences poor long-term treatment outcomes despite 50-60% response rate to SoC CP.

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

- Compared with SOC PCC, dostarlimab is an immunotherapy with a different, innovative, mechanism of action and toxicity profile. This allows dostarlimab to be used both in combination with PCC and continued as a monotherapy after SOC PCC for up to three years in total, to suppress any residual disease and extend remission.

- dMMR/MSI-H endometrial cancer is highly immunogenic and is more likely to respond to PD-1 blockade including anti-PD-1 therapies such as dostarlimab. The combination of increased T cell expression coupled with PD-1/PD-L1 expression, makes dMMR/MSI-H endometrial cancer an effective and innovative target for dostarlimab. Evidence of improved response to IO therapy has been observed in other cancers where patients express dMMR/MSI-H.[107]

- There is a need to address an inequality in access to innovative therapies in endometrial cancer compared with other cancer types. Immunotherapies have been available for several years for the first line treatment of patients with cancers such as melanoma, lung, and renal cell carcinoma, and have made a significant impact. [108–110]

B2.16 Conclusion

The efficacy and safety of dostarlimab in combination with CP compared with CP in the dMMR/MSI-H primary advanced or recurrent endometrial cancer population was demonstrated in the RUBY-1 trial. It acts as the most robust source of evidence due to the study being a direct head-to-head RCT aligned with the decision problem. The introduction of dostarlimab in combination with PCC in primary advanced or recurrent endometrial cancer patients would be a step change in treatment in this area of high unmet medical need where existing therapy confers modest but often short-lived benefits.

Bringing an IO therapy into earlier line settings will result in a greater number of patients being offered the treatment, which can be expected to delay time to disease progression in a greater proportion of patients.

B.3 Cost-effectiveness

Summary of cost-effectiveness analysis

- A *de novo* partitioned survival model with three health states (PFS, PD and death) was developed to evaluate the cost-effectiveness of dostarlimab in combination with PCC versus PCC for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer.
- The analysis was consistent with the NICE reference case: a cost-utility analysis with a NHS and PSS perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted.[111]
- Clinical outcomes (PFS, OS and TTD) were based on the dMMR/MSI-H population of the RUBY-1 trial, at the time of the first interim analysis (data cut off 8th September 2022).
- 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, 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 PCC was associated with [redacted] incremental costs and 4.26 incremental QALYs compared to PCC, which corresponds to an ICER of [redacted] per QALY gained i.e. <£20,000 per QALY gained.
- The probabilistic results are centred around the deterministic results and show that at a WTP threshold of £30,000 and £20,000, dostarlimab in combination with PCC has a 99.99% and 77.3% chance of being cost effective, respectively.
- 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 £23,000 per QALY gained for dostarlimab in combination with PCC versus PCC across all scenarios.

B3.1 Published cost-effectiveness studies

An economic SLR was undertaken on 10 November 2021 (with an update on 22 February 2023) to identify existing cost-effectiveness studies relevant to the decision problem. Full details of the methodology used to identify all relevant studies, results and quality assessment of the identified studies are presented in Appendix G.

Table 20 provides a summary of the published cost-effectiveness studies identified. Both studies utilised a Markov model with only a three- or four-year time horizon and therefore has limited generalisability to the decision problem. Furthermore, clinical inputs for both studies were highly uncertain, using digitized phase I/II outcomes' data from the literature.

Table 20: Summary list of published cost-effectiveness studies

Study	Summary of model	Patient population	Intervention	Comparator	QALYs intervention vs. comparator	Incremental costs intervention vs. comparator	ICER (per QALY gained)
Ackroyd, 2021[112]	Markov model US Healthcare perspective Three-year horizon Costs and utilities were discounted annually at 3%.	Advanced or recurrent endometrial cancer, specific stages: NR, subgroups: MSS or MSI-high	PEM + LEN	CB + PAC	-0.28	$212,670	NR [CB+PAC was considered the dominant treatment]
		Advanced or recurrent endometrial cancer, specific stages: NR, subgroup: MSI-high	PEM + LEN	CB + PAC	0.11	$313,487	$2,849,882/ QALY, USD inflated to 2020
Batman, 2021[113]	Markov US Societal perspective Four-year time horizon Costs and utilities were discounted annually at 3%.	HER2/neu-positive advanced or recurrent UPSC in one year, specific stages: NR, subgroup: NA	CB + PAC + TRA	CB + PAC	2,065	$144,335,895	$69,903/ QALY, USD inflated to 2019

Abbreviations: CB – carboplatin; HER2 – human epidermal growth factor receptor 2; ICER – incremental cost-effectiveness ratio; LEN – Lenvatinib; MSI – microsatellite instability; MSS – microsatellite stable; NA – not applicable; NR – not reported; PAC – paclitaxel; PEM – Pembrolizumab; QALYs – quality-adjusted life years; TRA – Trastuzumab; UPSC – uterine papillary serous carcinoma; USD – United States dollar

B3.2 Economic analysis

No existing economic studies of dostarlimab in combination with PCC in the primary advanced or recurrent endometrial cancer setting were identified in the economic SLR, therefore a *de novo* cost-effectiveness model (CEM) was developed in Excel version 2302 (Microsoft 365).

B3.2.1 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. The RUBY-1 trial was designed to collect data for both the ITT and dMMR/MSI-H population, however, since this submission focuses solely on the dMMR/MSI-H population, the economic model is aligned to this population.

B3.2.2 Model structure

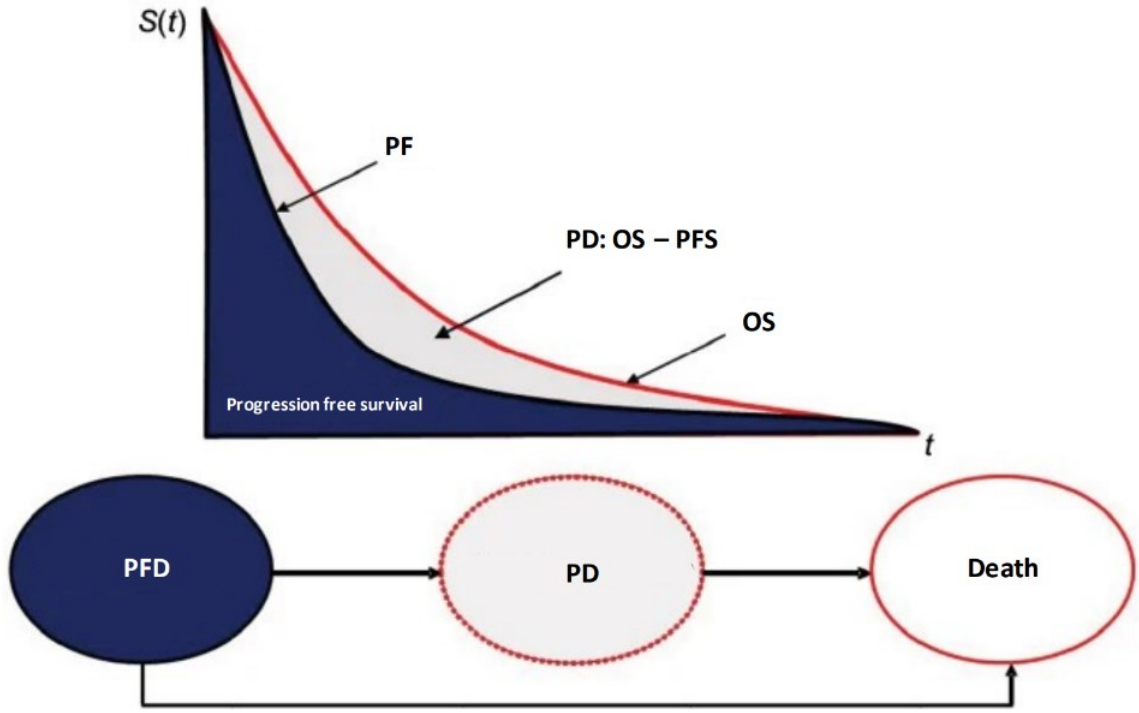
Partitioned survival models (PSM) are a well-established model framework used to assess the cost-effectiveness of oncology treatments, including advanced and metastatic cancers.[114] The use of a PSM structure is broadly accepted in oncology by HTA bodies and its application is well understood by clinical experts and health economists. In the UK, PSMs are considered standard practice, with 73% of recent (2017) oncology appraisals using the structure.[114]

The structure of a PSM model accurately captures the progressive nature of disease observed in oncology and has been used in previous appraisals, including for dostarlimab for the treatment of patients with recurrent or advanced dMMR/MSI-H in endometrial cancer that has progressed on or after platinum-based chemotherapy[74], and pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer.[115] A PSM model framework best utilises the available RUBY-1 PFS and OS data (primary efficacy endpoints). Limited follow up for post progression endpoints would be associated with high uncertainty using a Markov approach (see Section B2.6.3 and Section B2.6.4.1). In addition, a PSM approach allows for flexible scenario analysis across a range of various extrapolations.

The direct correspondence between frequently reported time-to-event endpoints such as PFS and OS and the survival functions that inform state membership estimates in partitioned survival analysis makes the models intuitively appealing. PSMs are easy to communicate and construct, allows for relatively easy replication of within-trial data, and means that the PSM can be constructed for these endpoints using either summary data or individual patient data (IPD).

A PSM is a type of economic model used to follow a theoretical cohort through time as they move between a set of exhaustive and mutually exclusive health states (see Figure 11).

Figure 11: PSM structure schematic



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

The model estimates the proportion of a cohort in each state based upon parametric survival equations. In the PSM model, PFS and OS data from the trial are directly used to model state occupancy using “progression-free disease”, “progressed disease” and “death” health states as shown in Table 21.

Table 21: PSM model inputs

Model input	Description
PFS	The proportion of patients in the pre-progression state is estimated by extrapolating PFS KM curves.
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).
Death	Survival is estimated by extrapolating OS KM curves (i.e., death = 1 - OS).

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

The proportion of patients in the PFS state over time is estimated directly from parametric survival curves of PFS, with the proportion of patients in the PD state estimated as the difference between parametric survival curves for PFS and OS. The model structure does not allow for 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 B3.3.3 and Section B3.3.4. Time to treatment discontinuation (TTD) curves were also modelled directly, informing the proportion of patients on treatment as described in Section B3.3.5.

PFS captures the costs and consequences of treatment, administration, monitoring, and adverse events, whilst PD captures the costs and consequences of subsequent treatments, monitoring and end of life care. Therefore, the model captures the key elements of care for patients with endometrial cancer from the time they begin treatment to when they complete subsequent treatment and enter terminal care.

Costs, life years (LYs) and quality-adjusted life years (QALYs) were accrued according to the proportion of patients in the PFS and PD health states over time to calculate total costs, LYs and QALYs for the two cohorts entering the model to receive dostarlimab in combination with PCC and PCC, respectively. The incremental cost-effectiveness ratio (ICER) of dostarlimab in combination with PCC versus PCC was evaluated in terms of the incremental cost per QALY and LY gained.

B3.2.3 Model characteristics

The analysis was conducted from the perspective of the UK NHS and Personal Social Services in England over a lifetime horizon. A cycle length of one week was adopted to sufficiently capture changes in costs and effects over time. Both costs and effectiveness estimates were discounted at 3.5% annually in line with the NICE reference case.[111]

Clinical outcomes (PFS, OS and TTD) for both dostarlimab in combination with CP and placebo in combination with CP were derived from the RUBY-1 trial. Full details of the clinical efficacy methodology and sources are provided in Section 0. Full details of the assumptions underlying the cost-effectiveness model are provided in Section B3.9.2.

HRQoL components considered within the economic analysis included age-adjusted health state utilities and adverse event disutilities. Full details of the methodology and sources are provided in Section B3.4.

Cost and health care resource use (HCRU) components considered within the economic analysis included treatment acquisition and administration costs, monitoring costs, AE costs, subsequent therapy costs and end of-life costs. Full details of the methodology and sources are provided in Section B3.5.

A summary of the key features from previous NICE TAs and for the *de novo* economic analysis with justification is provided in Table 22. Parameter selection was consistent with the NICE Reference Case[111] and UK clinical practice based on input from UK health care professionals with experience treating primary advanced or recurrent endometrial cancer.[4,5]

Table 22: Features of the economic analysis

Factor	Previous evaluation		Current evaluation	
	Dostarlimab post-platinum chemotherapy (TA779)[74]	**Lenvatinib+pembrolizumab (GID-TA10692)**[115]	**Chosen values**	**Justification**
Population and treatment	Adult patients with advanced or recurrent dMMR/MSI-H endometrial cancer that has progressed on or after platinum-based chemotherapy	Adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation	Adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer	Aligns with the NICE decision problem (see B1.1 Decision problem).
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime ([redacted] years)	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 dMMR/MSI-H patients in RUBY-1 trial was [redacted] years – assuming no patients survive beyond a mean age of 100 years.
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	NICE reference case.[111]
Discounting	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	NICE reference case.[111] Other discounting rates were tested as part of scenario analyses.
Cycle length	3 weeks	Weekly	Weekly	A weekly cycle (1/52nd of a year) captures all relevant costs and health outcomes. Longer cycle lengths increase the risk of over or under predicting costs per QALYs when averaging across cycle times. Due to the short cycle length, a half cycle correction was not applied to any costs or outcomes.

Health states	PFS, PD and death	PFS, PD and death	PFS, PD and death	The PSM structure is an established model framework to assess cost-effectiveness of oncology treatments and has enabled decision making in prior endometrial cancer NICE appraisals.[74,115] 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.
Source of utilities	EQ-5D-5L from GARNET study, cross-walked to the 3L	EQ-5D-5L from KEYNOTE-775 (interim data) mapped onto 3L	EQ-5D-5L from RUBY-1 trial ITT patient population, cross-walked to the 3L	EQ-5D HRQoL data aligned with the NICE reference case,[111] were available from the RUBY-1 trial for dMMR/MSI-H population. Due to the much larger number of observations (Section B3.4.1) in the ITT cohort the ITT population utilities were used to provide robust estimates (dMMR/MSI-H utilities used in a scenario analysis). Health state utilities were age-adjusted using the Hernández Alava, Pudney and Wailoo (2022).[116] Adverse event disutilities were included for the first cycle of the model as it is assumed patients experience adverse events in the first cycle following treatment initiation and are resolved through acute care. Adverse event rates of grade 3 and above were sourced from the RUBY-1 trial ITT patient population and AE disutility values from published literature.
Source of costs	BNF, eMIT, NHS reference costs, PSSRU	BNF, eMIT, MIMS, NHS reference costs	BNF, NHS reference costs, PSSRU	Costs were obtained from UK national resources to reflect the UK NHS and PSS perspective, aligned with the NICE reference case.[111] PSSRU pay and prices indices were used to inflate costs to 2022/23.[117]

Abbreviations: dMMR – DNA mismatch repair deficient; eMIT – electronic market information tool; HRQoL – health related quality of life; ITT – intention to treat; MIMS – monthly index of medical specialities; MSI-H – microsatellite instability high; NHS – National Health Services; NICE – National Institute for Health and Care Excellence; PSS – personal social service; PSSRU – Personal Social Services Research Unit; QALY – quality adjusted life year.

B3.2.3.1 Intervention technology and comparators

B3.2.3.2 Intervention: Dostarlimab in combination with platinum-containing chemotherapy (PCC)

Dostarlimab is administered through intravenous infusion. The dose of dostarlimab incorporated in the economic model is aligned with the draft SmPC (Appendix C) and the RUBY-1 study. In the intervention arm of the RUBY-1 study, patients received 500 mg of dostarlimab plus area under the curve (AUC) 5 mg/ml/min of carboplatin and 175 mg/m^2 of paclitaxel every three weeks 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 every six weeks until disease progression, unacceptable toxicity or up to three years (see Figure 2, page 29; for treatment duration of dostarlimab in combination with PCC modelled see Section B3.3.5).

B3.2.3.3 Comparators: Platinum-containing chemotherapy (PCC)

As discussed in Section B1.1, the only comparator for dostarlimab in combination with PCC is PCC, the comparator in the RUBY-1 trial. Therefore, PCC was included in the model as the only comparator in the base case. The comparator arm of the RUBY-1 trial, placebo in combination with CP, was used to inform the PCC arm in the model. 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 every three weeks for six cycles (i.e. weeks 1, 4, 7, 10, 12, 16), followed by (i.e. from week 19 onwards) placebo every six weeks for up to three years or until patient progression (for the treatment duration of PCC modelled see Section B3.3.5).

B3.3 Clinical parameters and variables

B3.3.1 Baseline characteristics

The patient baseline characteristics that are used as inputs in the CEM are provided in

Table **23**. These were based on the baseline characteristics in the dMMR/MSI-H population in the RUBY-1 trial.

Table 23: Patient baseline characteristics for the base-case economic analysis

Parameter	Value	Reference
Mean age (years)	[redacted]	RUBY-1 trial[71]
Mean weight (kg)	[redacted]	
Mean body surface area (m^2)	[redacted]	
GFR (ml/min)	[redacted]	Calculation based on RUBY-1 trial[71]

Abbreviations: GFR – Glomerular filtration rate. *Calculation: $142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \times (BSA/1.73)$ (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))

B3.3.2 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 from PFS, OS and TTD data. The NICE Decision Support Unit (DSU) Technical Support Document (TSD)[114] was considered when selecting the survival models for the base case analysis (see Appendix P for details). Survival analyses were conducted in weeks due to the model cycle length.

B3.3.3 Progression-free survival

In the RUBY-1 trial, IA PFS was the primary endpoint for the dMMR/MSI-H population. Table 24 shows the non-parametric and semi-parametric analysis results for IA PFS. Aligned with the RUBY-1 data presented in Section B2.6.2, data is more mature in the placebo in combination with CP arm compared with dostarlimab in combination with CP arm with 72% versus 36% of patients progressing over the follow-up period, respectively. Overall, the mean duration of follow up was similar in both arms ([redacted] weeks and [redacted] weeks for dostarlimab in combination with CP versus placebo in combination with CP calculated through the reverse censoring method). The median PFS was not reached in the dostarlimab in combination with CP arm but was [redacted] weeks in the placebo in combination with CP arm.

A statistically significant increase in IA PFS was observed for dostarlimab in combination with CP compared with placebo in combination with CP (unstratified HR

[95% CI] p-value = [redacted]; stratified HR [95% CI] p-value = 0.28 [0.16 – 0.50] <0.0001). Unstratified means that there are no covariates in the model except for treatment whereas stratified is in line with the randomisation stratification factors.

Table 24: Non-parametric and semi-parametric results for IA PFS

Treatment arm (N)	Dostarlimab in combination with CP (n=53)	Placebo in combination with CP (n=65)
Maturity (%) – n/N	35.85% (19/53)	72.31% (47/65)
Duration of follow up (weeks) Median (95% CI)	[redacted]	[redacted]
Duration of follow up (weeks) Restricted mean (SD)	[redacted]	[redacted]
Median (95% CI) (weeks)	NR [redacted]	[redacted]
Restricted mean (weeks), (SE)	[redacted]	[redacted]
HR unstratified* (95% CI; p-value)	[redacted]	
HR stratified (95% CI, p-value)	0.28 (0.16, 0.50; p<0.0001)	

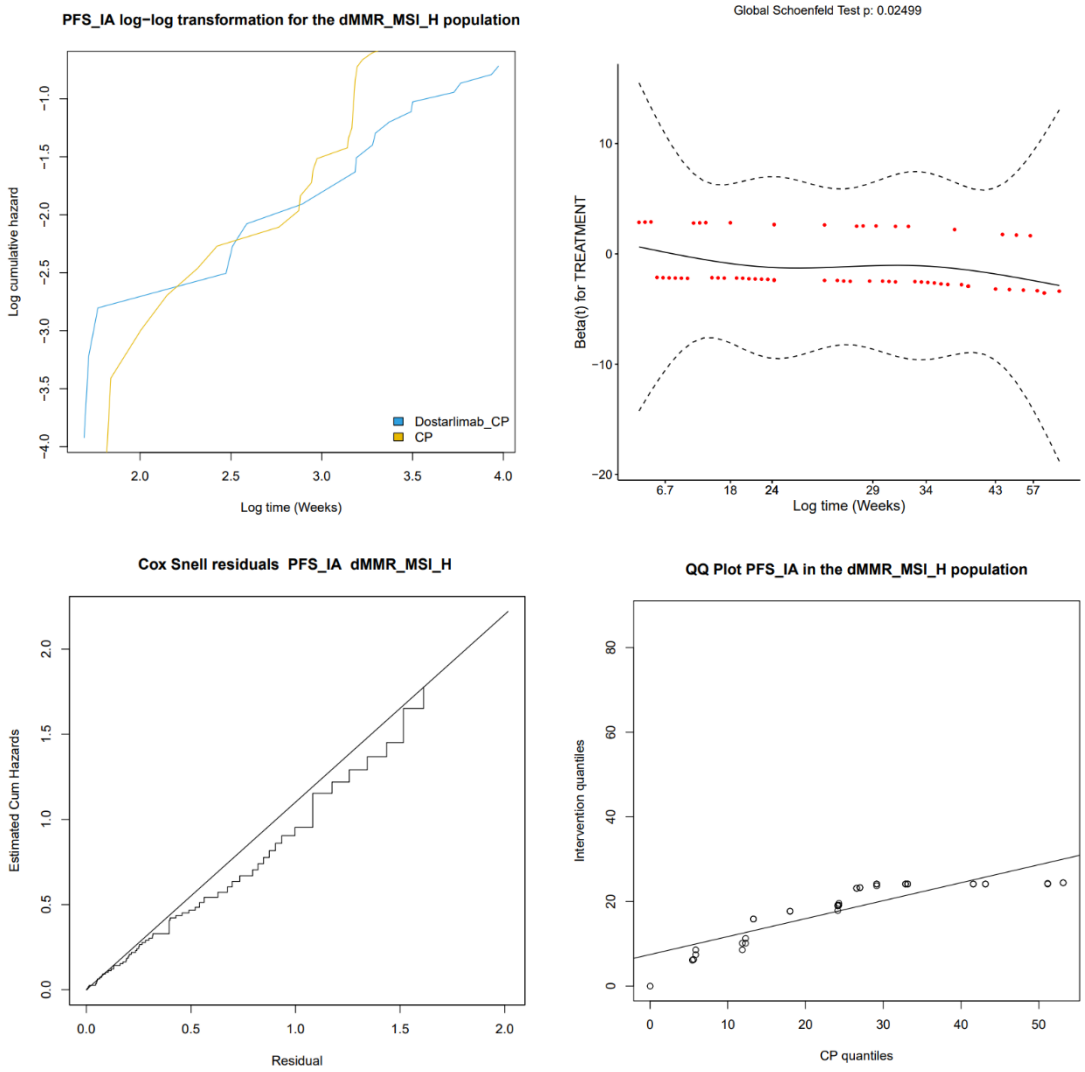
Non-parametric analysis includes percentage of data maturity, median and restricted mean follow up, median and restricted mean survival. The cox proportional hazards model (HR) is a semi-parametric model.
Abbreviations: CI – confidence interval; HR – hazard ratio; NR – not reported; SD – standard deviation; SE – standard error. *Unstratified cox proportional hazards model used to calculate HR.

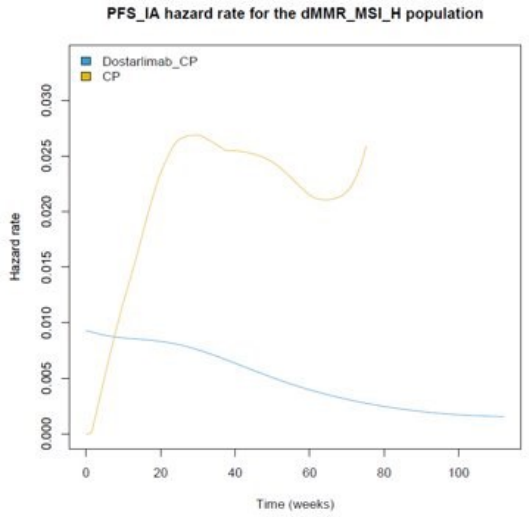
Several statistical tests were conducted to understand if the proportional hazards assumption and constant accelerated failure time (AFT) assumptions would be violated (

Figure 12). These tests are discussed in detail in Appendix P and suggest that the proportional hazard assumption between dostarlimab in combination with CP and CP may be rejected and the constant AFT assumption can also be rejected. The hazard rate plot for dostarlimab in combination with CP is shown to be monotonic with a

continuous decline in hazard rate whereas the hazard rate for placebo in combination with CP is non-monotonic.

Figure 12: Log-log plot, global Schoenfeld test, Cox Snell residuals, QQ plot and hazard rate plot for IA PFS





Abbreviations: dMMR – DNA mismatch repair deficiency; IA – investigator assessed; MSI-H – microsatellite instability-high; PFS – progression free survival; QQ – quantile-quantile

B3.3.3.1 Platinum-containing chemotherapy (PCC) progression-free survival

Standard parametric distributions were fitted to IA PFS from RUBY-1 for the placebo in combination with CP arm independently. Table 25 summarises the AIC and BIC values for each extrapolation.

The choice of curve in the base case was selected by visual analysis, considering UK clinical opinion and external data sources, alongside analysis of goodness-of-fit statistics such as AIC and BIC with a lower AIC or BIC value indicating a better fitting model.

Table 25: Summary of goodness-of-fit data for PCC for IA PFS (standard parametric independent models)

IA PFS	PCC	
Distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; IA – investigator assessment; PCC – platinum-containing chemotherapy; PFS – progression free survival.

UK clinicians were consulted on estimates for patients receiving PCC who are in PFS at various landmark timepoints.[4] Table 26 presents the estimated proportion of patients who would be progression-free at landmark timepoints from five UK clinicians along with the overall mean. In turn, Table 27 presents the overall mean estimate alongside the proportions estimated through standard parametric extrapolations. Figure 13 presents the standard parametric extrapolations with the observed placebo in combination with CP RUBY-1 data. The mean proportions from the UK clinicians were higher than the proportions estimated through standard parametric extrapolations and the extrapolations did not fit the observed RUBY-1 data. Progression free survival rates appear more optimistic in real world and clinical consensus compared to the results of the RUBY-1 trial due to differences in the inclusion criteria of the trial which included higher risk patients (see Section B2.3.1).

Table 26: Advisor estimates of the proportion of patients who would be progression free at landmark time points in the dMMR/MSI-H population in the RUBY-1 trial treated with PCC

Months (years)	dMMR/MSI-H					
	Mean	A1	A2	A3	A4	A5
24 (2)	23%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

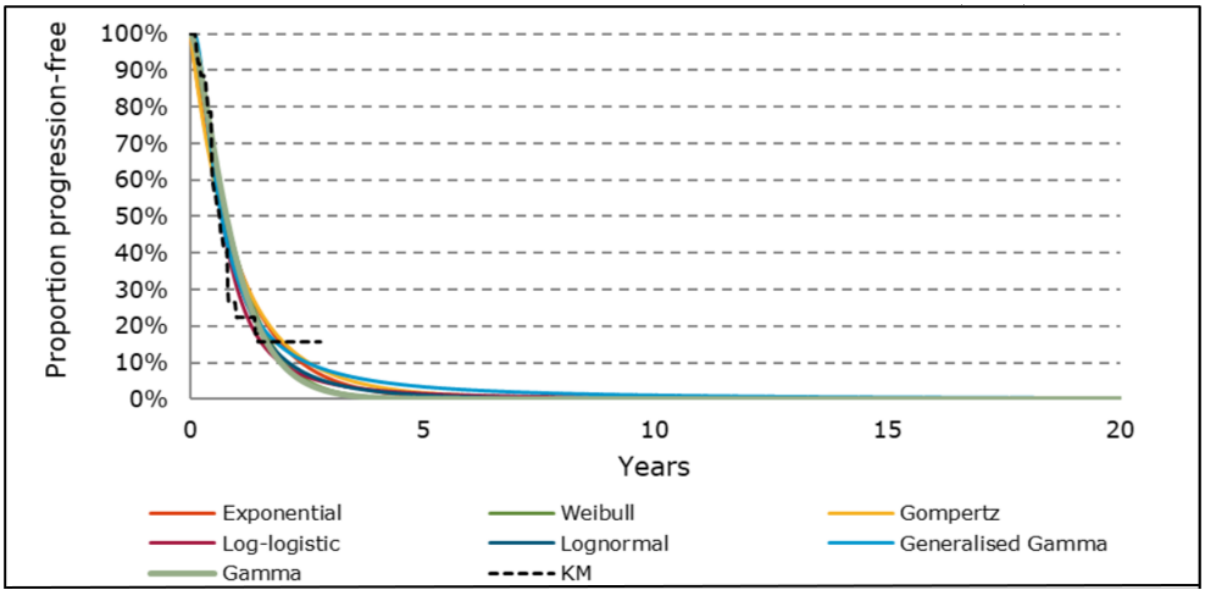
Abbreviations: A1-5 – advisor 1-5. Please note, advisor 4 was from Scotland.

Table 27: Advisor mean estimates and standard parametric estimates of the proportion of patients who would be progression-free at landmark time points in the dMMR/MSI-H population in the RUBY-1 trial treated with PCC

Months (years)	Advisors' mean	PCC						
		Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
24 (2)	23%	15%	11%	16%	10%	11%	14%	9%
36 (3)	15%	6%	2%	7%	4%	5%	8%	2%
60 (5)	9%	1%	0%	2%	2%	1%	3%	0%
120 (10)	7%	0%	0%	0%	0%	0%	1%	0%
240 (20)	6%	0%	0%	0%	0%	0%	0%	0%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

Figure 13:Standard parametric survival analyses for PCC for IA PFS



Abbreviations: IA –investigator assessed; KM – Kaplan-Meier; PCC – platinum containing chemotherapy; PFS – progression-free survival

As the independent standard parametric curves did not fit the observed RUBY-1 data or UK clinical expert estimates well, flexible approaches were explored. Of the approaches reviewed in NICE DSU TSD 21[118], the flexible spline was the most relevant to address the challenges seen with standard parametric extrapolation of the RUBY-1 data.

Flexible spline distributions were fit to the IA PFS from RUBY-1 for the placebo in combination with CP arm. In previous NICE HTA submissions for cancer therapies, use of spline models has resulted in better fits than traditional models.[74,115] Furthermore, spline models have been shown to perform well when extrapolating beyond observed oncology data. Recent literature, specific to immunotherapy and advanced cancers, have shown that spline models tended to demonstrate better fit to the observed hazard functions than standard parametric models.[119,120] Spline models have been specifically noted as an approach to consider when selecting models to inform economic evaluation of cancer IOs. The 12 flexible spline models were: Hazard knotts (k)=0,1,2,3; Odds, k=0,1,2,3; and Normal k=0,1,2,3. The choice of curve in the base case was selected by visual analysis, UK clinical opinion and consideration of external data sources, alongside analysis of goodness-of-fit statistics such as AIC.

The hazard rate for placebo in combination with CP was shown to be non-monotonic, which suggests that AFT models such as log-logistic, log-normal or generalised gamma should be used. For flexible distributions, the Odds and Normal curves are relatives of the log-logistic and log-normal curves. Therefore, the Odds and Normal curves were then compared to the UK clinical opinion estimates for PFS.

The AIC scores for Odds k=1,2,3 and Normal k=2,3 were within 3 points of each other, indicating that none of the models can be deemed statistically better fitting than the other (Table 28).[121] In addition, the Odds and Normal distributions aligned well with the observed data for IA PFS (Figure 13). The mean proportions from the UK clinicians aligned closest with proportions from the Odds k=2,3 and Normal k=2,3 curves (Table 29). **The Odds k=2 was selected for the base case based on reduced model complexity, had the lowest AIC value and provides the most appropriate proportion of patients in the PFS state for PCC to align with advisor estimates.**

Upon applying PFS in the model a rule was also applied whereby the PFS curve could not exceed the OS curve for both treatment arms.

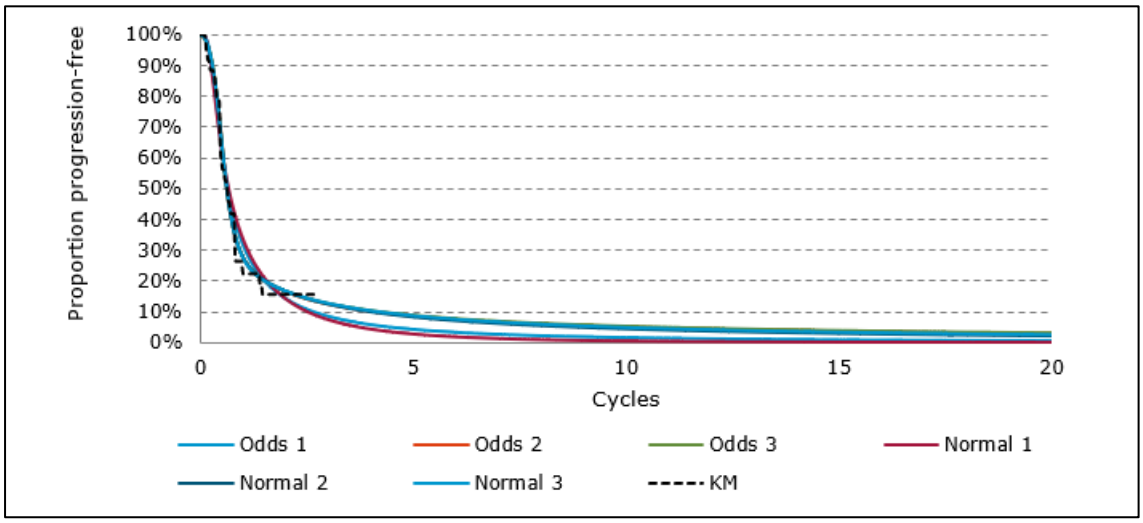
Table 28: Summary of goodness-of-fit data for PCC for IA PFS (flexible models)

IA PFS	**PCC**
Distribution	**AIC**
Odds k=1	[redacted]
Odds k=2	[redacted]
Odds k=3	[redacted]
Normal k=1	[redacted]
Normal k=2	[redacted]
Normal k=3	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; IA – investigator assessment; PCC – platinum-containing chemotherapy; PFS – progression free survival.

Figure 14:Flexible models for PCC for IA PFS



Abbreviations: IA – investigator assessment; KM – Kaplan Meier; PCC – platinum containing chemotherapy; PFS – progression free survival.

Table 29: Advisor mean estimates and flexible model estimates of the proportion of patients who would be progression-free at landmark time points in the dMMR/MSI-H population in the RUBY-1 trial treated with PCC

Months (years)	Advisors' mean	PCC					
		Odds k=1	Odds k=2	Odds k=3	Normal k=1	Normal k=2	Normal k=3
24 (2)	23%	14%	17%	17%	14%	17%	17%
36 (3)	15%	9%	13%	13%	7%	13%	13%
60 (5)	9%	4%	9%	9%	3%	8%	9%
120 (10)	7%	2%	5%	5%	1%	4%	5%
240 (20)	6%	1%	3%	3%	0%	2%	3%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

For scenario analyses, the following were explored to show the impact on results:

- IA PFS using Normal k=2 (next best fitting curve based on model complexity and AIC value).
- Odds k=1 and Normal k=1 (based on curves selected for the dostarlimab in combination with PCC arm, Section B3.3.3.2).

- A KM piecewise approach (modelling IA PFS for the full follow up period followed by the base case Odds k=2 curve).

- BICR PFS (using the base case Odds k=2 curve). BICR and IA PFS have a good correlation and results are shown to be consistent between PFS endpoints in gynaecological cancer trials.[122]

These scenarios had minimal impact on the ICERs, ICERs were similar irrespective of the choice of PFS curves.

B3.3.3.2 Dostarlimab in combination with platinum-containing chemotherapy (PCC) progression-free survival

Standard parametric distributions were fitted to IA PFS from RUBY-1 for the dostarlimab in combination with CP arm independently. Table 30 summarises the AIC and BIC values for each extrapolation.

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

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

Note: A small AIC or BIC value represents a better goodness of fit

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; IA – investigator assessment; PCC – platinum-containing chemotherapy; PFS – progression free survival.

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 AIC and BIC.

Table 31 presents the estimated proportion of patients who would be progression-free at landmark timepoints from five UK clinicians along with the overall mean. In turn, Table 32 presents the overall mean estimate alongside the proportions

Months (years)	dMMR/MSI-H					
	Mean	A1	A2	A3	A4	A5
24 (2)	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	56%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	46%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	36%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	30%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

estimated through standard parametric extrapolations.

Table 32Table 31: Advisor estimates of the proportion of patients who would be progression-free at landmark time points in the dMMR/MSI-H population in the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	Advisors' mean	Dostarlimab in combination with PCC						
		Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
24 (2)	60%	58%	59%	62%	58%	59%	61%	60%
36 (3)	56%	44%	50%	60%	49%	50%	56%	49%
60 (5)	46%	25%	36%	60%	38%	40%	51%	34%
120 (10)	36%	6%	18%	60%	25%	27%	45%	14%
240 (20)	30%	0%	6%	60%	15%	16%	40%	3%

Abbreviations: A1-5 – advisor 1-5; dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy. Please note, advisor 4 was from Scotland.

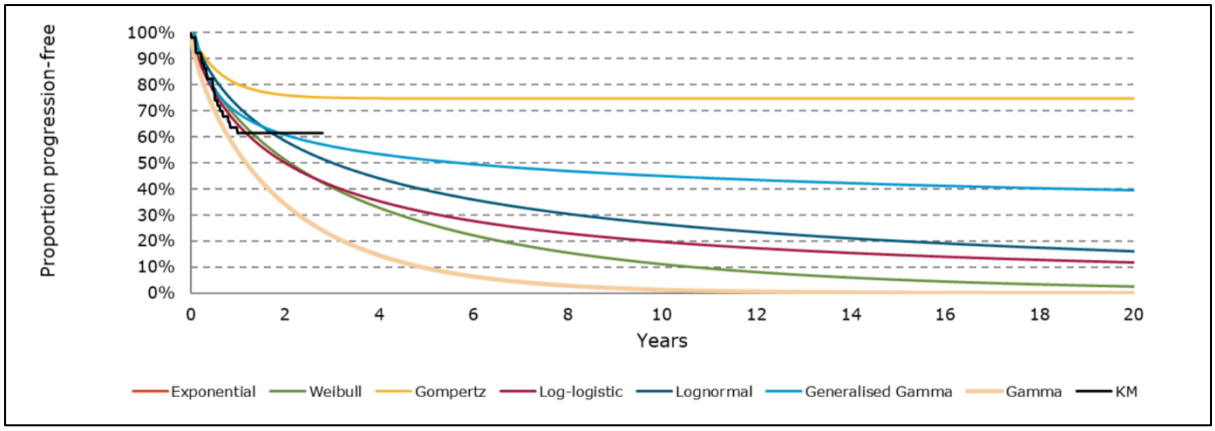
Months (years)	dMMR/MSI-H					
	Mean	A1	A2	A3	A4	A5
24 (2)	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	56%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	46%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	36%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	30%*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 32: Advisor mean estimates and standard parametric estimates of the proportion of patients who would be progression-free at landmark time points in the dMMR/MSI-H population of the RUBY-1 trial treated with dostarlimab in combination with PCC

Error! Reference source not found. presents the standard parametric extrapolations with the observed dostarlimab in combination with CP RUBY-1 data. The mean proportions from the UK clinicians did not align with proportions estimated through standard parametric extrapolations and neither did the extrapolations fit the observed RUBY-1 data.

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy. *Mean value was calculated using a value of 5% for advisor 4.

Figure 15: Standard parametric survival analyses for dostarlimab in combination with PCC for IA PFS



Abbreviations: IA – investigator assessed; KM – Kaplan-Meier; PCC – platinum containing chemotherapy; PFS – progression-free survival.

As the independent standard parametric curves did not fit the observed RUBY-1 data or UK clinical expert estimates well, flexible approaches were explored. For the same reasons outlined for the placebo in combination with CP data, the flexible spline was the most relevant modelling approach to address the challenges seen with standard parametric extrapolation of the RUBY-1 data.

Flexible spline distributions were fit to the IA PFS from RUBY-1 for the dostarlimab in combination with CP arm. The 12 flexible spline model were: Hazard, k=0,1,2,3; Odds, k=0,1,2,3; and Normal k=0,1,2,3. The choice of curve in the base case was selected by visual analysis, UK clinical opinion and consideration of external data sources, alongside analysis of goodness-of-fit statistics such as AIC.

Flexible models were explored to capture the plateau in risk associated with dostarlimab in combination with plus CP observed from the hazard rate plots. The distributions for dostarlimab in combination with PCC that were closest to UK clinical opinion for PFS and consistent with distributions selected for PCC were Odds and Normal.

The AIC scores for Odds k=1,2,3 and Normal k=1,2,3 were within 3 points of each other, indicating that none of the models can be deemed statistically better fitting than the other (Table 33).[121] In addition, the Odds and Normal distributions aligned well with the observed data for IA PFS (Figure 16). The mean proportions from the UK clinicians aligned closest with proportions from the Odds k=1 and Normal k=1 curves (Table 34). **The Odds k=1 was selected for the base case based on the lowest AIC value and provides the most appropriate proportion of patients in the PFS state to align with advisor estimates.**

Table 33: Summary of goodness-of-fit data for dostarlimab in combination with PCC for IA PFS (flexible models)

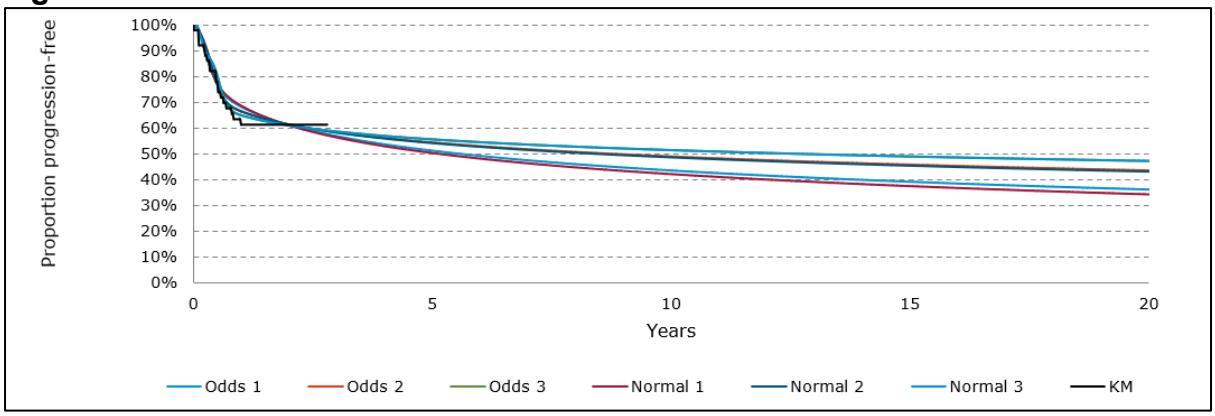
IA PFS	**Dostarlimab in combination with PCC**
Distribution	**AIC**
Odds k=1	[redacted]
Odds k=2	[redacted]
Odds k=3	[redacted]
Normal k=1	[redacted]

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

Note: A small AIC or BIC value represents a better goodness of fit

Abbreviations: AIC – Akaike information criteria; IA – investigator assessed; PCC – platinum containing chemotherapy; PFS – progression-free survival.

Figure 16: Flexible models for dostarlimab in combination with PCC for IA PFS



Abbreviations: IA – investigator assessed; KM – Kaplan Meier; PCC – platinum containing chemotherapy; PFS – progression-free survival.

Table 34: Advisor mean estimates and flexible model estimates of the proportion of patients who would be progression-free at landmark time points in the dMMR/MSI-H population in the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	Advisors' mean	Dostarlimab in combination with PCC					
		Odds k=1	Odds k=2	Odds k=3	Normal k=1	Normal k=2	Normal k=3
24 (2)	60%	61%	62%	61%	61%	61%	61%
36 (3)	56%	57%	58%	59%	56%	58%	59%
60 (5)	46%	51%	55%	56%	50%	54%	56%
120 (10)	36%	44%	49%	52%	42%	49%	52%
240 (20)	30%	36%	44%	47%	34%	43%	47%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

For scenario analyses, the following were explored to show the impact on results:

- IA PFS using Normal k=1 (next best fitting curve)

- Odds k=2 and Normal k=2 (based on curves selected for the CP alone arm, Section B3.3.3.1)

- A KM piecewise approach (modelling IA PFS for the full follow up period followed by the base case Odds k=1 curve)

- BICR PFS (using the base case Odds k=1 curve)

These scenarios had minimal impact on the ICERs, ICERs were similar irrespective of the choice of PFS curves.

B3.3.4 Overall survival

Table 35 shows the non-parametric and semi-parametric analysis results for OS. Aligned with the RUBY-1 data presented in Section B2.6.3, data is more mature in the placebo in combination with CP arm compared with dostarlimab in combination with CP arm with 37% versus 13% events occurring over the follow-up period, respectively. Overall, the mean duration of follow up was similar in both arms (weeks and weeks for dostarlimab in combination with CP versus placebo in combination with CP, respectively, calculated through the reverse censoring method). The median OS was not reached in either arm. Despite the immaturity of the data at present, there was a strong numerical trend in favour of the dostarlimab in combination with CP arm compared with the placebo in combination with CP, with an increase in OS observed (unstratified HR 95% CI nominal p-value = ; stratified HR 95% CI nominal p-value = 0.30 [0.13, 0.70]).

Table 35: Non-parametric and semi-parametric results for OS

Treatment arm (N)	Dostarlimab in combination with CP (n=53)	Placebo in combination with CP (n=65)
Maturity (%) – n/N	13.21% (7/53)	36.92% (24/65)
Duration of follow up (weeks) Median (95% CI)		
Duration of follow up (weeks) Restricted mean (SD)		

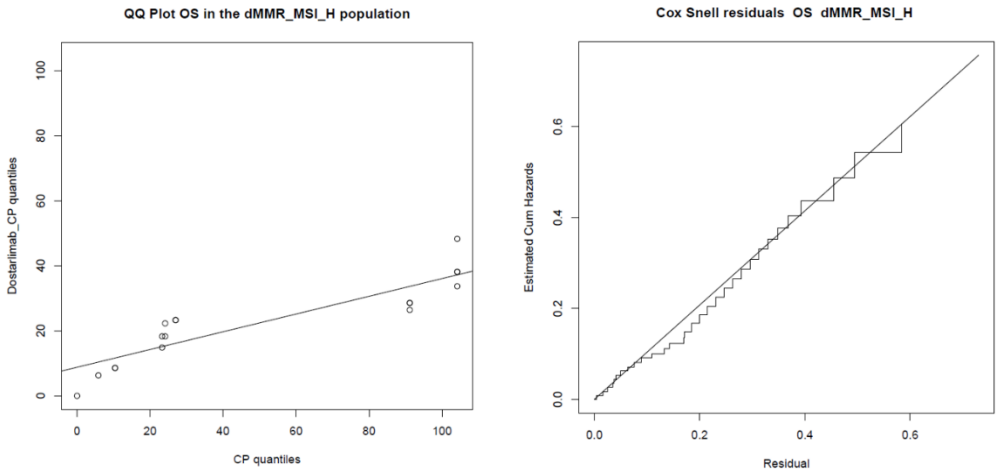
Median (95% CI) (weeks)	NR (NR, NR)	NR [redacted]
Restricted mean (weeks), (SE)	[redacted]	[redacted]
HR unstratified* (95% CI; nominal p-value)	[redacted]	
HR stratified (95% CI; nominal p-value)	0.30 (0.13, 0.70; [redacted])	

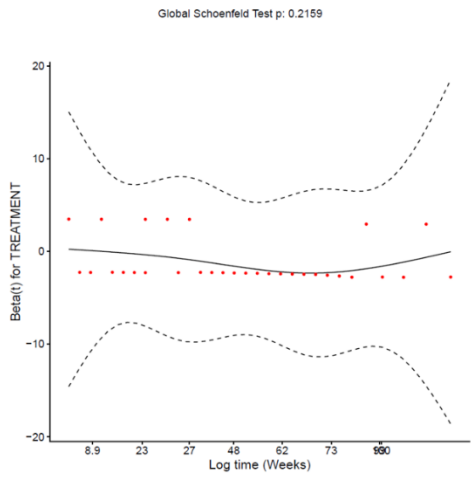
Non-parametric analysis includes percentage of data maturity, median and restricted mean follow up, median and restricted mean survival. The cox proportional hazards model (HR) is a semi-parametric model.

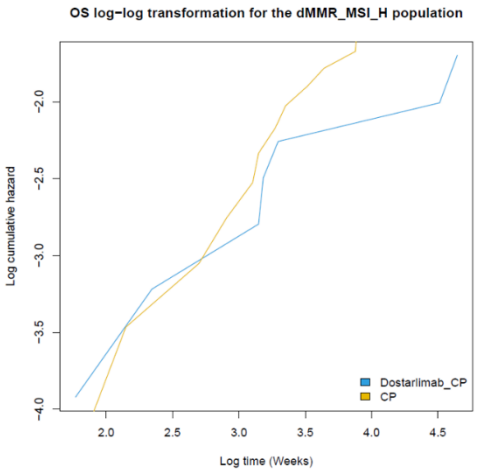
Abbreviations: CI – confidence interval; HR – hazard ratio; NR – not reported; SD – standard deviation; SE – standard error. *Unstratified cox proportional hazards model used to calculate HR.

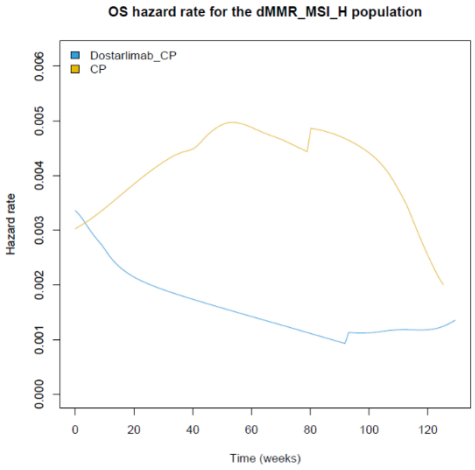
Several statistical tests were conducted to understand if the proportional hazards assumption and constant AFT assumptions would be violated (Figure 17). These tests are discussed in detail in Appendix P and suggest that the proportional hazard assumption between dostarlimab in combination with CP and CP may be rejected and the constant AFT assumption can also be rejected. The hazard rate plot for both dostarlimab in combination with CP and CP are non-monotonic, shown by the various turning points by both comparators. Due to the non-monotonicity of the curves, models with hazard functions that can be non-monotonic, such as the log-logistic, log-normal and generalised gamma, may be more suited to modelling OS in both arms.

Figure 17: Log-log plot, global Schoenfeld test, Cox Snell residuals, QQ plot and hazard rate plot for OS









Abbreviations: dMMR – DNA mismatch repair deficiency; IA – investigator assessed; MSI-H – microsatellite instability-high; PFS – progression free survival; QQ – quantile-quantile.

B3.3.4.1 Platinum-containing chemotherapy (PCC) overall survival

Standard parametric distributions were fitted to OS from RUBY-1 for the placebo in combination with CP arm independently. Table 36 summarises the AIC and BIC values for each extrapolation.

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 AIC and BIC.

Table 36: Summary of goodness-of-fit data for PCC for OS (standard parametric independent models)

OS	PCC	
Distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; IA – investigator assessment; PCC – platinum-containing chemotherapy; OS – overall survival.

Table 37 presents the estimated proportion of patients who would be alive at landmark timepoints from five UK clinicians along with the overall mean. In turn Table 38 presents the overall mean estimate alongside the proportions estimated through standard parametric extrapolations.

Figure 18 then presents the standard parametric extrapolations with the observed placebo in combination with CP RUBY-1 data. The lognormal, exponential and log-logistic curves have the lowest AIC/BIC values with the log-logistic aligning closest with proportions provided by the UK clinical experts.

Table 37: Advisor 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 PCC

Months (years)	dMMR/MSI-H					
	Mean	A1	A2	A3	A4	A5
24 (2)	58%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	46%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	17%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	13%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

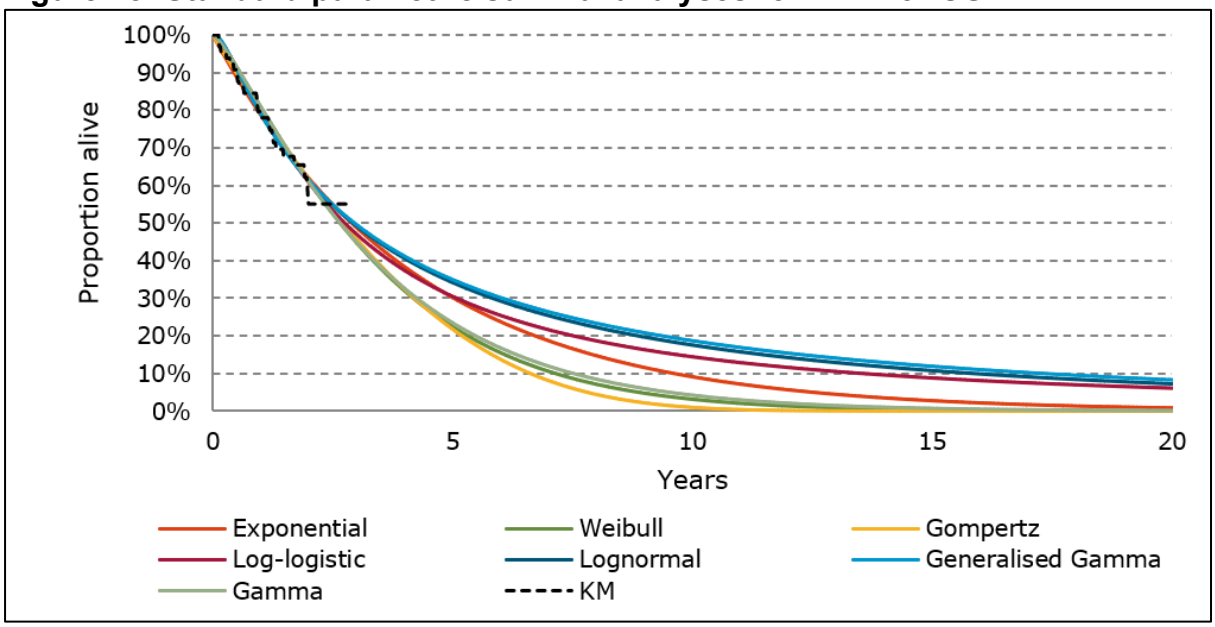
Abbreviations: A1-5 – advisor 1-5; dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy. Please note, advisor 4 was from Scotland.

Table 38: 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 PCC

Months (years)	Advisors' mean	PCC						
		Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
24 (2)	58%	62%	61%	62%	61%	61%	61%	61%
36 (3)	46%	49%	45%	46%	47%	49%	50%	45%
60 (5)	30%	30%	23%	22%	31%	34%	35%	24%
120 (10)	17%	9%	3%	1%	14%	18%	19%	4%
240 (20)	13%	1%	0%	0%	6%	7%	8%	0%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

Figure 18: Standard parametric survival analyses for PCC for OS



Abbreviations: KM – Kaplan-Meier; OS – Overall survival; PCC – platinum containing chemotherapy.

The hazard plots indicated that after the observed data a model with a non-monotonic hazard may be suitable for PCC, such as the log-logistic, log-normal, and generalised gamma curves. Based on goodness of fit and compared against UK clinical opinion the **log-logistic provided the closest estimates for OS PCC expected in clinical practice and is the base case**. To directly use all available RUBY-1 data that is available during the follow up period, **a piecewise approach utilising the KM for the follow up period (up to week 147) followed by the log-logistic standard parametric curve to extrapolate the remaining years was selected**. This piecewise approach was preferred to best use all available RUBY-1 data available during the follow-up period.

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 (applied in Figure 20).[123] Scenario analysis include implementation of the lognormal which was the second best fitting curve against the UK clinical opinion estimates and using the full extrapolated log-logistic curve (no use of KM for the follow up period).

B3.3.4.2 Dostarlimab in combination with platinum-containing chemotherapy (PCC) overall survival

Standard parametric distributions were fitted to OS from RUBY-1 for the dostarlimab in combination with CP arm independently. Table 39 summarises the AIC and BIC values for each extrapolation.

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 AIC and BIC.

Table 39: Summary of goodness-of-fit data for dostarlimab in combination with PCC for OS (standard parametric independent models)

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

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

Table 40 presents the estimated proportion of patients who would be alive at landmark timepoints from five UK clinicians along with the overall mean. In turn, Table 41 presents the overall mean estimate alongside the proportions estimated through standard parametric extrapolations.

Figure 19 presents the standard parametric extrapolations with the observed dostarlimab in combination with CP RUBY-1 data. The mean proportions from the UK clinicians did not align with proportions estimated through standard parametric extrapolations and neither did the extrapolations fit the observed RUBY-1 data. This is likely due to the low number of events in the RUBY-1 trial. The hazard plots indicated that a model with a non-monotonic hazard may be suitable for dostarlimab in combination with PCC. However, due to the low number of events, the log-logistic,

log-normal and generalised gamma curves overestimated the longer term OS for dostarlimab in combination with PCC compared with UK clinical opinion estimates.

Table 40: Advisor 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 dostarlimab in combination with PCC

Months (years)	dMMR/MSI-H					
	Mean	A1	A2	A3	A4	A5
24 (2)	82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	76%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	67%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	53%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	44%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

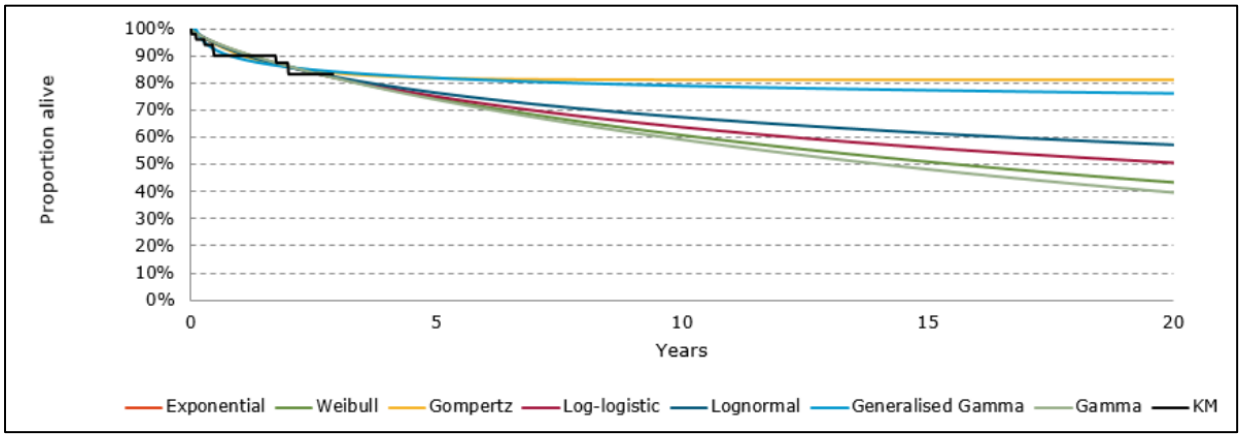
Abbreviations: A1-5 – advisor 1-5; dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy. Please note, advisor 4 was from Scotland.

Table 41: 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 dostarlimab in combination with PCC

Months (years)	Advisors' mean	PCC						
		Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
24 (2)	82%	86%	86%	86%	86%	86%	86%	86%
36 (3)	76%	80%	82%	84%	82%	82%	84%	82%
60 (5)	67%	69%	74%	82%	75%	76%	82%	74%
120 (10)	53%	47%	61%	81%	64%	67%	79%	59%
240 (20)	44%	22%	43%	81%	51%	57%	76%	40%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

Figure 19: Standard parametric survival analyses for dostarlimab in combination with PCC for OS



Abbreviations: KM – Kaplan-Meier; OS – overall survival; PCC – platinum containing chemotherapy.

As the independent standard parametric curves did not fit the observed RUBY-1 data well or UK clinical expert estimates, alternative approaches were explored. Flexible spline modelling was not applicable as it is unlikely to converge for OS due to the low number of events. The low number of events would not have enabled convergence on the minimum of three coefficients and the knots required for running a flexible curve for OS.

A conservative approach was to take the unstratified HR calculated for dostarlimab in combination with CP compared with placebo in combination with CP to show the reduced risk; (unstratified HR of [redacted] is more conservative than the stratified HR of 0.30). The placebo in combination with CP OS data is more mature compared with dostarlimab in combination with CP in the RUBY-1 data (37% versus 13%). As noted previously the log-logistic extrapolation of the PCC OS data provides a clinically validated estimate of long-term outcomes and represents a solid basis to apply the HR observed in RUBY-1 for dostarlimab in combination with CP. Application of the dostarlimab in combination with CP HR to an OS extrapolation for PCC is also potentially conservative when the mechanism of action of immunotherapies is considered. This approach assumes that the shape of the OS curve for dostarlimab in combination with PCC, and the risk of mortality over time mirrors that seen in the PCC alone extrapolation. This is a conservative assumption considering the early and durable plateau seen in the RUBY-1 dostarlimab in combination with CP OS KM.

The HR for dostarlimab in combination with CP accounts for the entire follow-up period (at [redacted] weeks), including the initial approximately 6 months of follow-up where there is limited separation between the dostarlimab in combination with CP and placebo in combination with CP OS KMs. The HR calculated for dostarlimab in combination with CP compared with placebo in combination with CP post 6 months would likely show an even further reduced risk of death. This is further supported by the shape of OS hazard curves (Figure 17) which show a continuous declining curve for dostarlimab in combination with CP arm unlike the placebo in combination with CP arm.

Within the base case, **the combination of the KM piecewise approach for the follow up period, in addition to the HR approach were used for the OS extrapolation.** The piecewise approach was preferred to best use all the available RUBY-1 data during the follow-up period. Table 42 presents the overall mean estimates from the UK clinicians alongside the proportions estimated through the HR approach with standard parametric extrapolations. Figure 20 presents the base case:

- Placebo in combination with PCC: KM piecewise approach, followed by log-logistic extrapolation, adjusted by general population mortality
- Dostarlimab in combination with PCC: KM piecewise approach, followed by unstratified HR approach applied to the placebo in combination with PCC log-logistic extrapolation, adjusted by general population mortality

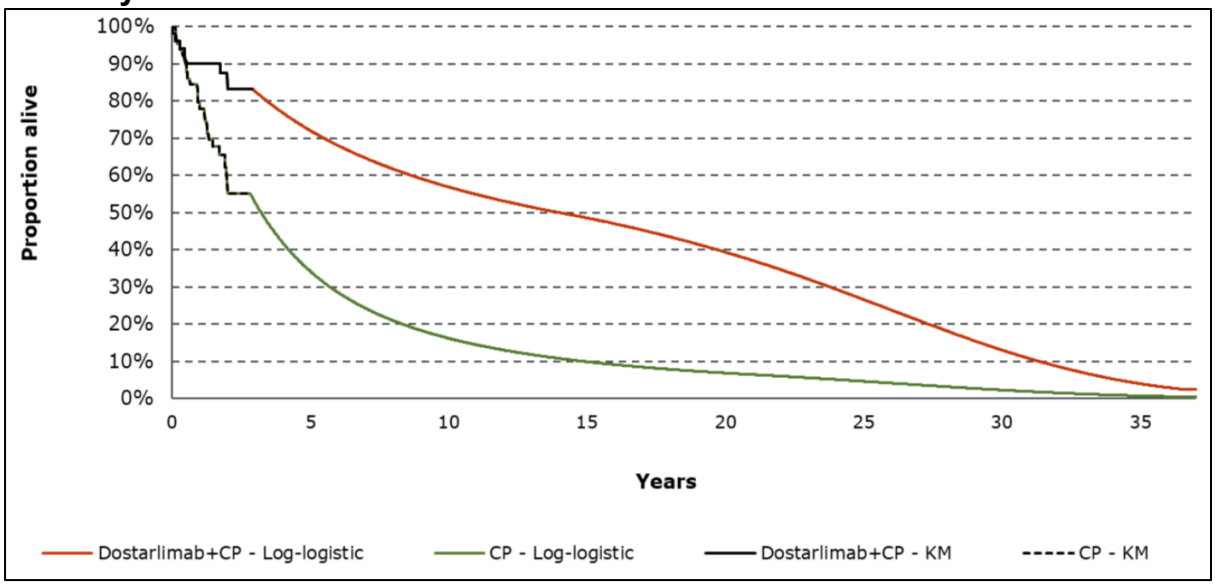
Table 42: Advisor mean estimates and HR approach estimates of the proportion of patients who would be alive at landmark time points in dMMR/MSI-H population in the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	Advisors' mean	Dostarlimab in combination with PCC HR approach	
		Unstratified HR applied to Log-logistic PCC	Unstratified HR applied to Lognormal PCC
24 (2)	82%	83%	83%
36 (3)	76%	83%	83%

120 (10)	53%	57%	60%
240 (20)	44%	39%	42%

Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

Figure 20: KM piecewise approach (follow up period) followed by HR approach with standard parametric extrapolation (log-logistic) for dostarlimab in combination with PCC and PCC for OS adjusted for general population mortality



Abbreviations: CP – carboplatin paclitaxel; HR – hazard ratio; KM – Kaplan Meier; OS – overall survival; PCC – platinum containing chemotherapy.

For scenario analyses, the following were explored to show the impact on results:

- Implementation of the stratified HR
- Unstratified HR applied to lognormal PCC OS curve (PCC OS second best fitting curve)
- Unstratified HR will full log-logistic parametric extrapolation (no KM piecewise)
- Log-logistic curve parametric approach (aligned with the curve used to model PCC OS base case)
- Lognormal curve parametric approach (aligned with the second-best fitting curve to model PCC)

- Weibull curve parametric approach (closest to the UK clinical opinion estimates).

The curves tested align with the curves selected in the scenario analyses for PCC and also show the impact of selecting parametric curves that are based on low number of events. Testing a range of scenarios and approaches to model OS quantifies the uncertainty and provides an upper bound of potential cost effectiveness estimates. All scenarios and approaches presented were highly cost effective (ICER <£23,000).

B3.3.5 Time to treatment discontinuation (TTD)

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

Table 43 shows the non-parametric and semi-parametric analysis results for TTD. Data is more mature in the placebo in combination with CP arm compared with dostarlimab in combination with CP arm with [redacted]% versus [redacted]% maturity over the follow-up period, respectively. Overall, patients remained on treatment for longer with dostarlimab in combination with CP versus placebo in combination with CP ([redacted] mean weeks versus [redacted]).

Table 43: Non-parametric and semi-parametric results for TTD

Treatment arm (N)	Dostarlimab in combination with CP (n=53)	Placebo in combination with CP (n=65)
Maturity (%) – n/N	[redacted]	[redacted]
Duration of follow up (weeks) Median (95% CI)	[redacted]	[redacted]
Duration of follow up (weeks) Restricted mean (SD)	[redacted]	[redacted]
Median (95% CI) (weeks)	[redacted]	[redacted]
Restricted mean (weeks), (SE)	[redacted]	[redacted]
HR* (95% CI; p-value)	[redacted]	

Non-parametric analysis includes percentage of data maturity, median and restricted mean follow up, median and restricted mean survival. The cox proportional hazards model (HR) is a semi-parametric model.

Abbreviations: CI – confidence interval; HR – hazard ratio; NR – not reported; SD – standard deviation; SE – standard error. *Unstratified cox proportional hazards model used to calculate HR.

Table 44 and Figure 21 show that patients were not treated beyond progression (assessed by IA) in either treatment arm. Therefore, the TTD curve should be below the IA PFS curve.

Table 44: TTD and IA PFS in each treatment arm

	Dostarlimab in combination with CP (n=53)		Placebo in combination with CP (n=65)	
	TTD	IA PFS	TTD	IA PFS
Restricted mean (weeks), (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Restricted mean IA PFS – restricted mean TTD (weeks)	[redacted]		[redacted]	
Median (95% CI) (weeks)	[redacted]	NR	[redacted]	[redacted]

Abbreviations: CI – confidence interval; CP – carboplatin-paclitaxel; IA – investigator assessed; NR – not reported; PFS – progression free survival; SE – standard error; TTD – time to treatment discontinuation.

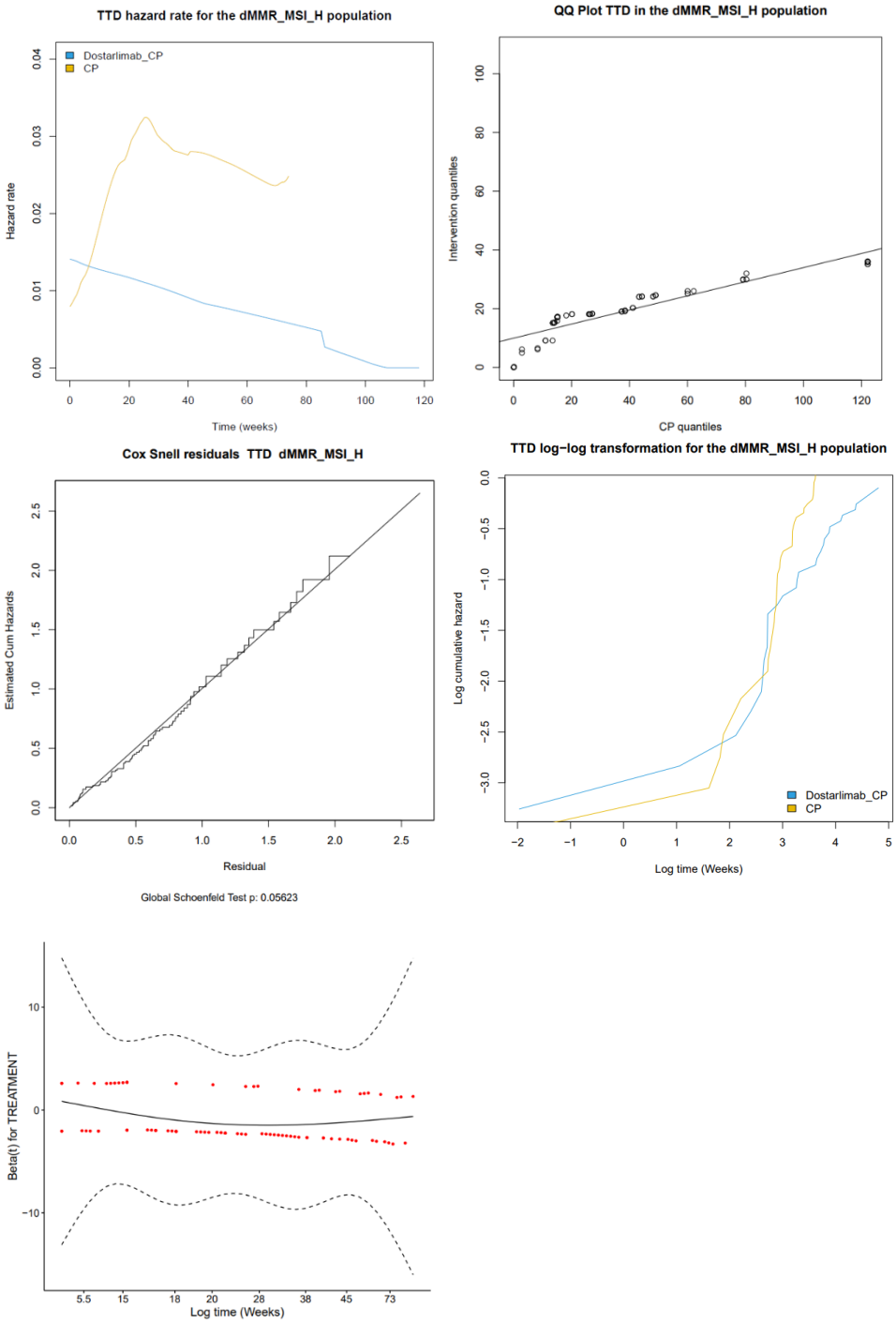
Figure 21: TTD and IA PFS KM curves

Abbreviations: CP – carboplatin-paclitaxel; IA – investigator assessed; KM – Kaplan-Meier; PFS – progression free survival; TTD – time to treatment discontinuation.

Several statistical tests were conducted to understand if the proportional hazards assumption and AFT assumption would be violated (Figure 22). These were the same tests performed for PFS, outlined in Section B3.3.3, and the tests suggested

violation of the proportional hazards and constant AFT assumptions, in alignment with PFS.

Figure 22: Log-log plot, global Schoenfeld test, Cox Snell residuals, QQ plot and hazard rate plot for TTD



Abbreviations: dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy; QQ – quantile quantile.

B3.3.5.1 *Platinum-containing chemotherapy (PCC) time to treatment discontinuation*

Standard parametric distributions were fitted to TTD from RUBY-1 for the placebo in combination with CP arm independently. Table 45 summarises the AIC and BIC values for each extrapolation.

The choice of curve in the base case was selected by visual analysis and UK clinical opinion, alongside analysis of goodness-of-fit statistics such as AIC and BIC, with a lower AIC or BIC value indicating a better fitting model.

Table 45: Summary of goodness-of-fit data for PCC for TTD (standard parametric independent models)

TTD	**PCC**	
Distribution	**AIC**	**BIC**
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

Note: A small AIC or BIC value represents a better goodness of fit. Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; PCC – platinum-containing chemotherapy; TTD – time to treatment discontinuation.

Figure 23 presents the standard parametric extrapolations with the observed placebo in combination with CP RUBY-1 TTD data.

Figure 23: Standard parametric survival analyses for PCC for TTD

Abbreviations: KM – Kaplan-Meier; PCC – platinum containing chemotherapy; TTD – Time to discontinuation.

As described in Section B1.2, patients on SoC are given 6 treatment cycles (where one treatment cycle is three weeks) of CP with response monitored after three treatment cycles.[43,63] The placebo in combination with CP TTD KM data includes time on treatment for three treatments: carboplatin, paclitaxel and placebo;

- Placebo: Though the placebo in combination with CP TTD KM and extrapolation continues beyond week 18, there is no cost assigned beyond week 18 during the placebo monotherapy phase (B3.5.2). **In the base case, beyond week 18 the KM curve is used for the follow up period and subsequently the Weibull standard parametric curve.**

- Carboplatin and paclitaxel: **In the base case the completion rates from RUBY-1 were applied for the first six treatment cycles** (where one treatment cycle is three weeks), with placebo continuing until year three (Table 46). A scenario analysis with completion rates switched off has been explored.

Table 46: Completion rates for CP per treatment cycle

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

3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

Abbreviations: CP – carboplatin-paclitaxel

B3.3.5.2 Dostarlimab in combination with platinum-containing chemotherapy (PCC) time to treatment discontinuation

Standard parametric distributions were fitted to TTD from RUBY-1 for the dostarlimab in combination with CP arm independently. Table 47 summarises the AIC and BIC values for each extrapolation.

Table 47: Summary of goodness-of-fit data for dostarlimab in combination with PCC for TTD (standard parametric independent models)

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

Note: A small AIC or BIC value represents a better goodness of fit. Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; PCC – platinum-containing chemotherapy; TTD – time to treatment discontinuation

Table 48 presents the estimated proportion of patients who would be on treatment at landmark timepoints from five UK clinicians along with the overall mean. In turn, Table 49 presents the overall mean estimate alongside the proportions estimated through standard parametric extrapolations. Figure 24 presents the standard parametric extrapolations with the observed dostarlimab in combination with CP RUBY-1 TTD data.

Table 48: Advisor estimates of the proportion of patients who would remain on treatment at landmark time points in dMMR/MSI-H populations in the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	dMMR/MSI-H					
	Mean	**A1**	**A2**	**A3**	**A4**	**A5**
12 (1)	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 (2)	49%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

36 (3)	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4)	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56 (5)	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

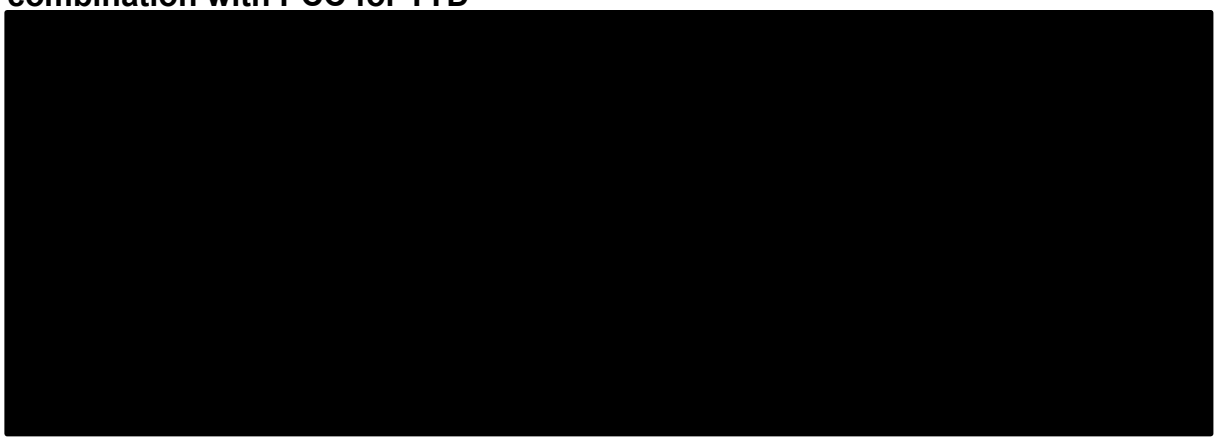
Abbreviations: A1-5 – advisor 1-5; dc – discontinued; dMMR – DNA mismatch repair deficiency; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy. Please note, advisor 4 was from Scotland.

Table 49: Advisor mean estimates and standard parametric estimates of the proportion of patients who would remain on treatment at landmark time points in dMMR/MSI-H population of the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	Advisors' mean	Dostarlimab in combination with PCC							
		KM	Exponential	Weibull	Gompertz	Log-logistic	Lognormal	Generalised Gamma	Gamma
12 (1)	60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 (2)	49%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (4)	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56 (5)	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*this is the last % on treatment in the KM curve at year 2 and 51 weeks. Abbreviations: dMMR – DNA mismatch repair deficiency; KM – Kaplan Meir; MSI-H – microsatellite-instability high; PCC – platinum containing chemotherapy.

Figure 24: Standard parametric survival analyses for dostarlimab in combination with PCC for TTD



Abbreviations: KM – Kaplan-Meier; PCC – platinum containing chemotherapy.

The Gompertz, log-logistic and Weibull curves have the lowest AIC/BIC values, however, the Gompertz and log-logistic curves have an unrealistic long tail compared with the UK clinical expert estimates. Therefore, the Weibull curve provides the best statistical fit coupled with clinical plausibility whilst also aligning with the Weibull curve used to model PCC.

Aligned with how PCC was modelled, completion rates from RUBY-1 were applied for the first six treatment cycles (see Table 46 and Table 50 for CP and dostarlimab completion rates respectively), followed by the KM for the follow up period and subsequently the Weibull standard parametric curve. In addition, a stopping rule of three years was applied to align with the draft SmPC (Appendix C), RUBY-1 trial data and feedback from clinicians given this is reflective of clinical practice.[4] Discontinuation will not impact efficacy since patients remain progression-free for longer than on treatment in the observed data. A scenario analysis with completion rates switched off has been explored along with using the full extrapolated Weibull curve (no use of KM for the follow up period).

Table 50: Completion rates for dostarlimab per treatment cycle

Dostarlimab completion rates per treatment cycle	Proportion receiving dose of dostarlimab (%)
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]

5	[redacted]
6	[redacted]

B3.4 Measurement and valuation of health effects

B3.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D-5L data collected within the RUBY-1 trial were analysed to estimate health state utility values. In the dMMR/MSI-H population of RUBY-1, [redacted] and [redacted] EQ-5D-5L VAS observations were available for the PFS and PD health states, respectively. In the ITT population of RUBY-1, there were [redacted] EQ-5D-5L VAS observations in total, with [redacted] and [redacted] available in the PFS and PD health states, respectively. Therefore, the ITT population is the preferred source of HRQoL data due to the larger available sample of patient data, particularly in the PD health state. For this analysis, patients included were required to be in the ITT population and have a baseline and post-baseline EQ-5D-5L assessment. The dMMR/MSI-H population utility values were tested as part of scenario analyses and the impact on the ICERs was minimal.

Currently, there is no approved value set for the EQ-5D-5L in England. Therefore, aligned with NICE preference, the EQ-5D-5L were mapped to EQ-5D-3L.[124] The EQ-5D-5L data from RUBY trial was mapped to the EQ-5D-3L data using the cross-walk approach by Hernández Alava M, Pudney S. (2017)[116] as recommended in NICE guidelines (2022).[111] The health state utility values from the RUBY trial analyses are [redacted] for PFS and [redacted] for PD for the ITT population (see Table 51).

Table 51: Health state utility values from RUBY trial

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

Abbreviations: dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PD – progressed disease; PFS – progression free survival; SD – standard deviation

B3.4.2 Health-related quality-of-life studies

An HRQoL SLR was undertaken on 10 November 2021 (with an update on 22 February 2023) 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 only one unique study evaluating health utilities in patients with advanced or recurrent endometrial cancer. The identified study from Hildebrandt et al. 2014[125] was a cross-sectional study of women with gynecological cancers from Germany that evaluated health utilities using the EQ-5D questionnaire in a subgroup of 27 patients with endometrial cancer compared to 62 healthy controls.[126]

Of the patients with endometrial cancer, only 12 women diagnosed with advanced disease had EQ-5D-3L data. Baseline demographic and clinical characteristics of enrolled patients with advanced or recurrent endometrial cancer were not reported. The median health utility scores in patients with advanced endometrial cancer was 0.8870 (range: 0.676-1) which was lower than compared to the health utility scores in healthy controls (median: 0.9995; range: 0.262-1), with no health state specific utilities reported. Due to small patient numbers (n=12) in this literature study, and lack of information regarding patients' characteristics, the RUBY-1 trial is used for the health state utilities in the economic analysis.

B3.4.3 Adverse reactions

Section B2.10 includes full details of AE data in the RUBY-1 trial.

As standard practice in CEMs, only grade 3 and above AEs were included in the model (see Section B2.10). AEs from the ITT population was the preferred source since there was more patient data available (see Appendix R Table 65). In addition, minimal differences were observed between the AEs observed in the ITT population and dMMR-MSI-H population (see Appendix R Table 62).

Whilst the application of AE disutilities may be considered as double counting, this ensures the model includes an impact on healthcare resource use, costs, or an impact on HRQoL due to AEs. A scenario analysis explored the impact of excluding AE disutilities. Utility decrements were applied on an absolute (rather than relative) basis and applied in the first model cycle per treatment arm, assuming that AEs were likely to occur rapidly after treatment and only require acute care. RUBY-1 events

were also more likely to happen in the combination phase and not in the monotherapy phase (see Section B2.10, and see Appendix R Tables 63 and 64).

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 52).

Table 52: Adverse event disutilities

Adverse event	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.[126] 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.[126]
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.[127] Assumed equal to responding plus fatigue.
Hypertension	−0.020	NICE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first line platinum-based chemotherapy. Published 17 February 2021. https://www.nice.org.uk/guidance/ta673/history. Accessed February 2023 [115]
Hypokalaemia	−0.074	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). Published 28 September 2016. https://www.nice.org.uk/guidance/ta411. Accessed March 2023[128]
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.[127] 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. https://www.nice.org.uk/guidance/ta411. Accessed March 2023[128]
Urinary tract infection	−0.010	Assumption
White blood cell decreased	0.000	Assumed to have no utility impact

B3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 53 summarises the utility values used in both the base-case and scenario analyses. Age-adjusted utilities were applied to reflect decreases in HRQoL seen in the general population and to make sure 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)[116]. The impact of removing this age-adjustment was explored as a scenario analysis.

Table 53: Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
PFS	**Base case (ITT):** [redacted] **Scenario analysis (dMMR/MSI-H):** [redacted]	[redacted] [redacted]	B.3.4.1 Health-related quality-of-life data from clinical trials. Page 123	EQ-5D-5L data from RUBY-1 trial were mapped to EQ-5D-3L aligned with NICE guidelines.[111] ITT data were used because there were four-fold more data available versus the dMMR/MSI-H subgroup.
PD	**Base case (ITT):** [redacted] **Scenario analysis (dMMR/MSI-H):** [redacted]	[redacted] [redacted]		

Age-adjusted utilities	**Base case:** Included **Scenario analysis:** Excluded	B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis. Page 126	Age adjusted utilities were applied to align with NICE guidelines .[111]
Adverse events			
Adverse events	**Base case:** Included **Scenario analysis:** Excluded	B3.4.3 Adverse reactions. Page 102	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; dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PD – progressed disease; PFS – progression free survival.

B3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was undertaken on 10 November 2021 (with an update on 22 February 2023) 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 ten publications from eight unique studies reporting on HCRU that met the inclusion criteria. All studies enrolled adult women diagnosed with endometrial cancer. Five studies were conducted in the US[129–134] and three studies were each conducted in Denmark[135], Italy[136], and the UK[137].

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 two studies covering the US.[130,136,137] The UK costs were reported at an aggregate level for two 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 (Chen et al. 2020).[132] Mean length of inpatient hospitalisation among patients with endometrial cancer was only reported in a predominantly Medicare fee-for-service population in the US (reported in Galaznik et al. 2019 only).[133] Only Pennington et al. 2016 reported UK resource use data,[137] detailing the number and proportion of patients which received medical procedures and prescription drugs.

None of the studies reporting resource use were used in the economic model due to either being US based or containing limited UK data 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.[102,117,138]

B3.5.1 Costs included in the model

The CEM was built from the perspective of the NHS and personal social service (PSS), in line with the NICE reference case,[111] and so NHS reference costs were deemed an appropriate source for the cost inputs for HCRU. Treatment costs were sourced from the BNF Formulary 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
- Adverse events
- 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 PSSRU.[139]

B3.5.2 Intervention and comparators' costs and resource use

B3.5.2.1 *Treatment acquisition costs*

Treatment acquisition costs were calculated using treatment prices and dosing schedules. The RUBY-1 trial and draft SmPC provided data for the dosing scheduled for dostarlimab in combination with PCC, and PCC. Treatment prices were sourced from the BNF.

Cost per unit was multiplied by dose per treatment cycle (where one cycle is three 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 B3.3.5 using TTD data from the RUBY-1 trial with completion rates applied for the first six treatment cycles and a discontinuation rule at three years.

B3.5.2.2 Dostarlimab in combination with platinum-containing chemotherapy (PCC)

The cost of 50 mg per 1 ml vial of dostarlimab was £5,887.33. Dostarlimab is administered intravenously 500 mg every 3 weeks for 6 doses on weeks 1, 4, 7, 10, 13, and 16, followed by 1,000 mg every 6 weeks from week 19 onwards up to a maximum of 3 years (see Figure 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.[9] Carboplatin is administered intravenously at a unit dose of area under the plasma or serum concentration-time curve 5 mg/ml/min every three weeks.

The cost of 100 mg vial of paclitaxel was £87.50.[10] Paclitaxel is administered intravenously at a unit dose of 175 mg/m^2 every three weeks (

Table 54).

B3.5.2.3 Platinum-containing chemotherapy (PCC)

Carboplatin and paclitaxel are administered intravenously for the first six cycles only. Table 54 and Table 55 summarise the treatment acquisition cost for dostarlimab in combination with PCC and PCC.

Table 54: Drug acquisition unit costs for dostarlimab and PCC 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	87.50	343.35	4	350.00	0	0

Abbreviations: PAS – patient access scheme; PCC – platinum containing chemotherapy.

Table 55: Total drug acquisition cost per treatment cycle with wastage

Cycle (week)	Dostarlimab	Carboplatin and Paclitaxel
	Acquisition cost per treatment cycle (£)	
Up to cycle 18	5,887.33 (list price) [redacted] (PAS price)	518.85
Cycle 19+	11,774.66 (list price) [redacted] (PAS price)	0.00

Abbreviations: PAS – patient access scheme

B3.5.2.4 Treatment administration cost

Administration costs for both dostarlimab in combination with PCC and PCC were sourced from NHS National cost collection data publication 2020/21 (Table 56). Costs were inflated to 2022/23 using the PSSRU.[117] Treatment administration costs were applied in addition to treatment acquisition costs to derive the total cost per treatment cycle (Table 56).

During the monotherapy phase (model cycle 19+ to three years maximum), administration of dostarlimab alone is a 30-minute IV infusion. This is a simple administration and the health research group (HRG) code typically used for subsequent chemotherapy administrations [SB15Z Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRGs, £495.36] may be too high a cost considering the simplicity.

In scenario analysis, a more representative infusion cost has been applied for the cost of administration for dostarlimab monotherapy cycle 19+. The HRG code based SB12Z [Deliver Simple Parenteral Chemotherapy at First Attendance) is applied [£281.28 from NHS reference costs 2020/21 and inflated to £296.07 2023 using the PSSRU].[117,140] This is consistent with the costing approach applied in previous NICE appraisals for pembrolizumab (TA357, TA366, TA766, TA837).[141–144] Also in scenario analysis the cost of administration for IV biologics for the treatment of rheumatoid arthritis, which accounts for a 60-minute IV infusion has been applied to dostarlimab administration after cycle 19. This cost [£154.00 per IV infusion (2012), inflated to £184.95 2023] was applied in TA715 and TA247.[145,146]

Table 56: 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 PCC	£449.23 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£495.36 [SB15Z – Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRGs]	£6,855.41 (list price) [redacted](PAS price)	£12,155.20 (list price) [redacted] (PAS price)	NHS. National Cost Collection Data Publication 2020/2021. https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/.Accessed February 2023[140] NICE. British National Formulary (BNF). https://bnf.nice.org.uk/. Accessed February 2023[140]
PCC	£449.23 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£0.00	£968.08	£0.00	NHS. National Cost Collection Data Publication 2020/2021. https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/. Accessed February 2023[140]

Abbreviations: NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PAS – patient access scheme; PCC – platinum containing chemotherapy.

B3.5.3 Health state unit costs and resource use

B3.5.3.1 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 B3.3.3) and PD health state (based on the difference between the PFS and OS modelled as described in Section B3.3.3 and B3.3.4, respectively).

UK clinical opinion was sought to provide estimates for resource use by health state, by treatment, and by treatment phase (up to model cycle 18 [combination] and model cycle 19+ [monotherapy]).[4] 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 2020/2021 and were inflated to 2022/23 costs. HCRU per weekly cycle applied per health state for dostarlimab in combination with PCC and PCC are presented in Table 57 and Table 58, respectively.

B3.5.3.2 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.

Terminal care costs are applied to the proportion of patients who transition to the death state and applied as a one-off cost. Costs were taken from Guest et al. 2006 and inflated to the 2023 cost year.[117,147] Guest et al. estimated the costs of palliative care associated with ovarian cancer to be £4,789 (2000/2001 UK setting).[147] 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 TA779 for dostarlimab in previously treated individuals with endometrial cancer, where this estimate was inflated from the 2000/2001 to 2018/2019 UK cost setting, resulting in an estimate of £8,104.88.[148] This cost was then inflated to 2022/23 to be £8,716.94.

Table 57: Cost and resource use per weekly model cycle for dostarlimab in combination with PCC

Resource	Unit cost (£)	Health state	Resource use (up to cycle 18)	Total costs (up to cycle 18) (£)	Resource use (cycle 19+)	Total costs (cycle 19+) (£)	Reference
Outpatient visit	187.19	PFS	0.30	56.16	0.13	24.33	NHS cost collection (2021)[140] inflated to 2022/2023 cost year [117]
		PD	0.12	22.46	0.12	22.46	
CT scan	156.74	PFS	0.13	20.38	0.06	9.40	
		PD	0.07	10.97	0.07	10.97	
Complete blood count	3.82	PFS	0.33	1.26	0.22	0.84	
		PD	0.09	0.34	0.09	0.34	
Specialist nurse visit	57.00	PFS	0.11	6.27	0.07	3.99	
		PD	0.10	5.70	0.10	5.70	
GP visit	46.00	PFS	0.00	0.00	0.01	0.46	
		PD	0.01	0.46	0.01	0.46	

Abbreviations: CT – computerized tomography; GP – General practitioner; NHS – National Health Service; PCC – platinum-containing chemotherapy; PD – progressed disease; PFS – progression free survival.

Table 58: Cost and resource use per weekly cycle for PCC

Resource	Unit cost (£)	Health state	Resource use (up to cycle 18)	Total costs (up to cycle 18) (£)	Resource use (cycle 19+)	Total costs (cycle 19+) (£)	Reference
Outpatient visit	187.19	PFS	0.30	56.16	0.08	14.98	NHS cost collection (2021)[140] inflated to 2022/2023 cost year [117]
		PD	0.12	22.46	0.12	22.46	
CT scan	156.74	PFS	0.13	20.38	0.05	7.84	
		PD	0.07	10.97	0.07	10.97	
Complete blood count	3.82	PFS	0.33	1.26	0.06	0.23	
		PD	0.09	0.34	0.09	0.34	
Specialist nurse visit	57.00	PFS	0.11	6.27	0.07	3.99	
		PD	0.10	5.70	0.10	5.70	
GP visit	46.00	PFS	0.00	0.0	0.01	0.46	
		PD	0.01	0.46	0.01	0.46	

Abbreviations: CT – computerized tomography; GP – General practitioner; NHS – National Health Service; PCC – platinum-containing chemotherapy; PD – progressed disease; PFS – progression free survival.

B3.5.4 Adverse reaction unit costs and resource use

In line with standard practice of modelling cost-effectiveness in oncology, and previous economic analyses in endometrial cancer, costs associated with the treatment of grade ≥3 AEs reported for each comparator are included in the CEM.[148]

Incidence of grade ≥3 AEs from the ITT population were used as there was more data available, and rates of AEs were similar to those seen in the dMMR/MSI-H population (see Section B2.10 and Appendix R Tables 62 and 65). 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 Section B2.10 and Appendix R Tables 63 and 64).

Table 59 and Table 60 summarise the costs for each AE and AE incidence for dostarlimab in combination with PCC and PCC, respectively, included in the cost-effectiveness analysis.

Table 59: List of AE unit costs, AE grade ≥3 incidence and summary of costs for dostarlimab in combination with PCC

Adverse event	Unit cost (£)	Incidence	Total costs (£)	Reference for cost
Anaemia	774.48	14.9%	115.69	NHS. National Cost Collection Data Publication 2020/2021.[140]
Neutropenia	702.43	9.5%	67.04	
Neutrophil count decreased	1,042.39	8.3%	86.51	
Hypertension	546.21	7.1%	38.53	NICE TA673 https://www.nice.org.uk/guidance/ta673/history. Accessed February 2023[115]
White blood cell count decreased	1,042.39	6.6%	69.20	Assumed same as neutrophil count decreased
Hypokalemia	2,204.06	5.0%	109.75	NHS. National Cost Collection Data Publication 2020/2021.[140]
Pulmonary embolism	2,147.67	5.0%	106.94	
Lymphocyte count decreased	1,042.39	5.4%	56.23	Assumed same as neutrophil count decreased

Abbreviations: AE – adverse event; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PCC – platinum-containing chemotherapy.

Table 60: List of AE unit costs, AE grade ≥3 incidence and summary of costs for PCC

Adverse event	Unit cost (£)	Incidence	Total costs (£)	Reference for cost
Anaemia	774.48	16.3%	125.93	NHS. National Cost Collection Data Publication 2020/2021.[140]
Neutropenia	702.43	9.3%	65.67	
Neutrophil count decreased	1,042.39	13.8%	144.07	
Hypertension	546.21	3.3%	17.76	NICE TA673 https://www.nice.org.uk/guidance/ta673/history. Accessed February 2023[115]
White blood cell count decreased	1,042.39	5.3%	55.09	Assumed same as neutrophil count decreased
Hypokalemia	2,204.06	3.7%	80.64	NHS. National Cost Collection Data Publication 2020/2021.[140]
Pulmonary embolism	2,147.67	4.9%	104.76	
Lymphocyte count decreased	1,042.39	7.3%	76.27	Assumed same as neutrophil count decreased

Abbreviations: AE – adverse event; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PCC – platinum-containing chemotherapy.

B3.5.5 Subsequent costs

Cost of subsequent treatments were included to account for the costs of treatment sequencing. Subsequent treatment data from UK clinical experts were used to inform the subsequent treatment regimens within the model in the base case. This is representative of approved SoC in England following discontinuation of primary treatment.

For patients who have not received prior treatment with an IO (i.e. the PCC arm only), lenvatinib plus pembrolizumab was recently approved in the post-platinum setting by NICE, and has been included within the base case as a subsequent treatment option based on the proportion of this regimen received in the RUBY-1 trial post-progression. A scenario analyses is provided to explore the impact of subsequent treatment without lenvatinib plus pembrolizumab. Dostarlimab monotherapy is recommended for use via the CDF for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.[148] A scenario has been included where dostarlimab is also included as a subsequent treatment option for patients who have not received prior treatment with

an IO (aligned with the proportion received in the RUBY-1 trial for lenvatinib plus pembrolizumab post-progression), as outlined in Appendix S.

The subsequent treatments captured in the RUBY-1 trial included several treatments not available as per UK SoC, and therefore this data is not appropriate to inform the range of treatments or proportion usage of subsequent treatments.

Table 61 presents the cost and percentage of patients treated with each subsequent treatment. The percentages for each subsequent treatments were reweighted to ensure the total sum of percentages for all subsequent treatment doesn't exceed 100%. The cost of management of AEs for subsequent treatments were calculated based on incidence and costs sourced from the literature, aligned with methodology described in Section B3.5.4. 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 Section B3.11.3.

The total subsequent treatment costs, inclusive of drug at list prices and AE costs, of dostarlimab in combination with PCC were £5,152.19. Total subsequent treatment costs of PCC were £14,035.19.

Table 61: Subsequent treatments (HCP opinion with lenvatinib plus pembrolizumab)

Second-line treatment	Carboplatin and paclitaxel	Doxorubicin	Pembrolizumab and lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	No treatment
Total cost per class for average total treatment duration (£)	6,869.51	7,664.18	118,677.26	6.75	190.48	2,975.84	0.00
Total cost of adverse events during subsequent treatment (£)	389.54	622.53	362.63	66.11	66.11	0.00	0.00
Percentage usage post dostarlimab in combination with PCC	46.9%	19.4%	0.0%	5.1%	5.1%	4.1%	19.4%
Percentage usage post PCC	43.8%	15.1%	[redacted]	4.5%	4.5%	7.6%	[redacted]

Abbreviations: PCC – Dostarlimab in combination with platinum-containing chemotherapy; HCP – Healthcare professional

B3.5.6 Miscellaneous unit 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.[18] As such, dMMR 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.[149]

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

B3.6 Severity

The lifetime QALY gain of patients in the PCC arm of the CEM and corresponding age and sex from the RUBY-1 trial (see Table 62) was used to understand the extent to which the disease impacts patient's remaining QALYs. Utility data are outlined in Section B3.4.1 (

Table 63).

Patients with primary advanced or recurrent endometrial cancer experience dire health outcomes, demonstrated by the absolute shortfall of almost 9 QALYs, which is a 73% proportional shortfall compared with patients in the general population (Table 64). 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 62: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	100% female	Section B3.3.1
Starting age	[redacted] years old	Section B3.3.1

Abbreviations: QALY – quality adjusted life year

Table 63: 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 64: 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 PCC	Absolute QALY shortfall	Proportional
RUBY trial	11.82	3.21	8.61	72.83%

Abbreviations: QALY – Quality adjusted life year; PCC – platinum containing chemotherapy

B3.7 Uncertainty

The dostarlimab in combination with CP OS KM data available for economic analysis are informed by a small number of OS events from the RUBY-1 trial, and the trial was powered for OS in the ITT population (see B2.4). This led to poorly fitting independent standard parametric curves for the dostarlimab in combination with PCC treatment arm. A conservative approach was taken which used the more mature PCC OS curve as a base to apply the unstratified HR for dostarlimab in combination with CP compared with placebo in combination with CP to show the reduced risk. This approach may underestimate the potential OS benefit of dostarlimab in combination with CP that could be observed in the trial. The additional piecewise approach utilised the OS KM data directly for the follow up period to make use of all available observed data. Uncertainty regarding OS has been explored via various scenarios as described in Section B3.3.4 with results presented in Section B3.11.3 in order to determine the impact of various scenarios on cost effectiveness.

B3.8 Managed access proposal

The Company's preference, considering the statistically significant PFS dMMR/MSI-H RUBY-1 results and the clinically beneficial trend seen in OS, is to enter routine commissioning. However, the Company's priority is rapid access for all appropriate

patients in the UK and therefore will consider entry into managed access. The managed access proposal is outlined in in Appendix M.

As noted previously, RUBY-1 is an ongoing study with another interim analysis data cut expected in [redacted]. Data is expected to be available in [redacted]. It is important to note that RUBY-1 is an event driven trial, and therefore these dates are subject to change. Further interim analysis and final data cuts are also planned, details can be found in the supplementary appendix Mirza et al. 2023.[101]

B3.9 Summary of base-case analysis inputs and assumptions

B3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 65.

Table 65: Summary of variables applied in the base-case economic model

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
Settings						
Time horizon	[redacted]	-	-	-	Not varied	B3.2.3
Age at baseline (years)	[redacted]	-	-	-	Not varied	B3.3.1
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	Varied using Gamma distribution	
Body surface area (m2)	[redacted]	[redacted]	[redacted]	[redacted]	Varied using Gamma distribution	
Discount rate costs and outcomes	3.5%	-	-	-	Varied in scenario analysis	B3.2.3
Clinical inputs						
PFS (dostarlimab in combination with PCC)	IA PFS, flexible Odds K=1	-	-	-	Each survival analysis sheet contains a calculation for probabilistic analysis	B3.3.3
PFS (PCC)	IA PFS, flexible Odds K=2	-	-	-		
OS (dostarlimab in combination with PCC)	Extrapolated PCC OS adjusted by unstratified HR (0.32) (KM for full follow up period)	-	-	-		B3.3.4

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
OS (PCC)	Log-logistic (KM for full follow up period)	-	-	-		
OS HR	[redacted]	-	[redacted]	[redacted]		
TTD (dostarlimab in combination with PCC)	Weibull (KM for full follow up period) three year stopping rule and completion rates applied	-	-	-		B3.3.5
TTD (PCC)	Weibull (KM for full follow up period) three year stopping rule and completion rates applied	-	-	-		
Cost inputs						
Dostarlimab cost (up to cycle 18)	[redacted]	-	-	-	Not varied	B3.5.2
Dostarlimab cost (up to cycle 19+)	[redacted]	-	-	-	Not varied	
Carboplatin cost (up to cycle 18)	£168.85	-	-	-	Not varied	
Paclitaxel cost (up to cycle 18)	£350.00	-	-	-	Not varied	
Dostarlimab administration cost (up to cycle 18)	£449.23	£89.85	£290.72	£641.69	Gamma distribution	B3.5.2.4
Dostarlimab administration cost (cycle 19+)	£495.36	£99.07	£320.57	£707.58	Gamma distribution	
PCC administration cost (up to cycle 18)	£449.23	£89.85	£290.72	£641.69	Gamma distribution	
Cost inputs – resource use costs						
Outpatient visit	£187.19	£37.44	£121.14	£267.39	Gamma distribution	B3.5.3
CT scan	£156.74	£31.35	£101.43	£223.88	Gamma distribution	
Complete blood count	£3.82	£0.76	£2.47	£5.46	Gamma distribution	
Blood pressure and heart rate	£249.13	£49.83	£161.22	£355.85	Gamma distribution	
Specialist nurse visit	£57.00	£11.40	£36.89	£81.42	Gamma distribution	
GP visit	£46.00	£9.20	£29.77	£65.71	Gamma distribution	

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
Cost inputs – resource use frequency per cycle dostarlimab in combination with PCC						
Outpatient visit (up to cycle 18) - PFS	0.30	0.06	0.19	0.43	Gamma distribution	B3.5.3
CT scan (up to cycle 18) - PFS	0.13	0.03	0.08	0.19	Gamma distribution	
Complete blood count (up to cycle 18) - PFS	0.33	0.07	0.21	0.47	Gamma distribution	
Specialist nurse visit (up to cycle 18) - PFS	0.11	0.02	0.07	0.16	Gamma distribution	
Outpatient visit (up to cycle 18) - PD	0.12	0.02	0.08	0.17	Gamma distribution	
CT scan (up to cycle 18) - PD	0.07	0.01	0.05	0.10	Gamma distribution	
Complete blood count (up to cycle 18) - PD	0.09	0.02	0.06	0.13	Gamma distribution	
Specialist nurse visit (up to cycle 18) - PD	0.10	0.02	0.06	0.14	Gamma distribution	
GP visit (up to cycle 18) - PD	0.01	0.00	0.01	0.01	Gamma distribution	
Outpatient visit (cycle 19+) – PFS	0.13	0.03	0.08	0.19	Gamma distribution	
CT scan (cycle 19+) – PFS	0.06	0.01	0.04	0.09	Gamma distribution	
Complete blood count resource use (cycle 19+) – PFS	0.22	0.04	0.14	0.31	Gamma distribution	
Specialist nurse visit (cycle 19+) – PFS	0.07	0.01	0.05	0.10	Gamma distribution	
GP visit r (cycle 19+) – PFS	0.01	0.00	0.01	0.01	Gamma distribution	
Outpatient visit (cycle 19+) – PD	0.12	0.02	0.08	0.17	Gamma distribution	
CT scan (cycle 19+) – PD	0.07	0.01	0.05	0.10	Gamma distribution	
Complete blood count (cycle 19+) – PD	0.09	0.02	0.06	0.13	Gamma distribution	
Specialist nurse visit (cycle 19+) – PD	0.10	0.02	0.06	0.14	Gamma distribution	
GP visit (cycle 19+) - PD	0.01	0.00	0.01	0.01	Gamma distribution	
Cost inputs – resource use frequency per cycle PCC						
Outpatient visit (up to cycle 18) - PFS	0.30	0.06	0.19	0.43	Gamma distribution	B3.5.3
CT scan (up to cycle 18) - PFS	0.13	0.03	0.08	0.19	Gamma distribution	

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
Complete blood count (up to cycle 18) - PFS	0.33	0.07	0.21	0.47	Gamma distribution	
Specialist nurse visit (up to cycle 18) - PFS	0.11	0.02	0.07	0.16	Gamma distribution	
Outpatient visit (up to cycle 18) - PD	0.12	0.02	0.08	0.17	Gamma distribution	
CT scan (up to cycle 18) - PD	0.07	0.01	0.05	0.10	Gamma distribution	
Complete blood count (up to cycle 18) - PD	0.09	0.02	0.06	0.13	Gamma distribution	
Specialist nurse visit (up to cycle 18) - PD	0.10	0.02	0.06	0.14	Gamma distribution	
GP visit (up to cycle 18) - PD	0.01	0.00	0.01	0.01	Gamma distribution	
Outpatient visit (cycle 19+) – PFS	0.08	0.02	0.05	0.11	Gamma distribution	
CT scan (cycle 19+) – PFS	0.05	0.01	0.03	0.07	Gamma distribution	
Complete blood count (cycle 19+) – PFS	0.06	0.01	0.04	0.09	Gamma distribution	
Specialist nurse visit (cycle 19+) – PFS	0.07	0.01	0.05	0.10	Gamma distribution	
GP visit (cycle 19+) – PFS	0.01	0.00	0.01	0.01	Gamma distribution	
Outpatient visit (cycle 19+) – PD	0.12	0.02	0.08	0.17	Gamma distribution	
CT scan (cycle 19+) – PD	0.07	0.01	0.05	0.10	Gamma distribution	
Complete blood count (cycle 19+) – PD	0.09	0.02	0.06	0.13	Gamma distribution	
Specialist nurse visit (cycle 19+) – PD	0.10	0.02	0.06	0.14	Gamma distribution	
GP visit (cycle 19+) - PD	0.01	0.00	0.01	0.01	Gamma distribution	
Cost inputs – AE cost						
Anaemia	£774.48	£154.90	£501.20	£1,106.27	Gamma distribution	B3.5.4
Neutropenia	£702.43	£140.49	£454.58	£1,003.36	Gamma distribution	
Neutrophil count decreased	£1,042.39	£208.28	£674.58	£1,488.95	Gamma distribution	
Hypertension	£546.21	£109.24	£353.48	£780.21	Gamma distribution	
White blood cell count decreased	£1,042.39	£208.48	£674.58	£1,488.95	Gamma distribution	

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
Hypokalemia	£2,204.06	£440.81	£1,426.35	£3,148.29	Gamma distribution	
Pulmonary embolism	£2,147.67	£429.53	£1,389.86	£3,067.73	Gamma distribution	
Lymphocyte count decreased	£1,042.39	£208.48	£674.58	£1,488.95	Gamma distribution	
Cost inputs – Subsequent costs						
Subsequent treatment cost dostarlimab in combination with PCC	£5,152.19	£1,030.44	-	-	Individual components varied	B3.5.5
Subsequent treatment cost with PCC	£14,035.19	£2,807.04	-	-	Individual components varied	
Total cost for average total treatment duration (£) pembrolizumab and lenvatinib	£118,677.26	£23,735.45	£76,801.66	£169,519.06	Gamma distribution	
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from PCC	7.9%	1.6%	5.1%	11.2%	Gamma distribution	
AE probabilities – dostarlimab in combination with PCC						
Anaemia	14.9%	3.0%	9.6%	21.2%	Beta distribution	B2.10
Neutropenia	9.5%	1.9%	6.1%	13.6%	Beta distribution	
Neutrophil count decreased	8.3%	1.7%	5.3%	11.8%	Beta distribution	
Hypertension	7.1%	1.4%	4.5%	10.1%	Beta distribution	
White blood cell count decreased	6.6%	1.3%	4.3%	9.5%	Beta distribution	
Hypokalemia	5.0%	1.0%	3.2%	7.1%	Beta distribution	
Pulmonary embolism	5.0%	1.0%	3.2%	7.1%	Beta distribution	
Lymphocyte count decreased	5.4%	1.1%	3.5%	7.7%	Beta distribution	
AE probabilities - PCC						
Anaemia	16.3%	3.3%	10.4%	23.1%	Beta distribution	B2.10
Neutropenia	9.3%	1.9%	6.0%	13.3%	Beta distribution	
Neutrophil count decreased	13.8%	2.8%	8.9%	19.7%	Beta distribution	

-	Value	SE	Lower bound	Upper bound	Within PSA varied by	Reference to section in submission
Hypertension	3.3%	0.7%	2.1%	4.6%	Beta distribution	
White blood cell count decreased	5.3%	1.1%	3.4%	7.5%	Beta distribution	
Hypokalemia	3.7%	0.7%	2.4%	5.2%	Beta distribution	
Pulmonary embolism	4.9%	1.0%	3.1%	7.0%	Beta distribution	
Lymphocyte count decreased	7.3%	1.5%	4.7%	10.4%	Beta distribution	
QoL inputs – health state utilities and AE disutilities						
PFS	[redacted]	[redacted]	[redacted]	[redacted]	Beta distribution	B3.4.4
PD	[redacted]	[redacted]	[redacted]	[redacted]	Beta distribution	
Anemia	0.119	0.024	0.076	0.169	Beta distribution	B3.4.4
Neutropenia	0.090	0.018	0.058	0.128	Beta distribution	
Neutrophil count decreased	0.000	0.000	0.000	0.000	Beta distribution	
Hypertension	0.020	0.004	0.013	0.029	Beta distribution	
White blood cell count decreased	0.000	0.000	0.000	0.000	Beta distribution	
Hypokalemia	0.074	0.015	0.047	0.105	Beta distribution	
Pulmonary embolism	0.320	0.064	0.202	0.451	Beta distribution	
Lymphocyte count decreased	0.000	0.000	0.000	0.000	Beta distribution	

Abbreviations: AE – adverse events; SE – standard error

B3.9.2 Assumptions

A summary of the CEM assumptions are presented in Table 66.

Table 66: Model assumptions

Category	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.	Aligned with the decision problem for this appraisal.

	CP (PCC) is an appropriate comparator for dostarlimab in combination with PCC.	Aligned with decision problem for this appraisal.
Model structure and settings	UK NHS and PSS	In line with NICE reference case.[111]
	Lifetime horizon	A [redacted]-year time horizon was chosen as the mean age of dMMR/MSI-H patients in RUBY-1 trial was [redacted] years – a lifetime horizon assuming no patients survive beyond a mean age of 100 years.
	The important costs and outcomes associated with primary advanced or recurrent endometrial cancer can be captured by PFS and PD health states	The PSM structure is an established model framework to assess cost-effectiveness of oncology treatments and has been enabled decision making in NICE submissions in endometrial cancer.[2,74] The health states are consistent with the natural disease progression in patients with advanced or recurrent dMMR/MSI-H endometrial cancer.
Clinical effectiveness	Treatment efficacy data sourced from RUBY-1 trial for treatments.	In line with the NICE reference case [111] and described in Section B2.6.
Cost and resource use inputs	Wastage of doses	In line with the treatment of primary advanced or recurrent 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 in combination with PCC and PCC aligned with RUBY trial discontinuation criteria and treatment SmPCs.	RUBY trial and SmPC discontinuation criteria reflect clinical practice as validated by UK clinicians.
	Excluded societal costs.	In line with the NICE reference case.[111]

	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	EQ-5D-5L data from RUBY-1 trial ITT population mapped to EQ-5D-3L.	In line with the NICE reference case.[111]
	Grade ≥ 3 AEs from RUBY-1 trial ITT population included 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; dMMR – mismatch repair deficient; EQ5D – 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

B3.10 *Base-case results*

B3.10.1 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 B1.2.

Total costs, LYs, QALYs, and the ICER for dostarlimab in combination with PCC versus PCC are presented in

Table 67. In the deterministic base-case analysis, dostarlimab in combination with PCC was associated with [redacted] incremental costs and 4.26 incremental QALYs compared to PCC, 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 68 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 in combination with PCC.

Table 67: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental QALYs (£/QALY)
Dostarlimab in combination with PCC	[redacted]	[redacted]	[redacted]	-	-	-	-
PCC (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.26	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; PCC – platinum containing chemotherapy; QALYs – quality-adjusted life years

Table 68: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Dostarlimab in combination with PCC	[redacted]	[redacted]				
PCC (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	4.26	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; PCC – platinum containing chemotherapy; QALYs – quality-adjusted life years.

B3.11 *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.

B3.11.1 Probabilistic sensitivity analysis

PSA involves drawing a value at random for each variable from its uncertainty distribution (see Table 65). 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) scatter plot (Figure 25), cost-effectiveness acceptability curve (CEAC) (

Figure 26) and cost-effectiveness acceptability frontier (CEAF) (Figure 27) were produced to graphically illustrate the level of variability and uncertainty in the results.

The results of the PSA including mean total costs, LYs, QALYs, and the ICER for dostarlimab in combination with PCC versus PCC are presented in Table 69. In the probabilistic base-case analysis, dostarlimab in combination with PCC was associated with [redacted] incremental costs and 4.23 incremental QALYs compared to PCC, which corresponds to an ICER of [redacted] per QALY gained i.e. <£20,000 per QALY gained.

Figure 25 to Figure 27 present the ICEP, CEAC and CEAF of dostarlimab in combination with PCC versus PCC. The probabilistic results are centred around the deterministic results and the CEAC and CEAF show that at a WTP threshold of £30,000 per QALY, dostarlimab in combination with PCC has a 99.99% chance of being cost effective and at a threshold of £20,000 per QALY, dostarlimab in combination with PCC has a 77.3% chance of being cost effective.

Table 69: PSA base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental QALYs (£/QALY)
Dostarlimab in combination with PCC	[redacted]	[redacted]	[redacted]	-	-	-	-
PCC (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.23	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; PCC – platinum containing chemotherapy; QALYs – quality-adjusted life years

Figure 25: Incremental cost-effectiveness plane

Abbreviations: PCC – platinum containing chemotherapy; QALY – quality adjusted life year.

Figure 26: Cost-effectiveness acceptability curve

Abbreviations: PCC – platinum containing chemotherapy

Figure 27: Cost-effectiveness acceptability frontier

Abbreviations: PCC – platinum containing chemotherapy.

B3.11.2 Deterministic sensitivity analysis

The OWSA varied one parameter at a time and assesses 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% confidence interval (CI), 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 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 65 presents the mean, standard error, 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 in combination with PCC versus PCC is presented in Figure **28, with tabulated results presented in**

Table 70. The model was most sensitive to the OS HR followed by the completion rates per cycle associated with dostarlimab in combination with PCC arm.

Figure 28: OWSA tornado diagram

Table 70: Tabulated OWSA results

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
OS HR			
Dostarlimab+CP: Dostarlimab completion rates per cycle (week) (cycle 16)			
Outpatient visit frequency per cycle Dostarlimab+CP in PF state from cycle 19+			
Outpatient visit unit cost			
Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib			
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP			
Admin cost cycle 19+ (£) Dostarlimab			
CT scan Dostarlimab+CP in PF state from cycle 19+			
Utility: PFS			
Outpatient visit CP in PD state from cycle 19+			

Abbreviations: CP – Carboplatin-paclitaxel; CT – computerised tomography; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; PD – progressed disease; PF – progression free; PFS – progression free survival; OS – overall survival.

B3.11.3 Scenario analyses

Scenarios analyses were conducted to test structural and parametric uncertainty and have been outlined throughout Section B.3. The results of these scenarios are summarised in Table 71.

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 £23,000 per QALY gained for dostarlimab in combination with PCC compared with PCC 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 alternative OS extrapolations and implementation of risk convergence on OS.

Risk convergence assumptions have been considered in NICE IO appraisals, and therefore risk convergence has been explored for completeness in scenario analysis within this economic analysis. The clinical benefit of immunotherapies such as dostarlimab in combination with PCC has been shown to extend beyond a patient completing their treatment. This is due to the mechanism of action and has been observed across several of the endpoints in RUBY (including efficacy endpoints [PFS separation from TTD, separation between treatments in PFS2, separation between treatments in OS] outlined in Section B2.6). Durability of IO efficacy following treatment discontinuation has been demonstrated in the relapsed, pre-treated, advanced or recurrent endometrial cancer setting (GARNET trial interim analysis 3, KEYNOTE-158). There is no clinical rationale why this durability would be anything other than improved in the frontline setting. The PFS and OS estimates selected within the CEM base case were clinically validated in the context of dostarlimab treatment discontinuation at maximum three years i.e. the long-term survival estimates provided by clinical experts considered the durability of efficacy after treatment discontinuation.

Within scenario analysis, the economic analysis allows a time at which treatment risk convergence starts and ends to be specified. UK clinical experts noted that following discontinuation of IO in other oncology indications benefits were seen *'2-3 years', '3-4 years'* and *'5-10 years'* after stopping immunotherapy.[4] Within scenario analysis, risk convergence starts three years after treatment discontinuation stopping rule. The risk gradually converges between years six and nine, and beyond year nine the risk entirely converges.

The PCC extrapolation acts as the baseline hazard function. The model uses linear interpolation to model a gradual decline of the dostarlimab in combination with PCC hazard towards the PCC hazard. Considering clinical plausibility and the UK clinical advisors estimates for long term OS and PFS, applying treatment risk convergence functionality results in a highly conservative and most improbable prediction of long-term survival outcomes for patients treated with dostarlimab in combination with PCC.

Table 71: Results for scenario analyses explored in the cost-effectiveness analysis

No.	Category	Base-case value	Scenario value	Deterministic				Probabilistic
				Inc. costs (£)	Inc. Lys	Inc. QALYs	ICER (£/ QALY)	ICER (£/ QALY)
1	Base case	-	-	[redacted]	[redacted]	4.26	[redacted]	[redacted]
2	Annual discount rate for costs and QALYs	3.50%	1.50%	[redacted]	[redacted]	5.45	[redacted]	[redacted]
3	Annual discount rate for costs and QALYs	3.50%	5.00%	[redacted]	[redacted]	3.61	[redacted]	[redacted]
4	Age-adjusted utilities	Age adjusted utilities included	Age adjusted utilities excluded	[redacted]	[redacted]	4.61	[redacted]	[redacted]
5	AE disutilities	AE disutilities included	AE disutilities excluded	[redacted]	[redacted]	4.26	[redacted]	[redacted]
6	Completion rates per cycle	Completion rates switched on	Completion rates switched off	[redacted]	[redacted]	4.26	[redacted]	[redacted]
7	Utility values source	Utility score ITT	Utility score dMMR/MSI-H	[redacted]	[redacted]	4.23	[redacted]	[redacted]
8	Treatment wastage	Wastage on	Wastage off	[redacted]	[redacted]	4.26	[redacted]	[redacted]
9	Subsequent treatment source	HCP feedback with lenvatinib + pembrolizumab	HCP feedback without lenvatinib + pembrolizumab	[redacted]	[redacted]	4.26	[redacted]	[redacted]
10	Subsequent treatment source	HCP feedback with lenvatinib + pembrolizumab	HCP feedback with lenvatinib + pembrolizumab and dostarlimab	[redacted]	[redacted]	4.26	[redacted]	[redacted]
11	PFS source	PFS IA (dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2)	PFS BICR (dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2)	[redacted]	[redacted]	4.24	[redacted]	[redacted]
12	PFS extrapolation	Flexible dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2	Flexible Odds k=1 for both arms	[redacted]	[redacted]	4.29	[redacted]	[redacted]

13	PFS extrapolation	Flexible dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2	Flexible Odds k=2 for both arms	[redacted]	[redacted]	4.30	[redacted]	[redacted]
14	PFS extrapolation	Flexible dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2	Flexible Normal k=1 for both arms	[redacted]	[redacted]	4.29	[redacted]	[redacted]
15	PFS extrapolation	Flexible dostarlimab in combination with PCC Odds k=1 and PCC Odds k=2	Flexible Normal k=2 for both arms	[redacted]	[redacted]	4.30	[redacted]	[redacted]
16	PFS extrapolation	Flexible dostarlimab in combination with Odds k=1 and PCC Odds k=2	IA PFS base case after KM piecewise for both arms	[redacted]	[redacted]	4.27	[redacted]	[redacted]
17	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	OS stratified HR (0.30)	[redacted]	[redacted]	4.36	[redacted]	[redacted]
18	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	Log-logistic curves for both arms	[redacted]	[redacted]	4.89	[redacted]	[redacted]
19	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	Weibull curves for both arms	[redacted]	[redacted]	5.48	[redacted]	[redacted]
20	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	Lognormal curves for both arms	[redacted]	[redacted]	4.98	[redacted]	[redacted]
21	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using lognormal curve	[redacted]	[redacted]	4.29	[redacted]	[redacted]
22	OS extrapolation	Dostarlimab extrapolated using 0.32 unstratified HR. PCC extrapolated using log-logistic	OS HR unstratified with full parametric extrapolation	[redacted]	[redacted]	4.22	[redacted]	[redacted]
23	PFS treatment risk convergence	No treatment risk convergence of PFS	PFS curves as per base case, treatment risk convergence from years 6-9	[redacted]	[redacted]	4.21	[redacted]	[redacted]

24	PFS and OS treatment risk convergence	No treatment risk convergence of PFS and OS	PFS curves as per base case, treatment risk convergence from years 6-9 and OS curves log-logistic for both arms and treatment risk convergence from years 6-9	[redacted]	[redacted]	3.29	[redacted]	[redacted]
25	TTD	KM for the follow-up period	Use full extrapolated Weibull curves	[redacted]	[redacted]	4.26	[redacted]	[redacted]
26	Administration cost	Dostarlimab monotherapy cycle 19+ administration cost using SB15Z	Dostarlimab monotherapy cycle 19+ administration cost using SB12Z	[redacted]	[redacted]	4.26	[redacted]	[redacted]
27	Administration cost	Dostarlimab monotherapy cycle 19+ administration cost using SB15Z	Dostarlimab monotherapy cycle 19+ administration cost using administration cost for IV biologics	[redacted]	[redacted]	4.26	[redacted]	[redacted]
28	Subsequent treatment cost	0% discount on list price of lenvatinib + pembrolizumab	25% discount on list price of lenvatinib + pembrolizumab	[redacted]	[redacted]	4.26	[redacted]	[redacted]
29	Subsequent treatment cost	0% discount on list price of lenvatinib + pembrolizumab	50% discount on list price of lenvatinib + pembrolizumab	[redacted]	[redacted]	4.26	[redacted]	[redacted]
30	Subsequent treatment cost	0% discount on list price of lenvatinib + pembrolizumab	75% discount on list price of lenvatinib + pembrolizumab	[redacted]	[redacted]	4.26	[redacted]	[redacted]

Abbreviations: BICR – blinded independent central review; CP – Carboplatin-paclitaxel; CT – computerised tomography; HCP – healthcare professional; HR – hazard ratio; IA – investigator assessed; ICER – incremental cost-effectiveness ratio; LYG – life years gained; PD – progressed disease; PF – progression free; PFS – progression free survival; OS – overall survival; QALYs – quality-adjusted life years

B3.12 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.

B3.13 Benefits not captured in the QALY calculation

Bringing an IO therapy 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.[85–87]

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.

B3.14 Validation

B3.14.1 Validation of cost-effectiveness analysis

Internal validity checks were performed by the model developers. This included a quality check of model codes, inputs including both a comparison to the original source and any calculations applied, and a check of model output. The model was further validated by an external health economist.

B3.14.2 Clinical expert validation

The company ran three advisory boards to seek clinical expert insights on the current treatment pathway in the UK, advice on the latest clinical data from the RUBY-1 trial and seek estimates of long-term survival outcomes (OS, PFS and TTD). A selection of clinicians with a breadth of experience across the UK geography were approached.

Advice was sought from clinical experts which included medical oncologists, clinical oncologists and a gynae-oncology surgeon, who are all involved in diagnosis and management of patients with primary advanced or recurrent endometrial cancer in the UK. As per the GSK due diligence process for engaging with external experts, conflicts of interests were declared. The specific rationale for each expert engaged is outlined in Appendix O. All experts were made aware that their input into the advisory boards will be used to support the HTA submission of dostarlimab in combination with PCC. Questions asked during the advisory boards are provided in the minutes.

B3.15 Interpretation and conclusions of economic evidence

B3.15.1 Summary of cost-effectiveness analysis

Over a lifetime time horizon, at a PAS price, deterministic base-case results showed that dostarlimab in combination with PCC accrued incremental QALYs of 4.26 with an incremental cost of [redacted] compared to PCC. The resulting ICER in the base case was [redacted] per QALY, which is well below the NICE threshold of £30,000 per QALY.

In the PSA, based on 1,000 iterations, the mean PSA results were aligned with the deterministic base case results. Dostarlimab in combination with PCC, when provided at the PAS price, was associated with an additional 4.23 QALYs and [redacted] incremental costs versus PCC which resulted in an ICER of [redacted] per QALY gained i.e., <£20,000 per QALY gain. The probability that dostarlimab in combination with PCC (with PAS) is cost-effective at a £30,000 and £20,000 WTP threshold is 99.9% and 77.3%, respectively.

In the OWSA, the parameters with the greatest effect on the base case ICER were the OS HR followed by the completion rates per cycle associated with dostarlimab in combination with PCC arm. Several scenario analyses investigated variation in model settings and approaches, and all resulted in dostarlimab in combination with PCC being cost-effective at the £30,000 per QALY threshold with the ICER remaining below £23,000 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.

B3.15.2 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 PCC, and thus PCC 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.

B3.15.3 Strengths of cost-effectiveness analysis

The economic evaluation is based on the patient population with dMMR/MSI-H from a robust phase III, RUBY-1 trial, which is representative of patients with primary advanced or recurrent endometrial cancer. The RUBY trial is the only trial that evaluated the efficacy and safety of dostarlimab in combination with PCC as a first line treatment in female adult patients with primary advanced or recurrent endometrial cancer (see Section B2.2). 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 validated 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 the exploration of flexible analysis where possible alongside all standard parametric analyses.

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.

B3.15.4 Limitations of cost-effectiveness analysis

A limitation of the economic analysis is the lack of events observed for OS to inform extrapolations. To overcome this limitation, UK clinical opinion was sought for estimating OS at year 2, 3, 5,10 and 20 to enable selection of the best fitting curve to anticipated clinical outcomes. In addition, a conservative approach was taken to extrapolate the OS curves for dostarlimab in combination with PCC.

B3.16 Conclusion

Currently, innovative treatment options for patients with primary advanced or recurrent endometrial cancer are restricted to patients who have experienced disease relapse. Patients with primary advanced or recurrent endometrial cancer speak to facing a constant fear of recurrence, such as a patient testimony saying “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.”[150] 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 represents a viable treatment option for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer. These patients currently face a poor prognosis, with limited treatment options in their treatment landscape.

Dostarlimab in combination with PCC provides patients the opportunity to receive IO licensed treatment for primary advanced or recurrent endometrial cancer. As an addition onto the established SoC, the regimen ensures that clinicians have the existing confidence and familiarity with the efficacy and side effects of the chemotherapy regimen when making a prescribing decision. The inclusion of an IO therapy in primary advanced or recurrent endometrial cancer increases patient’s accessibility to innovative

treatment earlier in their treatment journey, thus increasing the chances of survival and improving outcomes.

The results from the cost-effectiveness analysis demonstrate dostarlimab in combination with PCC 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 99.9% chance of dostarlimab in combination with PCC being cost-effective at a £30,000 per QALY threshold and at a threshold of £20,000 per QALY, dostarlimab in combination with PCC has a 77.3% chance of being cost effective.

For patients with primary advanced or recurrent dMMR/MSI-H EC, dostarlimab in combination with PCC 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]

B.4 References

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B.5 Appendices

The appendices included with this submission are as follows:

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource use 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: National Cancer Registration and Analysis Service (NCRAS) real-world evidence (RWE) study
- Appendix M: Managed access proposal
- Appendix N: Disease severity measures
- Appendix O: Advisory board summary
- Appendix P: Survival analyses
- Appendix Q: Supplementary data for patient-reported outcomes
- Appendix R: Supplementary data for adverse reactions
- Appendix S: Subsequent treatment costs
- Appendix T: Checklist of confidential 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 [ID3968]

Summary of Information for Patients (SIP)

18th July 2023

File name	Version	Contains confidential information	Date
	v1.0		

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

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

Dostarlimab (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 treat [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), 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.

The UK marketing authorisation has been submitted to the MHRA (the UK medicines' regulatory body) for consideration. The MHRA marketing authorisation for this current indication is expected late 2023.

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 Womb Cancer Trust are collaborating with GSK and The Eve Appeal to create a campaign to raise awareness of the symptoms of womb cancer in the general public. The aim of this campaign is to reduce the number of people being diagnosed with advanced endometrial cancer. This campaign will be released over 1 week from Sept 18th 2023, which is gynaecological cancer awareness month.

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. 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. These types of cancers 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 treat.(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 9,700 patients are diagnosed with endometrial cancer each year in the UK with around 2,900 of those being advanced disease. It is estimated that approximately 500 patients are diagnosed with primary advanced or recurrent dMMR/MSI-H endometrial cancer each year in the UK. (4)

For a full break down of how many patients there are, please see section 3.1 in the company's budget impact analysis submission.

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 [5]

The most common symptom of womb 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 (90%) are picked up because of post-menopausal or irregular vaginal bleeding. Therefore, womb cancer is often diagnosed early.

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

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

Diagnosis [6]

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[7]:

- 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 lining the womb)
- blood tests for womb 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)

The dMMR/MSI-H genetic marker 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 cancer is run through a laboratory to determine if it contains the dMMR/MSI-H biomarker.[8]

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 [9]

The treatment of endometrial cancer depends on the type of womb cancer, 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 [10]

For patients who are able to receive chemotherapy, the most common treatment following surgery is a combination of two chemotherapy drugs – carboplatin and paclitaxel. [11] These drugs destroy rapidly dividing cells, such as cancer cells. [12]

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, or 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". [13] 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. [14]

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. [15]

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 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. [16]

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. [14]

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

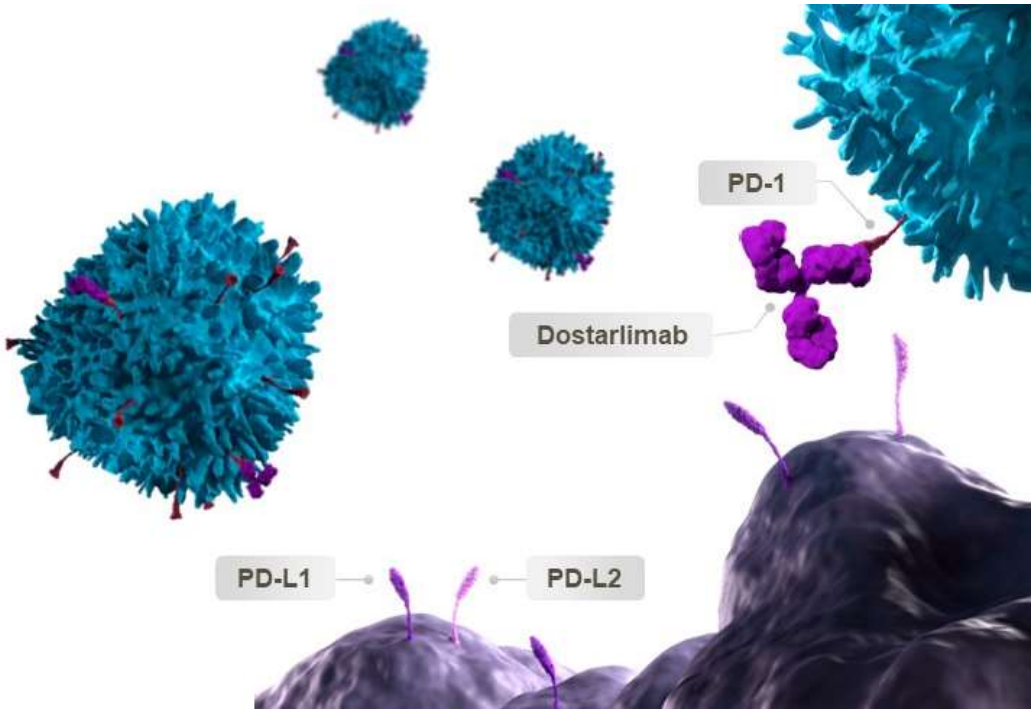
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

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. [17] In endometrial cancer, PD-1 is responsible for dampening (reducing) the body's anti-cancer immune response. [18-20] 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 1. Mechanism of action for dostarlimab [21]



Abbreviations: PD-1 – programmed death receptor-1; PD-L1 – programmed death ligand-1.

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.[22]

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

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. (23)

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. (10) 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. (24)

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. (25)

When carboplatin and paclitaxel are used together, they can have a more powerful effect on cancer cells than when used individually. (11) They target different aspects of cell division and growth, making the treatment more effective in killing cancer cells and reducing tumour size. (12)

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.

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) for about 30 minutes. [23, 26]

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), there will not be any significant changes in the way patients access their care. This means there will be no impact or additional burden to patients and their care givers.

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.[27] 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

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 (Section B1.10.3 of the company submission)

Progression free survival (PFS) is defined as the length of time during or after their 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 limitations to this data are that not all the data on when progression occurs is currently available. The trial needs to continue to run and to follow up these patients to collect longer term information on when progression occurs. The data collected so far 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 B1.10.4 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 OS results showed a trend favouring the dMMR/MSI-H patients who were receiving dostarlimab plus carboplatin paclitaxel. The analysis was performed when 26% 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 0.30. This hazard ratio of 0.30 suggests that for dMMR/MSI-H patients there is a 70% reduced risk of death for those receiving dostarlimab plus carboplatin paclitaxel compared to the patients who were only receiving carboplatin paclitaxel.

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 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

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. [28] 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. [29]

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.

The RUBY study was not designed to show a difference in this data but there is a clear difference seen between the results when these scores are mapped out on to a graph over time.

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. Gaining 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.

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 regardless of whether or not they were dMMR/MSI-H or not. In these patients the most common adverse reactions that happened in more than 10% of patients were:

- Rash (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 %).

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. Adverse reactions were serious in 5.8 % of patients; most serious adverse reactions were immune-related adverse reactions.

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.

This improvement in patients' health comes at no cost to a patient's quality of life, and the results of the RUBY trial even showed a numerical improvement in patient's quality of life as outlined in section 3f. 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 manageable. 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. Providing 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 a step forward.

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 does mean that patients will have to 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. [23, 26]

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. [23, 26]

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 main side effects that people taking dostarlimab should be aware of are listed above in Section 3g.

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.

Uncertainty

- As mentioned in section 3a, there is limited long term data available for dostarlimab in this primary advanced or recurrent dMMR/MSI-H population. There are only 34 months of data available from the RUBY trial, so any longer-term outcomes have been estimated out into the future creating some uncertainty.

Economic analysis

- All these considerations impact the decision on whether dostarlimab represents good value for money and a good use of NHS resources. The model developed by the company showed that there is enough of a benefit to patients, measured in quality adjusted life years (QALYs), to justify the additional cost of treatment with dostarlimab in combination with carboplatin and paclitaxel.

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 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. [30]

- There is a need to address an inequality in access to innovative therapies in endometrial cancer compared with other cancer types. Immunotherapies have been available for several years for the first line treatment of patients with cancers such as melanoma (skin cancer), renal cell carcinoma (cancer in the kidney) and, lung cancer and has made a significant impact. [31-33]

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, 34]

There are significant differences in survival rates among different ethnicities and socioeconomic backgrounds among endometrial cancer patients. [4, 35] To address these inequalities, it's important to make innovative treatments widely available throughout the UK.

Additionally, there is a need for new treatment options other than chemotherapy for primary advanced or recurrent endometrial cancer. Currently, innovative treatments are only available for patients whose disease has returned after treatment with chemotherapy.

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. [36]

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.
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 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.
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.
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 given 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.
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 – All References last accessed July 4th 2023

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

ID3968 Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

Clarification questions

September 2023

File name	Version	Contains confidential information	Date
ID3968 Dostarlimab Company response to EAG CQs 24082023 [CIC]	**V2**	**Yes (CIC throughout)**	**15th September 2023**

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

A0: Please could the company estimate PFS and OS hazard ratios for the effect of dostarlimab in the dMMR/MSI-H subgroup of RUBY 1 but which include parameters/are adjusted for age (under vs over 65) and weight (continuous), as we notice these terms are imbalanced between the dMMR/MSI-H treatment groups.

As per the RUBY trial protocol, stratification factors for randomisation were MMR–MSI status (dMMR–MSI-H or MMRp–MSS), previous external pelvic radiotherapy (yes or no), and disease status (recurrent, primary stage III, or primary stage IV). Based on these stratification factors, a stratified Cox regression was used to estimate the HRs of PFS and OS along with the confidence interval associated with the significance level for hypothesis testing. These stratified HRs are presented within the trial publication,[1] and within Tables 12 and 13, company submission Document B.

In addition, an unstratified Cox regression was used to estimate the HRs of PFS and OS, along with the confidence intervals, as part of the survival analysis conducted to support the cost effectiveness model. These unstratified HRs are presented within Tables 24 and 35, company submission Document B.

Adjusting the Cox regression for two specific factors (age and weight), is not methodologically appropriate. A more systematic approach would be completing a stepwise regression to identify independent variables to be included in the final model, with full reporting of the stepwise regression and covariate selection advised.[2,3] The results associated with two arbitrarily defined specific factors (age and weight) should therefore be interpreted with caution. The results as per the pre-defined stratification factors, or the unstratified HRs, are more relevant to inform this submission.

Table **1** below contains the PFS and OS hazard ratios for the effect of dostarlimab in the dMMR/MSI-H subgroup of RUBY-1 with the requested adjustments – adjusted for age (under vs over 65) and weight (continuous).

These results should therefore be interpreted with caution. With these limitations in mind, the comparative effectiveness is consistent across both variables controlled for, and the HRs for PFS and OS are consistent irrespective of stratification.

Table 1: Stratified PFS and OS hazard ratios, dMMR/MSI-H population RUBY-1

Hazard ratio (95% CI) [p value]	**PFS**	**OS**
Stratified	0.28 (0.16, 0.15) P<0.001	0.30 (0.13, 0.70) [redacted]
Unstratified	[redacted]	[redacted]
Stratified by Age[a]	[redacted]	[redacted]
by Weight[b]	[redacted]	[redacted]
by Weight and Age[c]	[redacted]	[redacted]

Stratified Cox Regression; in a model containing covariates:

a. treatment group and age group (<65 vs. >=65).
b. treatment group and weight (continuous).
c. treatment group, weight (continuous) and age group (<65 vs. >=65).

Source: SSDR103710

Data cutoff: 28 September 2022. Abbreviations: CI – confidence intervals; dMMR – DNA mismatch repair deficient; ECOG – Eastern Cooperative Oncology Group; HR – hazard ratio; MSI-H – microsatellite instability-high; PFS – progression-free survival; OS – overall survival

A1. Please fit Cox models to the dMMR/MSI-H population PFS and OS data including terms for treatment and treatment/weight interaction, and present output.

The company cautions considering one patient demographic characteristic in isolation. The summary of demographic characteristics included in Table 8 and disease history in Table 9, company submission, outlines patients' characteristics across both arms which are balanced with respect to age, BMI, ECOG performance

status, disease stage, disease histology and disease grade. Predefined prognostic stratification factors, outlined in Table 10 company submission, are also well balanced. Clinical experts confirmed that the RUBY trial baseline characteristics were representative of what the advisors encountered in their UK clinical practice.[4]

Furthermore, subgroups based on weight were not predefined within the RUBY-1 trial protocol for the assessment of OS or PFS. The dMMR/MSI-H population is already a subgroup of the broader ITT population. Due to the small number of patients within subgroups of the dMMR/MSI-H subgroup, results should be interpreted with caution.

Weight was included as categorical variable for the requested analysis. Two analyses were completed – weight <84 kg vs >=84kg and weight <89 kg vs >=89kg. [redacted]. Table 2 to Table 5 below outlines the results of the request analysis.

Table 2: Kaplan-Meier analysis of PFS (RECIST v.1.1 by investigator assessment) [weight <89 kg vs >=89kg dMMR/MSI-H patient population]

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number in subgroup <89kg (n)	[redacted]	[redacted]
PFS Events observed (n)	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
Number in subgroup >=89 kg(n)	[redacted]	[redacted]
PFS Events observed (n)	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
p-value from Interaction test*	[redacted]	

Source: SSDR103710_T3_km_pfs_ia_wgt. Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MMRp – mismatch repair proficient; HR – hazard ratio; MSI-H – microsatellite instability-high; MSS – microsatellite stable; PFS – progression-free survival

*Based on a Stratified Cox Regression model for the interaction of baseline weight (<89 vs >=89 kg) and treatment group in a model containing covariates: treatment and weight (<89 vs >=89) [redacted]

Table 3: Kaplan-Meier analysis of PFS (RECIST v.1.1 by investigator assessment) [weight <84 kg vs >=84kg dMMR/MSI-H patient population]

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number in subgroup <84kg (n)	[redacted]	[redacted]
PFS Events observed (n)	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
Number in subgroup >=84 kg(n)	[redacted]	[redacted]
PFS Events observed (n)	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
p-value from Interaction test*	[redacted]	

Source: SSDR103710_T4_km_pfs_ia_wgt2
Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MMRp – mismatch repair proficient; HR – hazard ratio; MSI-H – microsatellite instability-high; MSS – microsatellite stable; PFS – progression-free survival

*Based on a Stratified Cox Regression model for the interaction of baseline weight (<84 vs >=84 kg) and treatment group in a model containing covariates: treatment and weight (<84 vs >=84)
[redacted]

Table 4: Kaplan-Meier analysis of OS [weight <89 kg vs >=89kg dMMR/MSI-H patient population]

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number in subgroup <89kg (n)	[redacted]	[redacted]
OS Events observed (n)	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
Number in subgroup >=89 kg(n)	[redacted]	[redacted]
OS Events observed (n)	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	

Source: SSDR103710_T5_km_os_ia_wgt
Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MMRp – mismatch repair proficient; HR – hazard ratio; MSI-H – microsatellite instability-high; MSS – microsatellite stable; NE – not estimable; OS – overall survival

Table 5: Kaplan-Meier analysis of OS [weight <84 kg vs >=84kg dMMR/MSI-H patient population]

Category subcategory	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number in subgroup <84kg (n)	[redacted]	[redacted]
OS Events observed (n)	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	
Number in subgroup >=84 kg(n)	[redacted]	[redacted]
OS Events observed (n)	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	
p-value of 2-sided stratified log-rank test	[redacted]	

Source: SSDR103710_T6_km_os_ia_wgt2
Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; MMRp – mismatch repair proficient; HR – hazard ratio; MSI-H – microsatellite instability-high; MSS – microsatellite stable; NE – not estimable; OS – overall survival

Small patient numbers in each of the weight-based subgroups limits the interpretation of these results. The statistical analysis plan does not allow time-to-event analysis to be run in situations where less than five events have occurred in either arm. The OS HRs are therefore not estimable. The PFS HRs for the effect of dostarlimab in combination with CP are similar to the overall PFS HRs seen in the dMMR/MSI-H population, and do not vary widely based on weight subgroup. Furthermore, the interaction test values for PFS show that there is no interaction between weight and treatment effect, indicating that treatment effect of dostarlimab in combination with CP does not statistically significantly differ by the weight subgroups.

This analysis should be interpreted with caution; however, they do further support that comparative effectiveness is consistent across analysis. The HRs for PFS are consistent irrespective of stratification. In addition, the requested analysis presented in A0, Table 1, demonstrates HRs for the effect of dostarlimab in combination with CP on PFS and OS are not impacted when age (as a continuous covariate) is adjusted for within the cox regression.

A2. Please clarify how many patients in the dMMR/MSI-H population, by arm, were affected by each of the censoring rules as described in Table 11.

The number of patients affected by each censoring rule in the dMMR/MSI-H population is presented in Table 6. The most common reason for censoring, across each of the three censoring rules outlined below, was censoring due to ongoing

follow-up. As per section B.2.6 of the company submission, there were lower numbers of progression and overall survival events experienced by patients treated with dostarlimab in combination with carboplatin-paclitaxel (CP), and therefore there were more patients in this arm censored due to ongoing follow-up.

Table 6: dMMR/MSI-H population by censoring rule

Censoring	Dostarlimab in combination with CP (n=53)	Placebo in combination with CP (n=65)
PFS based on Investigator assessment and primary censoring rule		
Censored, total		[redacted]
Censored, follow-up ended	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
- Date of last tumour assessment before new anti-cancer therapy	[redacted]	[redacted]
- Date of last tumour assessment prior to ≥2 missed disease assessments	[redacted]	[redacted]
- Date of randomisation	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
PFS based on Investigator assessment and sensitivity censoring rule 1		
Censored, total	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
- Date of last tumour assessment before new anti-cancer therapy	[redacted]	[redacted]
- Date of randomisation	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
PFS based on Investigator assessment and sensitivity censoring rule 2		
Censored, total	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
- Date of randomisation	[redacted]	[redacted]
Censored, follow-up ongoing	[redacted]	[redacted]
- Date of last tumour assessment	[redacted]	[redacted]
Overall survival		
Censored, total	[redacted]	[redacted]
Censored, follow-up ended	[redacted]	[redacted]
- Last contact date	[redacted]	[redacted]

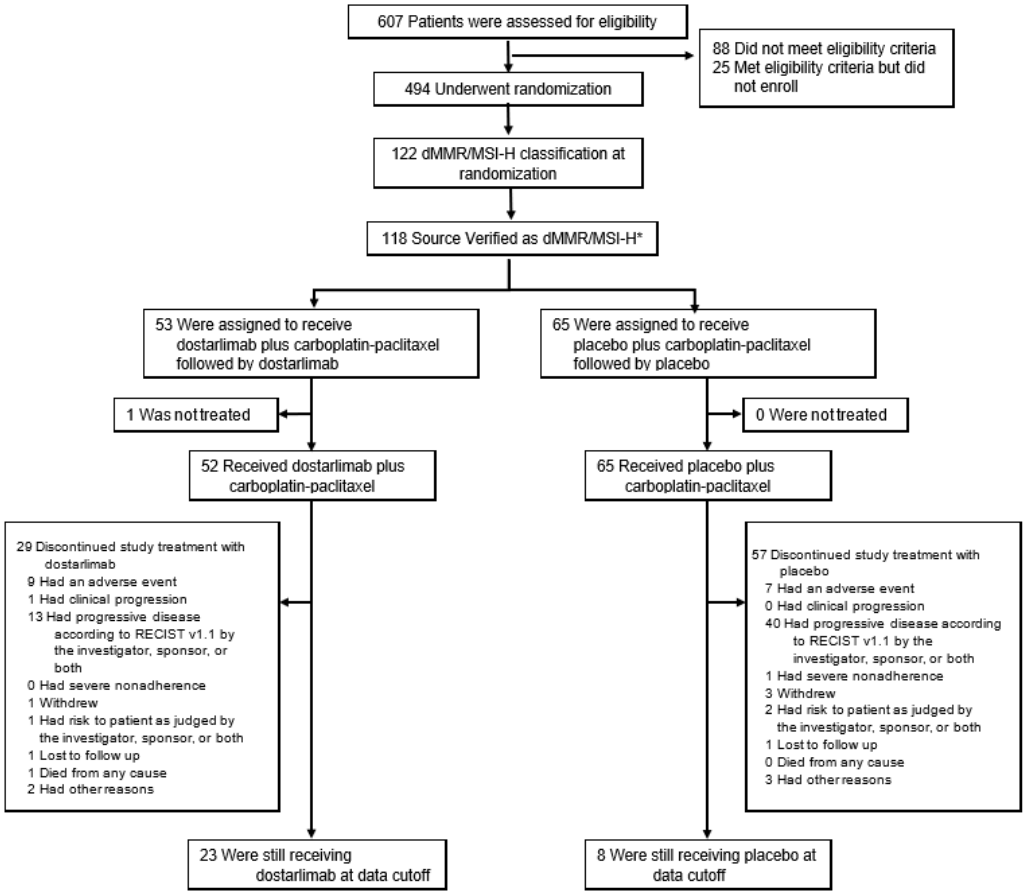
Censored, follow-up ongoing	[redacted]	[redacted]
- Last contact date	[redacted]	[redacted]

Source: CSR Table 14.2.1.44 Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair; MSI-H – microsatellite instability-high; PFS – progression-free survival

A3. Please provide the CONSORT flow diagram for the dMMR/MSI-H population, including information on issues of initial dMMR/MSI-H identification

The CONSORT flow diagram for the dMMR/MSI-H population is presented in Figure 1.

Figure 1: CONSORT diagram for dMMR/MSI-H population



*dMMR/MSI-H status confirmed via central laboratory using immunohistochemistry (IHC), next generation sequencing (NGS) or polymerase chain reaction (PCR) assays. These verification approaches align with UK NICE guidance for identification of dMMR/MSI-H endometrial cancer. The difference between the two MMR/MSI classifications was due to misclassification of MMR/MSI status at time of randomisation. Source: CSR Tables 14.1.1.3 and 14.1.1.6 Abbreviations: dMMR – DNA mismatch repair; MSI-H – microsatellite instability-high; RECIST - Response Evaluation Criteria in Solid Tumours.

A4. Please provide response related results (i.e. Table 15 and Table 16 of CS Doc B) for BICR based analyses.

Response related results for BICR based analyses are presented in

Table 7 and Figure 2. Objective response rate (ORR) and disease control rate (DCR) by BICR assessment consistently indicated a benefit in the dostarlimab in combination with CP arm compared with the placebo in combination with CP arm, consistent with the tumour response as assessed by investigator. Within the dMMR/MSI-H patient population, median duration of response (DOR) was [redacted] in the dostarlimab in combination with CP arm compared with [redacted] months (95% CI: [redacted]) in the placebo in combination with CP arm (Table 10). The 24-month probability of remaining in response was [redacted]% versus [redacted]%, respectively.

Table 7: Summary of Tumour Response - RECIST v1.1 for Subjects with Target Lesion or Non-target Lesion at Baseline based on BICR Assessment (dMMR/MSI-H patient population)

	Dostarlimab in combination with CP (N=53)	**Placebo in combination with CP (N=65)**
Patients with evaluable disease at baseline, n	**Dostarlimab in combination with CP** (N=[redacted]	**Placebo in combination with CP (N=[redacted]**
Best overall response by RECIST v1.1, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
Non-CR/Non-PD	[redacted]	[redacted]
No disease	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
ORR[a]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Disease Control Rate DCR[a]		
n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Source: CSR Table 14.2.1.13. Abbreviations: BICR – Blinded Independent Central Review; CI – confidence interval; CP – carboplatin/paclitaxel; CR – complete response; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; PD – progressive disease; PR – partial response; SD – stable disease.

a. DCR and ORR are defined as the percentage of patients with a RECIST v.1.1. CR, PR, SD and No disease, of patients with evaluable disease at baseline.

Figure 2: Graph of Kaplan-Meier Curves of Duration of Response – RECIST v1.1 based on BICR Assessment and Primary Censoring Rule (dMMR/MSI-H patient population)

Source: CSR Figure 15.1.10.
Data cutoff: 28 September 2022
Abbreviations: BICR – Blinded Independent Central Review; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high.

Table 8: Kaplan-Meier analysis of DOR – RECIST v.1.1. based on BICR Assessment and primary censoring rule, Interim Analysis (dMMR/MSI-H patient population)

Variable [n (%)]	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number of responders		
n	[redacted]	[redacted]
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	[redacted]	[redacted]
Duration ≥12 months	[redacted]	[redacted]
Probability of DOR (95% CI)		
Month 6	[redacted]	[redacted]

Variable [n (%)]	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
	[redacted]	[redacted]

Source: CSR Table 14.2.1.16
Data cutoff: 28 September 2022
Abbreviations: CI – confidence intervals; CP – carboplatin/paclitaxel; DOR – duration of response; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; NE – not estimable

A5. Please provide a tabular and graphical output (e.g. Figure 8 and Table 18 of CS Doc B) for EQ 5D 5L index values (summary values) from the RUBY-1 dMMR/MSI-H population, by arm of treatment and pooling across treatment arms.

Detailed EQ-5D-5L VAS results are provided in clarification response A15, in addition to detailed cross walked EQ-5D-3L results provided in clarification response B4.

EQ-5D-5L index values are not available since EQ-5D-5L values were cross-walked to EQ-5D-3L values for UK analysis. As agreed with NICE, completion rates for EQ-5D by domain and visit for the dMMR/MSI-H population by arm of treatment and pooling across treatment arms, have been provided in Table 9.

Table 9: Completion rate of EQ-5D by domain and visit (dMMR/MSI-H)

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
Baseline	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 4 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 6 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	n	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 10 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 14 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 18 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	n	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 22 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 26 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
End Of Treatment	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Safety Follow-Up	n	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 1	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 2	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 3	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 4	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 5	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Survival Follow-Up Assessment 7	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]
Total	n	[redacted]	[redacted]	[redacted]
	Mobility	[redacted]	[redacted]	[redacted]
	Self-Care	[redacted]	[redacted]	[redacted]

Visit		Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)	Total (N=118)
		Completion rate n (%)	Completion rate n (%)	Completion rate n (%)
	Usual Activities	[redacted]	[redacted]	[redacted]
	Pain/Discomfort	[redacted]	[redacted]	[redacted]
	Anxiety/Depression	[redacted]	[redacted]	[redacted]

Source: GSK data on file- Completion rate of EQ-5D by Domain and visit (ITT analysis set). Percentages are calculated based on the number of subjects expected to complete the questionnaire in that specific visit.

A6. Please provide a KM Plot for DOR, by arm of RUBY-1 dMMR/MSI-H patients, for both BICR and Investigator assessment, including a risk table.

The KM plot and risk table for DOR by Investigator assessment (IA) for the dMMR/MSI-H population are presented in Figure 3 and Table 10, respectively.

Figure 3: Kaplan-Meier curves of duration of response – RECIST v.1.1 based on IA (dMMR/MSI-H population)

Source: CSR Figure 15.1.9.
Data cutoff: 28 September 2022
Abbreviations: dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high

Table 10: Summary of Kaplan-Meier Analysis of Duration of Response - RECIST v1.1 based on IA and Primary Censoring (dMMR/MSI-H population)

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Number of responders		
n	38	40
DOR		
Status n (%)		
Events observed	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Death	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Estimates for DOR (months)		
Quartile (95% CI)		

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
25%	[redacted]	[redacted]
50%	NE (10.1, NE)	5.4 (3.9, 8.1)
75%	[redacted]	[redacted]
Duration ≥ 6 months, n (%)	[redacted]	[redacted]
Duration ≥ 12 months, n (%)	22 (57.9%)	7 (17.5%)
Probability of DOR (95% CI)		
Month 6	76.1% (59.0%, 86.8%)	46.2% (30.2%, 60.7%)
Month 12	62.1% (44.4%, 75.5%)	19.2% (8.6%, 33.1%)
Month 18	[redacted]	[redacted]
Month 24	62.1% (44.4%, 75.5%)	13.2% (4.6%, 26.3%)

Source: CSR Table 14.2.1.15 Data cutoff: 28 September 2022
Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; DOR – Duration of response; MSI-H – microsatellite instability-high; NE – not estimable

Response related results based on BICR assessment, including KM plot and risk table, are outlined in response to question A4 – Table 7, Table 8, and Figure 2. The response related results were generally similar based on assessment by IA or BICR.

A7. Please provide an overview of DOR for dMMR/MSI-H patients who achieved CR, by arm of RUBY 1.

In the RUBY-1 trial, when tumour response was assessed by IA in patients with evaluable disease at baseline almost one third (30.1%) of dMMR/MSI-H patients treated with dostarlimab in combination with platinum containing chemotherapy (PCC) achieved complete response, versus one in five patients (20.7%) treated with placebo in combination with PCC. Tumour assessment by BICR found a lower proportion of patients in both arms in complete response (CR), however the CR rate in the dostarlimab in combination with PCC arm remained higher [redacted].

As illustrated in the results below, patients who achieved a complete response had highly durable and extended durations of response. The KM plot and risk table for DOR for patients who achieved CR by IA for the dMMR/MSI-H population are presented in Figure 4 and Table 11, respectively.

Figure 4: Kaplan-Meier curves of duration of response for patients with CR – RECIST v.1.1 based on IA (dMMR/MSI-H population)

Source: SSDR103710_f_km_dor_inv.rtf
Data cutoff: 28 September 2022
Abbreviations: dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high

Table 11: Summary of Kaplan-Meier Analysis of Duration of Response - for patients with CR - RECIST v1.1 based on IA 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 complete response		
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]

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
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/paclitaxel; dMMR – DNA mismatch repair deficient; DOR – Duration of response; MSI-H – microsatellite instability-high; NE – not estimable

The KM plot and risk table for DOR for patients who achieved CR by BICR for the dMMR/MSI-H population are presented in Figure 5 and Table 12, respectively.

Figure 5: Kaplan-Meier curves of duration of response for patients with CR – RECIST v.1.1 based on BICR assessment (dMMR/MSI-H population)

Source: SSDR103710_f_km_dor_bicr.rtf
Data cutoff: 28 September 2022
Abbreviations: BICR – Blinded Independent Central Review; CR – complete response; dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high

Table 12: Summary of Kaplan-Meier Analysis of Duration of Response - for patients with CR - RECIST v1.1 based on BICR 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 complete response		
N	[redacted]	[redacted]
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: BICR – Blinded Independent Central Review; CI – confidence interval; CP – carboplatin/paclitaxel; CR – complete response; dMMR – DNA mismatch repair deficient; DOR – Duration of response; MSI-H – microsatellite instability-high; NE – not estimable

A8. Based on latest available data, what proportion of patients received dostarlimab beyond 3 years?

As per the most recent data available up to September 2022 (data cut for interim analysis 1), the maximum observed follow-up for time on treatment for the dMMR/MSI-H population was [redacted] weeks (< 3 years). No patients have received >156 weeks (>3 years) of treatment in either arm yet due to the limited follow-up time. The proportion of patients who had follow-up at 1 year, 2 years, and 3 years

was as follows: [redacted] in the dostarlimab in combination with CP arm vs placebo in combination with CP arm, respectively.

NOTE: The previous proportion of patients with follow-up at 1 year, 2 year and 3 years presented in company submission (Document B, section B2.10.1) were summary of duration of follow-up (expected) [CSR Table 14.1.1.34] rather than summary of duration of follow-up [CSR Table 14.1.1.33]. The expected follow-up is the duration from randomisation to cut off date. The actual follow-up is duration from randomisation to last contact date or death. The company requests that the actual trial reported values for follow-up, as per CSR Table 14.1.1.33 to be used as the more relevant values than expected values.

As per the time to treatment discontinuation (TTD) KM data at the maximum duration of follow-up (Document B, section B3.3.5, Figure 21) there were [redacted] on treatment with dostarlimab, and [redacted] patients censored at this time point. There were [redacted] on treatment with placebo in the comparator arm, with [redacted] patients censored at this time point.

Notably, an analysis of Kaplan-Meier data highlights that both progression-free survival (PFS) assessed by both IA and BICR consistently exceeds TTD at all observed intervals (Document B, section B3.3.5, Figure 21). This trend suggests that even when treatment discontinued, positive disease progression outcomes continue to be observed.

Insights gleaned from a clinical advisory board conducted in March 2023, underscored the inclination of UK clinicians to adhere to a three-year treatment stopping rule as per the RUBY trial study protocol.[5,6]

A9. Please provide summary information on subsequent treatments received by the dMMR/MSI-H subgroup of Ruby-1 and confirm whether this information has informed Table 61.

The company can confirm that Table 61 is based on insights gathered during advisory boards, in addition to the percentages of subsequent treatments received by the dMMR/MSI-H subgroup of RUBY-1 trial [7]

Company base case subsequent treatments

The key table informing the treatments in the base case is outlined in Table 13 below. The following points should be noted:

- The proportion of patients expected to receive dostarlimab monotherapy in second-line is expected to be 0%. This is because dostarlimab is only available through the Cancer Drugs Fund (CDF) and is therefore not routinely commissioned. Hence aligned to the NICE reference case, dostarlimab monotherapy cannot be considered a subsequent treatment within the analyses.

- At the time of submission, pembrolizumab monotherapy was subject to ongoing appraisal by NICE for use in the UK and had not yet been recommended. Therefore, the proportion of patients are 0% in the base case.[8]

- Bevacizumab monotherapy is not licensed for use in endometrial cancer in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), and the proportion of patients are therefore 0%.

- Pembrolizumab in combination with lenvatinib has recently been recommended as a treatment options by NICE in the relapse setting.[9] The percentage of patients who received pembrolizumab plus lenvatinib as a subsequent therapy in the dMMR/MSI-H cohort of the RUBY-1 trial has been used to inform the percentage of subsequent treatment use in the model.

- All other treatment percentages are based of UK clinical expert opinion. There is no standard of care regimen in the second-line treatment setting, with a wide range of treatments and combinations of treatments used.

    - For simplicity the proportion of use of the less frequently used regimens are combined in the ‘carboplatin and paclitaxel’ and the ‘doxorubicin’ proportions.

Since the proportion of patients on each treatment have been taken from different sources (pembrolizumab plus lenvatinib from the RUBY-1 trial, all others from UK clinical expert opinion), the total distribution does not sum to 100%. Therefore, the

proportion of patients on each treatment has been re-weighted. This has been calculated by dividing the percentage for a particular treatment by the sum of all treatments. The re-weighted percentages (Table 14) have then been applied in the cost-effectiveness model (CEM).

Table 13: Subsequent treatments base case: UK clinical expert opinion (with pembrolizumab in combination with lenvatinib from the RUBY-1 trial)

Second-line subsequent treatment	Dostarlimab + PCC	PCC	Source
Dostarlimab	0.00%	0.00%	Patients who receive dostarlimab in combination with PCC as a first-line treatment are not eligible to receive a subsequent IO in the relapse setting. Patients who receive PCC at first-line are not eligible to receive dostarlimab in the relapse setting, since dostarlimab is only available through the CDF.
Carboplatin and paclitaxel	46.0%*	58.0%**	UK clinical expert opinion.
Pembrolizumab	0.00%	0.00%	Pembrolizumab monotherapy was not recommended for use in relapsed endometrial cancer by NICE, hence usage is 0%.
Doxorubicin	19.0%#	20.0%##	UK clinical expert opinion.
Bevacizumab	0.00%	0.00%	Bevacizumab monotherapy is not approved for use in endometrial cancer the UK by the MHRA, hence usage is 0%.
Pembrolizumab plus lenvatinib[β]	0.00%	[redacted]%	Subsequent treatment use in RUBY-1 trial. Recommend as an option by NICE in the relapsed endometrial cancer setting.
Letrozole	5.00%	6.00%	UK clinical expert opinion (average of hormone therapy).
Medroxyprogesterone acetate	5.00%	6.00%	UK clinical expert opinion (average of hormone therapy).
Radiotherapy	4.00%	10.00%	UK clinical expert opinion.
Other	0.00%	0.00%	UK clinical expert opinion.
No treatment	19.00%	22.00%	UK clinical expert opinion.

Abbreviations: CDF – Cancer Drugs Fund; IO – Immuno-oncology; PCC – Platinum-containing chemotherapy; UK – United Kingdom
*31% carboplatin and paclitaxel + 13% paclitaxel + 2% carboplatin = combined to 46% carboplatin and paclitaxel [rounded]
**19% carboplatin and paclitaxel + 35% paclitaxel + 3% carboplatin = combined to 58% carboplatin and paclitaxel [rounded]
15% liposomal doxorubicin + 4% carboplatin and doxorubicin = combined to give 19% doxorubicin [rounded]
10% liposomal doxorubicin + 5% carboplatin and doxorubicin + 4% cisplatin and doxorubicin = combined to give 20% doxorubicin [rounded]
[β]The total proportion pembrolizumab plus lenvatinib from the full dMMR/MS-H population, regardless of treatment arm has been applied in this scenario to inform the percentage receiving dostarlimab monotherapy and pembrolizumab plus lenvatinib.

Table 14: Subsequent treatments base case: UK clinical expert opinion (with pembrolizumab plus lenvatinib) - Re-weighted* values used in model

	Dostarlimab	Carboplatin and paclitaxel	Pembrolizumab	Doxorubicin	Bevacizumab	Pembrolizumab plus lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	Other	No treatment
Dostarlimab+ PCC	0.0%	46.9%	0.0%	19.4%	0.0%	0.0%	5.1%	5.1%	4.1%	0.0%	19.4%
PCC	0.0%	43.8%	0.0%	15.1%	0.0%	[redacted]	4.5%	4.5%	7.6%	0.0%	[redacted]

Abbreviations: CP – carboplatin and paclitaxel; PCC – platinum-containing chemotherapy; UK – United Kingdom.

*Since the proportion of patients on each treatment has been taken from different sources, the total distribution does not sum to 100%. Therefore, the proportion of patients on each treatment has been re-weighted. This has been calculated by dividing the percentage for a particular treatment by the sum of all treatments

[redacted]

Subsequent treatment options explored in scenario analysis: RUBY-1 dMMR/MSI-H population: The model also contains the functionality to use different distributions of treatments received as subsequent treatment. The subsequent treatments used in the RUBY-1 trial, in the dMMR/MSI-H cohort post-progression, are outlined in Table 15 below, with the re-weighted values included in the CEM outlined in Table 16. This scenario was not included in the company base case as the treatments are not aligned with those available via routine commissioning and broadly used as standard of care in the UK. Furthermore, the number of dMMR/MSI-H patients who received follow-up anti-cancer therapy post-progression in the RUBY-1 trial was low (n=[redacted]% [[redacted] dostarlimab in combination with CP arm, [redacted] placebo in combination with CP arm]) due to limited duration of follow-up.

Table 15: Subsequent treatments scenario: RUBY-1 dMMR/MSI-H population – Unweighted raw values

	Dostarlimab	Carboplatin and paclitaxel	Pembrolizumab	Doxorubicin	Bevacizumab	Pembrolizumab and lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	Other	No treatment
Dostarlimab+ PCC (n=53) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCC (n=65) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (n=118) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR – mismatch repair deficient; MSI-H – microsatellite instability-high; PCC – platinum-containing chemotherapy.

Table 16:Subsequent treatments scenario: RUBY-1 dMMR/MSI-H population – Re-weighted* values used in model

	Dostarlimab	Carboplatin and paclitaxel	Pembrolizumab	Doxorubicin	Bevacizumab	Pembrolizumab and lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	Other	No treatment
Dostarlimab+ PCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR – mismatch repair deficient; MSI-H – microsatellite instability-high; PCC – platinum-containing chemotherapy.
*The proportion of patients on each treatment has been re-weighted to ensure the total is 100%. This has been calculated by dividing the percentage for a particular treatment by the sum of all treatments.

The results of these scenario analysis are shown in Table 17. The scenario results are consistent with the base case ICER (<£20,000 per quality-adjusted life year (QALY) gained), indicating that the analysis is not sensitive to changes in subsequent treatment assumptions.

Table 17: Subsequent treatment scenario analyses – dMMR/MSI-H population

			Deterministic							Probabilistic
Category	**Base case value**	**Scenario value**	**Dostarlimab + PCC**	**PCC**	**Dostarlimab + PCC**	**PCC**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£/ QALY)**	
			Total costs		**Total QALYs**		**Incremental results**			
Base case	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.26	[redacted]	[redacted]
Subsequent treatment distribution	Subsequent treatment based on UK expert opinion with lenvatinib + pembrolizumab	Subsequent treatment based on RUBY-1 trial data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.26	[redacted]	[redacted]

Abbreviations: dMMR – mismatch repair deficient; ICER – Incremental cost effectiveness ratio; MSI-H – Microsatellite instability-high; PCC – Platinum-containing chemotherapy; PSA – probabilistic sensitivity analysis; QALY – Quality adjusted life year; UK – United Kingdom

A10. The EAG is aware of the different definitions for TTD and Duration on Treatment/Exposure for the dMMR/MSI-H subgroup, however it is not clear why the difference between these measures for dostarlimab and placebo arms are in opposite directions. Please could you provide more information, with examples where patients have conflicting times that explain this difference.

Summaries of time to treatment discontinuation and duration on treatment are presented in Table 18 and Table 19. Table 18. Non-parametric and semi-parametric results for TTD (dMMR/MSI-H population)

Table 18. Non-parametric and semi-parametric results for TTD (dMMR/MSI-H population)

Treatment arm (N)	Dostarlimab in combination with CP (n=53)	Placebo in combination with CP (n=65)
Maturity (%) – n/N	[redacted]	[redacted]
Duration of follow-up (weeks) Median (95% CI)	[redacted]	[redacted]
Duration of follow-up (weeks) Restricted mean (SD)	[redacted]	[redacted]
Median (95% CI) (weeks)	[redacted]	[redacted]
Restricted mean (weeks), (SE)	[redacted]	[redacted]
HR* (95% CI; p-value)	[redacted]	

Non-parametric analysis includes percentage of data maturity, median and restricted mean follow-up, median and restricted mean survival. The cox proportional hazards model (HR) is a semi-parametric model.
Abbreviations: CI – confidence interval; dMMR – mismatch repair deficient; HR – hazard ratio; MSI-H – microsatellite instability-high; NR – not estimable; SD – standard deviation; SE – standard error. *Unstratified cox proportional hazards model used to calculate HR.

Table 19: Summary of duration on treatment (dMMR/MSI-H population)

Duration	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Duration of study treatment interval [n(%)][a]		
>Week 54	[redacted]	[redacted]
>Week 102	[redacted]	[redacted]
>Week 156	[redacted]	[redacted]
Overall duration of study treatment (weeks)[b]		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	76.50	31.86

Duration	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Q1, Q3	[redacted]	[redacted]
Min, Max	3.0, 150.3	3.0, 153.0
Number of cycles of study treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Source: CSR Table 14.1.1.24.
Data cutoff: 28 September 2022
a. Intervals are inclusive of the upper week number, e.g Week 1 - <= Week 3 is equivalent to day 1 to day 21 (inclusive). b. Overall duration of treatment is calculated as follows: If no >=C7 non-zero dose was infused: minimum of (Last dose date – Start dose date + 21) and (Death date – Start dose date + 1); If at least one >=C7 non-zero dose was infused: minimum of (Last dose date – Start dose date + 42) and (Death date – Start dose date + 1). Abbreviations: CP – carboplatin/paclitaxel; dMMR – mismatch repair deficient; Q – quartile; Max – maximum; Min – minimum; MSI-H – microsatellite instability-high; SD – standard deviation.

The median TTD and median time on treatment were [redacted] and 76.50 weeks, respectively, for dostarlimab in combination with CP. The median TTD and median time on treatment were [redacted] and 31.86 weeks, respectively, for placebo in combination with CP.

The company do not believe that this represents a significant difference between the TTD and the time on treatment measurement. The difference in definitions between the measures, and the difference in analysis methodology (including rounding to the nearest cycle for duration on treatment) would result in small discrepancies in results between the two methodologies*.

More importantly, the difference between the two measures does not have an impact on the assessment of clinical or cost effectiveness of the medicine. Dostarlimab drug costs within the model are based on TTD values. The TTD values were higher than the duration on treatment values for dostarlimab, therefore incorporating more cost of dostarlimab and a more conservative estimate of cost effectiveness.

Furthermore, beyond week 18 in the model the TTD and duration on treatment data for the comparator arm represents only the ongoing treatment with placebo. CP is received for a maximum of 18 model cycles (six chemotherapy cycles) as per the trial protocol and standard of care clinical guidelines in this setting. The model

includes a CP cost for a maximum of 18 model cycles only. Therefore, beyond week 18 the TTD for the comparator arm has no impact on cost effectiveness.

* TTD was defined as the time from the start of treatment to the date of treatment discontinuation or death, whichever occurs first and includes discontinuation from placebo.

Duration on treatment/exposure was defined as:

- If no dose >=Cycle 7 has been given, duration of treatment = minimum of (Date of last administration of study treatment – Date of first administration of study treatment + 21) and (Death date – Date of first administration of study treatment + 1).
- If at least one dose >=Cycle 7 has been given, duration of treatment = minimum of (Date of last administration of study treatment – Date of first administration of study treatment + 42) and (Death date - Date of first administration of study treatment + 1).

A11. Were there earlier phase 1 or phase 2 trials for dostarlimab with PCC?

There are no Phase 1 or Phase 2 trials for dostarlimab in combination with PCC specifically in patients with endometrial cancer. The only relevant trial for dostarlimab in combination with PCC is the IO-Lite study (NCT03307785), which includes a mixed population with advanced or metastatic solid tumours.[10]

The IO-Lite study was a Phase 1b, multi-arm, open-label, dose-finding study across four parts, where only Part B was relevant to dostarlimab in combination with PCC. The study aimed to determine the recommended Phase 2 dose, safety, and pharmacokinetic profile of dostarlimab in combination with previously approved anti-cancer therapies in advanced or metastatic solid tumours. Secondary efficacy endpoints included ORR, DOR, DCR, and PFS.

The overall study population was 55 patients with advanced or metastatic solid tumours. In Part B, 14 patients were evaluated and received the regimen relevant to this submission. No patients in the Part B cohort had advanced or metastatic endometrial cancer. In the Part B cohort, patients received dostarlimab 500 mg Q3W for four cycles, followed by 1,000 mg Q6W until disease progression or unacceptable toxicity up to 2 years, in combination with carboplatin (area under the plasma or serum concentration-time curve [area under curve (AUC)] five or six, determined by the investigator, Q3W) and paclitaxel (175 mg/m^2 Q3W) for four to six cycles.

In the Part B cohort an ORR of 42.9% (n=6) was observed (90% CI, 20.6–67.5%) with a DCR of 57.1% (n=8; 90% CI, 32.5–79.4%). The PFS rate was 58.7% (95% CI, 27.4–80.4%) at 6 months, and was unchanged at 12 months, suggesting responses to dostarlimab in combination with carboplatin and paclitaxel were durable.

In the Part B cohort, 12 patients were evaluable for safety. One patient experienced a dose limiting toxicity (grade 3 aspartate aminotransferase increased) and the recommended dose for Phase 2 dose was confirmed.

The GARNET study (NCT02715284) is a Phase I/II trial evaluating the efficacy and safety of dostarlimab (as a monotherapy) in patients with advanced or recurrent endometrial cancer. The GARNET study does not provide earlier Phase 1 or 2 data for dostarlimab with PCC, however it does provide valuable data in the relevant tumour type (advanced/recurrent dMMR/MSI-H endometrial cancer).[11] Furthermore, the GARNET study has been underway since 2016, and therefore provides a longer duration of follow-up than the available interim analysis 1 data from RUBY-1 (median follow-up cut off date of November 1, 2021, 27.6 months). A total of 143 patients with dMMR/MSI-H EC were evaluated for efficacy. ORR was 45.5% (n=65), with median DOR not reached. The 12-, 24- and 36-month probability of PFS and overall survival (OS) are outlined in Table 20 below.

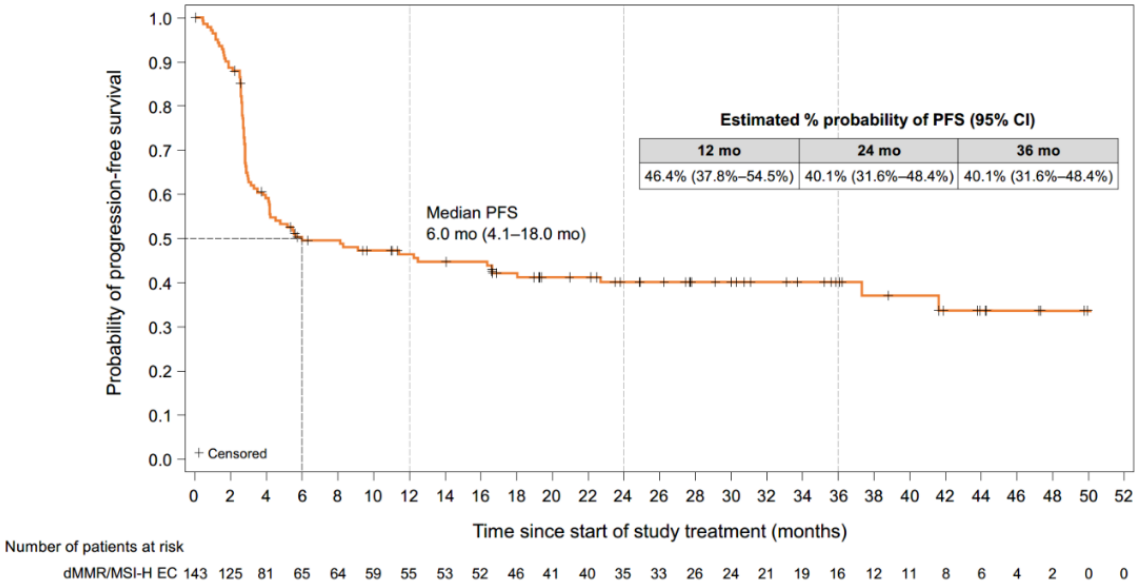
Table 20: Estimated probability of PFS and OS in dMMR/MSI-H patients with pre-treated advanced or recurrent endometrial cancer treated with dostarlimab monotherapy

	Estimated probability of PFS (95% CI)	Estimated probability of OS (95% CI)
12 months	46.4% (37.8%-54.5%)	73.3% (65.2%-79.8%)
24 months	40.1% (31.6%-48.4%)	60.5% (51.5%-68.4%)
36 months	40.1% (31.6%-48.4%)	58.4% (49.2%-66.5%)

Abbreviations: CI – confidence interval; dMMR - mismatch repair deficient; MSI-H - microsatellite instability-high; OS – overall survival; PFS – progression-free survival.

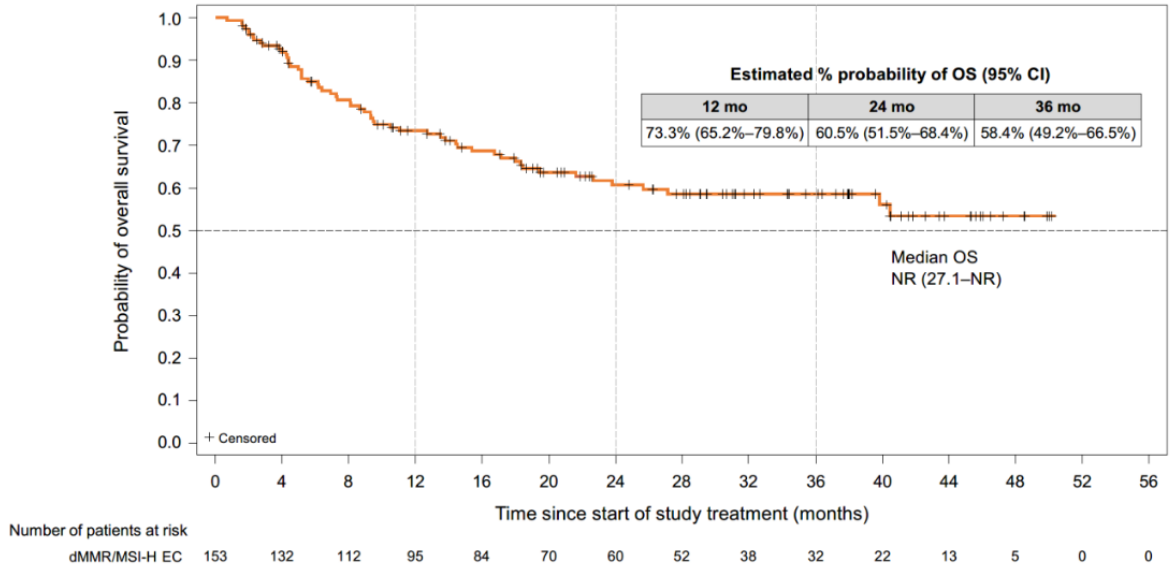
Durable efficacy has been demonstrated for patients treated dostarlimab in the GARNET trial, with plateaus seen in the PFS and OS KM data out to the maximum follow-up of 50 months (Figure 6 and Figure 7).

Figure 6. PFS in dMMR/MSI-H patients with pre-treated advanced or recurrent endometrial cancer treated with dostarlimab monotherapy



Abbreviations: CI – confidence interval; dMMR - mismatch repair deficient; EC – endometrial cancer; MSI-H - microsatellite instability-high; PFS – progression-free survival.

Figure 7. OS in dMMR/MSI-H patients with pre-treated advanced or recurrent endometrial cancer treated with dostarlimab monotherapy



Abbreviations: CI – confidence interval; dMMR - mismatch repair deficient; EC – endometrial cancer; MSI-H - microsatellite instability-high; OS – overall survival.

Furthermore, the safety profile of dostarlimab as observed in the GARNET trial was consistent with previous reports.[11,12]

A12. Were there any instances of hyperprogression in Ruby-1?

Investigator impression of hyperprogression is not collected in the eCRF (Electronic Case Report Form), and hence this information was not collected for the RUBY-1 study.

A13. Please could you provide the subgroup analyses for 'anti-cancer surgery' vs none for the dMMR/MSI-H populations referred to on CS page 10?

The company can confirm that the evidence does not allow for meaningful conclusions to be drawn from the analysis, due to the limited size of the patient cohort. Within the dMMR/MSI-H RUBY-1 trial cohort, [redacted] of patients in the dostarlimab in combination with CP arm, and [redacted] of patients in the placebo in combination with CP arm, did not receive prior anti-cancer surgery for endometrial cancer. In the CSR prior anti-cancer surgery for endometrial cancer is captured as a 'yes/no' variable and therefore the type and/or outcome of surgery is not readily available. The trial protocol did not outline any specific inclusion or exclusion criteria related to surgery. The trial was also not designed to evaluate outcomes dependent on surgical intervention and therefore the company believes that presenting data for the subgroup is not informative.

Furthermore, across three clinical advisory boards relating to this trial and this appraisal, people who have had primary debulking surgery versus people who have not, was not raised by any of the clinical experts as a subgroup of patients of clinical importance.[4,6,13]

A14. In Ruby-1 there were 5 UK sites, how many UK participants were included and how many had the subtype of interest? Please also provide the names of the 5 UK sites, the Mirza 2023 publication reports 3 UK sites.

In total, five UK sites were included for recruiting patients for the RUBY trial:

- Cambridge University Hospitals NHS Foundation Trust
- University College London Hospitals NHS Foundation Trust
- Brighton and Sussex University Hospitals NHS Trust
- Royal Cornwall Hospital NHS Trust

- Guy's and St Thomas' NHS Foundation Trust

At the time of the RUBY-1 interim analysis 1 data cut in September 2022, only three UK sites (Cambridge University Hospitals NHS Foundation Trust, University College London Hospitals NHS Foundation Trust and Brighton and Sussex University Hospitals NHS Trust) had recruited patients. In total, three patients were recruited from these UK sites for the RUBY-1 trial (two patients had dMMR/MSI-H endometrial cancer and one had MMRp/MSS endometrial cancer).

A15. Please tabulate the EQ-5D VAS values of each point and its 95% confidence interval for the dMMR/MSI-H population of Ruby-1 and also tabulate the equivalent values for the ITT population.

Tabulated EQ-5D VAS values for each point and the corresponding 95% confidence interval for the dMMR/MSI-H population and ITT population from the RUBY-1 trial are presented in Table 21 and Table 22, respectively. In the dMMR/MSI-H population, the focus of this appraisal, the mean quality of life (QoL) point estimate is greater for the dostarlimab arm than the control arm across all treatment cycles. In additional to the preferred base case utility scores from the larger ITT population, for completeness, the company have also provided a scenario (Document B, section B3.11.13) exploring the inclusion of utility scores for progression-free and progressed disease based on the dMMR/MSI-H population.

EQ-5D VAS outputs per treatment have not been pooled as per study statistical analysis plan (SAP) and supplementary SAP and therefore not available to present. The company's response to questions B3, B4 and B5 includes utility values by progression state. These utility values are pooled across treatments for the EAG's reference.

Table 21: EQ-5D VAS values at each time point and its 95% CI for the dMMR/MSI-H population of RUBY-1 (N=118)

Timepoint	Number of people		Mean QoL Dostarlimab in combination with CP	Mean QoL Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]	[redacted]
C23	[redacted]	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]	[redacted]
C25	[redacted]	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]	[redacted]
C27	[redacted]	[redacted]	[redacted]	[redacted]
C28	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Number of people		Mean QoL Dostarlimab in combination with CP	Mean QoL Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
SVFU5	[redacted]	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR Table 14.4.1.8 and Table 14.4.1.9
Data cutoff: 28 September 2022
Abbreviations: C – cycle; CI – confidence interval; dMMR – mismatch repair deficient; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; MSI-H – microsatellite instability-high; NC – not calculated; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit; VAS – visual analogue scale.

Table 22: EQ-5D VAS values at each time point and its 95% CI for the ITT population of RUBY-1 (N=494)

Timepoint	Number of people		Mean QoL Dostarlimab in combination with CP	Mean QoL Placebo in combination with CP
	Eligible	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]	[redacted]
C23	[redacted]	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Number of people		Mean QoL Dostarlimab in combination with CP	Mean QoL Placebo in combination with CP
	Eligible	Reporting (N)	Score (95% CI)	Score (95% CI)
C25	[redacted]	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]	[redacted]
C27	[redacted]	[redacted]	[redacted]	[redacted]
C28	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]	[redacted]
SVFU5	[redacted]	[redacted]	[redacted]	[redacted]
SVFU6	[redacted]	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]	[redacted]
SVFU8	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR Table 14.4.1.8 and Table 14.4.1.9
Data cutoff: 28 September 2022
Abbreviations: C – cycle; CI – confidence interval; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; ITT – intention to treat; NE – not estimable ; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit; VAS – visual analogue scale.

A16. Please could you reproduce Tables 8 and 9 (baseline characteristics) separately for the grade 3, grade 4 and recurrent subgroups for the dMMR/MSI-H population.

The RUBY-1 trial was powered to show statistical significance for PFS in both ITT and dMMR/MSI-H populations. The RUBY-1 trial was also powered to show statistical significance for OS in the ITT population. OS in the dMMR/MSI-H population was a predefined analysis in the RUBY trial. No further subgroups were powered to show statistical significance for OS or PFS. The dMMR/MSI-H population is already a subgroup of the broader ITT population. Due to the small number of patients within subgroups of the dMMR/MSI-H subgroup, results should be interpreted with caution.

The demographic baseline characteristics and disease history for primary Stage 3, primary Stage 4, and recurrent dMMR/MSI-H patients are presented in Table 23 to Table 28. The demographic baseline characteristics and disease history of the subgroups were largely similar to that of the overall dMMR/MSI-H population.

Table 23: Demographic characteristics for Primary Stage 3 dMMR/MSI-H patients (n=24)

Disease status: Primary Stage 3		
Characteristic	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	10	14
Child-bearing status, n(%)		
Child-bearing potential	[redacted]	[redacted]
Non-child-bearing potential	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Age Group, n (%)		
<=18	[redacted]	[redacted]
19-64	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Age group 2, n (%)		
<65	[redacted]	[redacted]
65-74	[redacted]	[redacted]
>=75	[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	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BSA (m^2)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ECOG Performance Status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: BMI – body mass index; BSA – body surface area; cm – centimetre; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ECOG – Eastern Cooperative Oncology Group; kg – kilograms; max – maximum; min – minimum; MSI-H – microsatellite instability-high; Q – quartile; SD – standard deviation

Table 24: Disease history for Primary Stage 3 dMMR/MSI-H patients (n=24)

Disease status: Primary Stage 3		
Category, n (%)	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	10	14
FIGO Stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at diagnosis		
Carcinosarcoma	[redacted]	[redacted]

Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]
Other	[redacted]	[redacted]
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Time since initial diagnosis (Months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[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]
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	[redacted]	[redacted]
No	[redacted]	[redacted]
PD-L1		
Negative	[redacted]	[redacted]
Low/High	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	[redacted]	[redacted]

Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; FIGO – Federation of Gynaecology and Obstetrics; MSI-H – microsatellite instability-high; PD-L1 – programmed death-ligand 1; SD – standard deviation

Table 25: Demographic characteristics for Primary Stage 4 dMMR/MSI-H patients (n=35)

Disease status: Primary Stage 4		
Characteristic	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	16	19
Child-bearing status, n(%)		
Child-bearing potential	[redacted]	[redacted]
Non-child-bearing potential	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]

Min, Max	[redacted]	[redacted]
Age Group, n (%)		
<=18	[redacted]	[redacted]
19-64	[redacted]	[redacted]
>=65	[redacted]	[redacted]
Age group 2, n (%)		
<65	[redacted]	[redacted]
65-74	[redacted]	[redacted]
>=75	[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	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
BSA (m^2)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ECOG Performance Status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: BMI – body mass index; BSA – body surface area; cm – centimetre; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ECOG – Eastern Cooperative Oncology Group; kg – kilograms; max – maximum; min – minimum; MSI-H – microsatellite instability-high; Q – quartile; SD – standard deviation

Table 26: Disease history for Primary Stage 4 dMMR/MSI-H patients (n=35)

Disease status: Primary Stage 4		
Category, n (%)	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	16	19
FIGO Stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at diagnosis		
Carcinosarcoma	[redacted]	[redacted]
Endometrioid carcinoma (Adenocarcinoma or adenocarcinoma-variants)	[redacted]	[redacted]
Mixed carcinoma with >=10% of carcinosarcoma, clear cell or serous histology	[redacted]	[redacted]
Other	[redacted]	[redacted]
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Time since initial diagnosis (Months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[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]
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	[redacted]	[redacted]
No	[redacted]	[redacted]
PD-L1		
Negative	[redacted]	[redacted]
Low/High	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; FIGO – Federation of Gynaecology and Obstetrics; MSI-H – microsatellite instability-high; PD-L1 – programmed death-ligand 1; SD – standard deviation

Table 27: Demographic characteristics for recurrent dMMR/MSI-H patients (n=59)

Disease status: Recurrent		
Characteristic	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	27	32
Child-bearing status, n(%)		
Child-bearing potential	[redacted]	[redacted]
Non-child-bearing potential	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]

Native Hawaiian or other Pacific Islander		
Unknown		
Not Reported		
Ethnicity, n (%)		
Hispanic or Latino		
Not Hispanic or Latino		
Unknown		
Not Reported		
Age (years)		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Age Group, n (%)		
<=18		
19-64		
>=65		
Age group 2, n (%)		
<65		
65-74		
>=75		
Weight (kg)		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Height (cm)		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
BMI (kg/m^2)		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
BSA (m^2)		

Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
ECOG Performance Status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: BMI – body mass index; BSA – body surface area; cm – centimetre; CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; ECOG – Eastern Cooperative Oncology Group; kg – kilograms; max – maximum; min – minimum; MSI-H – microsatellite instability-high; Q – quartile; SD – standard deviation

Table 28: Disease history for recurrent dMMR/MSI-H patients (n=59)

Disease status: Recurrent		
Category, n (%)	**Dostarlimab in combination with CP (N=53)**	**Placebo in combination with CP (N=65)**
Number of patients in the subgroup	16	19
FIGO Stage at initial diagnosis		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Histology at diagnosis		
Carcinosarcoma	[redacted]	[redacted]
Serous adenocarcinoma	[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]
Grade at diagnosis		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]
Time since initial diagnosis (Months)		
Mean (SD)	[redacted]	[redacted]

Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Most recent histology		
Serous adenocarcinoma	[redacted]	[redacted]
Undifferentiated carcinoma	[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]
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	[redacted]	[redacted]
No	[redacted]	[redacted]
PD-L1		
Negative	[redacted]	[redacted]
Low/High	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Oestrogen receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Progesterone receptor status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Abbreviations: CP – carboplatin/paclitaxel; dMMR – DNA mismatch repair deficient; FIGO – Federation of Gynaecology and Obstetrics; MSI-H – microsatellite instability-high; PD-L1 – programmed death-ligand 1; SD – standard deviation

A17. Please could you reproduce Figures 4 and 5 (PFS and OS Kaplan-Meier plots) separately for the grade 3, grade 4 and recurrent subgroups for the dMMR/MSI-H population and estimate respective hazard ratios of dostarlimab treatment effect.

The company ran the subgroup analyses for primary Stage 3, primary Stage 4, and recurrent patient populations according to the predefined SAP. As noted previously, running these analysis produces smaller patient numbers as each are 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.

The hazard ratio analysis for PFS and OS has been completed within these subgroups, as per the pre-specified SAP. The KM plots for OS and PFS are not available for Stage 4 and recurrent subgroups as the low number of patients and events would make these difficult to interpret.

The SAP does not allow time-to-event analysis to be run in situations where less than five events have occurred. The OS HR and the OS KM plot for the Stage 3 subgroup is therefore not evaluable. The KM plot for PFS is not available for the Stage 3 subgroup as the low number of patients and events would make it difficult to interpret.

The respective PFS and OS HRs for the recurrent, Stage 3 and Stage 4 subgroups are presented in Figures 9 and 10 in the submission document B.

Although PFS and OS benefit in the dostarlimab in combination with PCC arm were generally consistent across the protocol-specified subgroups, extended follow-up is required to observe a treatment effect in the subgroup of patients with primary stage III disease. Lower PFS maturity was observed for patients with stage III disease (41.6%) compared with Stage IV (60.0%) and recurrent patients (59.3%). In addition, there was a lower number of patients with stage III disease (N=24) compared with Stage IV (n=35) and recurrent (n=59). Although there is low event maturity and limited sample size in the stage III subgroup, patients with stage III endometrial cancer have responded to treatment as expected in the trial. Therefore, there is no biological rationale as to why patients with stage III disease would respond differently

to treatment with Stage IV or recurrent disease which is supported by the literature.[14–16]

Section B: Clarification on cost effectiveness data

B0. The external assessment group has requested access to the utility values which were used in Technology Appraisal 779. TA779 included a very similar population and the EAG feels that it will be useful for the committee to consider the utility values used in that appraisal.

NICE TA779 assessed the use of dostarlimab (monotherapy) as an option for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency in adults who have had prior platinum-based chemotherapy. The key clinical evidence which informed the QoL data referred to by the EAG was based on the GARNET study (NCT02715284). It is important to note that the population, and the place in the treatment pathway, included within the GARNET study is different to that of the RUBY-1 study. GARNET included patients in the relapsed setting, who have already received treatment with platinum-based therapy and whose disease has relapsed. In the GARNET study, 63.9%, 25% and 11.1% of patients with dMMR/MSI-H endometrial cancer had received one, two and three lines of prior therapy, respectively. Pre-treated patients with relapsed disease have poorer survival and health related quality of life (HRQoL) outcomes when compared to patients undergoing front line treatment for primary advanced/recurrent endometrial cancer.[1,11,17,18]

Therefore, the company do not believe that HRQoL outcomes collected in GARNET are relevant for this appraisal, in the primary advanced treatment setting. The RUBY-1 trial patient reported outcome (PRO) data has been analysed and provided in support of this appraisal. The company believe that this data is robust given that it captured in a large patient population and aligns with the exact patients who are modelled for the efficacy data. The company has also provided substantial additional analysis on the RUBY-1 HRQoL data as per EAG clarification questions to resolve any additional uncertainties regarding the RUBY-1 HRQoL results.

Provided below, as requested, are the tables (TA779 company response to clarification questions, Tables 20-23) from TA779 committee papers.[19]

Table 29: GARNET results of regression analyses (N=[redacted]) (predicting utilities by progression)

	Coefficient	Standard error	P>Z
Baseline utility	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]

Source: GARNET TA779 committee papers Table 20, Page 275.[19] Footnote: Values presented to 3 decimal places

Table 30: GARNET results of regression analyses (N=[redacted]) (predicting utilities by progression and time to death)

	Coefficient	Standard error	P>Z
Baseline utility	[redacted]	[redacted]	[redacted]
TTD>5 cycles	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]

Source: GARNET TA779 committee papers Table 21,Page 275.[19] Footnote: Values presented to 3 decimal places. Abbreviations: TTD: time to death.

Table 31: GARNET health state utility values (N=[redacted]) (progression)

Health state	Estimate
Pre-progression	[redacted]
Progressed disease	[redacted]

Source: GARNET TA779 committee papers Table 22. Page 275.[19] Footnote: Values presented to 7 decimal places

Table 32: GARNET health state utility values (N=[redacted]) (progression and time to death)

Health state	Estimate
Pre-progression >5 cycle from death	[redacted]
Pre-progression ≤5 cycle from death	[redacted]
Post-progression >5 cycle from death	[redacted]
Post-progression ≤5 cycle from death	[redacted]

Source: GARNET TA779 committee paper Table 23, Page 275. [19]

The progression-free utility score reported in GARNET ([redacted]) is very closely aligned with the progressed utility scores reported in RUBY ([redacted] for ITT and [redacted] for dMMR/MSI-H, company submission Table 51). This is expected given that the patients who have progressed on front line treatment in RUBY then move on to treatment of their relapsed disease i.e. they become a GARNET patient and would be considered as pre-progression in the GARNET study.

B1. Please confirm that the Gompertz and Gamma models fitted in Figure 15 successfully converged and are fitted to the correct dataset. If not, please re-fit and update the economic model.

The company can confirm that the Gompertz and Gamma models presented in Figure 15 of the CS were incorrect due to linkage error for these specific survival coefficients. In response to the EAG's question, the company have updated the economic model and Figure 15 (please see Figure 8 below) to reflect the correct dataset. The change has had no impact on the base case or scenario analyses results.

Figure 8: Standard parametric survival analyses for dostarlimab in combination with PCC for IA PFS

Abbreviations: IA – investigator assessed; PCC – platinum-containing chemotherapy; PFS – progression-free survival

B2. Please implement a waning effect within the economic model where the overall survival and progression-free survival hazard rates of the intervention arm are replaced by the respective hazard rates of the control arm at, and beyond, a point in time specified by the user. If not feasible, please instead implement the same waning effect that can be specific to begin from 3, 5, 7 and 10 years.

The company do not believe that it is appropriate to implement a treatment waning (treatment risk convergence) effect within the economic model. The reasons are outlined below including RUBY-1 efficacy, conservative OS modelling approaches

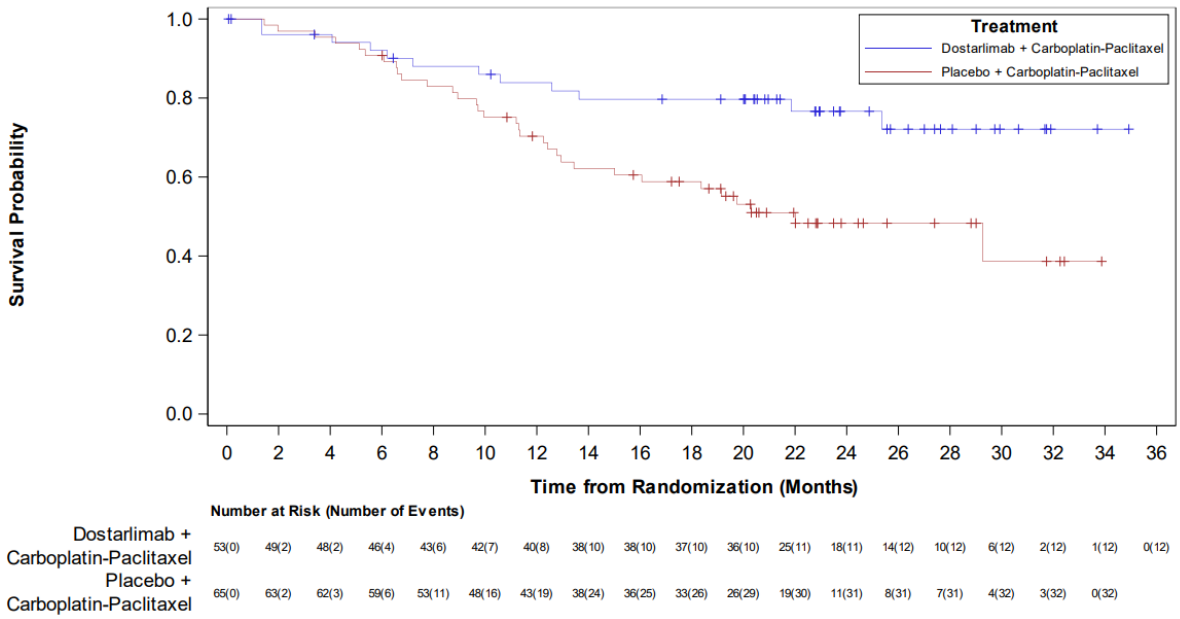
applied in the company base case, evidence of sustained treatment effect in relapsed advanced/recurrent endometrial cancer, treatment waning accepted beyond 7-9 years in ID4036 and UK clinical expert opinion.

RUBY-1 efficacy

Within the RUBY-1 trial, OS for dostarlimab in combination with PCC shows a substantial treatment benefit over PCC alone. In addition, post-progression benefits are further demonstrated by progression-free survival 2 (PFS2) and post-progression survival (PPS) HRs, and evidence of sustained separation of the dostarlimab in combination with PCC arm from the PCC arm. Therefore, the company consider that there is sufficient evidence for not including OS treatment waning in the base case.

PFS2 is defined as the time from the date of treatment randomisation to the date of assessment of progression on the first subsequent anti-cancer therapy following study treatment discontinuation or death by any cause, whichever is earlier by IA. Aligned to the PFS primary analysis, the KM curve of PFS2 showed separation in favour of the dostarlimab in combination with PCC treatment arm in the dMMR/MSI-H patient population (Figure 9). The PFS2 results indicate that the benefit of dostarlimab combination therapy extended beyond first progression, leading to long term benefits, and further supports the trend observed for OS. This is further supported by the HR of 0.37 (95% CI: 0.19, 0.73) (Table 33).

Figure 9: Kaplan-Meier curves of PFS2 – Interim Analysis (dMMR/MSI-H patient population)



Source: CSR Figure 15.1.11
Data cutoff: 28 September 2022
Abbreviations: dMMR – DNA mismatch repair deficient; MSI-H – microsatellite instability-high; PFS – progression-free survival.

Table 33: Summary of Kaplan-Meier of PFS2 – Interim Analysis (dMMR/MSI-H patient population)

	Dostarlimab in combination with PCC (N=53)	Placebo in combination with PCC (N=65)
Hazard ratio (95% CI)	0.37 (0.19, 0.73)	
Median PFS2, months (95% CI)	[redacted]	[redacted]
PFS2 Probability at 24 months (95% CI)	[redacted]	[redacted]

Source: CSR Table 14.2.1.39
Data cutoff: 28 September 2022
Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR – mismatch repair deficient; MSI-H – microsatellite instability-high; NR – Not reached; PFS – progression-free survival.

PPS is defined as the time to first documentation of disease progression per IA to date of death due to any cause. PPS provides further evidence for excluding treatment waning within the analysis. Aligned with PFS and PFS2, the KM curve of PPS showed separation in favour of the dostarlimab in combination with PCC treatment arm in the dMMR/MSI-H patient population (Figure 10). This is further supported by a HR of [redacted] (Table 34).

Figure 10: Kaplan-Meier- curves of PPS– Interim Analysis (dMMR/MSI-H patient population)

Source: GSK Data on file
Data cutoff: 28 September 2022
Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR – mismatch repair deficient; IA – investigator assessed; MSI-H – microsatellite instability-high; PPS – post-progression survival.

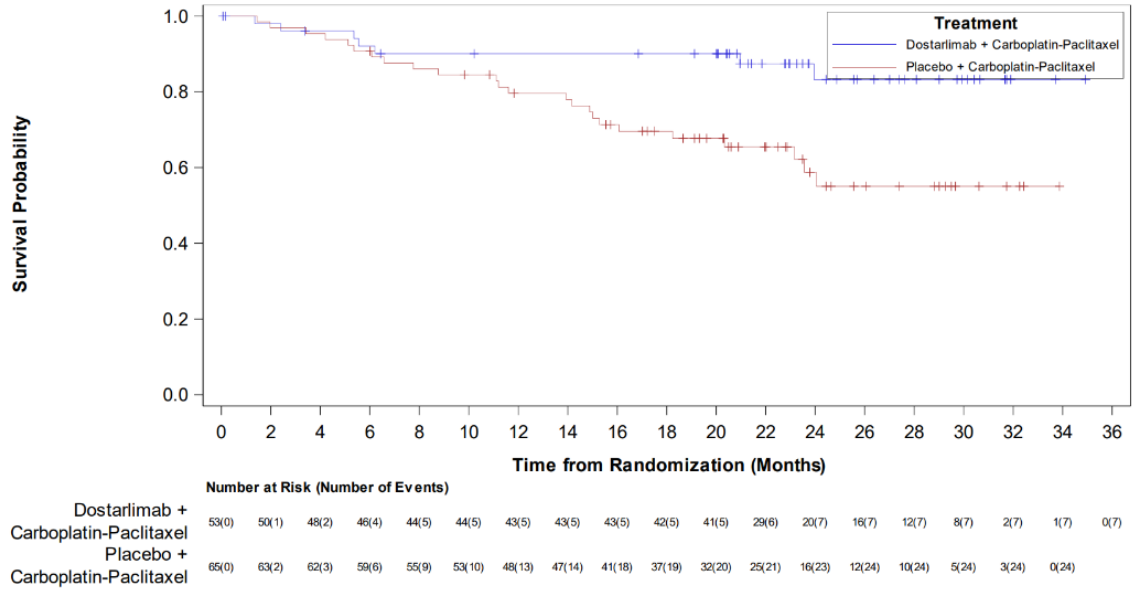
Table 34: Summary of Kaplan-Meier of PPS – Interim Analysis (dMMR/MSI-H patient population)

	Dostarlimab in combination with PCC (N=53)	Placebo in combination with PCC (N=65)
Hazard ratio (95% CI)	[redacted]	
Median PPS, months (95% CI)	[redacted]	[redacted]

Source: GSK Data on file
Data cutoff: 28 September 2022
Abbreviations: CI – confidence interval; CP – carboplatin/paclitaxel; dMMR –mismatch repair deficient; MSI-H – microsatellite instability-high; PPS – post-progression survival.

Furthermore, OS treatment waning was not considered in the base case because dostarlimab in combination with PCC demonstrates a survival benefit over PCC alone. This is demonstrated by the separation of curves in Figure 11 and the OS HR. The median OS was [redacted], however, despite the immaturity of the data at present, there was a strong numerical trend in favour of the dostarlimab in combination with the PCC arm compared with the placebo in combination with PCC, with an increase in OS observed (unstratified HR 95% CI nominal p-value = [redacted]; stratified HR 95% CI nominal p-value = 0.30 [0.13, 0.70] [redacted]).

Figure 11: Kaplan-Meier curves of OS– Interim Analysis (dMMR/MSI-H patient population)



Source: CSR- Figure 15.1.8.Abbreviations: dMMR – mismatch repair deficient; MSI-H – microsatellite instability-high; OS – overall survival.

Table 35: Non-parametric and semi-parametric results for OS (dMMR/MSI-H patient population)

Treatment arm (N)	Dostarlimab in combination with PCC (n=53)	Placebo in combination with PCC (n=65)
Maturity (%) – n/N	13.21% (7/53)	36.92% (24/65)
Duration of follow-up (weeks) Median (95% CI)	[redacted]	[redacted]
Duration of follow-up (weeks) Restricted mean (SD)	[redacted]	[redacted]
Median (95% CI) (weeks)	[redacted]	[redacted]
Restricted mean (weeks), (SE)	[redacted]	[redacted]
HR unstratified* (95% CI; nominal p-value)	[redacted]	
HR stratified (95% CI; nominal p-value)	0.30 (0.13, 0.70; [redacted])	

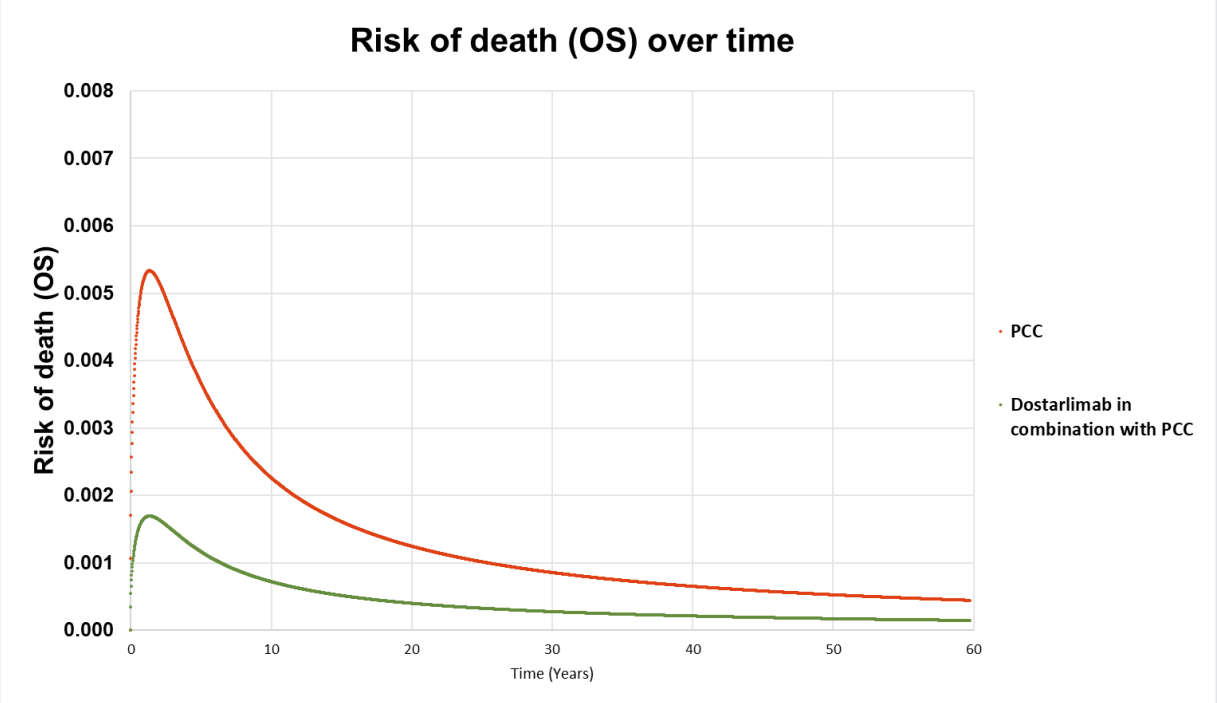
Non-parametric analysis includes percentage of data maturity, median and restricted mean follow-up, median and restricted mean survival. The cox proportional hazards model (HR) is a semi-parametric model.
Abbreviations: CI – confidence interval; dMMR – mismatch repair deficient; HR – hazard ratio; MSI-H – microsatellite instability-high; NR – not reported; SD – standard deviation; SE – standard error. *Unstratified cox proportional hazards model used to calculate HR.

Conservative OS modelling approaches applied in the company base case

A conservative approach has already been adopted in the company base case within the model, by using the PCC OS curve extrapolation as a baseline and applying a HR for dostarlimab in combination with PCC OS. Figure 13 shows the risk of death used in the model, which uses the PCC OS extrapolation curve and applies the unstratified OS HR of [redacted] for the dostarlimab in combination with PCC arm.

Figure 13 shows that using this approach, the dostarlimab in combination with PCC risk of death follows the same shape as the PCC OS risk of death, with an initial increase followed by a gradual decrease.

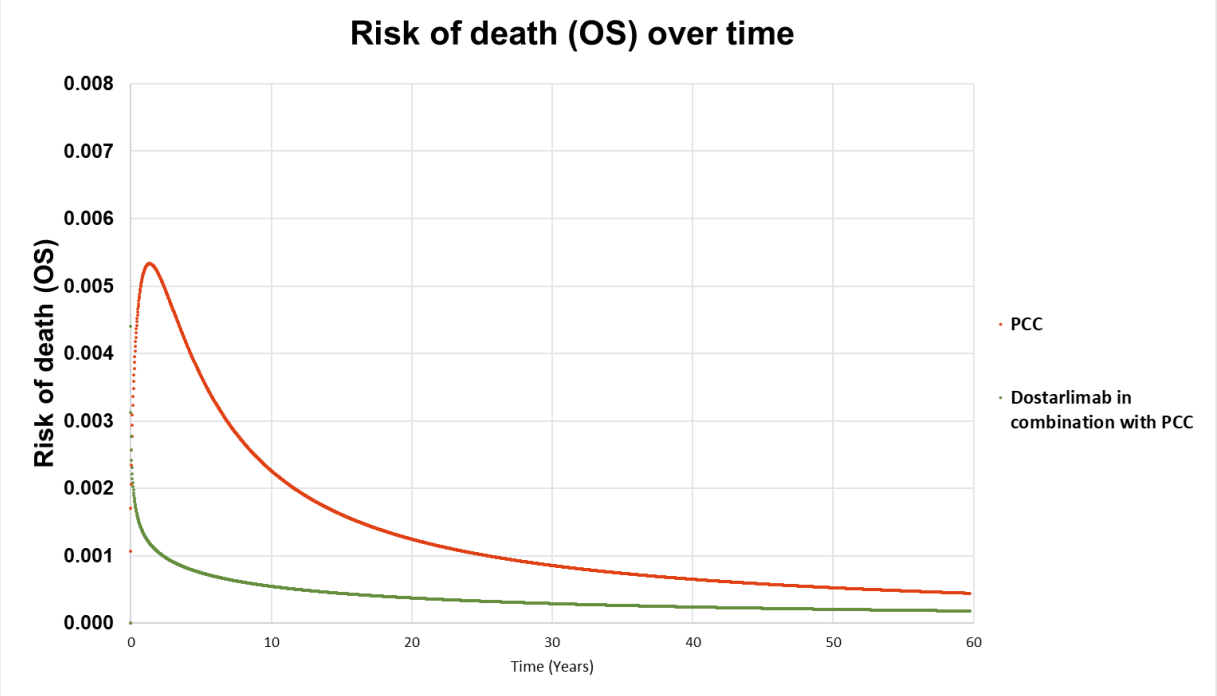
Figure 12: Risk of death (OS) over time- Dostarlimab + PCC extrapolation approach: Extrapolated PCC OS adjusted by HR



Abbreviations: CI – confidence interval; HR – hazard ratio; OS – overall survival; PCC – platinum-containing chemotherapy.

Since PCC is a chemotherapy and dostarlimab is an IO therapy, there are different mechanisms of action and thus different expected risks of death and different shaped curves for risk of death. Figure 13 shows the risk of death when extrapolating the dostarlimab in combination with PCC arm separately to the PCC arm. This shows a different shape for dostarlimab in combination with PCC compared with Figure 13 and PCC alone, showing a decrease in risk of death throughout the entire time period.

Figure 13: Risk of death (OS) over time- Dostarlimab + PCC extrapolation approach: Extrapolated dostarlimab + PCC OS



Abbreviations: CI – confidence interval; HR – hazard ratio; OS – overall survival; PCC – platinum-containing chemotherapy.

In summary, the company base case approach for modelling dostarlimab in combination with PCC OS is already a conservative approach, incorporating the early increased risk of death seen with PCC.

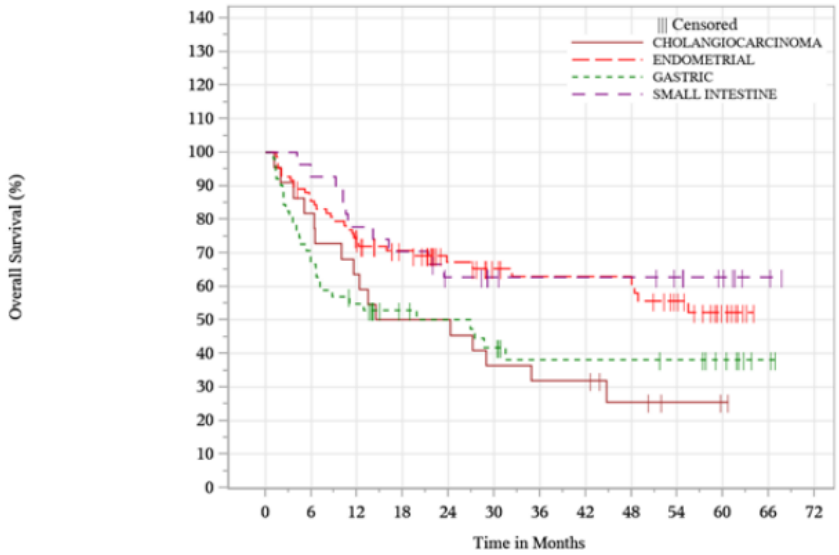
Evidence of sustained treatment effect in relapsed advanced/recurrent endometrial cancer

Sustained treatment effect in the relapsed advanced/recurrent endometrial cancer setting also supports the durability of efficacy in the primary advance setting, with both the GARNET trial and KEYNOTE-158 trial showing sustained efficacy up to and beyond five years.[8,11] Since these populations are likely to have poorer prognosis due to pre-treatment and the recurrent nature of the disease, it is reasonable to assume that the outcomes and sustained treatment effect with IO monotherapy in second-line will be no less prominent for an IO in combination with chemotherapy in the first-line.

Figure 6 and Figure 7, PFS and OS KM figures from the GARNET study, (EAG clarification question A10) show the sustained efficacy of dostarlimab monotherapy, with a PFS and OS plateau from 40 months still observed up to 50 months.

In addition, in the recent appraisal of pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency (ID4036), the KEYNOTE-158 trial was outlined. Within this trial, in the dMMR/MSI-H advanced/recurrent endometrial cancer cohort, a sustained treatment effect is observed following treatment with pembrolizumab with a plateau from 54 months, still observed at 60 months for OS and PFS (Figure 14 and Figure 15). Furthermore, median OS was not reached for the endometrial tumour site cohort in the trial, providing further evidence of sustained treatment effect.[8]

Figure 14: KM estimates of OS by tumour site (KEYNOTE-158 trial)[8]



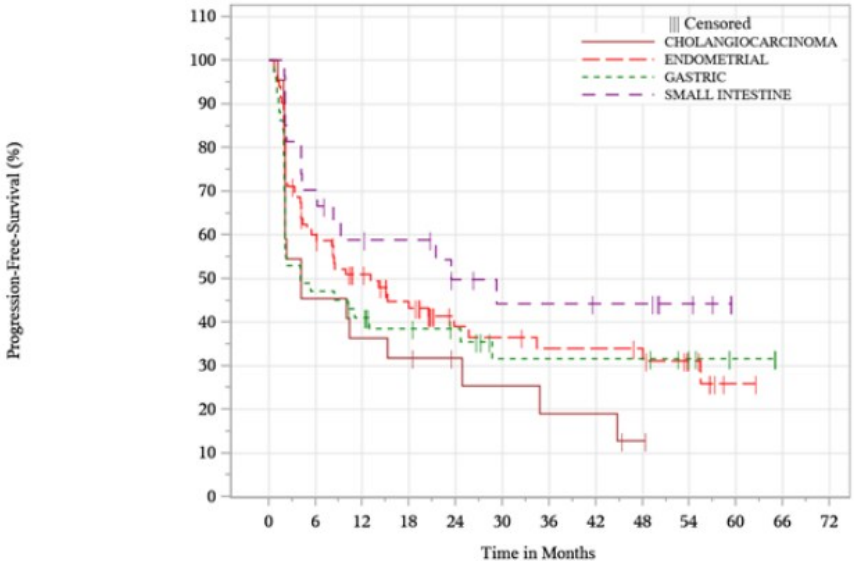
n at risk

CHOLANGIOCARCINOMA	22	18	14	11	11	8	7	7	4	2	1	0	0
ENDOMETRIAL	83	70	58	48	35	29	26	26	26	19	9	0	0
GASTRIC	51	34	27	20	18	15	11	11	11	10	7	2	0
SMALL INTESTINE	27	25	21	19	15	12	11	11	11	9	6	2	0

Notes: Database cutoff date: 15OCT2021.

Abbreviations: KM – Kaplan-Meier; OS – Overall survival

Figure 15: KM estimates of PFS by tumour site (KEYNOTE-158 trial) [8]



Abbreviations: KM – Kaplan-Meier; PFS – progression-free survival

Based on the data observed above, it is reasonable to assume the PFS and OS effect trajectory observed in the relapsed setting would also apply to the first-line setting for dostarlimab in combination with PCC.

Treatment waning accepted in ID4036 [8]

Within the recently published final appraisal determination document for pembrolizumab in ID4036, mentioned previously, the committee concluded "that applying treatment waning from 7 to 9 years was a reasonable and potentially conservative assumption based on the data provided for this particular indication." [8]

This committee conclusion was based on longer term follow-up, up to year six and following a two-year stopping rule, from KEYNOTE-158 (outlined above).

It wouldn't be appropriate to apply a more pessimistic treatment effect to dostarlimab in combination with PCC in the front line setting, than that which has been observed and accepted as conservative for pembrolizumab monotherapy in the treatment of relapsed advanced/recurrent endometrial cancer.

UK clinical expert opinion

As noted in B.3.11.3 of the CS, UK clinical experts expected that following discontinuation of IO in other oncology indications benefits were seen *'2-3 years', '3-*

4 years' and *'5-10 years'* after stopping IO.[6] Furthermore, the UK clinical advisers estimates for long term OS and PFS do not align well with long term OS and PFS estimates from the model when treatment waning is applied to the company base case settings. The estimates for long term OS and PFS provided by UK clinical advisers were in the consideration of a three-year stopping rule for dostarlimab, and therefore the durability of dostarlimab's treatment effect beyond treatment discontinuation is incorporated into the responses.

Application of treatment waning within the model is highly conservative and provides most improbable prediction of long term survival outcomes for patients treated with dostarlimab in combination with PCC. However, to satisfy the EAG request, and to allow model users to explore potential scenarios, treatment waning functionality is available within the model for both PFS and OS to apply either:

- An immediate waning to the CP arm at the end of the observed period
- A gradual linear waning to the CP arm, initiating and ending at user defined timepoints.

By selecting the dostarlimab treatment waning approach in cells D12 and D32 of the 'Clinical inputs' sheet, the user can specify the waning effect for PFS and OS respectively. Within the company submission, several scenarios were modelled which explored PFS and OS treatment waning (scenario 22-23 of Table 71).

B3. Re: Figure 8 of CS Doc B - Please clarify what proportion of patients contributing to EoT and subsequent quality of life (QoL) assessments have progressed disease versus have completed or otherwise stopped treatment. Please clarify if patients who contribute to the EOT/right-side of the figure are immediately excluded from the cycle-based/left-side of the plot.

Table 36 presents the completion rates of EQ-5D by disease progression status at the end of treatment, safety follow-up and a range of survival follow-up assessments. The company acknowledges that the below information completion rates show that a high proportion of patients completing EQ-5D responses are in the progressed disease/death progression status for both treatment arms. The higher proportion of

patients in the progressed disease/death status compared to the progression-free disease status explains the poor HRQoL reported.

Table 36: Completion Rate of EQ-5D by Domain, Visit and Disease Progression Status based on RECIST v1.1 by IA (dMMR/MSI-H subgroup)

Visit	Category	Dostarlimab + PCC (N=53)		Placebo + PCC (N=65)		Total (N=118)	
		Progression-free [N (%)]	Progressed disease [N (%)]	Progression-free [N (%)]	Progressed disease [N (%)]	Progression-free [N (%)]	Progressed disease [N (%)]
End of treatment	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety follow-up	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up assessment 1	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up assessment 2	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up assessment 3	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Category	Dostarlimab + PCC (N=53)		Placebo + PCC (N=65)		Total (N=118)	
		Progression-free [N (%)]	Progressed disease [N (%)]	Progression-free [N (%)]	Progressed disease [N (%)]	Progression-free [N (%)]	Progressed disease [N (%)]
Survival follow-up assessment 4	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up assessment 5	Number of patients expected to complete	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: [GSK Data on file]- Supplementary EQ-5D Data. Table 1. Completion Rate of EQ-5D by Domain, Visit and Disease Progression Status based on RECIST v1.1 by IA (ITT Analysis Set)- Pages 111, 114-116. Note - percentages are calculated based on the number of subjects expected to complete the questionnaire in that specific visit. Reason for non-completion can include death event during that time period. Abbreviations: CP – carboplatin/ paclitaxel; dMMR – DNA mismatch repair deficient; EQ-5D – EuroQol 5 dimensions; MSI-H – microsatellite instability-high

The PRO measures on the left-hand side of the graph, per cycle, are specifically for patients who remain on treatment. The PRO measurement was recorded for each patient for the appropriate cycle and timepoint. A patient may continue treatment until disease progression, death, unacceptable toxicity, subject withdrawal, or based on the investigator's decision, whichever occurred first.

When a patient discontinued treatment during the trial follow-up period and was available to complete a PRO questionnaire at that point in time, this PRO measurement then contributed to the EOT value in the graph. The patients' results move immediately to the right-hand side of the graph for their next PRO assessment following treatment discontinuation.

B4. Please tabulate the EQ-5D-5L index scores cross walked to the EQ-5D-3L UK value set, by progression status health state separately for (1) the ITT population of Ruby-1, (2) the dMMR/MSI-H population and (3) the ITT advanced population and (4) the ITT recurrent population.

The EQ-5D-5L data collected within the RUBY-1 trial were analysed to estimate progression status health state utility values as outlined in company submission (section B.1.1.1). Aligned with NICE preference, the EQ-5D-5L were mapped to provide EQ-5D-3L index scores using the crosswalk approach proposed by Hernández Alava M, Pudney S. (2022).[20]

The RUBY-1 trial was powered to show statistical significance for PFS in both ITT and dMMR/MSI-H populations. The trial was not powered to show statistical significance in HRQoL in the overall population or within any subgroups, and therefore HRQoL data for subgroups should be interpreted with caution.

Within the cost effectiveness analysis, the ITT population is the preferred source of HRQoL data due to the larger available sample of patient data, particularly in the progressed disease (PD) health state. The dMMR/MSI-H population was explored in scenario analysis as an alternative source of HRQoL data.

The EQ-5D index scores, on a cycle-by-cycle basis, have been for each of the requested populations, including primary advanced population [i.e., all patients with primary Stage 3 and primary Stage 4 disease status] (n=258) and the ITT recurrent population (n=236)]. These scores are presented in Table 37 - Table 40 below.

The cycle-by-cycle index values reported below demonstrate that there are only minor differences in values reported across the populations, across the time horizon captured. This gives further confidence that HRQoL results are consistent across the RUBY trial population.

Table 37. EQ-5D index scores dMMR/MSI-H population (cross walked to 3L and using UK value set)

Timepoint	Number of people		Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Number of people		Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
C23	[redacted]	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]	[redacted]
C25	[redacted]	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]	[redacted]
C27	[redacted]	[redacted]	[redacted]	[redacted]
C28	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]	[redacted]
SVFU5	[redacted]	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3.010201 Summary Statistics of EQ-5D Utility Scores by Visit UK Value Set ITT dMMR/MSS-H Population Data cutoff: 28 September 2022 Abbreviations: C – cycle; CI – confidence interval; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; ITT – intention to treat; NE – not estimable; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit; VAS – visual analogue scale.

Table 38. EQ-5D index scores ITT population (cross walked to 3L and using UK value set)

Timepoint	Number of people		Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Number of people		Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
C4	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]	[redacted]
C23	[redacted]	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]	[redacted]
C25	[redacted]	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	Number of people		Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Eligible (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
C27	[redacted]	[redacted]	[redacted]	[redacted]
C28	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]	[redacted]
SVFU5	[redacted]	[redacted]	[redacted]	[redacted]
SVFU6	[redacted]	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 3.010201 Summary Statistics of EQ-5D Utility Scores by Visit UK Value Set ITT dMMR/MSS-H Population Data cutoff: 28 September 2022 Abbreviations: C – cycle; CI – confidence interval; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; ITT – intention to treat; NE – not estimable; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit; VAS – visual analogue scale.

Table 39. EQ-5D index scores ITT recurrent population (cross walked to 3L and using UK value set)

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
C6	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]
C23	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]
C25	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]
C27	[redacted]	[redacted]	[redacted]

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
C28	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]
SVFU5	[redacted]	[redacted]	[redacted]
SVFU6	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]

Source: Table 3.010101 Summary Statistics of EQ-5D Utility Scores by Visit - ITT Recurrent Population UK Value Set Data cutoff: 28 September 2022 Note - For the recurrent ITT and advanced ITT subgroups the number of patients reporting EQ-5D values at each timepoint is available, however the number of patients eligible at each timepoint is not available. Abbreviations: C – cycle; CI – confidence interval; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; ITT – intention to treat; NE – not estimable; NE – not estimable; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit;

Table 40. EQ-5D index scores ITT advanced population (cross walked to 3L and using UK value set)

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
C6	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]
C9	[redacted]	[redacted]	[redacted]
C10	[redacted]	[redacted]	[redacted]
C11	[redacted]	[redacted]	[redacted]
C12	[redacted]	[redacted]	[redacted]
C13	[redacted]	[redacted]	[redacted]
C14	[redacted]	[redacted]	[redacted]
C15	[redacted]	[redacted]	[redacted]
C16	[redacted]	[redacted]	[redacted]
C17	[redacted]	[redacted]	[redacted]
C18	[redacted]	[redacted]	[redacted]
C19	[redacted]	[redacted]	[redacted]
C20	[redacted]	[redacted]	[redacted]
C21	[redacted]	[redacted]	[redacted]
C22	[redacted]	[redacted]	[redacted]
C23	[redacted]	[redacted]	[redacted]
C24	[redacted]	[redacted]	[redacted]
C25	[redacted]	[redacted]	[redacted]
C26	[redacted]	[redacted]	[redacted]
C27	[redacted]	[redacted]	[redacted]
C28	[redacted]	[redacted]	[redacted]

Timepoint	Number of people	Mean utility score Dostarlimab in combination with CP	Mean utility score Placebo in combination with CP
	Reporting (N)	Score (95% CI)	Score (95% CI)
EOT	[redacted]	[redacted]	[redacted]
SFV	[redacted]	[redacted]	[redacted]
SVFU1	[redacted]	[redacted]	[redacted]
SVFU2	[redacted]	[redacted]	[redacted]
SVFU3	[redacted]	[redacted]	[redacted]
SVFU4	[redacted]	[redacted]	[redacted]
SVFU5	[redacted]	[redacted]	[redacted]
SVFU6	[redacted]	[redacted]	[redacted]
SVFU7	[redacted]	[redacted]	[redacted]

Source: Table 3.010101 Summary Statistics of EQ-5D Utility Scores by Visit - ITT Recurrent Population UK Value Set Data cutoff: 28 September 2022 Note - For the recurrent ITT and advanced ITT subgroups the number of patients reporting EQ-5D values at each timepoint is available, however the number of patients eligible at each timepoint is not available. Abbreviations: C – cycle; CI – confidence interval; EOT – end of treatment; EQ-5D-5L – EuroQol five dimensions 5 levels; ITT – intention to treat; NE – not estimable; NE – not estimable; NR – not reported; QoL – quality of life; SFV – safety follow-up visit; SVFU – survival follow-up visit;

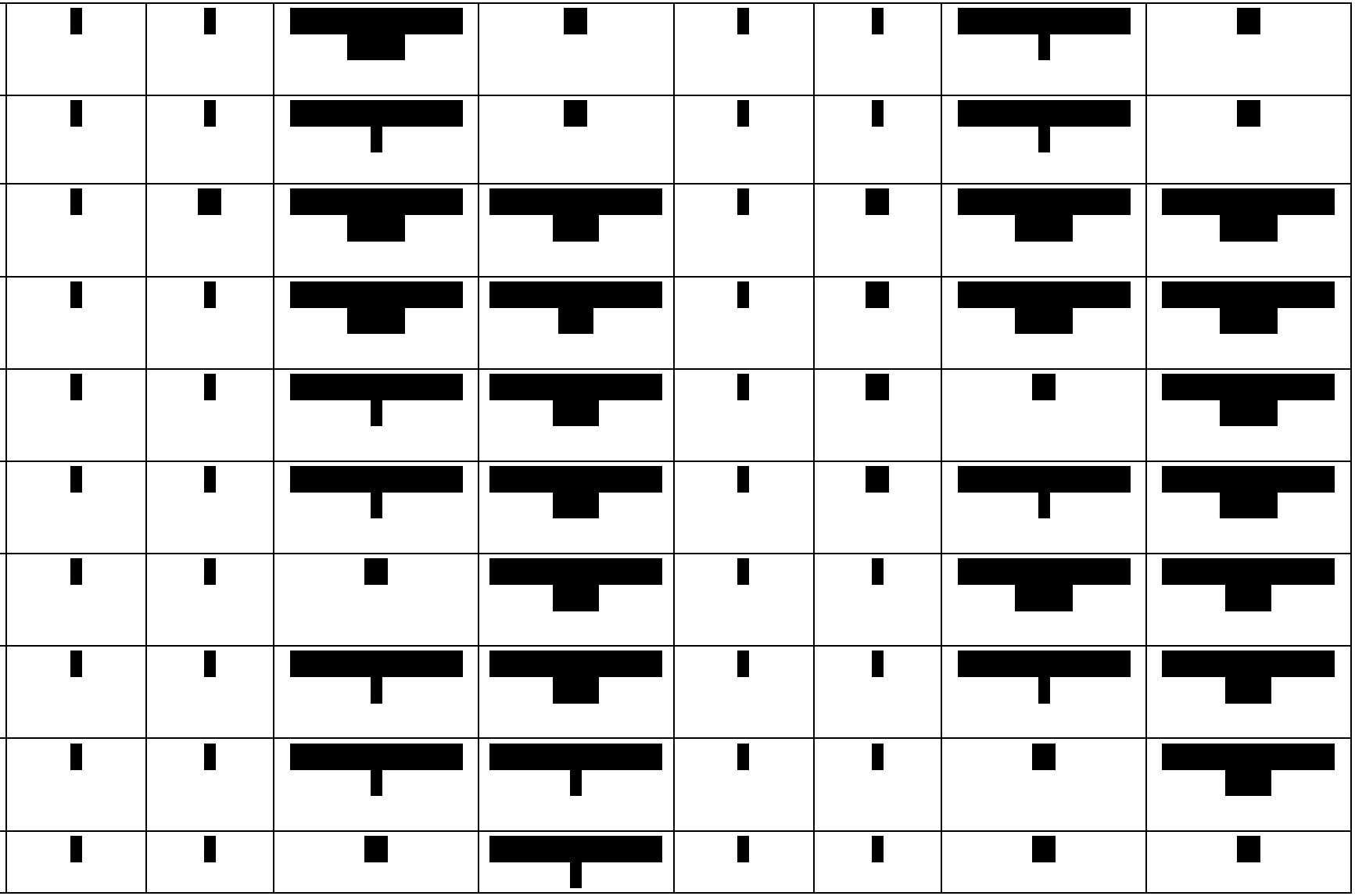
Additional analysis reporting the EQ-5D index scores, on a cycle-by-cycle basis, and also by disease progression status have been provided for each of the requested populations, including primary advanced population [i.e., all patients with primary Stage 3 and primary Stage 4 disease status] and the ITT recurrent population. These scores are presented in Table 41 to Table 44 below. The analyses further demonstrate that there are only minor differences in values reported across the populations when values are presented by progression health state. This gives further confidence that HRQoL results are consistent across the RUBY trial population.

Table 41: EQ-5D index scores dMMR/MSI-H population (cross walked to 3L and using UK value set) by disease status

Timepoint	Dostarlimab in combination with CP				Placebo in combination with CP			
	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed disease)	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed-disease)
	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C7								
C8								
C9								
C10								
C11								
C12								
C13								
C14								
C15								
C16								

C17								
C18								
C19								
C20								
C21								
C22								
C23								
C24								
C25								
C26								

C27								
C28								
EOT								
SFV								
SVFU1								
SVFU2								
SVFU3								
SVFU4								
SVFU5								
SVFU7								

Source: GSK data on file- ru_uk_t_stsat_p6
Abbreviations: CI – confidence interval; CP – carboplatin paclitaxel; NE – not estimable; SVFU – survival follow-up

Table 42: EQ-5D index scores ITT population (cross walked to 3L and using UK value set) by disease status.

Timepoint	Dostarlimab in combination with CP				Placebo in combination with CP			
	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed disease)	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed-disease)
	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C7								
C8								
C9								
C10								
C11								
C12								
C13								
C14								
C15								
C16								

C17								
C18								
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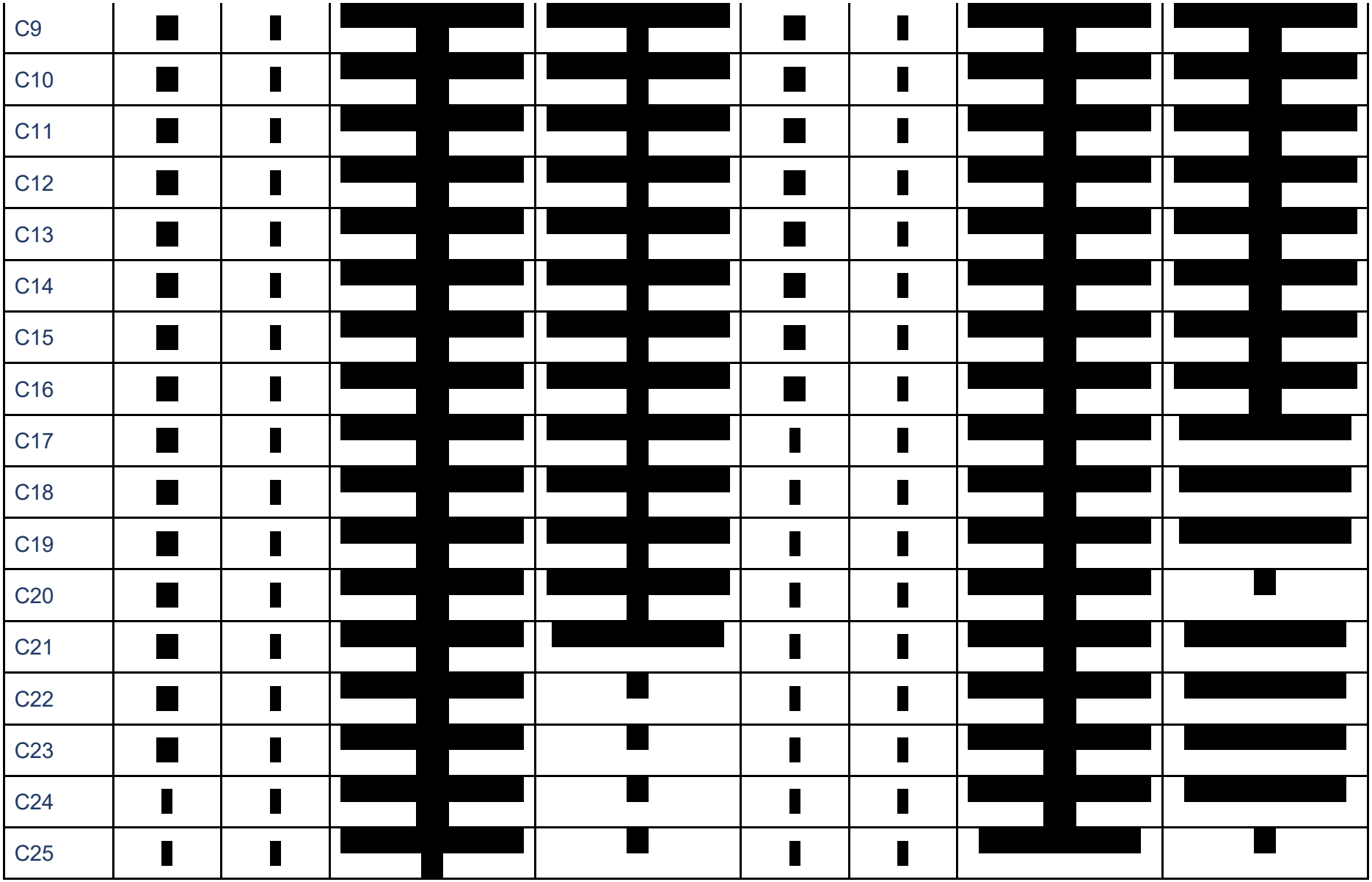
SVFU7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SVFU8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK data on file- ru_uk_t_stsat_p5
Abbreviations: CI – confidence interval; CP – carboplatin paclitaxel; NE – not estimable; SVFU – survival follow-up

Table 43: EQ-5D index scores ITT recurrent population (cross walked to 3L and using UK value set) by disease status

	Dostarlimab in combination with CP				Placebo in combination with CP			
Timepoint	Number of people (PF)	Number of people (PD)	Mean utility score (PF)	Mean utility score (PD)	Number of people (PF)	Number of people (PD)	Mean utility score (PF)	Mean utility score (progressed-disease)
	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]


C9
C10
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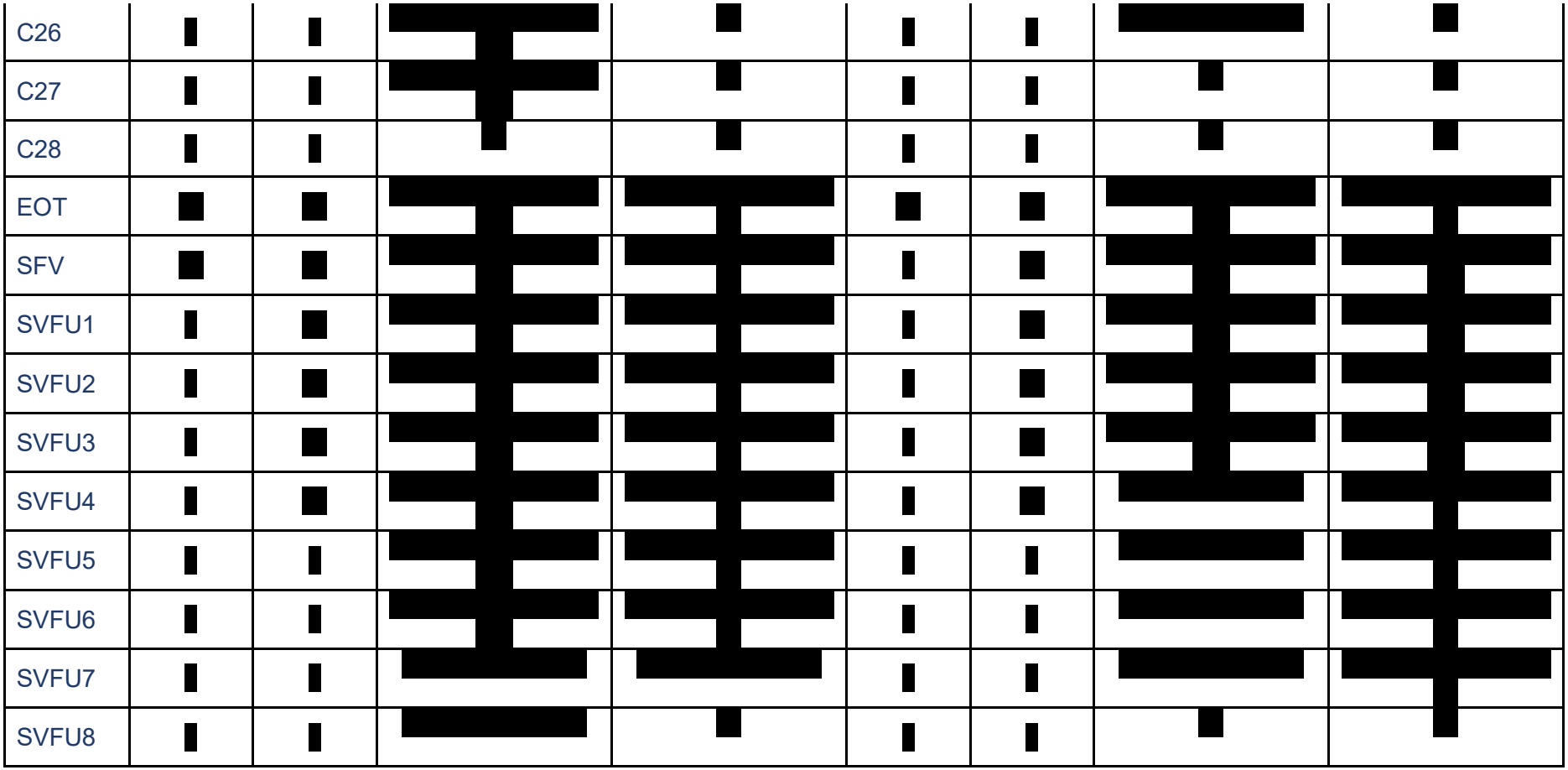

Source: GSK data on file- ru_uk_t_stsat_p7 Abbreviations: CI – confidence interval; CP – carboplatin paclitaxel; NE – not estimable; SVFU – survival follow-up

Table 44: EQ-5D index scores ITT advanced population (cross walked to 3L and using UK value set) by disease status

	Dostarlimab in combination with CP	Placebo in combination with CP

Timepoint	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed disease)	Number of people (progression-free)	Number of people (progressed disease)	Mean utility score (progression-free)	Mean utility score (progressed-disease)
	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)	Reporting (N)	Reporting (N)	Score (95% CI)	Score (95% CI)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C8								
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SVFU2								
SVFU3								
SVFU4								
SVFU5								
SVFU6								
SVFU7								

Source: GSK data on file- ru_uk_t_stsat_p8
Abbreviations: CI – confidence interval; CP – carboplatin paclitaxel; NE – not estimable; SVFU – survival follow-up

B5. Please provide health state utility values for PFS and PD health states as estimated from the Ruby-1 study for the following subgroups:

- ITT advanced

- ITT recurrent

- ITT recurrent and grade 4

The health state utility values by progression status have been calculated for the ITT primary advanced population [i.e., all patients with primary Stage 3 and primary Stage 4 disease status] (n=258) and the ITT recurrent population (n=236), and around outlined in Table 45. The overall ITT and dMMR/MSI-H health state utility values by progression status are included below for completeness.

Table 45. Health state utility values from RUBY trial

Health state	dMMR/MSI-H, mean (SE*)	ITT, mean (SE*)	ITT primary advanced population, mean (SE*)	ITT recurrent population, mean (SE*)
PFS	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PD – progressed disease; PFS – progression-free survival; SD – standard deviation. Note. Progression status determined by investigator. *SE calculated from lower and upper bounds assuming the a normal distribution. Source: CS, Table 51; GSK Data on File 'Table 3.060101 ru_uk_t_modest_pfsinv_m1_p2.rtf'; GSK Data on File 'Table 3.060201 ru_uk_t_modest_pfsinv_m1_p1.rtf'

The health state utility values for the ITT 'recurrent and primary Stage 4 patients' are not available. The HRQoL results for primary Stage 4 patients are included within the ITT advanced population utility values, in addition to patients with primary Stage 3 disease.

The utility values reported in Table 45 demonstrate that there are only minor differences between utilities reported for PFS health states (+/- 0.04) and the utilities reports for PD health states (+/- 0.05) across each of the provided populations and subgroups. This gives confidence that the utility value for PFS and PD is consistent across the RUBY trial population. Any further analysis of subgroups is not informative.

Furthermore, the RUBY-1 trial has demonstrated numerical benefits in HRQoL for patients treated with dostarlimab in combination with CP, in both the ITT and dMMR/MSI-H subgroups. These statistically significant results included the results

for patients with recurrent, primary Stage 3 and primary Stage 4. The utility analysis provided above aims to provide further clarity as requested by the EAG, while also aligning with the broad patient population in whom HRQoL was assessed in the RUBY-1 trial.

Section C: Textual clarification and additional points

C1. In the reference pack, we are not sure whether or not the document files for three of the 'data on file' references have been supplied:

46. [GSK Data on File]. Dostarlimab MOA for Jemperli. 2023b., which is cited as a source in CS Doc B for Figure 1: Mechanism of action for dostarlimab.

The reference has now been provided under the title '[GSK Data on File] Dostarlimab mechanism of action'.

71. [GSK Data on file] A Phase 3, Randomised, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)., which is cited as a source in CS doc B Table 23: Patient baseline characteristics for the base case economic analysis and section B1.4.1.1 Chemotherapy (PCC) second paragraph.

The reference for Table 23 should be replaced with the reference already provided named '[GSK Data on File] RUBY CSR'.

102. [GSK Data on file] UK Advisory Board: Advanced Endometrial Cancer Survival Outcomes. April 2023., which is cited as a source in CS Doc B for section B2.7.1 Subgroup analysis of PFS and OS paragraph 4, section B3.5 Cost and healthcare resource use identification, measurement and valuation in paragraph 4, and section B3.16 Conclusion final paragraph. This may be a duplicate reference to CS Doc B reference 4 filename 'GSK 2023b', which has a relevant looking title on the title page within the PDF, but says March 2023 on the title page (whereas this reference includes the date April 2023). Note that

there is a different PDF with filename '[GSK Data on File] UK Advisory Board Advanced Endometrial Cancer Survival Outcomes', but on opening this file, the title is 'GSK UK Advisory Board: External Insights into the RUBY Data'

The company appendices mention collecting healthcare resource use (HCRU) data from a panel of clinical experts following the meeting in April 2023. The EAG is unable to find any compilation of output from this activity, nor an example data capture form.

Please supply any missing documents or clarify which files in the reference pack relate to these references.

The provided PDF named '[GSK Data on File] UK Advisory Board Advanced Endometrial Survival Outcomes' has been wrongly named and should be named '[GSK Data on File] GSK UK Advisory Board: External Insights into the RUBY Data' as is stated on the title page of the document, which is also the same PDF as that of 'GSK 2023a'. This is the document to be referred to as both the source in Section B2.7.1 and for healthcare resource use.

The collected healthcare resource use data has now been provided in the Excel document titled '[GSK Data on File] HCRU Output Data'.

C2. Clinical SLR: Please provide a list of SR references (and PDFs if available) that were checked in this part of the search: 'checking references of up to five of the most comprehensive, recent, relevant SRs found via database searches'.

The list of SLRs that were searched as part of the citation-chasing exercise is presented in Table 46. As a correction, a total of 12 SLRs were searched instead of five as previously stated.

Table 46: SLRs searched – Clinical SLR

Author	Publication
Yi, L., Zhang, H., Zou, J., Zhang, J.[21]	Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 2018 Jun;149(3):612-619. doi: 10.1016/j.ygyno.2018.03.004. Epub 2018 Mar 9. PMID: 29530332.

Author	Publication
Ao, M., Ding, T., Xi, M.[22]	Efficacy and Toxicity of Adjuvant Therapies for High-Risk Endometrial Cancer in Stage I-III: A Systematic Review and Network Meta-Analysis. Med Sci Monit. 2020 Sep 20;26:e925595. doi: 10.12659/MSM.925595. PMID: 32950998; PMCID: PMC7526341.
Chen, H., Liang, M, Min, J.[23]	Efficacy and Safety of Bevacizumab-Combined Chemotherapy for Advanced and Recurrent Endometrial Cancer: A Systematic Review and Meta-analysis. Balkan medical journal. 2021 Jan 1;38(1).
Vale, C.L., Tierney, J., Bull, S.J., Symonds, P.R.[24]	Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma. Cochrane Database of Systematic Reviews. 2012(8).
Xiang, X., Wang, J., Ding, Z.[25]	Efficacy of chemotherapy versus chemoradiotherapy for locally advanced endometrial cancer: a systematic review and meta-analysis. Precision Radiation Oncology. 2021 Mar;5(1):43-9.
Dahl, L., Wittrup, I., Vaeggemose, U., Petersen, L. K., Blaakaer, J.[26]	Life after gynecologic cancer-A review of patients quality of life, needs, and preferences in regard to follow-up. International Journal of Gynecological Cancer. 2013. 23(2):227-234
Narasimhulu, D.M, Block, M.S., Weaver, A.L., McGree, M., Kumar, A., Langstraat, C., Petersen, I., Mariani, A., Glaser, G.[27]	Sequencing chemotherapy before radiotherapy for women with stage IIIC endometrial cancer. Int J Gynecol Cancer. 2021 May;31(5):702-708. doi: 10.1136/ijgc-2020-002158.
Pourrahmat, M.M., Kim, A., Kansal, A.R., Hux, M., Pushkarna, D., Fazeli, M.S., Chung, K.C.[28]	Health state utility values by cancer stage: a systematic literature review. The European Journal of Health Economics. 2021 Nov;22(8):1275-88.
Winarto, H.,Ibrahim, N. A. A.,Putri, Y. M.,Adnan, Fdsf,Safitri, E. D..[29]	Adjuvant chemoradiotherapy versus chemotherapy or radiotherapy in advanced endometrial cancer: a systematic review and meta-analysis. PeerJ. 2022. 10:e14420
Maiorano, B. A.,Maiorano, M. F. P.,Cormio, G.,Maglione, A.,Lorusso, D.,Maiello, E..[30]	How Immunotherapy Modified the Therapeutic Scenario of Endometrial Cancer: A Systematic Review. Frontiers in Oncology. 2022. 12:844801
Cao, S.Y., Fan, Y., Zhang, Y.F., Ruan, J.Y., Mu, Y., Li, J.K.[31]	Recurrence and survival of patients with stage III endometrial cancer after radical surgery followed by adjuvant chemo- or chemoradiotherapy: a systematic review and meta-analysis. BMC Cancer. 2023 Jan 9;23(1):31. doi: 10.1186/s12885-022-10482-x. PMID: 36624407; PMCID: PMC9827697.

Author	Publication
Kok, P.S., Antill, Y.C., Scott, C.L., Lee, C.K.[32]	The impact of single agent PD-1 or PD-L1 inhibition on advanced endometrial cancers: meta-analysis. ESMO Open. 2022 Dec;7(6):100635. doi: 10.1016/j.esmoop.2022.100635. Epub 2022 Nov 18. PMID: 36410086; PMCID: PMC9808459.

Abbreviations: SLR – systematic literature review

C3. Clinical SLR: A number of relevant conferences are listed in CS Appendices Table 4. Please clarify if these conferences were searched directly via each conference website in addition to the Embase search.

The searches were conducted by reviewing gynaecological cancer-related conference proceedings from the past three years, with cross-reference checks from relevant published SLRs. Where applicable, indexed conference abstracts were searched directly in Embase, while those that were not indexed were searched in abstract books. Conferences indexed in Embase were searched directly in Embase for efficiency, with no additional searches conducted via the conference website. The platforms used for each search are detailed in Table 47.

Table 47: Conference searches – Original SLR and SLR refresh

Source	Original SLR (10 November 2021)	SLR refresh (22 February 2023)
AACR	2019-2021: Embase (via OvidSP)	2021: All listed meetings were held before 10 November 2021, therefore they were already searched and screened in the original SLR 2022: Embase (via OvidSP) 2023: Not held yet
ASCO	2019-2021: Embase (via OvidSP)	
ESMO	2019-2021: Embase (via OvidSP)	
ESGO	2019-2020: Embase (via OvidSP) 2021: https://ijgc.bmj.com/content/31/Suppl_3	
IGCS	2019-2020: Embase (via OvidSP) 2021: https://igcs.org/education-resources/global-meeting/	
NCCN	2019: https://jnccn.org/view/journals/jnccn/17/3.5/jnccn.17.issue-3.5.xml 2020: https://jnccn.org/view/journals/jnccn/18/3.5/jnccn.18.issue-3.5.xml 2021: https://jnccn.org/view/journals/jnccn/19/3.5/jnccn.19.issue-3.5.xml	
SGO	2019-2021: Embase (via OvidSP)	

Source	Original SLR (10 November 2021)	SLR refresh (22 February 2023)
SITC	2018-2020: Embase (via OvidSP)	2021: Embase (via OvidSP) 2022: Embase (via OvidSP) 2023: Not held yet
ISPOR	2019-2020: Embase (via OvidSP) 2021: https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2021/program/posters (held virtually May 17–20)	
BGCS	2019: https://www.bgcs.org.uk/wp-content/uploads/2021/01/BGCS-2019-Abstract-Book-18.07.19335-1.pdf 2020: meeting cancelled for 2020. 2021: https://www.bgcs.org.uk/wp-content/uploads/2021/05/BGCS-2021-Book-of-Abstracts.pdf	2021: Meeting was held before Nov 10 in 2021, therefore it was already searched and screened in the original SLR 2022: https://www.bgcs.org.uk/wp-content/uploads/2022/07/BGCS-2022-Book-of-Abstracts-.pdf 2023: Not held yet

Abbreviations: AACR - American Association for Cancer Research; ASCO - American Society of Clinical Oncology; BGCS - British Gynaecological Cancer Society; ESGO - European Society of Gynaecological Oncology; ESMO - European Society for Medical Oncology; IGCS - International Gynecologic Cancer Society; ISPOR - International Society for Pharmacoeconomics and Outcomes Research; NCCN - National Comprehensive Cancer Network; SGO - Society of Gynecologic Oncology; SITC - Society for Immunotherapy of Cancer; SLR - systematic literature review

C4. All SLRs: thank you for providing tables of records excluded at full text (with reasons) from database searches. For each SLR, please provide a table or list of records excluded at full text (with reasons) from other sources.

A list of excluded studies from grey literature sources for each SLR question are presented in Excel documents.[33–36] No relevant studies were identified or excluded from grey literature sources for the HRQoL SLR.

Section D: References

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34. GSK. [GSK data on file] Excluded studies from grey literature sources - Cost and healthcare resource use studies SLR.

35. GSK. [GSK data on file] Excluded studies from grey literature sources - Cost-effectiveness studies SLR.

36. GSK. [GSK data on file] Excluded studies from grey literature sources - Clinical SLR.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer ID3968

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Peaches Womb Cancer Trust
3. Job title or position	Trustee
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.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Peaches Womb Cancer Trust has received several payments from GlaxoSmithKline (GSK) over the past few years. These grants are unrelated to a product mentioned in the stakeholder list except for review of the 'Jemperli' booklet (point 3. below): 1. £2512 payment received in Oct 2023 for employee and trustee time spent on an awareness campaign that involved collaboration with GSK and another gynae charity. 2. £9,960 grant received in Jan 2023 to create a series of bite-sized videos that will be hosted on Peaches website to provide support to people affected by womb cancer. 3. £240 payment received in May 2022 for review of 'Jemperli' (dostarlimab) booklet. 4. £180 payment received in Dec 2021 for a presentation on womb cancer delivered to GSK employees. 5. £8000 grant received in 2021 to fund merchandise and distribution costs of Clinical Nurse Specialist information packs for patients. Peaches Womb Cancer Trust also received a £100 honorarium from Eisai in Oct 2022 for a trustee's attendance at an endometrial cancer advisory meeting.

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?	This submission has been compiled from information obtained from members of Peaches Patient Voices, Peaches' patient and public involvement group for people affected by womb cancer. As well as including information obtained via focus group and questionnaire that informed our previous submission (ID3811), we recently conducted a further focus group and asked women with lived experience of advanced or recurrent endometrial cancer to complete a questionnaire. The focus groups included women with stage 3 and 4 endometrial cancer and, in the recent focus group, two carers of women with stage 4 endometrial cancer who had undergone primary treatment with surgery and/or chemotherapy and radiotherapy. The questionnaire was completed by six women: three with stage 3 endometrial cancer, one who had twice undergone investigations for possible recurrence, one whose mother had died following distant (gastric) recurrence of endometrial cancer, and one with recurrent endometrial cancer who has experience of the technology. This woman was initially treated for stage 3 endometrial cancer with a total hysterectomy, six cycles of carboplatin and paclitaxel, and 25 sessions of external beam radiotherapy. Recurrence in both her vagina and lungs 14 months later was inoperable. This recurrence has so far been treated with dostarlimab and four cycles of carboplatin and paclitaxel. A scan carried out after the third cycle of chemotherapy showed a reduction in size of her lung lesions and no new tumours. The focus group discussions and questionnaire responses focused on living with advanced or recurrent endometrial cancer and experiences with current treatments and, in the case of the woman treated with dostarlimab with carboplatin and paclitaxel for recurrence, their perspective so far on the advantages and disadvantages of the technology.

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. One of the women with stage 4 disease had ascites 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. Following her diagnosis of recurrence, she also required bilateral nephrostomies due to ureteric obstruction, which impacted her physically, reducing her mobility. Many women experienced diagnosis-induced feelings of terror and fear at having to face one's own mortality, and many 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. *"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 taking [an anti-depressant], something I never thought I would do. I was a successful [professional] for 19 years and coped well with everything that was thrown at me, I had [treatment for] breast cancer [several years ago] but sailed through it, this has been so much harder. " *"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."* 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?**	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 try and reduce the side effects, but found they also experienced other side effects from the additional 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 not being able to work face to face or requiring time off work, or unable to go out and spend time with family and friends or 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."* Long term side effects of current first line treatments for 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: *"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."* Furthermore, many 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. *"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."*

	"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".* A small number of women were unable to live fully independently due to physical symptoms and limited mobility, meaning they 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. Treatments including hysterectomy and radiotherapy also significantly impacted on sexual intimacy due to vaginal discomfort, bleeding and the vulnerability that comes with repeated intimate examinations.

	Furthermore, current treatments impacted on women's lives financially, both through the time it takes to receive treatment and the long-term side effects. This included; cost of travel to and parking at hospital, long term sick leave with implications to pay, and cost of living at home (e.g. heating) and alternative therapies. *"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."*

8. Is there an unmet need for patients with this condition?	Many women expressed frustration, disappointment, anger and feelings of being abandoned due to limited effective first line treatment options for advanced and recurrent endometrial cancer. They felt that women affected by endometrial cancer had fewer effective treatment options compared with other cancers. *"Endometrial cancer, with a predominately older woman, post-menopausal demographic, is considered something of an old woman's cancer and of little interest to society."* *"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 that would be offered to me in the NHS would be 'bog standard chemotherapy' as first line, filled me with dread and fear."* "*The UK has some of the poorest cancer survival rates as compared to Europe. However, where improvements in cancer survival rates are seen [it] is in those cancer[s] where a combined treatment approach is clinically available on the NHS, involving traditional chemotherapy plus newer targeted type treatments. In many cancer[s], 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 these newer cancer treatments may offer."* *"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 which will further reduce the chance of the cancer recurring."* *"[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."* *"Recurrent cancer is just given top up chemotherapy and there are very little alternatives available. There are little or no options available especially specific to womb cancer."*

Advantages of the technology **9. What do patients or carers think are the advantages of the technology?**	Patients want access to a first line targeted treatment that reduces the chance of recurrence and extends progression free survival, but also one that gives them a better overall quality of life, time with family and friends, and hope of living a meaningful life: *"[I want] the cancer to be gone and the risk of recurrence to be hugely, (ideally completely), eliminated"* *"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."* The patient who is currently being treated with the technology describes how she is: *"Hopeful [that] this new regime will be kinder and more effective. The new immunotherapy drug has given me a glimmer of hope. I want to live. I want a reasonable quality of life for a good few years. I am hoping this gives me a longer chance of progression free survival."* Although dostarlimab and carboplatin with paclitaxel cause side effects, the woman with recurrence explained how she was: *"Willing to put up with the short term side effects if it gives me a [better] chance of survival."* She described how access to this technology has given her hope of living long enough to attend her youngest son's wedding and to be able to support her elderly parents. She also hopes to hear her grand-daughter say 'granny' and see her start school, to see her grandsons start secondary school, and to be well enough to help with the school run and have the grandchildren stay for sleepovers. She is also hopeful that she can resume her plans plans for retirement, including spending time with family and friends and enjoying activities such as travelling, skiing, riding her mountain bike and playing tennis. *"All of this hope would have been dashed without the dostarlimab. Until I heard I'd got this new drug, I didn't actually expect to see Christmas! It's given the whole family a glimmer of hope that I might be around for a few more years and well enough to enjoy those years."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients find treatment with carboplatin and paclitaxel challenging due to the side effects described above and the requirement spend all day in the chemotherapy unit on the day of infusions: *"It's a long day, eight hours every three weeks."* She describes how she has experienced worse fatigue than when her primary tumour was treated and how there have been some effects on her blood magnesium levels and haemoglobin: *"I have one complete day when I can do nothing, I get exhausted walking up stairs."* *"I'm taking magnesium supplements for low levels which hasn't happened before, and I know my haemoglobin levels are low."* However, once the course of chemotherapy has finished, it is anticipated that ongoing treatment with dostarlimab will be less burdensome although uncertainty around continuing side effects due to dostarlimab causes concern: *"It's the fear of the unknown, not knowing what side effects I might get, how they might be controlled."* *"I do worry about the side effects of the dostarlimab, it's hard to know what is causing what!*

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.	Certain subgroups of endometrial cancer tumours have been shown to have a better response to the technology than others. In particular, that includes those tumours with mismatch repair deficiency.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There are limited effective treatment options for women with first line advanced and recurrent endometrial cancer, leaving them feeling frustrated, hopeless and abandoned. • Women want equal opportunity for effective treatment options as others suffering from different cancers • Women want treatment options that will increase life expectancy and give them hope of living a meaningful life for longer. • The impact of current treatments differs between individuals, but many would accept some increase in treatment side effects for improved long-term survival.

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External assessment group report for dostarlimab with platinum-containing chemotherapy for primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

Produced by *Warwick Evidence*

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Rider on responsibility for report
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Executive Summary

0 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

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 0.5 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 (beginning on page 17).

All issues identified represent the EAG's view, not the opinion of NICE.

0.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID3968	Summary of issue	Report sections
1	No comparison to pembrolizumab + lenvatinib. A comparison is not possible however this is a relevant comparator for a subgroup of patients.	1.3, 2.3
2	Suitability of RUBY-1 trial to provide a reliable estimate of the relative benefit additional treatment with dostarlimab in the dMMR/MSI-H subgroup due to limited follow-up, small sample size, low average population age, randomisation issues and a lack of information for subgroups described in the decision problem.	2.2
3	Lack of efficacy in the primary stage III subgroup, consistent across the dMMR and MMRp subgroups of the RUBY-1 trial.	2.2.3.7
4	The extent of progression-free survival benefit modelled by company is not justified from the trial follow-up	3.2.6.2
5	The extent of overall survival benefit modelled by company is not supported by the observed trial follow-up	3.2.6.3
6	Lack of data on adverse events (AEs). Trial follow-up is unlikely to capture full extent of AEs. Additional monitoring costs associated with immune related AEs are not captured in company base case.	3.2.7.1, 3.2.8
7	Lack of data on subsequent treatments received for both arms, and their potential impact on costs and benefits.	3.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

The company prefers PFS and OS extrapolations which predict a large benefit associated with dostarlimab+CP.

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 progression-free survival and overall survival

Overall, the technology is modelled to affect costs by:

- Its higher unit cost, and it is taken in addition to the comparator
- Additional monitoring costs for treatment related adverse events

The modelling assumptions that have the greatest effect on the ICER are:

- The magnitude of benefit of overall survival

0.3 The decision problem: summary of the EAG's key issues

Issue 1: Lack of comparison to pembrolizumab+lenvatinib

Report section	1.3, 2.3
Description of issue and why the EAG has identified it as important	The EAG understands that patients who receive adjuvant or neo-adjuvant chemotherapy alongside surgery may be eligible for either dostarlimab+CP or pembrolizumab + lenvatinib. This is a likely to be a minority of patients, however patients would prefer to receive the most efficacious treatment as it is unlikely they would be eligible to receive both treatments based on the expected treatment pathway and licensing restrictions.
What alternative approach has the EAG suggested?	No comparison is possible due to a lack of data availability for the relevant subgroups from the trials of interest.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	More detailed reporting of existing trials (RUBY-1 and KEYNOTE-775) may permit an indirect treatment comparison. Otherwise a comparison will require additional data generation.

0.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2: Suitability of RUBY-1 data for estimating benefit of dostarlimab+CP

Report section	2.2
Description of issue and why the EAG has identified it as important	The EAG is concerned with the suitability of RUBY-1 trial to provide reliable estimate of benefit of dostarlimab therapy received in addition to chemotherapy in the dMMR/MSI-H population. The small sample size and limited follow-up, combined with randomisation issues, lower average age at recruitment and lack of data to allow exploration of subgroups described in the decision problem, mean there is uncertainty over the suitability of the currently available data.
What alternative approach has the EAG suggested?	The EAG is unable to resolve many of these associated limitations, as it did not identify any other data sources for these. However, increasing the age at baseline to 67.1 years was supported by several alternative literature sources and EAG clinical expert opinion.
What is the expected effect on the cost-effectiveness estimates?	Increasing age of the population at baseline increases the ICER by £[redacted]. The other factors influencing trial suitability could not be explored in the economic model. The true benefit gained from dostarlimab+CP may be very different to what has been observed for this subgroup of the RUBY-1 trial.
What additional evidence or analyses might help to resolve this key issue?	Further follow-up from RUBY-1 combined with novel data generation would reduce the uncertainty in the estimates of long-term efficacy and allow exploration of key subgroups

Issue 3: Lack of efficacy in people with stage III disease

Report section	2.2.3.7
Description of issue and why the EAG has identified it as important	The EAG notes a lack of efficacy in RUBY-1 study among people with stage III disease. This effect is persistent across the dMMR/MSI-H and MMRp subgroups. This observation could have occurred by chance or may indicate that people with stage III disease gain little or no benefit from additional dostarlimab therapy.
What alternative approach has the EAG suggested?	The EAG has not been able to exclude these patients from the clinical or cost-effectiveness analyses.
What is the expected effect on the cost-effectiveness estimates?	The effect could not be explored in the economic model. If dostarlimab therapy was proven not to be effective in this population then excluding these people from consideration would likely improve cost-effectiveness in the remaining population, however prognostic differences may act as confounders.
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up from RUBY-1 and novel data generation designed to explore this hypothesis would reduce the uncertainty on this issue.

0.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4: Uncertain degree of progression-free survival benefit

Report section	3.2.6.2
Description of issue and why the EAG has identified it as important	The company models a substantial benefit of progression-free survival for dostarlimab which is sustained for the duration of the model. The EAG regard this as implausible as there is no rationale why the long term PFS rates would differ between people with good responses to either treatment.
What alternative approach has the EAG suggested?	The EAG has selected a different approach to extrapolating PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred PFS assumptions to the company's base case increases the ICER by: [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up and novel data collection would assist with reducing the uncertainty about the future PFS benefit.

Issue 5: Uncertain degree of overall survival benefit

Report section	3.2.6.3
Description of issue and why the EAG has identified it as important	The company models a substantial survival benefit for dostarlimab which is sustained for the duration of the model. The EAG regard this as inconsistent with the currently available data, and without justification as to why the long term hazard rate would differ for people who respond well to either treatment.
What alternative approach has the EAG suggested?	The EAG use a different approach for extrapolation of OS. (1) For placebo+CP, the EAG maintain a log-logistic extrapolation but do not use a piecewise approach. (2) For dostarlimab+CP the EAG applies an exponential model and converges the hazard rates over a 3-year period from 80 weeks.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG's preferred OS assumptions to the company's base case increases the ICER by: (1) [redacted] and (2) [redacted] (note cumulative change of 1 & 2, as 2 could not be applied without 1)
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up and novel data collection would assist with reducing the uncertainty about the future OS benefit.

Issue 6: Unknown usage, costs and effects of subsequent therapies

Report section	3.2.7.1, 3.2.8
Description of issue and why the EAG has identified it as important	Robust information on subsequent treatment use is not available. RUBY-1 data is immature and may not be generalisable to England. Treatments could substantially influence the cost-effectiveness
What alternative approach has the EAG suggested?	The EAG explores some scenarios varying the costs of subsequent therapies.
What is the expected effect on the cost-effectiveness estimates?	Current sensitivity analyses suggest the costs have a small effect on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Data collection in the UK could reduce this uncertainty.

Issue 7: Underrepresentation of Adverse Events

Report section	3.2.8
Description of issue and why the EAG has identified it as important	The current limited follow-up and sample size mean it is likely that AEs are under-reported and their impact underestimated in the company's base case. The risk of immune related adverse events is associated with additional patient monitoring, which is not captured in the company's base case.
What alternative approach has the EAG suggested?	The EAG (1) applies AE disutilities for a broader profile of adverse events at grade 3 and above and (2) incorporates additional monitoring costs into the EAG base
What is the expected effect on the cost-effectiveness estimates?	These changes increase the company base case ICER by: (1) [redacted] and (2) [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up from RUBY-1 and greater consultation over the potential implementation of dostarlimab+CP may reduce the uncertainties associated with AEs.

0.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	4.26	[redacted]
Starting age at baseline 67.1 years. Issue 2, suitability of RUBY-1 data for estimating benefit of dostarlimab+CP	[redacted]	3.93	[redacted]
EAG prefer a different approach to extrapolating PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation. Issue 4, uncertain degree of PFS benefit	[redacted]	4.10	[redacted]
EAG prefer a different approach to the extrapolation of OS. The EAG maintain a log-logistic extrapolation for placebo+CP, but do not use a piecewise approach. Issue 5, uncertain degree of OS benefit	[redacted]	4.22	[redacted]
EAG prefer a different approach to the extrapolation of OS. The EAG applies an exponential model for dostarlimab+CP and converges the hazard rates over a 3-year period from 80 weeks. (The log-logistic extrapolation without piecewise approach is maintained for placebo+CP in this analysis). Issue 5, uncertain degree of OS benefit	[redacted]	1.55	[redacted]
The EAG prefer inclusion of a broader range of AE disutilities at grade 3 and above. Issue 7, underrepresentation of adverse events	[redacted]	4.26	[redacted]
The EAG prefer higher estimates of resource use for outpatient visits in the dostarlimab+CP arm (increased to 0.23 outpatient visits per week from cycle 19+) to reflect more appropriate monitoring costs due to AEs in this treatment arm. Issue 7, underrepresentation of adverse events.	[redacted]	4.26	[redacted]
EAG's preferred base case (incorporating all EAG preferences as outlined)	[redacted]	1.50	[redacted]

Abbreviations

AE	Adverse events
BMI	Body mass index
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CP	Carboplatin-Paclitaxel
CR	Complete response
CS	Company Submission
CSR	Clinical study report
DOR	Duration of response
dMMR/MSI-H	Mismatch repair deficient or high microsatellite instability high
EAG	External Assessment Group
EC	Endometrial Cancer
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol five dimension
ESMO	European Society for Medical Oncology
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State Utility value
HTA	Health Technology Assessments
ICER	Incremental Cost-Effectiveness Ratios
IPI	International Prognostic Index
IQR	Interquartile range
irAE	Immune related adverse events
IRC	Independent review committee
ITC	Indirect treatment comparisons
KM	Kaplan-Meier
LY	Life Year
MMRp/MSS	Mismatch repair proficient or microsatellite stable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OR	Odds ratio
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Time from randomisation until progression on subsequent treatment
PICOS	Population, intervention, comparators, outcomes, and study design
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes

PS	Performance status
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCTs	Randomised controlled trials
RWE	Real-world evidence
SD	Standard deviation
SLR	Systematic literature review
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

Remit of the appraisal

To appraise the clinical and cost effectiveness of dostarlimab in combination with carboplatin and paclitaxel (dostarlimab+CP) within its marketing authorisation for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency.

Condition, symptoms and economic burden

Endometrial cancer (EC) originates in the endometrium, which is the lining of the uterus. It is sometimes referred to as uterine cancer, which is a general name for a group of cancers of which endometrial is the most common.[1]

EC is associated with a range of symptoms, however usual presentation involves abnormal or sustained vaginal bleeding.[2, 3] Quality of life can be affected a reduction in the ability to perform daily activities and in confidence.[4, 5] Additionally, endometrial cancer is associated with menopausal like symptoms, anxiety and sexual dysfunction.[6-8]

The company reports that roughly 8,000 cases of endometrial cancer are diagnosed each year, with just over quarter of these being primary advanced or recurrent disease. Within this group it is estimated that 20-25% will have high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) endometrial cancer and be eligible for this indication if they are not suitable for surgery.

Further details can be found in the CS sections B1.3-1.4.

1.2 Background

Critique of the company's description of the health condition

The EAG broadly agrees with the description of the underlying health condition. CS Section B1.3.1 to B1.3.3 provide a summary overview of EC and the main types.

The description of the clinical presentation for primary advanced or recurrent EC appears to appropriately reflect the types of symptoms people can have. The company's description of disease severity and staging of EC reflect internationally recognised approaches.[9, 10] The CS describe stage III or stage IV EC as advanced disease cancer where complete surgical resection is not possible and there is some residual tumour remaining, which appears to be appropriate from the source and clinical information given to the EAG.[11] The CS report that disease recurrence is where disease that is not detectable after primary treatment then becomes either radiologically or histologically detected again at a later point in time.[12] The EAG add that this recurrence was stated to be within a period of three years of follow-up in the cited publication and that for the radiological detected recurrences this was the case when no concomitant cancer could explain the finding.[12] The EAG clinical expert confirmed that recurrence is usually detected by CT scanning and clinical examination.

The CS describes the molecular classification of EC, reflecting international guidelines appropriately [11, 13] highlighting in particular the importance of considering these in establishing appropriate treatments for someone with EC. The focus of the CS discussion of molecular classifications is on dMMR/MSI-H, as appropriate to the NICE scope (see Section 1.3).

The company reports that people with advanced or recurrent disease have poorer outcomes and that these people are treated with a low potential for cure by radiotherapy, surgery, alone or in combination (CS 1.3.3.5). This links to the population in the pivotal trial used in the CS (see Section 2.2.2.1). Clinical advice to the EAG is that there is no clear definition for 'low potential for cure' and that in the NHS a multi-disciplinary team discussion would be required to determine if surgery or salvage radiotherapy are appropriate options for people with stage III and stage IV EC. The EAG was also advised that in recurrent disease people who were previously stage I, II and III may be suitable for radiotherapy.

Critique of the company's overview of the position of the technology in the treatment pathway

The CS describes the clinical pathway for people with advanced or recurrent EC in Section B1.4.2.4 and Figure 2. The EAG notes that this is a simplification of what is a complicated treatment pathway, and highlight the following:

- People with advanced EC (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 EC will have surgery +/- neoadjuvant/adjuvant treatment. These people would then be monitored and first line treatment considered subsequently. People with stage IV EC 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 EC.
- The potential positioning of dostarlimab as an addition to carboplatin and paclitaxel at first line therapy is appropriate, although the number of cycles of carboplatin and paclitaxel used in UK practice may differ from the use in the pivotal trial informing the CS (Section 2.2.2.2).

1.3 Critique of company's definition of decision problem

The decision problem provided by the company (CS Section B1.1) is broadly consistent with the NICE scope with the EAG main issue relating to the population as described in Table 3.

Table 3: 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 high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)	Adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer and who are candidates for systemic therapy.	Population updated to align with regulatory approach and anticipated license indication [NB this was in response to the original NICE final scope which was updated by NICE after the submission of the CS. The original final scope stated: people with primary advanced or recurrent endometrial cancer].	The EAG agrees that the population is generally consistent with the NICE final scope. The CS decision problem has included a focus on people with EC who are candidates for systemic therapy. The EAG has been unable to identify any specific criteria to identify people who would be a candidate for systemic therapy in the submitted evidence (see 2.2.2.1). The EAG clinical advisor confirmed that there is no objective criteria and that clinical judgement is used depending on factors including the characteristics of the patient, their disease and their clinical status and the anticipated clinical benefit / intention of the systemic therapy. While not stated in the decision problem 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. The EAG notes this may not fully reflect the anticipated NICE scoped population, in particular with regards to people with stage III advanced EC. This is discussed in 2.2.4 where the EAG also raises other areas of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				concern regarding the generalisability of the clinical evidence to the anticipated eligible population in England and Wales.
Intervention	Dostarlimab with platinum-containing chemotherapy	As per scope	NA	The EAG agrees that the intervention is consistent with the NICE final scope.
Comparators	1 Platinum-based doublet chemotherapy For people who had neoadjuvant or adjuvant platinum-based doublet chemotherapy: 2 Pembrolizumab plus lenvatinib*	Platinum containing chemotherapy – Carboplatin and paclitaxel	The company acknowledges that there is a potential overlap, for a small number of patients who had neoadjuvant or adjuvant platinum-based doublet chemotherapy, between the pembrolizumab plus lenvatinib recommended population (TA904) and the dostarlimab in combination with platinum containing population. However, there are a few limitations when conducting any economic analysis within this patient cohort: Within the dMMR/MSI-H cohort of the RUBY-1 trial data, very low numbers of patients received prior platinum containing doublet chemotherapy, in the dostarlimab group [redacted] and in the carboplatin-paclitaxel group [redacted] Any	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. The EAG discusses in Section 2.2.2.2 the use of carboplatin + paclitaxel across the two arms of the pivotal trial presented by the CS. The EAG agrees with the company that although there is a potential for a comparison with pembrolizumab + lenvatinib in people who had neoadjuvant or adjuvant therapy with a platinum-based doublet chemotherapy, there is no available evidence in this population from the pivotal trial (KEYNOTE-775), Section 2.3

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			further subgroup analysis of RUBY based on these patient numbers would be highly uncertain and unfeasible. There is no published evidence that the company is aware of from the KEYNOTE-775 trial (pivotal trail investigating pembrolizumab plus lenvatinib in this setting) regarding dMMR/MSI-H patients who specifically received prior platinum-doublet chemotherapy. The manuscript for the KEYNOTE-775 trial notes the proportion of patients who had previously received systemic treatment only as neoadjuvant or adjuvant therapy, though this is broader than prior platinum doublet chemotherapy noted in the scope.[14] No outcomes or baseline characteristics are published for this cohort. In addition, there is no information available within published TA904 committee papers [15]	The EAG has not been able to identify any real world evidence comparing dostarlimab + carboplatin + paclitaxel with pembrolizumab + lenvatinib (Section 2.3). The CS expert advisory board does not appear to have been questioned on their views of the effects of dostarlimab + carboplatin + paclitaxel compared with pembrolizumab + lenvatinib in people having had neoadjuvant or adjuvant therapy with a platinum-based doublet chemotherapy.
Outcomes	The outcome measures to be considered include:	As per scope, with the addition of disease control rate (DCR) and time to	DCR and PFS2 are two additional secondary efficacy	The EAG agrees that the outcomes presented by the company are in line

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Progression-free survival • Overall survival • Response rates • Duration of response • Adverse effects of treatment Health-related quality-of-life.	second objective disease progression (PFS2)	outcomes evaluated in the RUBY trial.	with the NICE final scope. The outcomes reported are, however, from an ongoing trial and as such are from a (pre-planned) interim analysis. Results therefore may be subject to change as the trial progresses. The EAG has included the two additional outcomes within their critique for consistency with the company decision problem.
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope	N/A	The EAG is satisfied that the economic analysis performed by the company is conducted in line with the NICE reference case and therefore as per scope. The EAG discusses the source and validity of inputs used for key model parameters in Section 3.2. Results of economic analyses performed by the EAG using commercial arrangements for comparator/subsequent treatment technologies are provided to the Committee in a confidential appendix.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	• Local versus metastatic recurrence • People who had primary debulking surgery vs people who have not	The company do not believe that additional economic analysis in these subgroups will aid decision making or reduce uncertainty within this appraisal. Any further subgroups within the dMMR/MSI-H subgroup will have small sample size which will not provide meaningful analysis.	**Local versus metastatic recurrence**: Within the clinical study report recurrence was captured as a 'yes/no' variable and therefore the type and/or location of recurrence is not readily available. Within the dMMR/MSI-H RUBY trial population, n=27 (50.9%) in the dostarlimab group and n=32 (49.2%) patients in the carboplatin-paclitaxel group had recurrent disease. Recurrent disease status was analysed as a pre-defined subgroup within the dMMR/MSI-H subgroup, with a HR of [redacted] for	The company has not been able to explore the subgroups specified in the decision problem. It is possible that these subgroups may correlate with treatment efficacy or prognostic outcomes. The EAG notes that efficacy of dostarlimab+CP has not been demonstrated in patients with stage III.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			PFS IA and a HR of [redacted] for OS. Based on the efficacy demonstrated across the entire recurrent cohort, the company do not believe that further subgroup analysis within this subgroup will aid decision making and reduce uncertainty. **People who had primary debulking surgery vs people who have not:** Within the clinical study report prior anti-cancer surgery for endometrial cancer is captured as a 'yes/no' variable and therefore the type and/or outcome of surgery is not readily available. The trial protocol did not outline any specific inclusion or exclusion criteria related to surgery, patients were eligible for inclusion regardless of the type of surgical intervention or lack thereof. The trial was not designed to evaluate outcomes dependent on	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			surgical intervention and therefore the company believe that presenting data for the subgroup is not informative. Within the dMMR/MSI-H RUBY trial population, most patients, [redacted] in the dostarlimab group and [redacted] in the carboplatin-paclitaxel group, had prior anti-cancer surgery for endometrial cancer. Furthermore, across three clinical advisory boards relating to this trial and this appraisal, people who have had primary debulking surgery versus people who have not, was not raised by any of the clinical experts as a subgroup of clinical importance (the CS cites the following documents provided with in the CS reference pack '[GSK Data on file] Endometrial Cancer RUBY Advisory Board. July 2022.', '[GSK Data on file] UK Advisory Board: Advanced Endometrial Cancer Survival Outcomes. March 2023.' and '[GSK Data on file] UK Advisory Board: External	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			Insights into the RUBY Data. April 2023.'	

*Note: Pembrolizumab with lenvatinib was subject to an ongoing appraisal at the time of the decision problem meeting, and achieved recommendation by NICE in June 2023.[16]
Abbreviations: DCR – disease control rate; dMMR – DNA mismatch repair; DNA – deoxyribonucleic acid; IA – Investigator assessed; ITT – intent to treat; 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.

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

The EAG reviewed the methods used in the company submission to search for, assess eligibility, extract data, assess the risk of bias and synthesise the evidence in support of the clinical effectiveness of dostarlimab+CP for people with advanced (stage III or IV) or recurrent endometrial cancer.

The company undertook a systematic literature review (SLR) of interventional studies relating to clinical effectiveness of dostarlimab+CP. The EAG assessed the quality of the SLR review using a modification of the ROBIS tool.[17]

2.1.1 Searches

Reasonably comprehensive searches in four relevant bibliographic databases were undertaken on 10 November 2021 (and updated on 22 February 2023). Suitable terms, including both thesaurus headings and free-text terms, were combined appropriately. Database search strategies were suitable for finding studies on the intervention and comparators, combining terms for the population and stage of disease. For MEDLINE and Embase, a pragmatic RCT filter from a recognised source (SIGN) was applied (the EAG note that this is not the most sensitive available filter, but it is a reasonable choice for this CS). A summary of supplementary searches is provided, including checking references of “the most comprehensive, recent, relevant systematic reviews found via database searches” (CS Appendix D.2.1). Twelve systematic reviews were chosen and citations have been provided in response to clarification questions. Note that with the inclusion of stage of disease, any very broad systematic reviews of endometrial cancer may not have been retrieved. Relevant records in a number of specific conferences were sought in Embase using the subject search and full names or acronym terms for the conference in fields cf (conference Information) and cg (conference publication). The same conferences are also listed in CS Appendices Table 4. The company have clarified (in response to clarification question C3) that, for efficiency, the Embase search was the sole source for some conferences/years if they were indexed in the

Embase database. Other conferences/years were searched via the conference websites. The EAG notes that this approach may not be as comprehensive as searching all relevant conference abstracts directly via handsearching conference websites.[18] In addition, the CS states that searches of HTA bodies and a trials register (ClinicalTrials.Gov) were undertaken. While the sources for these grey literature searches are listed, full details of the searches (e.g. search date, search terms or browsing categories used, number of hits retrieved for each term) are not provided.

2.1.2 ROBIS Assessment of Company SLR

Overall the EAG found the SLR to be of unclear quality, although it is likely to have identified all studies relevant to the company's decision problem (See 2.3 for EAG updated search results).

Table 4 provides a summary of the EAG critique and cross-references to the relevant section in the CS. The full EAG assessment of the SLR quality and the full EAG assessment of risk of bias (ROB) of the included evidence can be found in the appendices (Table 37).

Table 4: Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS section B2.1 Appendix D, Table 5	Unclear concern
Searches and selection of studies	CS section B2.1 Appendix D, Section D2; D3.1; D3.2	Unclear concern
Data extraction and risk of bias assessment	CS Appendix D, Section D3.3	Unclear concern
Evidence synthesis	CS section B2.3 Appendix D, Section D4.5	Unclear concern

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The source of evidence for the assessment of clinical effectiveness of dostarlimab+CP comes from a single RCT, the RUBY-1 trial. The RUBY-1 trial is an ongoing study (NCT03981796) and interim results have been published.[19] RUBY-1 was an international multi-centre, double-blind, randomised Phase III trial.

The study compromised 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. Median duration of follow-up for the interim analysis was 24.79 months. Table 5 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.

The CS also reports data from a real-world evidence (RWE) study conducted using the National Cancer Registration and Analysis Service (NCRAS) data to provide context to the results of the RUBY-1 trial, however this RWE study is not used to make any meaningful contribution to the company submission or economic analysis.

Table 5: Summary of the RUBY-1 methodology

Method step	Summary details	Section(s) of CS of relevance
Method of randomisation	Randomization 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 B2.3.1.3

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	CA Section B2.3.1.5
Primary endpoints of relevance to the decision problem	Progression free survival Overall survival	CS Section 2.3.1.6 CS Table 7
Key secondary endpoints of relevance to the decision problem	Objective response rate (ORR) Duration of response (DOR) HRQoL Adverse events	CS Section 2.3.1.6 CS Table 7
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 B2.4

2.2.1 Risk of bias of included study

The company assessed the ROB of RUBY-1 using the checklist provided in the NICE STA user guide for company evidence submissions.[20] The EAG assessed the ROB using the NICE STA questions and also for completeness using the Cochrane ROB2 tool.[21] A comparison of the company assessment and the EAG assessment of ROB in RUBY-1 is presented in Table 38. Although the randomisation process for the overall population in the trial appears appropriate, the EAG has some concerns regarding the adequacy of this for the relevant subgroup (see Table 38). There appears to be some differences between arms in some potential prognostic factors at baseline for the subgroup, although the impact of these differences is unclear. Some of the secondary outcome measures listed on the trial register for the study have not been reported, but details have been provided for all key outcomes relevant

to this appraisal. Despite the uncertainties described in Table 38, the EAG considers that the overall risk of bias assessed using Cochrane ROB2 in RUBY-2 is low. The ROB assessment of RUBY-1 can be found in the appendices (Section 8).

2.2.2 Overview and Critique of RUBY-1

2.2.2.1 Eligibility criteria

The CS reports the key eligibility criteria for the RUBY-1 trial in CS Table 6 and CS Section B2.3.1.3. 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 RUBY-1 protocol provided with the CS (cited in CS Doc B as '[GSK Data on file] Ruby Clinical Study Protocol 4010-03-001 Version 4.0. Dec 2022. Mar 2022') refers to: CancerMPact®: Patient Metrics, Kantar Health, 26 October 2018 but this appears to be to support the statement that 20% of patients are diagnosed with advanced or metastatic disease (Stage III or IV) for which surgical cure is not possible rather than why. This may be relevant in particular for people with Stage III EC. The EAG clinical expert concurs with some of the CS clinical experts discussions (provided with the CS and cited in CS Doc B as '[GSK Data on file] Endometrial Cancer RUBY Advisory Board. July 2022.') that some Stage III endometrial cancers are amenable to cure. In the RUBY-1 trial, in the dMMR population, the proportion with stage III endometrial cancer was approximately 20% (see

Table 6). There is not enough detail of these people presented to explore if they would be surgically treated in the real world. The EAG clinical advice is that reasons for not surgically treating people with stage III can include those with bulky nodules, excessive weight, comorbidities, excessive bleeding (2.2.3.7). It is also not clear from the evidence reported if any of these people would be candidates for radiotherapy in the real-world setting.

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 CS decision problem focuses on people with EC who are candidates for systemic therapy (Section 0.3). There are no specific eligibility criteria in the RUBY-1 trial relating to candidacy for treatment and the CS and the CSR do not report how this is established. 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 (see CS Section B2.3.1.3 for further details). 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')).

Although no other studies met the eligibility criteria for the company decision problem the EAG considered the inclusion criteria of the trials of carboplatin / paclitaxel that the CS identified but were subsequently excluded (CS Appendix D, Table 7) as a validation exercise for the RUBY-1 trial eligibility given these were also trials of populations at the same line of treatment. Although there were one or two differences for example the specific cell types that were eligible, the eligibility criteria of these trials were similar in terms of stage of disease, ECOG PS, and the prior use of treatments where relevant.

2.2.2.2 Cycles of carboplatin and paclitaxel

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 B1.3), combination carboplatin and paclitaxel. Clinical advice to the EAG is that carboplatin with paclitaxel is the most commonly used doublet 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 46 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] (the CSR refers to additional data that were not submitted) which may not be reflective of typical practice in the real world, see further discussion on generalisability (2.2.4). Section 2.2.3.9 describes additional information on delays and discontinuations of treatments.

2.2.2.3 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 3). During the placebo period it is not reported what treatments could have been, or were, received in each arm. The EAG are particularly interested in what subsequent anti-cancer therapies were taken. The EAG were unable to establish what subsequent therapies were given from the sources initially available (RUBY-1 schedule of events, the RUBY-1 protocol and the CSR) but was aware that there was the potential for subsequent anti-cancer treatments.. The EAG requested summary information on subsequent treatments received by the dMMR/MSI-H subgroup of RUBY-1. In clarification response A9 the number of dMMR/MSI-H

patients who received follow-up anti-cancer therapy post-progression in the RUBY-1 trial to date was incomplete (total [redacted] due to limited duration of follow-up. In the dostarlimab + CP arm the proportion receiving subsequent anti-cancer therapy was [redacted], the rate was [redacted] in the placebo + CP arm. Further treatments most commonly used in the dostarlimab+CP arm were [redacted]. Further treatments most commonly used in the placebo+CP arm were [redacted]. The EAG notes that in the dostarlimab+CP arm there were instances of treatment with an [redacted] but the impact on this treatment to the results is unclear. The EAG also notes that the duration of treatment with these subsequent treatments is currently unknown.

CS section B3.5.5 reports subsequent anti-cancer therapies costed in the economic model post progression and include carboplatin with paclitaxel, doxorubicin, and pembrolizumab with lenvatinib (See Section 3.2.8) but the EAG is unable to fully validate the use of these subsequent treatments. Clarification response A9 reports that these were from insights gathered during the company advisory boards with the exception of pembrolizumab with lenvatinib which was informed by use in the RUBY-1 trial (Section 2.2.2.3). The justification for not using subsequent treatments from the RUBY-1 trial was reportedly because these included several treatments not available as per UK standard of care (CS page 138). However, the company provided scenario analyses with the subsequent anti-cancer therapies used in RUBY-1.

Owing to the short follow-up of RUBY-1 the subsequent anti-cancer treatment data is immature, however, it can be seen that there was a higher proportion receiving a subsequent anti-cancer therapy in the PCC in combination with placebo arm, and that the specific anti-cancer therapies used differed between the two arms.

2.2.3 Trial Results

The RUBY-1 trial recruited a broader population than the dMMR/MSI-H subgroup that is under consideration within this appraisal. However, the trial design included a hierarchical approach to the hypothesis testing, with the first hypothesis testing for a

difference between investigator assessed (IA) progression-free survival (PFS) specifically in the dMMR/MSI-H subgroup. The other hypotheses factored into the study design investigated differences in PFS and overall survival (OS) in the whole trial population. All hypotheses present here assumed one-sided testing, assuming a benefit for dostarlimab.

2.2.3.1 Baseline characteristics

There were a total of 494 participants in the ITT (overall population) and 118 participants in the dMMR/MSI-H subgroups, of whom 53 were randomised to dostarlimab+CP and 65 to the comparator arm. The study recruited from 164 sites from 19 countries globally, [redacted] of the sites were from the UK although only [redacted] currently have recruited participants (clarification response A14), of which [redacted] participants were in the dMMR/MSI-H subgroup.

Baseline characteristics for the dMMR/MSI-H subgroups and the ITT population by study arms are provided in

Table 6. As noted in the EAG risk of bias assessment for RUBY-1 there were some slight imbalances in the subgroup arms, as acknowledged in CS p42 BMI is higher in the placebo arm and the proportion with ECOG PS 1 is higher in the dostarlimab arm. In addition, the EAG considers that the proportion aged ≥65 years appears higher in the placebo arm (see

Table 6 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 the mean age and mean BMI in the ITT populations are not reported in the available sources of evidence.

Table 6: Baseline characteristics for RUBY-1

Characteristic	dMMR/MSI-H dostarlimab + CP (N=53)	dMMR/MSI-H CP + placebo (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)

Source: CS Table 9 and RUBY-1 publication [19] 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

2.2.3.2 Results Overview

The outcomes presented by the company are all relevant to the dMMR/MSI-H subgroup, and the majority have not been adjusted for any consideration of multiple testing. Several analyses were pre-specified for the dMMR/MSI-H subgroup including PFS by blinded independent central review (BICR), overall response rate (ORR), duration of response (DOR), disease control rate (DCR), PFS2 and multiple patient reported outcome measures (PROMs), however an analysis of OS in this subgroup did not appear prespecified in the original protocol provided to the EAG though it appeared to be added as a sensitivity analysis in a later protocol change. Caution should be taken when interpreting p-values and confidence intervals for comparisons beyond the pre-planned primary PFS analysis, which was the only one to be included in the trial design with a specified significance level. All analyses are based on the first interim data-cut with a mean follow-up of [redacted] for the dMMR/MSI-H subgroup. Note that all analyses and comparisons, unless otherwise specified, do not adjust for any baseline differences between the two groups.

An overview of the analyses presented by the company are shown in Table 7.

Table 7: Overview of Clinical Outcomes from RUBY-1 for dMMR/MSI-H subgroup

Outcome	**Arm/Response**	**Median (95% CI)**	**Hazard Ratio (95% Confidence Interval); one sided p-value**
Investigator Assessed PFS	Dostarlimab Placebo	[redacted]	0.28 (0.16, 0.50); p<0.0001
BICR PFS	Dostarlimab Placebo	[redacted]	0.29 [redacted]
PFS2	Dostarlimab Placebo	[redacted]	0.37 (0.19, 0.73)
OS	Dostarlimab Placebo	[redacted]	0.30 (0.13, 0.70); [redacted]
		Dostarlimab (N=53)	**Placebo (N=65)**
Best Response (data taken from CSR)	No Disease Complete Response Partial Response Stable Disease Progressed Disease Not evaluable	[redacted] 15 (28%) 23 (43%) 6 (11%) 2 (4%) [redacted]	[redacted] 12 (18%) 28 (43%) 10 (15%) 4 (6%) [redacted]
Disease Control Rate	n (%)	[redacted]	[redacted]
Objective Response Rate	n (%)	38/49 (78%)	40/58 (69%)
Duration of Response	Median (months)	Not Reached (10.1, NR)	5.4 (3.9, 8.1)

2.2.3.3 Progression-free survival

The hazard ratio for IA PFS was 0.28 (95% CI: 0.16, 0.50), which was similar to the BICR PFS hazard ratio of 0.29 [redacted]. The prespecified value for statistical significance of [redacted] was exceeded by the statistical test performed on the IA PFS, meaning dostarlimab+CP demonstrated superiority to placebo plus CP. The Kaplan-Meier plots of IA and BICR PFS are shown in Figure 1 and Figure 2 respectively. Whilst again similar, there is a difference in the plateau [redacted] for dostarlimab and placebo

respectively, whilst IA PFS plateaus at 0.61 and 0.15 respectively. The BICR assessed PFS results in a smaller incremental difference between arms which might be influential when data are used for extrapolation.

The EAG had concerns over the censoring rules utilised by the company. Within the dMMR/MSI-H subgroup, there were [redacted] patients in each arm who were censored for PFS when they began new anticancer therapy despite not having progressed disease and there were a further [redacted] patients in each arm who were censored at the beginning of follow-up due to no baseline disease assessment. The influence of these patients is hopefully negligible, however given the small sample size and already uneven balance of baseline characteristics, it's possible that the censoring of these patients is influential on the effect size estimates and subsequent extrapolations.

In the CSR the company performed some sensitivity analyses varying the assumptions around PFS censoring. One analysis considered treatment discontinuation or starting a new anti-cancer treatment as a PFS event rather than censored, and that a death or progression event following 2 or more missed disease assessments was recorded to have occurred on the date of death or recorded disease rather than be censored on the date of their previous assessment. This sensitivity analysis produced a hazard ratio for PFS of [redacted]

When this sensitivity analysis was repeated using the dMMR/MSI-H as defined at initial randomisation rather than the subsequently verified classification, the hazard ratio was [redacted].

The EAG additionally requested a PFS analysis that adjusted for the effect of weight and age as these were imbalanced at baseline across the treatment arms of the dMMR/MSI-H subgroup. The company fitted the requested models, and whilst full output was not provided, the coefficient of the estimated hazard ratio of treatment effect was stable.

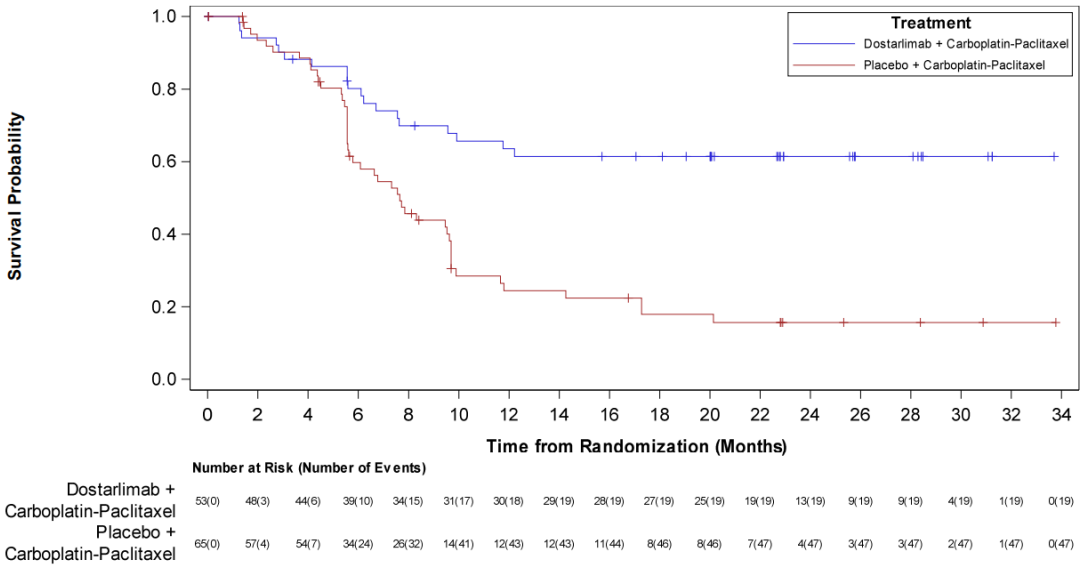

Figure 1: Kaplan-Meier plot of investigator assessed PFS follow-up for dMMR/MSI-H subgroup of RUBY-1 (Figure 4 of Company Submission)

[redacted]

Figure 2: Kaplan-Meier plot of BICR PFS follow-up for dMMR/MSI-H subgroup of RUBY-1 (from CSR)

2.2.3.4 PFS2

The CSR also reported the PFS2 outcome which was defined as the time from randomisation until either disease progression on a subsequent therapy following the therapies received in the RUBY-1 trial or death. This outcome was not in the NICE scope and it is unclear whether this outcome was IA or BICR assessed. For PFS2, dostarlimab demonstrated a benefit over placebo (HR = 0.37; 95% CI: 0.19, 0.73), however the magnitude of benefit is reduced compared to the previous PFS

outcomes and the confidence interval is wider. The Kaplan-Meier plot for PFS2 is shown in Figure 3. Details on subsequent treatments are not fully reported due to the immaturity of the data and it is not clear whether they can be considered well-balanced across arms.

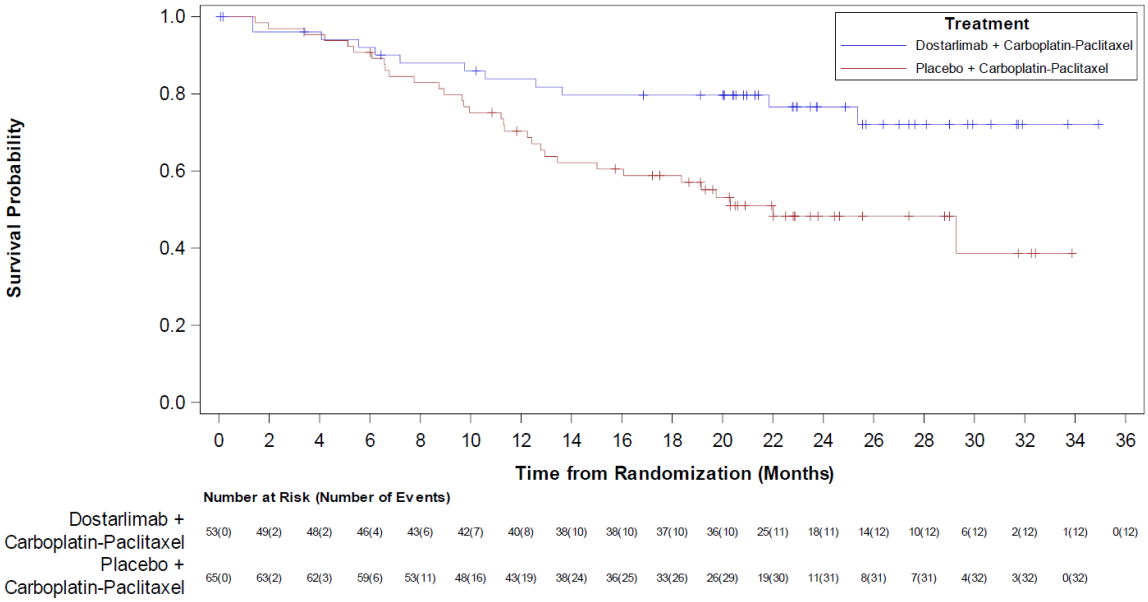

Figure 3: Kaplan-Meier plot of PFS2 follow-up for dMMR/MSI-H subgroup of RUBY-1 (from CSR)

2.2.3.5 Overall Survival

An analysis of overall survival in the dMMR/MSI-H subgroup of the RUBY-1 population showed a benefit in favour of dostarlimab. The hazard ratio for OS was 0.30 (95% CI: 0.13, 0.70), which is comparable to magnitude of benefit for PFS, however the confidence interval for OS is much wider. Median OS was not reached in either arm.

The EAG additionally requested an OS analysis that adjusted for the effect of weight and age as these were imbalanced at baseline across the treatment arms of the dMMR/MSI-H subgroup. As with PFS, the hazard ratio appeared stable to these adjustments.

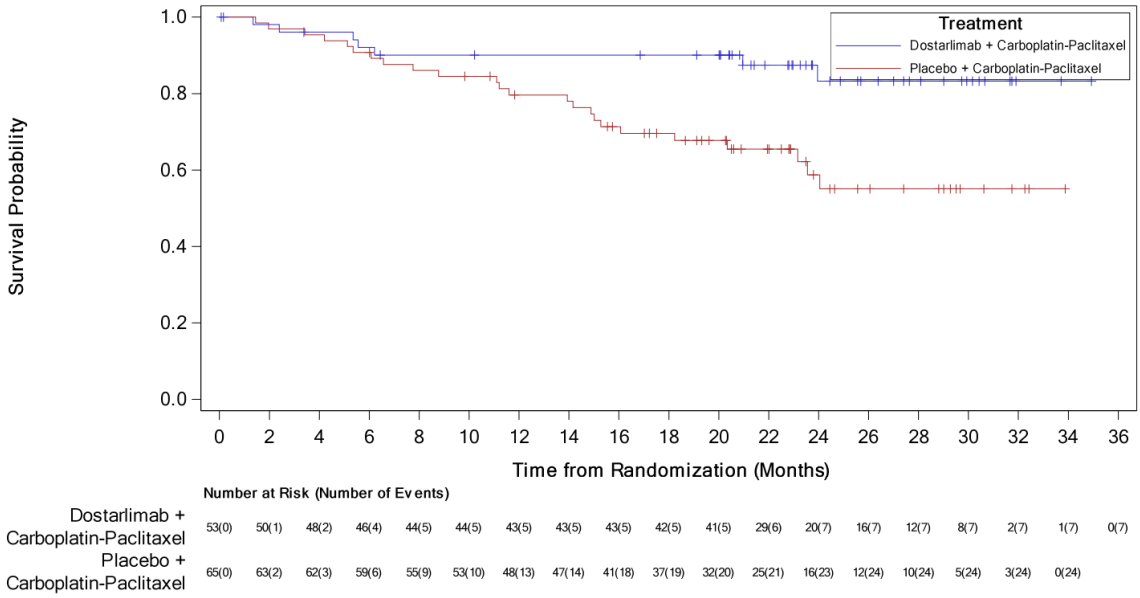

Figure 4: Kaplan-Meier plot of OS follow-up for dMMR/MSI-H subgroup of RUBY-1 (from Company Submission Figure 5)

2.2.3.6 Response related outcomes (Best response, ORR, DCR, DOR)

The RUBY-1 CSR reported several response-based outcomes which were all IA. The EAG notes that the company submission has minor discrepancy with the CSR on the classification of patients classed as “Not Evaluable” and those with “No Disease”. The EAG has presented numbers based on the CSR figures. The CS states that 4 and 7 patients in the dMMR/MSI-H subgroups of dostarlimab and placebo arms respectively had no evaluable disease at baseline, which accounts for almost 10% of the key population. People without evaluable disease are unlikely to be eligible for treatment according to the EAG’s clinical expert.

The best overall response (Table 7) was similarly distributed across the treatment arms.

DCR was defined as the number of participants who achieved one of the following response: CR, PR, SD or no disease. On this outcome, the two arms also performed similarly (dostarlimab vs placebo: [redacted]).

Meanwhile, ORR combined patients with complete or partial response, where a minor difference in favour of the dostarlimab arm was noted (78% vs 69%).

DOR looked at the length of the response for patients who achieved a best response of PR or CR. The company’s analysis shows a clear benefit for dostarlimab. Median DOR was 5.4 months for the placebo arm whilst it was not reached for dostarlimab.

A Kaplan-Meier plot of DOR is shown in Figure 5. As the DOR excluded patients without disease as reported by the CSR, without clarity over these patients, there is a potential of bias against the placebo arm in this outcome.

The EAG requested the results of BICR assessed response related outcomes, and the results were broadly consistent with the IA versions.

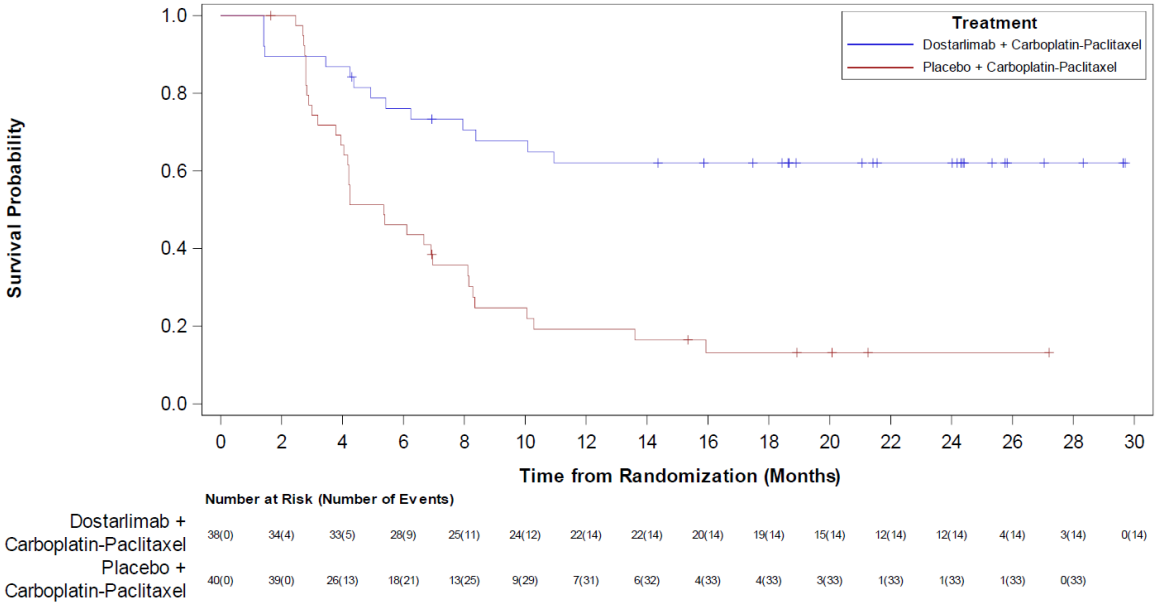

Figure 5: Kaplan-Meier plot of DOR follow-up for dMMR/MSI-H subgroup of RUBY-1 (from CSR)

The EAG also requested the company present DOR for the dMMR-MSI-H subgroup who achieved CR (Figure 6). A plateau is evident for both arms, although the numbers in each arm are small.

Figure 6: Kaplan Meier plot of DOR for CR of dMMR/MSI-H subgroup of RUBY-1 (from Company Clarification Response Figure 4)

2.2.3.7 Subgroup Analyses

The company presented a series of further subgroup analyses for IA PFS and OS within the dMMR/MSI-H subgroup of RUBY-1. The EAG shows the forest plot for the IA PFS in Figure 7. Across most analyses, the hazard ratio for dostarlimab+CP versus placebo+CP is comparable to the hazard ratio of effect in the whole subgroup. However, in the population with primary stage III disease status, the hazard ratio is 0.92 (95% CI: 0.26, 3.28; n=24). In the CSR for RUBY-1, the company provided an equivalent plot for the MMRp/MSS population, where the equivalent group had a hazard ratio of [redacted]. For whole ITT population, the hazard ratio is 1.03 (0.56, 1.89; n=92).

For OS, no hazard ratio was provided by the company for stage III subgroup of the dMMR population, however for the whole ITT population it was [redacted]. The EAG is aware of the large degree of uncertainty surrounding these estimates, however it notes a consistent difference in the efficacy of dostarlimab+CP in the stage III subpopulation, relative to those with stage 4 or recurrent disease and is concerned about the efficacy and potential cost-effectiveness of dostarlimab+CP in this group. The EAG requested Kaplan-Meier plots for the disease stage subgroups, however the company did not present these, stating that there would be too few

events for these to be interpretable. It is not clear why the company were willing to present hazard ratios in their subgroup analyses but not provide Kaplan-Meier plots.

The NICE scope listed the following two subgroups:

- local vs metastatic recurrence
- people who had primary debulking surgery vs people who have not

The company reports that neither of these were possible, both due to specific information on type of recurrence and type of prior surgery not being collected in RUBY-1.

The EAG requested a more general subgroup analysis of people who received any previous anti-cancer surgery vs people who did not, however the company stated a meaningful comparison could not be performed due to the small number of patients who did not have prior anti-cancer surgery ([redacted])

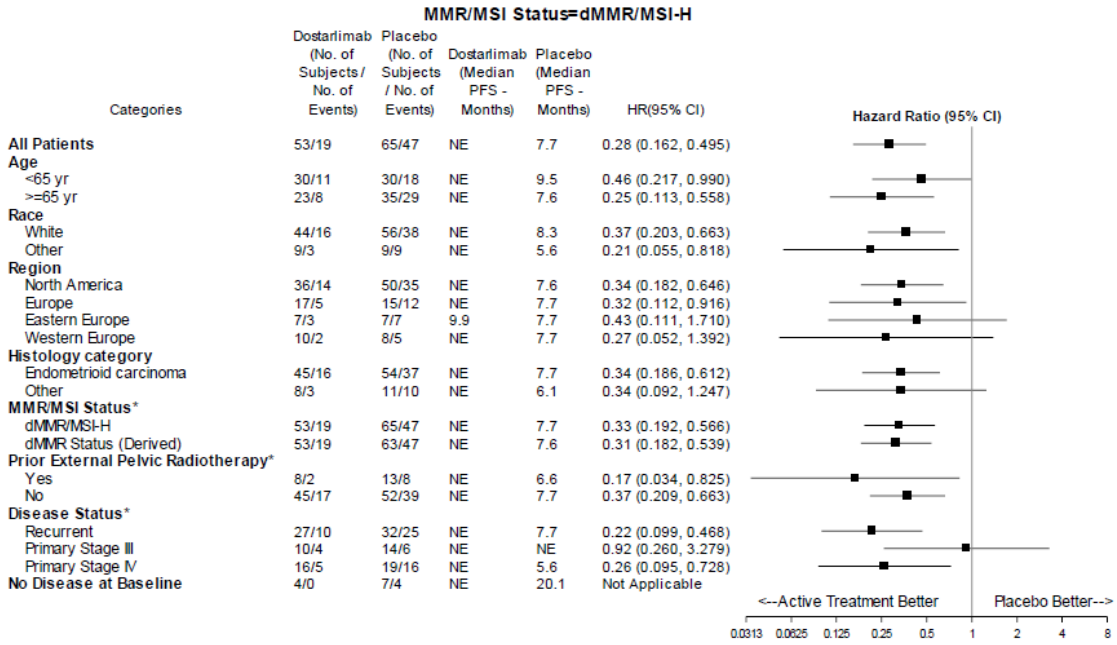

Figure 7: Forest plot of IA PFS for dMMR/MSI-H subgroup of RUBY-1, taken from CS Figure 9.

2.2.3.8 Patient Reported Outcome Measures (PROMs)

In the trial protocol, the company reported that they planned to collect three PROMs outcomes: EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-EN24. The EQ-5D-5L usually produces two outputs per patient, a visual analogue scale (VAS) score and a question-based score. The EORTC QLQ-C30 has a total of 15 outcomes that can be reported from the 30 questions it contains, whilst the EORTC QLQ-EN24 can report 13 outcomes from its 24 questions.

In both the CSR and company submission, the EAG could only identify results for the EQ-5D VAS and the global score from EORTC QLQ-C30. These outcomes are general indicators of health and may not capture specific differences between the treatment arms such as those linked with adverse events.

The scores for the EORTC QLQ-C30 global score for the dMMR/MSI-H subgroup are shown in Figure 8. A similar figure was presented by the company for the EQ-5D VAS (Figure 8, company submission). From the PROMs evidence they have presented, the company conclude that the improved PFS observed for dostarlimab was not associated with a reduction in quality of life. The EAG has concerns with the presented QoL data and thus this conclusion. Firstly, there is high drop-out on both arms and it is not clear whether the patients contributing information are comparable, nor whether the patients remaining are representative of the original population. Secondly, dostarlimab patients do not appear to have any worsening in QoL despite receiving 6 cycles of chemotherapy. Thirdly, equivalent information for the complete set of QoL outcomes has not been presented, meaning there may be differences between the treatments in certain aspects of quality of life that are not captured in the general measures presented.

Figure 8: Change from baseline in EORTC QLQ-C30 global score for dMMR/MSI-H subgroup of RUBY-1 (from Figure 7 of Company Submission)

2.2.3.9 Adverse Events

Adverse events from RUBY-1 were reported in CS Section B2.10 and Appendix R. The EAG has summarised key data from the adverse events reported in RUBY-1. Adverse events are summarised for both the dMMR/MSI-H subgroup of relevance to the decision problem and for the ITT (overall) population due to the larger sample size.

2.2.3.9.1 Treatment Exposure and Interruption to Treatment

Duration on treatment and interruption to treatment is summarised in Table 8. Duration of treatment and proportion of people with at least 54 weeks and 102 weeks of study treatment was greater in the dostarlimab+CP arm. No participants in either arm of the dMMR/MSI-H subgroup (and [redacted]) have received more than 3 years of treatment due to limited follow-up. 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.

Infusion delays (not clearly stated in the CS but assumed to be of any drug component) lasting at least 3 days were slightly more common in the

dostarlimab+CP arm, with one incident being the most common. Infusion delays were due to adverse events in around two-thirds of both arms (other reasons not defined). The company states that in the dMMR/MSI-H population, the proportion of participants who had at least 4 incidents of infusion interruption was [redacted] versus [redacted] in the dostarlimab+CP and placebo+CP arms, respectively (CS B2.10.2). The EAG notes the proportion with zero incidents was [redacted] in the placebo+ CP arm: [redacted] versus [redacted], respectively.

Table 8: **Treatment exposure and interruption to treatment**

	dMMR/MSI-H		**Overall population**	
	Dostarlimab + CP (N=53)	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Duration of dostarlimab/placebo weeks, median (range); mean (SD)	76.50 (3.0–150.3); [redacted]	31.86 (3.0–153.0); [redacted]	43.00 (3.0–150.9); NR	36.00 (2.1–165.1); NR
Duration of study treatment, > 54 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Duration of study treatment, 102 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: CS Appendix Tables 55 and 56; CSR section 5.6.1; Mirza 2023 [19] Table S3.

2.2.3.9.2 Treatment Emergent Adverse Events

An overview of treatment emergent adverse events (TEAEs) for the dMMR/MSI-H subgroup and the overall population are summarised in Table 9. The company states (referring to the dMMR/MSI-H subgroup) "all safety outcomes including Grade ≥3 TEAEs and treatment-related Grade ≥3 TEAEs were comparable between arms although generally numerically higher in the dostarlimab+CP arm compared with the placebo+CP arm" (CS B2.10.3). The EAG notes that immune-related TEAEs are higher in the dostarlimab arm (Table 9); these are reported further below.

In the overall population, in addition to immune-related TEAEs, the proportion with any grade ≥3 TEAEs and any serious adverse event appears higher in the dostarlimab+CP arm, these are discussed further below.

Table 9: **Overview of treatment emergent adverse events**

	dMMR/MSI-H		**Overall population**	
Adverse event category	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Any TEAE	[redacted]	[redacted]	241 (100%)	246 (100%)
Any Grade ≥3 TEAEs	[redacted]	[redacted]	170 (70.5%)	147 (59.8%)
Any TEAE with outcome of death[a]	[redacted]	[redacted]	5 (2.1%)	0
Any serious adverse event	[redacted]	[redacted]	91 (37.8%)	68 (27.6%)
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	[redacted]	[redacted]	[redacted]	[redacted]

Any immune-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any infusion-related reactions	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 19; CSR Table 33; Mirza 2023 [19]

[a] assessed by the investigator to be not related to carboplatin or paclitaxel, and only related to dostarlimab or placebo (CS Appendix Table 71)

2.2.3.9.3 Grade ≥ 3 Treatment Emergent Adverse Events

In the dMMR/MSI-H population TEAEs of at least grade 3 were similar across arms, apart from neutrophil count decreased which was higher in the placebo+CP arm. Grade ≥3 TEAEs in the overall population are summarised in Table 10. TEAEs occurring in at least 5% of patients in the overall population were used in the company's economic model; the EAG has extracted additional TEAEs from the CSR (see Table 10).

Table 10: **Summary of Grade ≥3 TEAEs**

	dMMR/MSI-H		**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 in ≥5% of patients (used in the CS economic model)				
Anaemia	[redacted]	[redacted]	36 (14.9%)	40 (16.3%)
Neutropenia	[redacted]	[redacted]	23 (9.5%)	23 (9.3%)
Neutrophil count decreased	[redacted]	[redacted]	20 (8.3%)	34 (13.8%)
Hypertension	NR	NR	17 (7.1%)	8 (3.3%)
White blood cell count decreased	NR	NR	16 (6.6%)	13 (5.3%)
Hypokalemia	NR	NR	12 (5.0%)	9 (3.7%)
Pulmonary embolism	NR	NR	12 (5.0%)	12 (4.9%)

Lymphocyte count decreased	[redacted]	[redacted]	13 (5.4%)	18 (7.3%)
Selected TEAEs Grade ≥3 occurring in ≥2% of patients in the overall population AND with proportion higher in the dostarlimab + CP arm				
[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]

From CS Appendix Tables 62 and 65; CSR Table 37; CSR 7.1.2

2.2.3.9.4 Deaths and Serious Adverse Events

There were five people with any TEAE with the outcome of death in the dostarlimab+CP arm, and none in the placebo+CP arm. Two of the deaths were judged to be related to dostarlimab (myelosuppression and hypovolemic shock, [redacted] and three were judged not to be related to dostarlimab (general physical health deterioration, COVID-19, and an opiate overdose).

In addition to those five deaths, the CS states that the most frequent cause of death was disease progression, and this occurred more frequently in the placebo+CP arm compared to the dostarlimab+CP arm ([redacted]) and lead to an overall higher death rate in the placebo arm ([redacted]). The EAG has been unable to validate these values against the CSR.

Serious adverse events are summarised in Table 11. Sepsis was more frequently reported in the dostarlimab+CP arm in the dMMR/MSI-H subgroup and the overall population. The CS notes that the most frequently reported SAEs with were higher in the placebo+CP arm versus the dostarlimab+CP arm were urinary tract infection, anaemia, asthenia, and pulmonary embolism, but the EAG notes the differences in the overall population are slight and frequency is low.

Table 11: **Serious TEAEs in ≥1% in either group**

	dMMR/MSI-H		Overall population	
Adverse event category	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Any serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	8 (3.3%)	1 (0.4%)
Pulmonary embolism	[redacted]	[redacted]	6 (2.5%)	5 (2.0%)
Pyrexia	[redacted]	[redacted]	6 (2.5%)	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]	3 (1.2%)	5 (2.0%)
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]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]

2.2.3.9.5 From CS B2.10.9 and Mirza 2023 [19] and CSR Table 43Dostarlimab- or Placebo-related Treatment Emergent Adverse Events

TEAEs (of any grade) considered related to dostarlimab or placebo only and not related to carboplatin or paclitaxel were higher in patients in the dostarlimab + CP arm compared with the placebo + CP arm in both the dMMR/MSI-H subgroup and overall population. This was mainly due to more participants in the dostarlimab + CP arm experiencing gastrointestinal disorders, rash, or hypothyroidism (Table 12). Of the gastrointestinal disorders, diarrhoea considered related to dostarlimab/placebo (and not to carboplatin or paclitaxel) occurred in [redacted] of the dostarlimab + CP arm of overall population, and nausea considered related to dostarlimab/placebo occurred

in [redacted]. These proportions in the placebo + CP arm of the overall population were [redacted] each, respectively. Treatment-related TEAEs related to any study drug are presented in CS Appendix Table 58.

Table 12: **Treatment-related adverse events related to dostarlimab or placebo only (occurring in >8% of either arm)**

	dMMR/MSI-H		Overall population	
Adverse event category	**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 Table 61, CSR Table 40

2.2.3.9.6 Immune-related Adverse Events

Immune-related adverse events (irAEs) (defined as Grade ≥2) occurring in the overall population are presented in

Table 13, and a detailed breakdown of those occurring in the dMMR/MSI-H subgroup is presented in Appendix Table 39. The most common irAE in both arms of the overall population was arthralgia (dostarlimab + CP 13.3%, placebo + CP 12.6%). The most common dostarlimab-related irAE was hypothyroidism (overall population 11.2%; dMMR/MSI-H subgroup [redacted]%). CS Appendix Tables 69 and 70 report summary irAEs in the dMMR/MSI-H populations for the two RUBY-1 trial arms respectively and the EAG has combined these data as seen in Appendix Table 39.

Table 13: **Immune-related TEAEs (defined as Grade ≥2)**

	Dostarlimab + CP (N=241)		**Placebo + CP (N=246)**	
	All events	**Dostarlimab-related**	**All events**	**Placebo-related**
Any immune-related AE	**137 (56.8%)**	[redacted]	**8 (35.8%)**	[redacted]
Arthralgia	32 (13.3%)	[redacted]	31 (12.6%)	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	27 (11.2%)	[redacted]	8 (3.3%)	[redacted]
Hypersensitivity/ Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Rash	21 (8.7%)	[redacted]	6 (2.4%)	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	15 (6.2%)	[redacted]	2 (0.8%)	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR Table 57

2.2.3.9.7 Adverse events from Phase I/II studies

In clarification response A11, the company provided details of two phase I/II studies.

The IO-Lite study (NCT03307785) [22] was an open label dose finding study of dostarlimab in combination with CP for a mixed population with advanced or metastatic solid tumours. Twelve patients were assessed for safety and one patient experienced a dose limiting toxicity (grade 3 aspartate aminotransferase increased) (clarification A11).

The GARNET study (NCT02715284) [23] is a Phase I/II trial evaluating the efficacy and safety of dostarlimab as a monotherapy in patients with advanced or recurrent endometrial cancer (n=209), and also presents safety data for n=515 with solid tumours. The GARNET study was used to inform NICE TA779.[24]

Among the n=515 with solid tumours, the most common ('selected') grade ≥3 adverse events were anaemia (8.7%), transaminases increased (2.5%), nausea (1.9%), vomiting (1.5%), diarrhoea (1.2%) and rash (1.2%).

Among the n=290 with endometrial cancer, the most common treatment-related adverse events of grade ≥3 were anaemia (2.8%), ALT increased (1.4%), diarrhoea (1.4%), fatigue (1.4%), amylase increased (1.4%), and lipase increased (1.4%).

Immune-related treatment related adverse events (grade ≥2) included hypothyroidism (6.9%), diarrhoea (3.8%), amylase increased (2.4%), AST increased (2.1%), ALT increased (1.7%), lipase increased (1.7%), hyperthyroidism (1.7%), colitis (1.4%) and hyperglycaemia (1.4%). Some of these events were not reported in RUBY-1 (diarrhoea, amylase increase, colitis, hyperglycaemia and lipase increased, see Table 15).

The MHRA Treatment Protocol [25] notes that severe or fatal immune-related adverse reactions can occur in patients treated with antibodies blocking the programmed cell death protein-1 / programmed death-ligand 1 (PD-1/PD-L1) pathway, including dostarlimab. These include immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies, hypothyroidism and hyperthyroidism, adrenal insufficiency, immune-related nephritis, immune-related rash, immune-related arthralgia, and other, potentially serious, immune related reactions. (e.g. myositis, myocarditis, encephalitis, demyelinating neuropathy (including Guillain Barré syndrome), sarcoidosis)

2.2.4 Trial Generalisibility

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 multinational study with only [redacted] UK sites currently having recruited participants and at the present interim analysis there are only [redacted] 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 is higher than the RUBY-1 trial population (Section 3.2.3).

EC is associated with obesity and commonly in the UK 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 2.2.3.6), but in the UK only those with evaluable disease would be treated. Patients with stage III disease typically have a good potential for cure by radiation therapy or surgery, however according to the eligibility criteria the patients with stage III disease in RUBY-1 had a low potential for cure. This means they are likely to be different in some way, although it is not clear how. One hypothesis is treatment resistance (Section 2.2.3.7).

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, but this varies in other countries. According to the EAG clinical expert, some of the trialists are known not to use radiotherapy in grade III patients at all. The number of cycles of CP used in RUBY-1 is likely to be higher than used in UK clinical practice (Section 2.2.2.2), and the subsequent anti-cancer treatments are also likely to be different (Section 2.2.2.3).

2.3 Additional work on clinical effectiveness undertaken by the EAG

The EAG undertook update searches for additional studies of relevance on 14th August 2023. The EAG used the company original search, limiting to studies published from 2023, duplicates of the CS included and excluded results were removed. This left 150 results. Two EAG reviewers independently screened these against the decision problem, full texts of three publications were retrieved for further scrutiny. Two EAG reviewers independently screened these full papers. The EAG

identified one conference abstract of RUBY-1 that had not been included by the company but this had no additional detail of the RUBY-1 trial. One additional publication of the dMMR/MSI-H subgroup of the KEYNOTE-775 trial comparing pembrolizumab+lenvatinib with CP was checked for eligibility but there were no data of relevance from the subgroup of those having neoadjuvant or adjuvant CP. One additional publication was excluded. This was an RCT of pembrolizumab monotherapy at a similar line of therapy to dostarlimab, but does not meet the NICE scope, see section 3.2.3 below.

2.3.1 Ongoing Trials

CS section B2.11 reports that RUBY-1 is an ongoing study with another interim analysis data cut expected in [redacted] Data is expected to be available in [redacted], with OS being followed up to reach maturity (PFS is final with primary endpoint met). Two ongoing RCTs in populations comparable to RUBY-1 were identified by the company's searches but were not summarised in the CS.

1. Phase 3 open-label RCT to evaluate efficacy and safety of dostarlimab versus CP in people with dMMR/MSI-H recurrent or advanced endometrial cancer in the first-line setting (DOMENICA), NCT05201547.

- Population, key differences from RUBY-1: adenocarcinoma; dMMR/MSI-H
- Intervention: dostarlimab 500 mg, every 3 weeks for 4 cycles and then 1000 mg every 6 weeks up to maximum 2 years
- Comparator: Carboplatin-paclitaxel for 6 cycles. Cross over is allowed from the CT arm to the dostarlimab arm at first progression.
- Estimated enrolment: 260
- Estimated completion: April 2026
- Key outcomes: PFS, OS, PFS2, EQ-5D-5L, EORTC QLQ C30
- Sponsor: GlaxoSmithKline

https://classic.clinicaltrials.gov/ct2/show/NCT05201547;
https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002124-21/ES/#A
https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.TPS5630?role=tab;
https://meetings.asco.org/abstracts-presentations/225946

2. Phase 3 open-label RCT of pembrolizumab versus CP in people with dMMR advanced or recurrent endometrial carcinoma in the first-line setting (KEYNOTE-C93/GOG-3064/ENGOT-EN15), NCT05173987.

- Population, key differences from RUBY-1: endometrial carcinoma or carcinosarcoma, dMMR
- Intervention: pembrolizumab 400 mg every 6 weeks for up to 18 cycles (up to approximately 2 years)
- Comparator: Carboplatin-paclitaxel for 6 cycles.
- Estimated enrolment: 280 (350 according to JCO abstract)
- Estimated completion: July 2026
- Key outcomes: PFS, OS, ORR, DOR, PFS2, EORTC QLQ C30
- Sponsor: Merck Sharp & Dohme LLC

https://clinicaltrials.gov/study/NCT05173987;
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.TPS5623

RUBY-2

The EAG also notes that the RUBY-2 trial is ongoing. The second part of the RUBY trial (RUBY-2) was added following the initiation of Part 1. Participants from Part 1 cannot participate in Part 2. RUBY-2 aims to evaluate the efficacy and safety of dostarlimab + CP followed by dostarlimab + niraparib versus placebo +CP followed by placebo in people with recurrent or primary advanced (Stage III or IV) endometrial cancer.

The design of RUBY-2 is similar to that of RUBY-1, but with the addition of niraparib to dostarlimab (for up to 3 years) after the 6 cycles of dostarlimab + CP. Niraparib is a poly-ADP ribose polymerase (PARP) inhibitor used to treat some types of ovarian, fallopian tube or primary peritoneal cancer. The starting dose of niraparib is 300 mg orally in people with an actual body weight ≥77 kg and platelet count ≥150,000/μL; and 200 mg orally in people with an actual body weight <77 kg or platelet count <150,000/μL or both.

Participants are randomised in a 2:1 ratio to the intervention and comparator arms, with randomisation stratified as per RUBY-1.

Differences in eligibility criteria are as follows:

Inclusion criteria, Part 2 only:

- Normal blood pressure or adequately treated and controlled hypertension.
- Be able to take medication orally, by mouth.

Exclusion criteria, Part 2 only:

- Prior therapy with a PARP inhibitor.
- Clinically significant cardiovascular disease.
- Any known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukaemia.
- Increased bleeding risk due to concurrent conditions.
- Participated in Part 1 of this study.

Approximately 270 participants are planned for enrolment. The estimated completion date is November 2026.

2.4 Conclusions of the clinical effectiveness section

The CS presents evidence from RUBY-1, an international multi-centre double-blind phase III RCT of dostarlimab+CP versus placebo+CP for patients with primary advanced or recurrent EC and who are candidates for systemic therapy. The population defined in the NICE scope, i.e. those with dMMR/MSI-H EC, are a pre-planned subgroup of this trial.

The first interim analysis of the RUBY-1 dMMR/MSI-H subgroup at a mean follow-up of [redacted], found a benefit of dostarlimab+CP over placebo+CP for the primary outcome of PFS, and also for PFS2, OS and DOR. DCR was similar between arms and ORR was slightly higher with dostarlimab. HRQoL was similar between arms. Serious adverse events, grade ≥3 adverse events, and immune-related adverse events where higher in the dostarlimab arm.

The EAG has concerns regarding the evidence provided. These include the small sample size of the relevant subgroup (n=118), potential randomisation issues, imbalances in baseline characteristics, subsequent treatments received, limited

follow-up, missing HRQoL results, and a lack of evidence for the subgroups specified in the NICE scope. No evidence was available for the comparison with pembrolizumab + lenvatinib. The EAG noted a lack of efficacy among patients with stage III disease, which was consistent across dMMR/MSI-H and MMRp subgroups.

There are also uncertainties regarding the generalisability of the dMMR/MSI-H subgroup in RUBY-1 to the population in England and Wales who would be eligible for first line treatment for advanced or recurrent EC. Issues include the age and ECOG score of the participants, the representativeness of the stage III patients, the use of other treatments and the number of CP cycles.

3 COST EFFECTIVENESS

3.1 EAG comment on company's review of cost-effectiveness evidence

The CS (Appendices G, H and I) provides detailed reports of 3 systematic reviews, aimed at identifying relevant; a) cost-effectiveness studies; b) health state utilities; c) cost and resource use.

3.1.1 Search strategy

Searches for all three SRs were conducted separately on 10 November 2021 (with an update on 22 February 2023) in a relevant range of databases. They sought English language literature published since 2011. All three searches combined terms for the population and stage of disease with a set of relevant study type terms (known as a search filter). For most concepts, suitable terms including both thesaurus headings and free-text terms were combined appropriately. However, the search filters used for the cost-effectiveness studies and HRQoL searches were arguably overly focussed (e.g. not searching for thesaurus terms), which resulted in a relatively small number of hits. Searches of recent, relevant conferences and the websites of selected HTA bodies are listed as additional sources, potentially helping to broaden the overall search strategy, but full details of these searches (e.g. search date, search terms or browsing categories used, number of hits retrieved for each term) are not provided, making it difficult to say if this is the case. The EAG tested the MEDLINE HRQoL search without the stage of disease terms and found no additional, relevant studies. The EAG also sought recent literature added to databases since the CS update search.

The EAG update searches did not find any additional relevant studies to inform cost-effectiveness inputs or outcomes for this appraisal. Studies excluded by the company in the reviews conducted were excluded correctly according to the criteria set, but studies were difficult to decipher even at the full text stage due to unclear descriptions of the treatment lines. Summary of the identified studies is provided in Table 14.

The EAG did find several studies useful for face validity checks on company economic model (CEM) inputs and for scenario analyses (discussed later in relevant sections of the report).

Table 14: List of published cost-effectiveness studies (Company submission Table 20)

Study	Summary of model	Patient population	Intervention	Comparator	QALYs intervention vs. comparator	Incremental costs intervention vs. comparator	ICER (per QALY gained)
Ackroyd, 2021[26]	Markov model US Healthcare perspective Three-year horizon Costs and utilities were discounted annually at 3%.	Advanced or recurrent endometrial cancer, specific stages: NR, subgroups: MSS or MSI-high	PEM + LEN	CB + PAC	-0.28	$212,670	NR [CB+PAC was considered the dominant treatment]
		Advanced or recurrent endometrial cancer, specific stages: NR, subgroup: MSI-high	PEM + LEN	CB + PAC	0.11	$313,487	$2,849,882/ QALY, USD inflated to 2020
Batman, 2021[27]	Markov US Societal perspective Four-year time horizon Costs and utilities were discounted annually at 3%.	HER2/neu-positive advanced or recurrent UPSC in one year, specific stages: NR, subgroup: NA	CB + PAC + TRA	CB + PAC	2,065	$144,335,895	$69,903/ QALY, USD inflated to 2019

Abbreviations: CB – carboplatin; HER2 – human epidermal growth factor receptor 2; ICER – incremental cost-effectiveness ratio; LEN – Lenvatinib; MSI – microsatellite instability; MSS – microsatellite stable; NA – not applicable; NR – not reported; PAC – paclitaxel; PEM – Pembrolizumab; QALYs – quality-adjusted life years; TRA – Trastuzumab; UPSC – uterine papillary serous carcinoma; USD – United States dollar

3.2 Summary and critique of the company's submitted economic evaluation by the EAG

The following sections summarise components of the economic evaluation submitted by the company and provide EAG critique.

3.2.1 NICE reference case checklist

The EAG assessment against the NICE reference case checklist [28] is presented in Table 15.

Table 15: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
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
Synthesis of evidence on health effects	Based on systematic review	Yes
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

Element of health technology assessment	Reference case	EAG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company used a de-novo cost-utility partitioned survival model (PSM) with a weekly cycle length and time horizon of [redacted] years. The model consists of three health states: progression free survival (PFS), progressed disease (PD) and death (as an absorbing state). All patients start in the PFS state and remain there until disease progression or death. Patients in the PD health state remain there until death as shown in Figure 9.

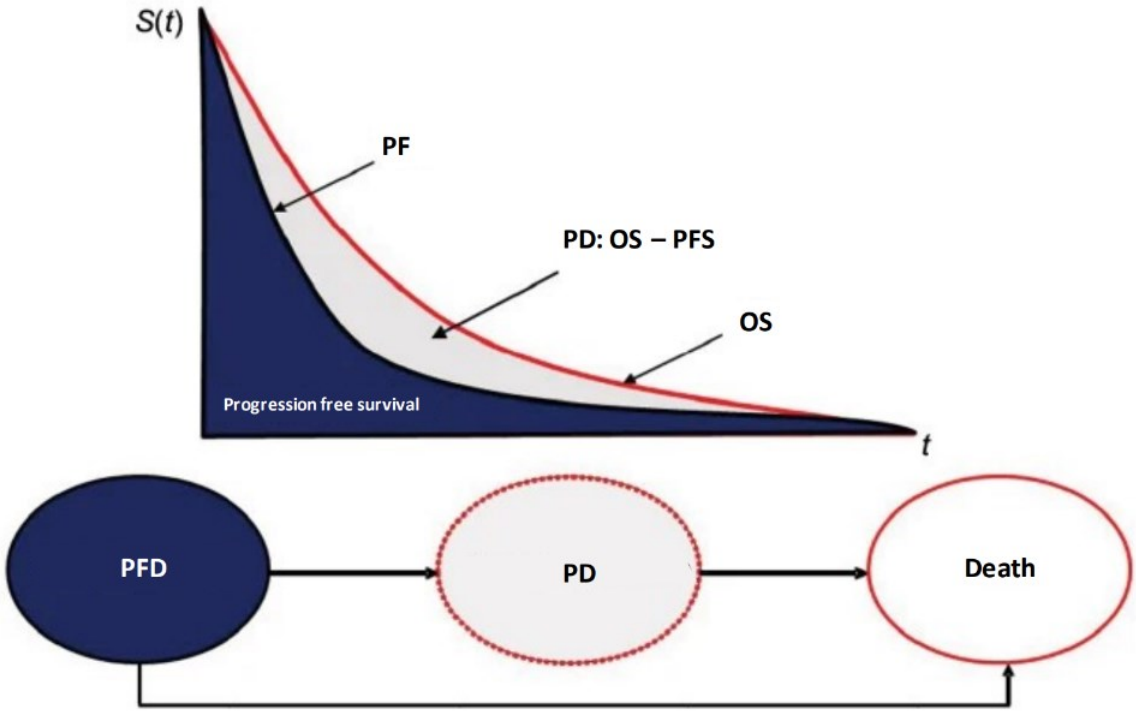

Figure 9: PSM structure (source CS doc B, fig. 11)

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

The PSM method uses an “area under the curve” approach, where the number of patients in each state at a given time point is taken directly from survival curves fitted to the clinical data. The PFS curve shows the proportion of patients who have not progressed or died at each given time point, whilst the OS curve shows the proportion of patients who are alive at each time point. The proportion of the patients in the PD state is calculated as the difference between the proportion of living patients (OS health state) and the proportion of patients who are both living and pre-progression (PFS health state). Details on how the PFS and OS curves were modelled are described in section 3.2.6.

EAG Comments:

- The PSM structure was sufficiently well-justified for use in this appraisal by the company. The health states capture the two important clinical endpoints of

PFS and OS, which are relevant to this disease area and have been used in previous technology appraisals.

- The weekly cycle length was short enough to capture relevant changes over the time interval.
- The life-time horizon of [redacted] years was long enough to capture important differences in costs and clinical outcomes. However, immaturity of key data sources requires substantial assumptions to be made and introduces significant uncertainty when extrapolated over such an extensive time period (see section 3.2.6).

3.2.3 Population

The population considered within the model are adult patients with primary advanced or recurrent dMMR/MSI-H EC and who are candidates for systemic therapy. The RUBY-1 trial collected data for both ITT and dMMR/MSI-H populations which was used to inform the economic model. The submission focuses on the dMMR/MSI-H population alone, therefore the economic model is aligned to this population, but uses some outcomes from the ITT population to gain advantage of data from a larger sample size.

The mean age of the dMMR/MSI-H population within RUBY-1 was used as the baseline age in the CEM ([redacted]).

The clinical expert for the EAG advised this was not unrepresentative of patients seen in clinical in England and Wales, as although there are younger patients with advanced or recurrent EC, many undergoing treatment were in their seventies. The EAG looked to compare mean age of the dMMR/MSI-H trial population with those of the ITT population in RUBY-1 but this information was not reported (see

Table 6). The EAG felt this was unusual as the company used the ITT population to inform other parameters within the model and a simple point of reference to assess against baseline figures used. See section 2.2.4 for further discussion.

The EAG consulted the literature retrieved across their clinical and cost searches to identify alternative sources to inform starting age which might be considered more appropriate in this appraisal. Table 16 summarises the sources retrieved and mean age of the population.

Table 16: Overview of sources of alternative starting population age

Source	Mean age (yrs)	Population	EAG comments
RUBY-1 trial [19]	[redacted]	dMMR/MSI-H population (n=118)	Only [redacted] patients recruited from UK sites. Trial ongoing. EAG clinical opinion likely healthier population than seen in UK practice.
Pennington (2016) [29]	67.1	Participants enrolled in UKCTOCS subsequently diagnosed with advanced stage III and IV EC patients (n=39)	Most relevant population to England & Wales although small sample size. Supports clinical expert opinion and reflects preferences of TA904 Committee in recent appraisal.
Eskander (2023) [30]	66	dMMR population (n=225)	Larger dMMR population, however multinational RCT
Sorbe (2008) [31]	67.9	Carboplatin and paclitaxel study, n=66	Small sample population but line of therapy close to the DP. European population. Median follow-up of 57 months
TA 904 [16]	67	Patients with previously treated advanced, metastatic or	Committee determined 67 years to be the most appropriate

		recurrent endometrial cancer	age for use in model – used in both company and EAG revised base cases
Clinical expert for EAG	>65	EC patients undergoing treatment in England NHS Trust	Feedback on mean age of patients in practice emphasising real world population rather than generally younger, fitter trial populations. More realistically later 60's as a mean but not less than 65 years.

Pennington and colleagues [29] estimated long-term secondary care costs of EC using data from a prospective cohort study nested within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Baseline characteristics of women participating in UKCTOCS and subsequently diagnosed with EC following enrolment (2001–2005) and prior to 31st Dec 2009 were included. This consisted of 34 patients diagnosed at stage III and five diagnosed at stage IV. The mean age of these patients was 67.1 years, all of whom resided in England.

In TA904 [16] pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer, clinical experts thought the most accurate age for patients was likely to be around 67. This lay between the key trial data and EAG's estimate and was close to what was reported in the real-world studies analysed. Both the company and EAG went on to use a mean age of 67 years in their revised base cases, which the committee concluded was most appropriate.

The EAG believe 67.1 years is a more representative starting age of patients in the economic model. Despite limitations of sample size (39) [29] and later treatment line (2nd line),[16] are the preferred source of figure as they are directly representative of the population in England and Wales [29] and has been deemed most appropriate for use in the advanced or recurrent EC population by prior NICE committee.[16] The EAG

performed a range of sensitivity analyses (see Table 32) to determine the impact of age at base line on the company base case ICER. When starting age in the model was implemented at 67.1 years the company ICER increased by [redacted] to [redacted] per QALY.

EAG comments

- The CEM is aligned with the relevant population for this appraisal.
- The EAG has some concerns about the definition of 'candidates for systemic therapy' in this population and the generalisability of clinical evidence from RUBY-1 patients to the anticipated eligible population in England and Wales (see section 2.2.2.1).
- The EAG finds the baseline age used within the company model too young to be representative of real-world clinical practice in England and Wales. This is supported by clinical expert opinion and alternative evidence sourced from the literature.

3.2.4 Interventions and comparators

The intervention within this appraisal is dostarlimab in combination with platinum-containing chemotherapy. The comparator is platinum-containing chemotherapy.

The comparator used by the company, carboplatin + paclitaxel in combination is consistent with the NICE final scoped comparator of platinum-based doublet chemotherapy.

As highlighted in the decision problem (Table 3), the EAG agrees with the company that although there is a potential for a comparison with pembrolizumab + lenvatinib in people who had neoadjuvant or adjuvant therapy with a platinum-based doublet chemotherapy, there is no available evidence in this population from the pivotal trial (KEYNOTE-775). Therefore, this has not been included within the company's economic analysis.

3.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE reference case,[28] with benefits from a patient perspective and costs from an NHS and personal social services (PSS) perspective. In the base case, costs and benefits were discounted at an annual rate of 3.5% in line with NICE reference case. The [redacted]-year time horizon is sufficient to capture the extrapolated OS curves given the model cohort age.

3.2.6 Treatment effectiveness and extrapolation

The company extrapolated time-to-event data from the dMMR/MSI-H subgroup of RUBY-1 to inform their partitioned survival economic model. For PFS and OS, the data used are the same as the company presented in the clinical section of their submission. The following section of the EAG report summarises and critiques the company's approach to these extrapolations.

3.2.6.1 Overview

The RUBY-1 dMMR/MSI-H subgroup has a median follow-up of 24.79 months. The time-to-event outcomes were extrapolated for [redacted] years, meaning the vast majority of the estimated treatment benefit is coming from extrapolations and not observed data. As these analyses focus on a subgroup, the starting number of patients is low and often leaves few patients contributing information late on. The company did not account for any baseline differences in their original extrapolations and it is possible that benefits from differences in age and weight and other unmeasured confounders are being carried into the extrapolations, inflating the benefit of dostarlimab.

The company fitted a series of parametric and flexible parametric models to the data, and selected their preferred model through a comparison of the statistical goodness of fit (Akaike/Bayesian information criterion (AIC/BIC)) and plausibility of the extrapolations. To assess the plausibility of extrapolations, the company assembled a panel of five clinical experts, who made predictions of long-term performance for both arms of RUBY-1 for both PFS and OS outcomes.

3.2.6.2 Progression-Free Survival

The company uses IA PFS in their base case analysis, however it was possible to implement survival models fitted to BICR PFS within the economic model. This critique focuses on evidence presented by the company which is relevant to IA PFS.

The company first assessed whether the assumption of proportional hazards held within the observed period of RUBY-1 through investigation of several plots, included smoothed hazard rates and Cox-Snell residuals. The EAG agrees with the company's conclusion that the assumption of proportionality does not hold, and so it is appropriate to fit independent models to each arm of data. The downside to this approach is that there is no borrowing of information between the two arms, meaning both are more susceptible to the influence of small numbers of patients which may lead to the capture of trends that are not representative of routine use. This risk of this is bigger in a case such as this when the starting population sample size is relatively small. PFS was modelled such that there could not be more patients in the progression-free health state than there were alive in the model.

3.2.6.2.1 PFS Placebo+CP

The company first fitted standard parametric models to the IA PFS data and compared these to the predictions made by their clinical experts. The company ruled out the standard parametric models as all the predictions were too negative, and instead fitted flexible parametric restricted cubic spline models. The 2-knot and 3-knot models fitted similarly (Figure 10), and the company selected the 2-knot normal extrapolation as it was associated with slightly superior goodness of fit statistics.

The EAG consulted their own clinical experts who provided similar predictions for long term PFS in the placebo+CP population (Table 17). Hence, the EAG accepts the company's choice of PFS extrapolation.

The company additionally explored scenarios using other curves, using a piecewise approach combining KM estimates and extrapolation, and using BICR PFS. However, scenarios using alternative censoring rules were not explored.

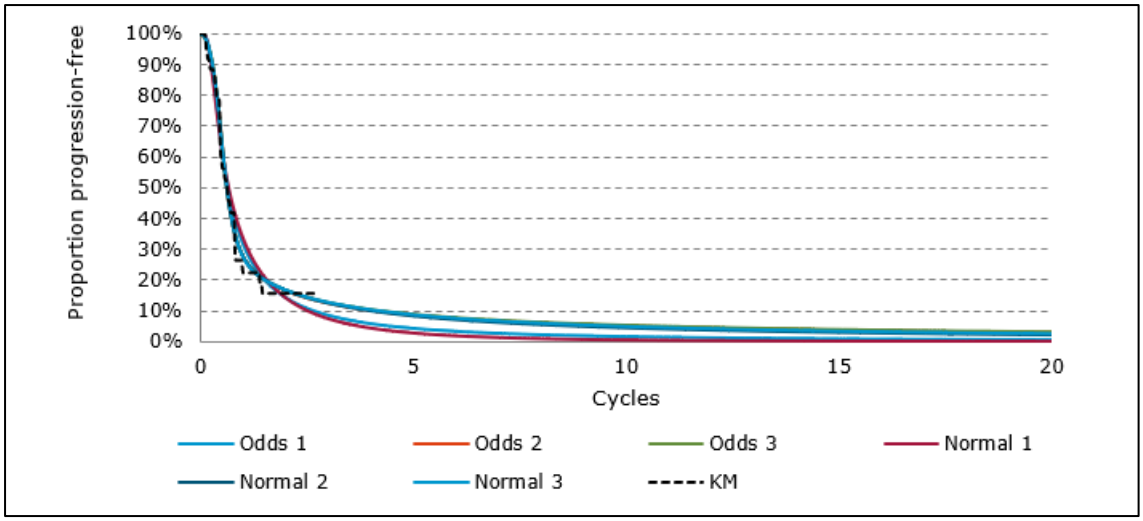

Figure 10: Spline extrapolations of placebo+CP PFS (taken from Fig 14 Company Submission)

Table 17: Estimates of PFS for people receiving placebo+CP

Months (years)	Company Advisors' mean	EAG Adviser	Company and EAG Preferred (spline odds 2 knot)
24 (2)	23%	18%	17%
36 (3)	15%	10%	13%
60 (5)	9%	8%	9%
120 (10)	7%	5%	5%
240 (20)	6%	3%	3%

3.2.6.2.2 PFS Dostarlimab+CP

For dostarlimab+CP, the company employed a similar approach. Standard parametric models were again fitted and rejected for their inconsistency with predictions made by clinical experts consulted by the company.

The EAG notes that the predictions made by the company's experts are much more optimistic than those provided by the EAG's clinical expert. Additionally, the company's preferred extrapolation is more optimistic than the predictions made by their experts.

Figure 11 shows the hazard rates from the company's preferred models for both arms, and Figure 12 shows the combined effective hazard ratio. It is apparent that hazard rate for dostarlimab is considerably lower for the full duration of the

extrapolation. The resulting extrapolations are shown in Figure 13. The EAG questions the validity of this implied assumption as comments from the EAG's clinical expert suggested that people who respond well to chemotherapy and remain progression-free will be very similar people with an equivalent response who have received dostarlimab+CP, and there is no reason why these groups would have a different hazard rate.

Hence, the EAG concludes that the magnitude of PFS benefit suggested by the company's approach is an overestimation of the expected benefit in real world use.

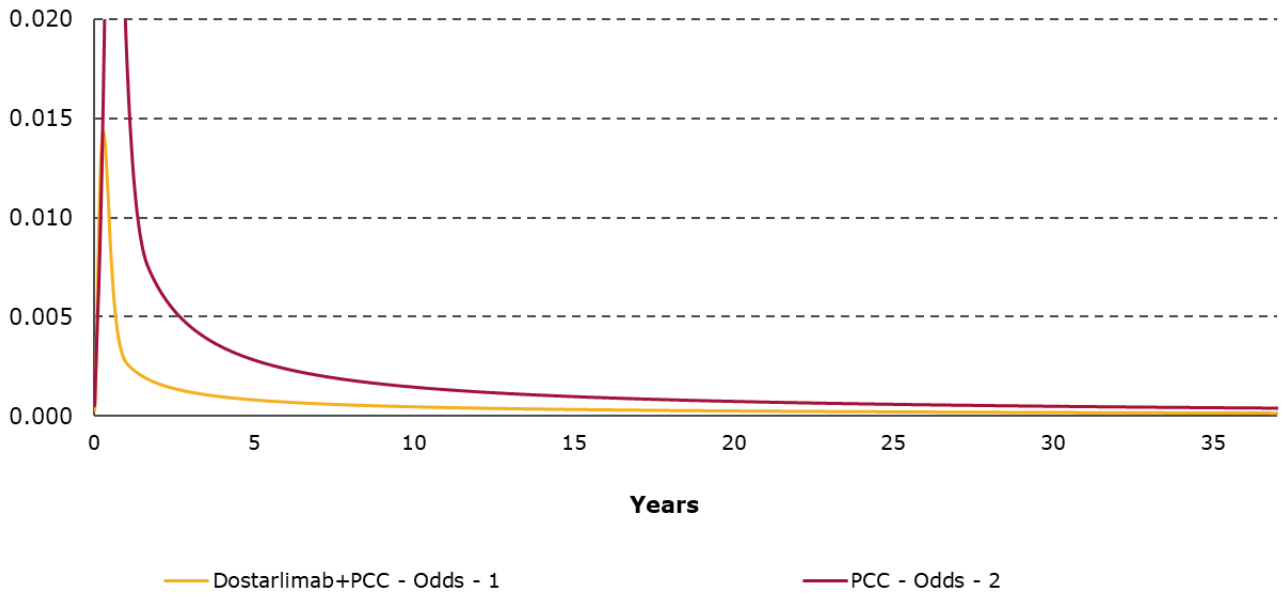

Figure 11: PFS Hazard Rates for company preferred extrapolations

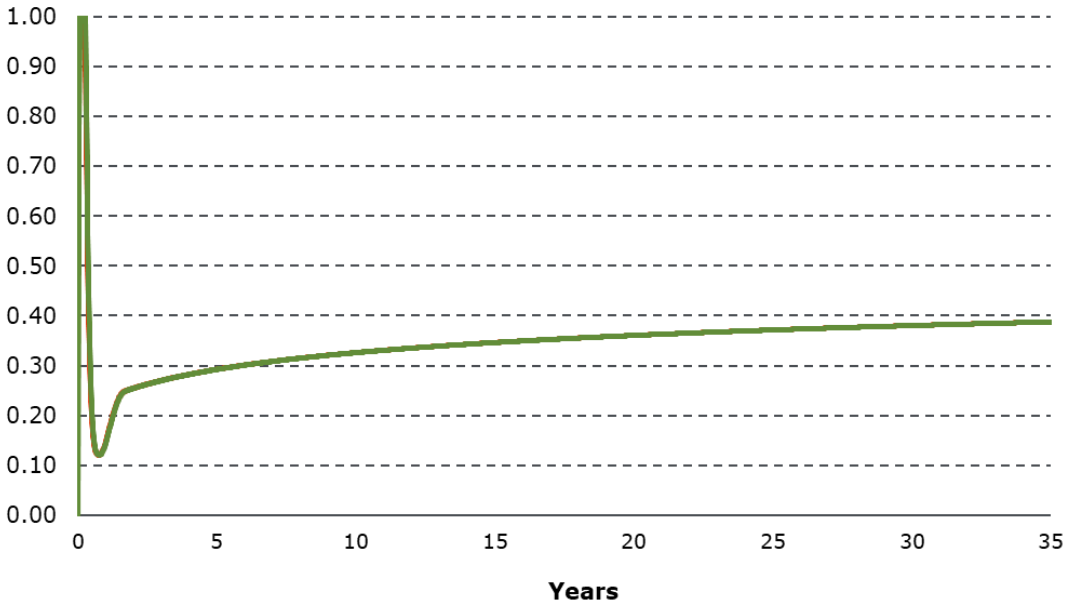

Figure 12: PFS Hazard ratio for company preferred extrapolation

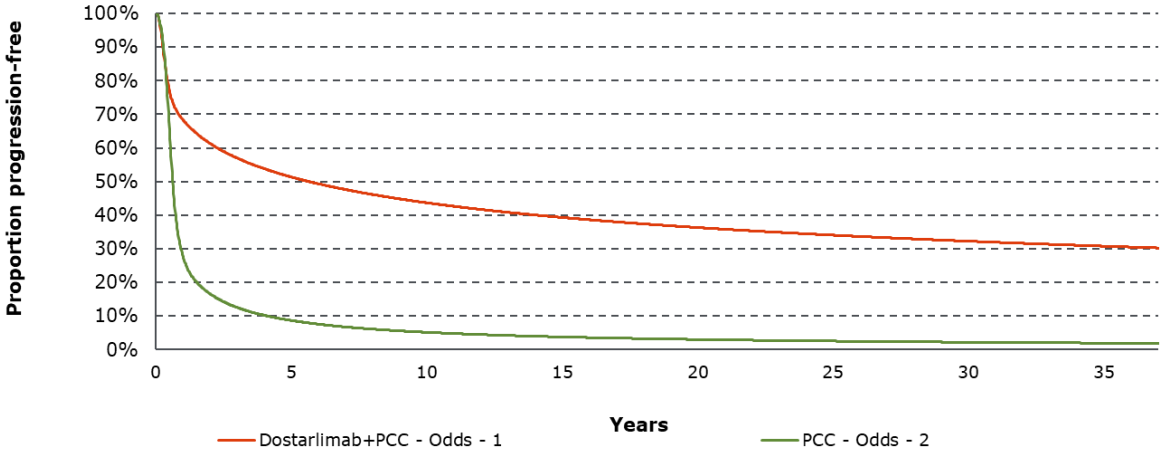

Figure 13: Corresponding PFS extrapolations from company's preferred assumptions, prior to OS capping

The EAG preferred approach is to use a Weibull model for the initial extrapolation period, as this was the most consistent model with the predictions of their clinical expert. At the point that the hazard rates cross, the EAG assumes the hazard rate for the dostarlimab population will follow the hazard rate for the chemotherapy population, which occurs at roughly 5 years. The corresponding hazard rates and hazard ratio are shown in Figure 14 and Figure 15 respectively. A comparison of the preferred approaches and predictions is show in Table 18, and the resulting EAG extrapolation is shown in Figure 16.

The EAG also considered fitting a log-logistic model as it was the next closest fitting model to the predictions made by the EAG clinical expert, including the same assumption of equivalent hazard rate beyond the crossing point. Both of these parametric models were close fits to the Kaplan-Meier estimator prior to the plateau (CS Figure 15). The data is too immature to provide a reliable estimate of any potential plateau.

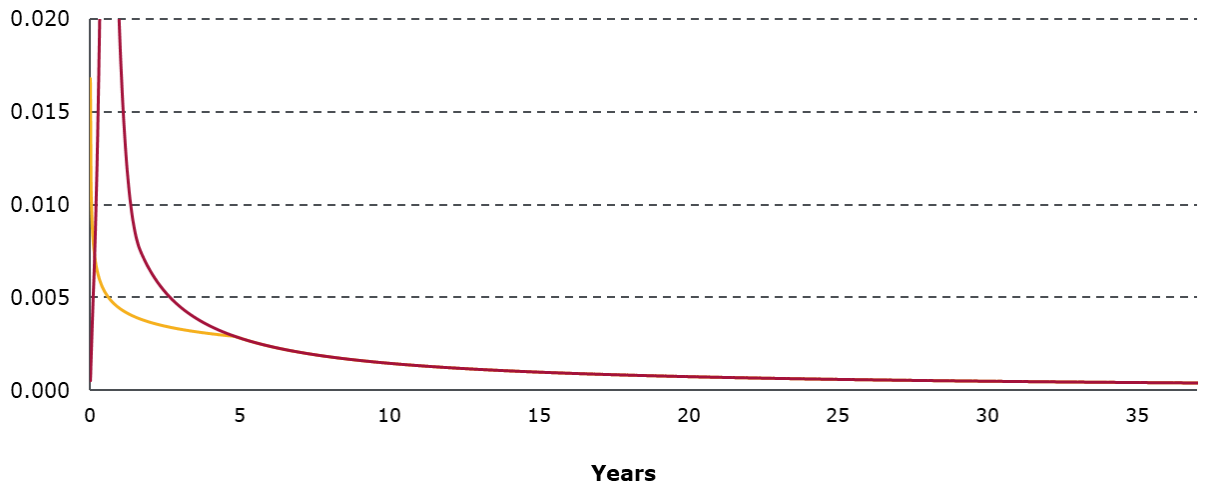

Figure 14: PFS hazard rates for EAG preferred base case (dostarlimab+CP yellow, placebo+CP red)

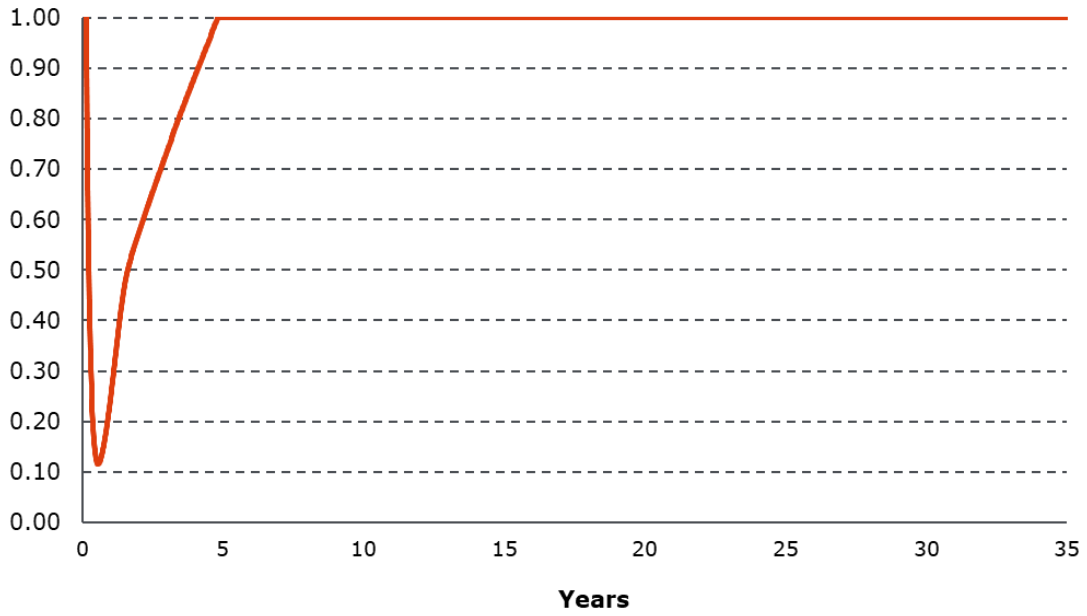

Figure 15: PFS hazard ratio for EAG preferred base case

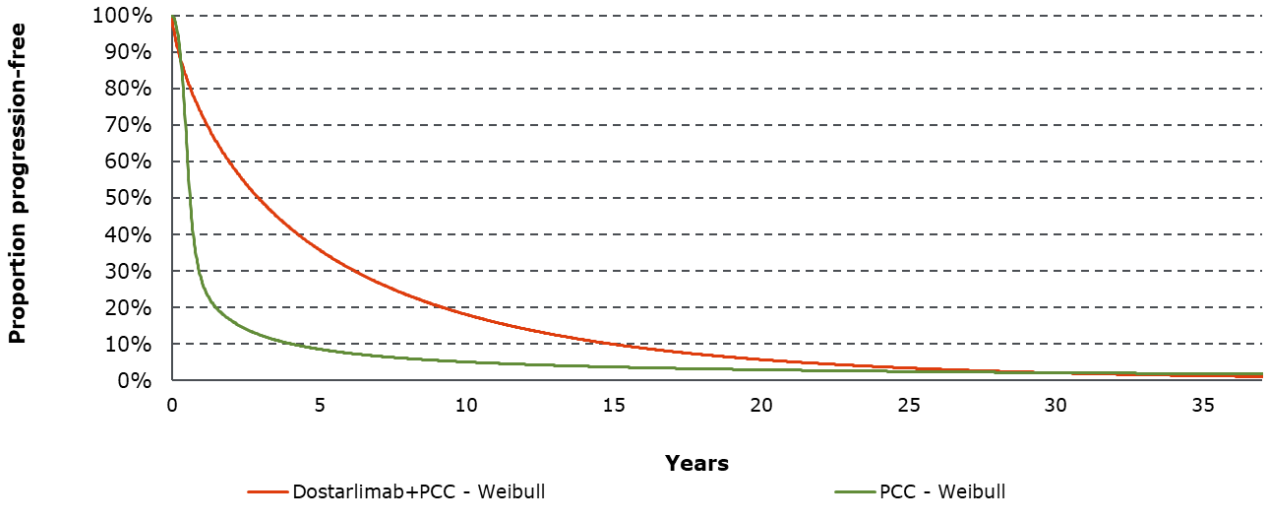

Figure 16: Corresponding PFS extrapolations from EAG's preferred assumptions

Table 18: Estimates of PFS for people receiving dostarlimab+CP

Months (years)	Company Advisors' mean	EAG Adviser	Company Preferred (spline odds 2 knot)	EAG preferred (Weibull/equal)	EAG alternative (log-logistic/equal)
24 (2)	60%	60%	61%	59%	58%
36 (3)	56%	40%	57%	50%	49%
60 (5)	46%	20%	51%	36%	38%
120 (10)	36%	15%	44%	21%	25%
240 (20)	30%	10%	36%	12%	15%

3.2.6.3 Overall Survival

The company uses the overall survival data for the relevant dMMR/MSI-H subgroup from the RUBY-1 trial.

The company first assessed whether the assumption of proportional hazards held within the observed period of RUBY-1 through investigation of several plots, included

smoothed hazard rates and Cox-Snell residuals. Whilst the immaturity of the data makes a firm conclusion impossible, the EAG accepts the company's conclusion that the assumption of proportionality does not hold, and so it is appropriate to fit independent models to each arm of data.

3.2.6.3.1 OS Placebo+CP

The company fitted parametric models to the placebo+CP arm data and after consideration of multiple factors, including goodness-of-fit criteria and consistency with the extrapolations from their clinical experts, they were content with the fit of the log-logistic model. Spline models were not considered due to the suitability of the standard parametric models. Despite the good fit to the data, the company preferred to use the extrapolation in a piecewise nature, and use the Kaplan-Meier estimates of survival for the duration of trial follow-up, and thereafter extrapolate based on a log-logistic parametric curve . The EAG is not supportive of this approach when the model fits well to the data, as it can be highly influenced by the tail of the Kaplan-Meier plot when few people are contributing information to the curve.

The EAG accepts the choice of the log-logistic model, but prefers to utilise it for the full duration of the economic model, rather than in combination with the Kaplan-Meier estimates. A comparison of these approaches is shown in Table 19.

Table 19: Estimates of OS for people receiving placebo+CP

Months (years)	Company Advisors' mean	EAG Adviser	Company Preferred (KM + log-logistic)	EAG preferred (log-logistic)
24 (2)	58%	60%	55%	61%
36 (3)	46%	30%	53%	47%
60 (5)	30%	10%	34%	31%
120 (10)	17%	5%	16%	14%
240 (20)	13%	3%	7%	6%

3.2.6.3.2 OS Dostarlimab+CP

The company considers extrapolation using standard parametric models fitted to the dostarlimab dMMR/MSI-H subgroup of the RUBY-1 trial. It is the EAG's interpretation that Figure 19 of the company submission suggests that these models fit well to the limited observed follow-up, however the company disagrees and also concludes that the models all disagree with the predictions made by their clinical experts.

The company instead explores an alternative approach where they apply the unstratified hazard ratio (HR=[redacted]) of relative efficacy for dostarlimab+CP vs placebo+CP to their preferred extrapolation for placebo+CP. This is claimed to be a conservative approach as the hazard ratio is slightly higher than the stratified hazard ratio (HR=0.30). This approach assumes that the magnitude of benefit is sustained for the full time horizon of the model, unless influenced by background mortality which influences the dostarlimab+CP extrapolation from just before 15 years. The EAG considers this to be implausible given that the effect size was not constant even in the trial period, and actually decreased within the observed follow-up (Company Submission Figure 17E). Furthermore, it does not account for the potential effects of subsequent treatments available.

It is unclear people who have responded well to CP will have a different hazard rate to those who respond well to dostarlimab+CP, though the numbers of people in each population may differ. The company's preferred extrapolation and the magnitude of the benefit modelled was deemed implausible by the EAG's clinical expert. The OS hazard rates for the company's preferred assumptions are shown in Figure 17, and the corresponding extrapolations are shown in Figure 18. A consequence of the company's modelling is that the post-progression survival health state ceases to exist beyond 22 years in the time horizon.

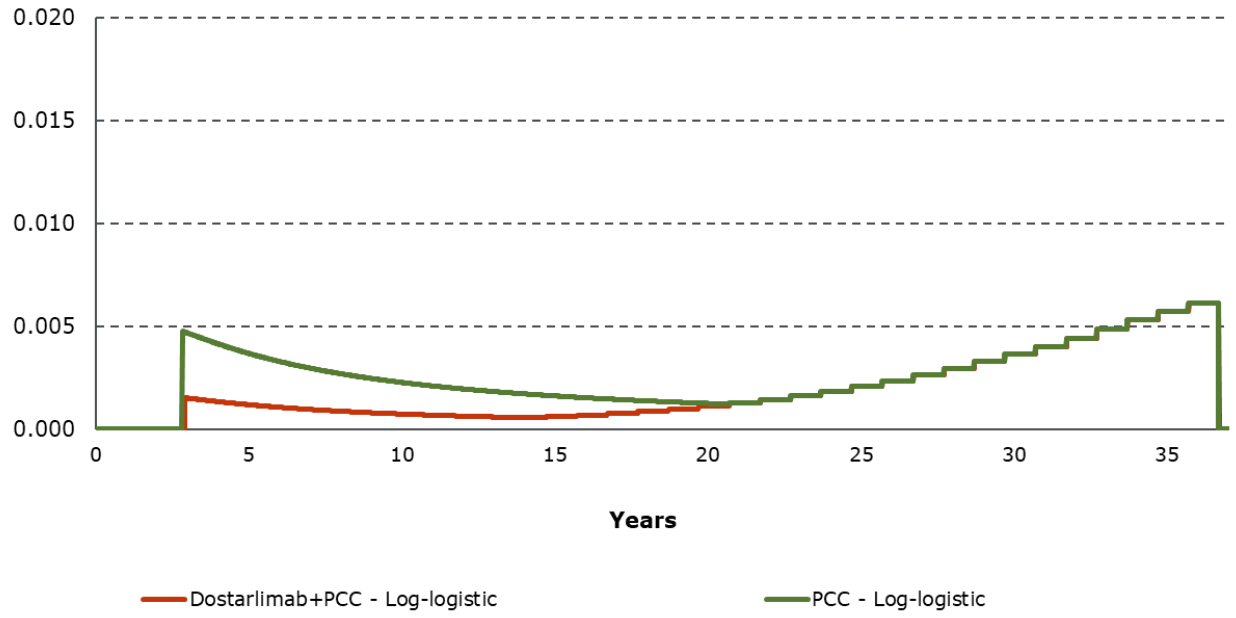

Figure 17: OS hazard rates for company preferred extrapolation

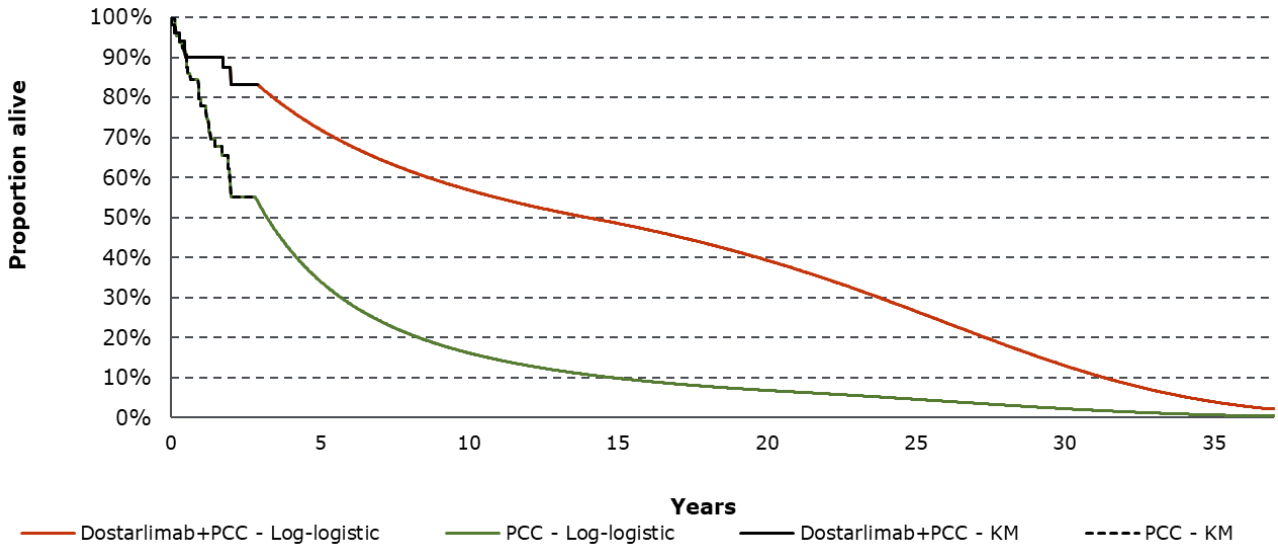

Figure 18: Corresponding OS extrapolations from company's preferred assumptions

The EAG preference is to select an exponential distribution, as this reflects the constant hazard rate observed within the trial data. To do this, the EAG applied a gradual converging effect of the hazard rates where the hazard rate for dostarlimab+CP begins to converge to the hazard rate of placebo+CP from 80 weeks and converges across a period of 3 years (Figure 19). This is to reflect the convergence of hazard rates witnessed within the trial follow-up, and to obtain an

extrapolation that sits within the survival predictions made by the EAG and company's clinical experts. An additional consideration was to preserve the presence of a post-progression survival health state across the model time horizon. A comparison of preferred approaches and clinical predictions is shown in Table 20. The EAG explores scenarios which vary the start and duration of the convergence period. The resulting extrapolations for the EAG's preferred assumptions are presented in

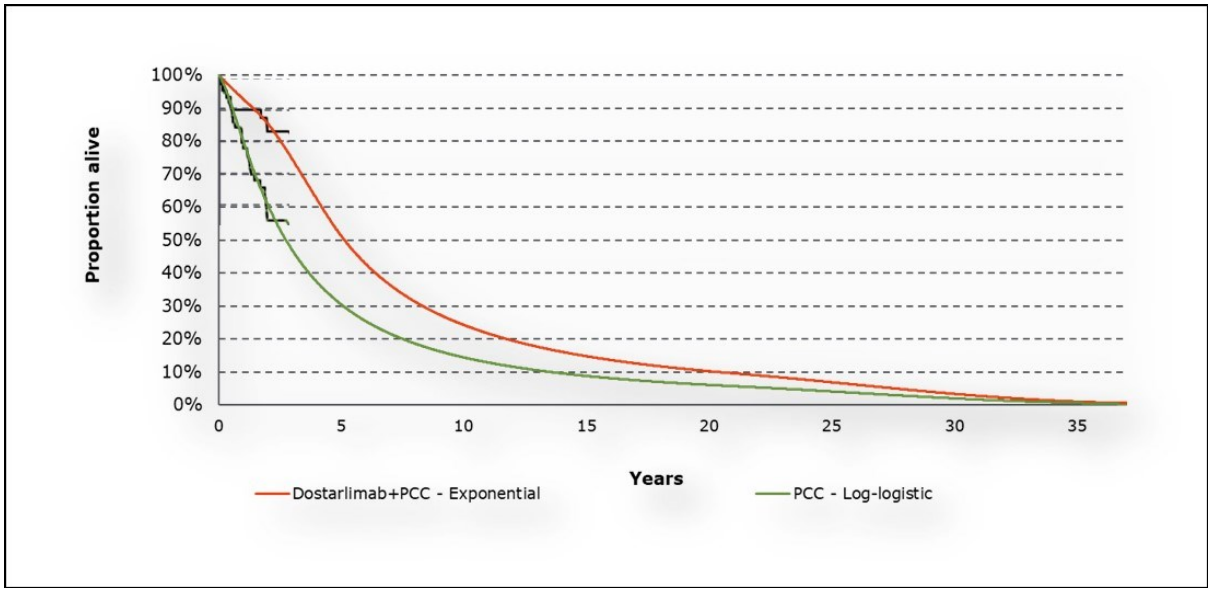

Figure 20.

Table 20: Estimates of OS for people receiving dostarlimab+CP

Months (years)	Company Advisors' mean	EAG Adviser	Company Preferred (KM + HR)	EAG preferred (exponential with convergence)
24 (2)	82%	80%	83%	85%
36 (3)	76%	50%	83%	75%
60 (5)	67%	20%	72%	51%
120 (10)	53%	10%	57%	24%
240 (20)	44%	8%	39%	10%

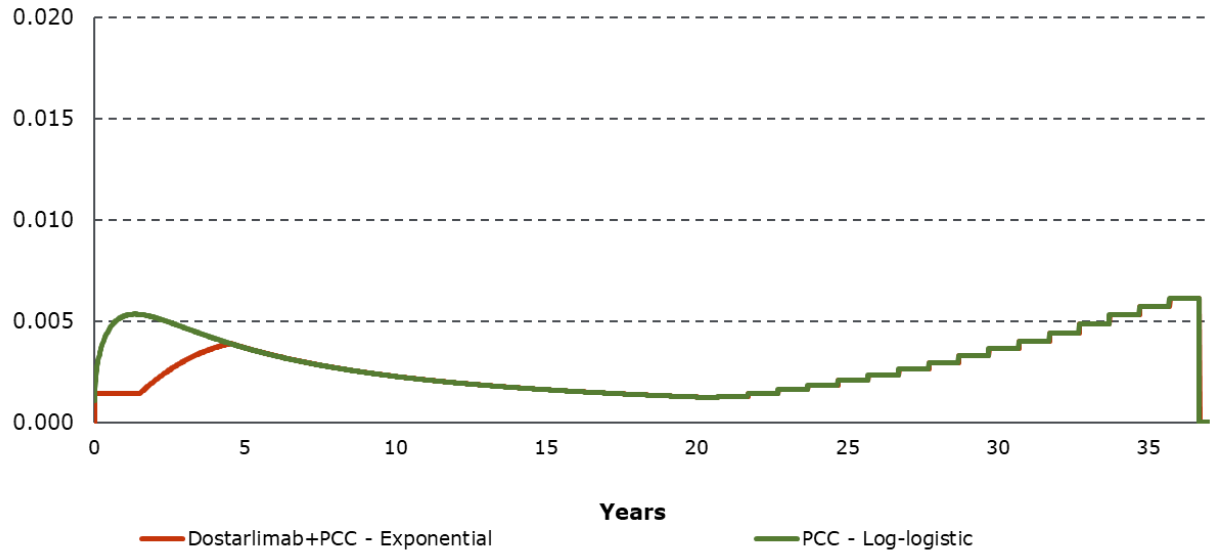

Figure 19: OS hazard rates from EAG's preferred assumptions

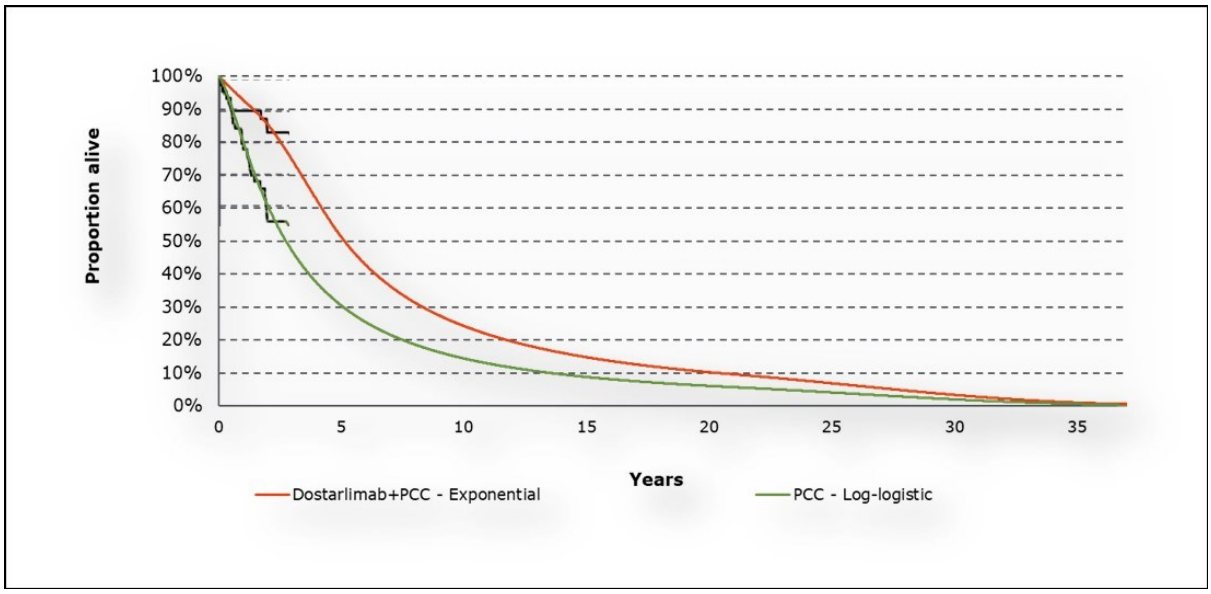

Figure 20: Corresponding OS extrapolations from EAG's preferred assumptions

3.2.7 Health related quality of life

Health-related quality of life (HRQoL) utility values were estimated from EQ-5D-5L data collected within the RUBY-1 trial.

The company preferred to use values for the ITT population rather than the dMMR/MSI-H population due to the larger available sample of patient data within RUBY-1, particularly in the PD health state. In the company submission the number

of observations available in each population at both PFS and PD health states was presented to support this. However, these were the number of EQ-5D-5L VAS observations rather than complete health index observations which were used in the model.

The reporting of HRQoL outcomes in the company submission was limited. Only changes from baseline and confidence intervals in EQ-5D-5L VAS scores of the dMMR/MSI-H patient population were presented (see Figure 8, CS doc B) along with changes from baseline and confidence intervals in EORTC QLQ-C30 global QoL scores in this population (see Figure 7, CS doc B). Neither of these measures are used in economic modelling, nor can the threshold for clinically meaningful change in either measure be applied. However, they appear to be the only subcategories which suggest a more favourable HRQoL profile for the dostarlimab+CP arm.

During the clarification process, the EAG requested the omitted EQ-5D health index scores (cross walked to the 3L UK value set) per cycle for the ITT population for both treatment arms, and those of the dMMR/MSI-H population for comparison. The tables of results can be found in Table 32 and Table 31 of the company clarification response document, respectively. It is clear from this data that there are no observed differences in HRQoL between the dostarlimab+CP and placebo+CP arms in either the ITT or dMMR/MSI-H populations at each treatment cycle/measurement point.

Within this PSM, utility values are assigned to disease states independently of treatment arm. Therefore, pooled data from across the dostarlimab+CP and placebo+CP treatment arms for patients in the PFS and PD states were used to calculate the respective mean health state utility values for use in the economic model. To be included in the analysis, patients were required to be in the ITT population and have a baseline and post-baseline EQ-5D-5L assessment. EQ-5D-5L data was mapped to the recommended EQ-5D-3L valuation set as per current NICE reference case guidance.[28] This produced health state utility values from the RUBY trial analyses of [redacted] for PFS and [redacted] for PD for the ITT population (Table 21).

Age-related disutility was applied to the estimates using general female population utility values for the UK taken from Hernández Alava et al, 2022.[32]

Table 21: Health state utility values from RUBY trial (source Table 51, CS doc B, pg. 123)

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

Abbreviations: dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PD – progressed disease; PFS – progression free survival; SD – standard deviation

The mean values obtained for both ITT and dMMR/MSI-H populations were similar (see Table 21), with a marginally greater difference between PFS and PD states in the ITT population ([redacted]). This was explored in a sensitivity analysis and made little impact on results ([redacted] v [redacted] incremental QALYs with ICERs of [redacted] v [redacted] using ITT and dMMR/MSI-H values respectively).

The EAG also sought equivalent data for the ITT primary advanced (Stage III and IV) and ITT recurrent populations from the RUBY-1 trial (see Table 22). Whilst showing slight deviations from the full ITT population, the difference between the health states within each comparison remained similar.

Table 22: Health state utility values from RUBY trial for primary advanced and recurrent ITT populations (adapted from Table 35, company clarification response)

Health state	ITT primary advanced population, mean (SE*)	ITT recurrent population, mean (SE*)	Source:
PFS	[redacted]	[redacted]	RUBY-1 trial
PD	[redacted]	[redacted]	

Abbreviations: dMMR – DNA mismatch repair deficient; ITT – intention to treat; MSI-H – microsatellite instability-high; PD – progressed disease; PFS – progression-free survival; SD – standard deviation. Note. Progression status determined by investigator. *SE calculated from lower and upper bounds assuming a normal distribution. Source: CS, Table 51; GSK Data on File 'Table 3.060101 ru_uk_t_modest_pfsinv_m1_p2.rtf'; GSK Data on File 'Table 3.060201 ru_uk_t_modest_pfsinv_m1_p1.rtf'

The EAG agrees with the company's observations that there are only minor differences between utilities reported for PFS health states (+/- 0.04) and the utilities reports for PD health states (+/- 0.05) across each of the provided populations and subgroups, suggesting the utility value for PFS and PD is reasonably consistent across the RUBY trial population. Consequently, the difference in mean health utility values between the PFS and PD states is consistent, between +/- 0.5 and +/- 0.6.

A SLR was conducted to identify any HRQoL studies from the literature (see section 3.1.1). The company justified use of trial data in the economic model as findings returned only one, small sample, study evaluating health utilities in patients with advanced or recurrent endometrial cancer [33] (see CS doc B, pg 124 for company's full critique).

The EAG support the use of health utility values derived from the ITT population of the RUBY-1 trial for use in the economic model. As trial data this is the most relevant available source, with use of the ITT population values appropriate due to inherent sample size advantages, the EAG believe this clinically reasonable to apply to the dMMR/MSI-H population.

With the paucity of data available in the published literature, the EAG performed a validity check on values from the recent NICE TA779 [24] which assessed the use of dostarlimab (monotherapy) in the EC population who have had prior platinum-based chemotherapy. The key clinical evidence which informed the QoL data was based on the GARNET study (NCT02715284), and whilst the place in the treatment pathway in the GARNET study is different to that of the RUBY-1 study, GARNET included patients in the relapsed state as the entry point.

It would be expected that patients who have moved on from front line treatment in RUBY i.e. those in the PD state, would align with patients entering GARNET (in the PFS) and utility scores would be comparable between cohorts.

The company provided the health state utility values from the GARNET trials as requested during the clarification process (see Table 23).

Table 23: GARNET health state utility values (N=[redacted]) (progression) (Source: Table 25, company clarification response)

Health state	Estimate
Pre-progression	[redacted]
Progressed disease	[redacted]

Source: GARNET TA779 committee papers Table 22. Page 275.[24] Footnote: Values presented to 7 decimal places

The EAG is satisfied the PFS utility score reported in GARNET ([redacted]) is very closely aligned with the PD scores reported in RUBY ([redacted] for ITT and [redacted] for dMMR/MSI-H (see Table 21). In the EAG opinion, this anchor point suggests face validity of the

health utility values for the EC population in the UK and is appropriate for use in this appraisal.

3.2.7.1 Adverse Events

The company included disutility decrements in the model for TEAEs of grade 3 and above in >5% of the RUBY-1 trial ITT population. The company state that 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 (CS doc B, pg. 125). These values and sources are summarised in Table 24. The EAG noted these values were used in TA779.[24]

Table 24: Adverse event disutilities used in CEM (Source: Table 52, CS doc B)

Adverse event	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.[34] 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.[34]
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.[35] Assumed equal to responding plus fatigue.
Hypertension	−0.020	NICE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first line platinum-based chemotherapy. Published 17 February 2021. https://www.nice.org.uk/guidance/ta673/history. Accessed February 2023.[36]
Hypokalaemia	−0.074	NICE. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). Published 28 September 2016. https://www.nice.org.uk/guidance/ta411.[37]

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.[35] 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. https://www.nice.org.uk/guidance/ta411.[37]
Urinary tract infection	−0.010	Assumption
White blood cell decreased	0.000	Assumed to have no utility impact

The EAG are satisfied the utility decrements identified by the company are appropriate for use in the analysis. However, the EAG are concerned the AEs included in the model are too limited and do not reflect the breadth of AEs at grade 3 and above experienced by patients on treatment for advanced and recurrent EC. This is particularly the case for immune-related AEs which are more likely to affect those in the dostarlimab+CP treatment arm. See sections 2.2.3.9.2 and 2.2.3.9.3 for detailed clinical discussion.

The EAG prefers to include the additional grade 3 and above TEAEs from Table 10 which were extracted by the EAG from the CSR and were recorded in >2% of patients, rather than just those at the >5% patient threshold applied by the company. This broadened the variety of AEs represented in the model, with the additions shown in Table 25. The EAG noted disutilities and costs for UTI, lipase increase, and abdominal pain had already been sourced within the CEM though were not used as they did not exceed the >5% cut off used. These were validated and retained by the EAG and disutility values sourced for the remaining AEs.

Table 25: Disutility estimates and sources for grade 3 and above AEs experienced by >2% patients in RUBY-1 ITT population

Adverse event category	Disutility	Source
[redacted]	0.010	Company assumption (CEM)
[redacted]	0.069	Assumed equal to abdominal pain
[redacted]	0.045	EAG assume equal to [redacted]
[redacted]	0.000	EAG assume no disutility
[redacted]	0.045	TA779[24] and Lloyd (2006) [38]
[redacted]	0.010	Company assumption (CEM)
[redacted]	0.116	EAG assume equal to hand and foot syndrome, Lloyd (2006)[38]

EAG sensitivity analysis showed addition of these AE disutilities and their associated costs (see section 3.2.8.3), at the proportions reported in Table 10, made negligible difference to the company base case ICER and imperceptible difference to incremental QALYs (see Table 32). A detailed explanation of EAG modelling methodology to include these AEs within the model is provided in addendum appendix 8.4.

The overall incidence of any grade TEAEs related to dostarlimab or placebo only, is substantially higher in dostarlimab only (see Table 12), and further illustrated by the proportion of the immune-related TEAEs (discussed in detail in section 2.2.3.9.6 and shown in full in Table 13). The most common dostarlimab-related irAE was hypothyroidism (overall population 11.2%; dMMR/MSI-H subgroup [redacted]%). This was also highlighted by clinical experts for both the EAG and the company as an important and commonly encountered AE in clinical practice in those treated with dostarlimab, and substantiated by additional phase I/II trial outcomes.

Despite the frequency of irAEs, they do not feature as TEAEs at grade 3 or above. The EAG cannot therefore justify including them in the economic model as this would not align with common/standard methodology for inclusion in NICE TA. However, it is important to emphasise the outcomes from a clinical perspective and recognise the potential impact of these irAEs, even when classified below grade 3.

The nature of irAEs experienced mean that regular monitoring of symptoms is required and medications to manage, mitigate and resolve symptoms may be prescribed and subject to ongoing review. The EAG is not aware of available data to inform whether certain AEs e.g. hypothyroidism, are reversible issues even when at grade 2.

The EAG preferred estimates for outpatient resources use/monitoring costs (discussed in section 3.2.8.2) go some way towards addressing the costs of irAEs whilst avoiding double counting within the model.

EAG comments:

- The EAG agrees health utility values for PFS and PD health states sourced from the RUBY-1 trial are the most appropriate for use in this appraisal.
- The EAG supports the use of ITT figures due to sample size advantages and believe to be clinically reasonable in the dMMR/MSI-H population.
- The values derived for the PD state show face validity against data from comparable cohorts of EC patients in another recent trial.
- Reporting of HRQoL outcomes in the original company submission was misleading and did not include EQ-5D health index values.
- Health utility index values for both ITT and dMMR/MSI-H populations show no difference in HRQoL between people in the dostarlimab + CP arm and placebo + CP arm at each equivalent treatment cycle/time point.
- Health utility values are pooled across treatment arms to derive values for the PFS and PD health states. Poorer HRQoL scores are a result of progressed disease status, not treatment received.
- Increase in QALYs in the dostarlimab + CP arm is due to the additional life years projected to occur in the company's survival extrapolations rather than any measurable improvement in HRQoL in the dostarlimab + CP arm.

- The EAG preferred to include the additional grade 3 and above TEAEs experienced by >2% of the population. This made a negligible impact on the ICER.

3.2.8 Resources and costs

The company conducted an economic SLR to identify available HCRU evidence relevant to the decision problem, however none of the data retrieved was used in the company economic model (CEM). The company instead used UK clinical opinion for HCRU inputs and sourced costs from British National Formulary (BNF) [39] and National Health Service (NHS) reference costs [40] where applicable. The company preferred this approach as the studies identified were either US based or contained limited UK data not relevant to the model inputs. A targeted literature review was also conducted to identify acute care costs to treat AEs specific to the RUBY-1 trial.

Costs inputs were for the 2022/23 cost year, using inflation indices annual percentage increase for adult services published by PSSRU [41] to inflate prices where necessary.

Costs included in the company economic model comprised:

- Treatment acquisition costs of intervention and comparator treatments in decision problem and subsequent treatments
- Treatment administration costs of intervention and comparator treatments in decision problem and subsequent treatments
- Monitoring costs for intervention and comparator treatments
- Adverse events applied as a one-off cost in the first model cycle per treatment arm for grade 3 and above TEAEs
- End-of-life care as a one-off cost on entry to the death state

The company model did not include:

- Monitoring costs for subsequent treatments (the company state these are captured in the health state costs applied to the PD health state (CEM).
- Adverse event costs for the most frequent immune-related adverse events.
- Diagnostic testing costs using immunohistochemistry to identify tumours with dMMR.

3.2.8.1 Treatment acquisition and administration costs

Treatment acquisition costs were calculated using treatment prices sourced from the BNF [39] and dosing schedules from the RUBY-1 trial and draft SmPC which provided data for the dosing scheduled for dostarlimab in combination with CP. The company applied the patient access scheme (PAS) discount of [redacted] with a net price of [redacted] per 50 mg per 1 ml vial of dostarlimab.

Cost per unit was multiplied by dose per treatment cycle (where one cycle is three weeks) to calculate the treatment cost per cycle. Wastage was assumed in the base case. Duration of treatment was modelled using TTD data from the RUBY-1 trial with completion rates applied for the first six treatment cycles and a discontinuation rule at three years.

Table 26: Acquisition and administration costs per treatment cycle (source: Table 56, CS doc B)

	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	£449.23 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£495.36 [SB15Z – Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRGs]	£6,855.41 (list price) [redacted](PAS price)	£12,155.20 (list price) [redacted] (PAS price)	NHS. National Cost Collection Data Publication 2020/2021. https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/.Accessed February 2023[140] NICE. British National Formulary (BNF). https://bnf.nice.org.uk/. Accessed February 2023[140]
CP	£449.23 [SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs]	£0.00	£968.08	£0.00	NHS. National Cost Collection Data Publication 2020/2021. https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/. Accessed February 2023[140]

Abbreviations: NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PAS – patient access scheme;

3.2.8.2 Monitoring costs

The clinical expert for the EAG advised that ongoing monitoring for those on immunotherapy treatment was especially resource intensive and already impacting significantly on their clinics following recommendations for their use as a second line treatment for this indication. Treatment related AEs were a major factor in this, requiring more regular outpatient follow up than patients treated with CP alone. The EAG clinical expert informed that those on immunotherapy treatment are seen every 3-6 weeks in clinic, with many irAEs occurring after several months of sustained treatment. This contrasts with patients on CP who are reviewed every 3 months. Subsequently, the EAG believe the ongoing monitoring costs for those continuing with dostarlimab monotherapy from the dostarlimab+CP arm have been significantly underestimated in the CEM.

The incidence of any TEAEs related to dostarlimab or placebo only (occurring in >8% of either arm) is approximately [redacted] higher in the dostarlimab arm ([redacted] v. [redacted]) in the ITT population and nearly [redacted] higher in the dMMR/MSI-H population ([redacted]) v.[redacted]) (see Table 12).
The overall profile of these TEAEs is reflected in in the immune-related TEAEs (discussed in detail in section 2.2.3.9.6 and shown in full in

Table 13) and impact of these further substantiated by additional trial outcomes.

Expert advice to the EAG highlighted the need for active monitoring and early management of these irTEAEs which involved clinic visits, regular blood tests and in the case of hypothyroidism, prescription and modification of medication. The relevance of hypothyroidism (and other irAEs including colitis, pneumonitis, hepatitis and nephritis) was also reflected in feedback to the company from their clinical advisors on adverse events (GSK data on file: Subsequent treatment distributions, Adverse Events sheet of economic model)

Costs and resource use for these elements have not been adequately captured within the model and the individual costs of these interventions may be relatively small. However, the requirement for more intensive monitoring and consequent resource use is a significant factor from both a clinical and cost perspective.
The EAG identified estimates for weekly outpatient visit frequency in the literature in addition to calculating estimates based upon the EAG clinical expert advice, which are compared in Table 27.

Table 27: Resource use estimates and sources for outpatient monitoring

Resource use estimate (outpatient visits per week for PFS state cycle 19+)	**Source**
0.13	Company clinical expert opinion as per company base case – EAG unable to verify figures from company submission documents
0.23	TA904 [15] also used in TA620.[42]
0.25	EAG clinical expert. Average weekly rate calculated by EAG assuming 3-weekly visits for 6 months and 6-weekly visits for 6 months

Sensitivity analysis was performed using values from these alternative sources (see Table 32). Increased frequency of outpatient visits for the dostarlimab + CP arm from cycle 19+ increased the ICER by over [redacted] in both alternative analyses.

The EAG believe the very similar estimates obtained from the literature [15, 42] and the EAG clinical expert are more representative of real-world monitoring resource use in patients who receive ongoing dostarlimab therapy. The EAG feel the use of these values in the analysis are more appropriate and also serve to incorporate some of the costs associated with management of lower grade, but significant, irAEs not included within the company analysis.

3.2.8.3 Adverse events costs

The EAG found the unit costs for grade 3 and above AEs included within the CEM to be sourced and inflated to current cost year appropriately. However, as discussed in detail in section 3.2.7.1, the EAG believe the AEs included by the company are restrictive and do not fully capture the breadth of AEs experienced by patients or costs involved in their management. This is particularly relevant as inputs are calculated under the assumption that AEs are likely to occur rapidly after treatment and only require acute care (CS, doc B, pg 135).

The EAG sourced cost estimates for the additional AEs included in Table 10 experienced by >2% of RUBY-1 ITT population. These are summarised below in Table 28.

Table 28: Cost estimates and sources for grade 3 and above AEs experienced by >2% patients in RUBY-1 ITT population

Adverse event category	Disutility cost per incident (£)	Source
[redacted]	1,042.39	Company assumption (CEM)
[redacted]	591.53	TA779 [24]
[redacted]	2,426.93	Company estimate (CEM)
[redacted]	664.75	TA567 [43]
[redacted]	719.00	National Cost Collection Data [40] PJ66B Rash or Other Non-Specific Skin Eruption, with CC

		Score 1-2, Total HRG

3.2.8.4 Subsequent treatment costs

Subsequent treatment costs used in the CEM are reported to be calculated based on resource use estimates provided by UK experts (CS doc B, pg. 136). The company cited a document from an Advisory Board meeting with clinical experts as the source of the HCRU data (confirmed at clarification as filename GSK 2023a, entitled '[GSK Data on File] GSK UK Advisory Board: External Insights into the RUBY Data' supplied with the CS reference pack). The EAG requested these during clarification, but only estimated percentages of subsequent treatments by each of the 5 experts, and a single line response from each to an unreported question on AEs included, was reported (filename 'GSK data on file - subsequent treatment distributions' supplied with the response to clarification questions reference pack).

Total subsequent treatment costs were calculated as cost per class for average total treatment duration using drugs at list prices, and total AE costs during subsequent treatment. These combined figures generated total subsequent treatment costs for dostarlimab+CP of £5,152.19 and for CP £14,035.19.

The EAG find the values used by the company for subsequent treatment costs highly uncertain.

Firstly, there is no established standard 2nd line treatment for these patients.[24] The company therefore sought UK clinical expert opinion on the proportions of those receiving treatment after progression from the dostarlimab+CP and placebo+CP arms, as well as the proportions likely to receive each of the identified subsequent treatment options (GSK data on file - subsequent treatment distributions). Mean values for both of these parameters were used to inform the CEM, however estimates provided by the five experts varied significantly. The substantial differences in responses between experts suggests a high degree of variability in real world practice (estimates range between 55-90% of patients who have dostarlimab+CP as 1st line will receive subsequent 2nd line treatment and 70-90% of

patients with 1st line CP to receive 2nd line treatment) (GSK data on file - subsequent treatment distributions).

Secondly, the application of subsequent treatment costs as a one-off, total cost using average total treatment duration for each treatment regime. Some references were provided in version 2 of the CEM (supplied at clarification) to literature sources suggesting these were where average treatment durations were derived, but the EAG found these vague and were unable to fully validate figures or their appropriateness within the timescale of this review. It is unclear what is meant by 'average treatment duration' so the EAG cannot determine if this method may under or over-estimate the total costs.

The EAG was unable to find any alternative evidence sources to reduce uncertainty in these estimates, so undertook a series of sensitivity analyses to explore the impact of subsequent treatment costs on the ICER (see Table 32). The EAG were satisfied that changes to these cost inputs only have a small effect on the ICER.

3.2.8.5 End-of-life costs

End-of-life care was applied as a one-off cost on entry to the death state. The company used costs from Guest (2006).[44] Whilst appropriately uplifted to the current cost year for use, this was a relatively old source. The EAG therefore conducted sensitivity analysis using estimates from Georghiou (2014),[45] also used in the recent TA904.[15] The inflated cost used by the EAG of £6,956.95 made only minimal difference on the ICER (see Table 32).

EAG comments:

- The EAG was satisfied with the acquisition and administration cost inputs, end-of-life care costs, and omission of diagnostic costs using immunohistochemistry in the company base case.
- Unit costs for AEs and category of monitoring intervention were sourced and inflated appropriately for use in the CEM.

- The EAG believe ongoing monitoring costs for those continuing with dostarlimab monotherapy from the dostarlimab+CP arm have been significantly underestimated in the CEM.
- The EAG prefer estimates sourced from the literature and EAG clinical expert to inform resource use for outpatient visits, thereby informing monitoring costs.
- There remains considerable uncertainty over subsequent treatment costs included within the model.
- The application of costs and disutility decrements in the first cycle of the model, on the assumption that AEs are likely to occur rapidly after treatment and only require acute care, does not fully capture the nature of immune related AEs. This underestimates both monitoring and management costs.
- The EAG believes the selection of AEs at grade 3 and above was restrictive, therefore costs of AEs are underestimated in the company base case.
- The EAG preferred to include costs for a broader range of AEs at grade 3 and above in their base case.
- Costs of the additional AE categories included by the EAG made negligible difference on the ICER.
- Increased resource use of outpatient visits and thus subsequent costs of monitoring patients on dostarlimab therapy made a moderate impact on the ICER.

3.2.9 Severity

The company did not submit a case for a 'severity modifier' to be applied as the QALY shortfall analysis they conducted concluded that primary advanced or recurrent endometrial cancer does not qualify for any severity modifier. Therefore, no adjustments to the QALYs in the economic model were made.

The EAG agreed with the figures calculated by the company (see CS doc B, section 3.6 for full details of their analysis) and that no severity modification is appropriate in this case.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

The company's preferred assumptions that make up their base case analysis are summarised in

Table 29. Corresponding deterministic results are shown in Table 30 and Table 31.

Table 29: Summary of company base-case inputs and assumptions (Source: section B3.9, CS doc B)

Category	Base-case value
Time horizon	[redacted]
Age at baseline (years)	[redacted]
Weight (kg)	[redacted]
Body surface area (m2)	[redacted]
Completion rates per cycle	Completion rates for RUBY-1 trial switched on
Utility values source	Grade ≥ 3 AEs from RUBY-1 trial ITT population included and assumed occur in the first cycle of the model time horizon.
Treatment wastage	Wastage on
Subsequent treatment source	HCP opinion on treatment with lenvatinib + pembrolizumab
PFS (dostarlimab in combination with CP)	IA PFS, flexible Odds K=1
PFS (CP)	IA PFS, flexible Odds K=2
OS (dostarlimab in combination with CP)	Extrapolated CP OS adjusted by unstratified HR ([redacted]) (KM for full follow up period)
OS (CP)	Log-logistic (KM for full follow up period)
OS HR	[redacted]
TTD (dostarlimab in combination with CP)	Weibull (KM for full follow up period) three year stopping rule and completion rates applied
TTD (CP)	Weibull (KM for full follow up period) three year stopping rule and completion rates applied
PFS treatment risk convergence	No treatment risk convergence of PFS
PFS and OS treatment risk convergence	No treatment risk convergence of PFS and OS
Resource use	Estimates provided to company by UK clinical experts based on treatment phase, health state and treatment.
Costs	Obtained from key UK sources: NHS list prices,[40] BNF [39] and literature.[44, 46]

Table 30: Company deterministic base-case results (Source Table 67, CS Doc B)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental QALYs (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.26	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years

Table 31: Net health benefit and net monetary benefit at £20,000 threshold (Source: Table 68, CS Doc B)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NMB at £20,000 (£)
Dostarlimab in combination with CP	[redacted]	[redacted]				
CP (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	4.26	[redacted]	[redacted]

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; NMB – net monetary benefit; QALYs – quality-adjusted life years.

4.2 Company's sensitivity analyses

The company conducted a range of deterministic and probabilistic sensitivity analyses (PSA) on the base case. PSA included 1000 Monte Carlo simulations with appropriate sampling distributions fitted for all inputs. Only treatment costs for primary advanced or recurrent EC were fixed.

Compared to CP alone, dostarlimab+CP has a [redacted]% chance of being cost effective at a WTP threshold of £20,000 per QALY (**Figure 21** and **Figure 22**).

Abbreviations: PCC – platinum containing chemotherapy; QALY – quality adjusted life year.

Figure 21: Probabilistic cost-effectiveness results, dostarlimab + CP vs CP: 1000 simulations (with PAS price for dostarlimab) (Source: Figure 25, CS doc B)

Abbreviations: PCC – platinum containing chemotherapy

Figure 22: Base-case cost-effectiveness acceptability curve dostarlimab + CP vs CP (with PAS price for dostarlimab) (Source: Figure 26, CS doc B)

Deterministic one-way sensitivity analysis (OWSA) was conducted by varying single parameter at a time. The company presented the top 10 parameters which impact incremental costs and QALYs in the form of a tornado diagram (Figure 23). The model was most sensitive to the OS HR, completion rates per cycle associated with dostarlimab+CP arm, and both outpatient visit frequency per cycle for dostarlimab+CP in PFS state from cycle 19+ and outpatient visit unit cost. (For tabulated results see Table 70 in CS document B)

Figure 23: One-way sensitivity analysis on company base-case (Source: Figure 28, CS Doc B)

4.3 Model validation and face validity check

The EAG undertook extensive review of the CEM submitted.

The model appears to reflect the assumptions made by the company. The EAG were able to reproduce the analyses provided by the company and obtained comparable PSA results using the CEM base case values (QALY difference [redacted], ICER £[redacted] per QALY)

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG's main exploratory analyses informed the base case and are described below (section 5.3). In addition, the EAG conducted sensitivity analyses surrounding a range of parameters presented in Table 32.

Table 32: EAG exploratory and additional sensitivity analyses

Parameter variation and section of report discussed	Incremental Costs (£)	Incremental QALYs	Deterministic ICER (£/QALY)
Age at baseline			
67.1 years [16, 29]	[redacted]	3.93	[redacted]
66.0 [30]	[redacted]	4.03	[redacted]
67.9 [31]	[redacted]	3.84	[redacted]
End of life costs			
Alternative estimate of end of life costs used in TA904 [15, 45]	[redacted]	4.26	[redacted]
Subsequent treatment data source			
UK expert opinion with Lenvatinib, pembrolizumab and pembrolizumab monotherapy (CEM v2)	[redacted]	4.26	[redacted]
Subsequent treatment costs varied			
Subsequent treatment costs excluded	[redacted]	4.26	[redacted]

Subsequent treatment costs increased by 50%	[redacted]	4.26	[redacted]
Subsequent treatment costs reduced by 50%	[redacted]	4.26	[redacted]
Outpatient visit resource use for dostarlimab+CP arm from cycle 19+			
0.23 outpatient visits per week [15]	[redacted]	4.26	[redacted]
0.25 outpatient visits per week (EAG clinical expert opinion)	[redacted]	4.26	[redacted]
AE disutilities from broader range			
Inclusion of AE disutilities grade 3 and above from >2% of population (see Table 10)	[redacted]	4.26	[redacted]

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 33 summarises the main issues highlighted by the EAG throughout this report that could impact the cost-effectiveness of dostarlimab for use in this indication.

It shows the expected direction of bias introduced by these issues and whether these are examined in any exploratory analyses or incorporated in the EAG base-case.

Table 33: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses
Comparators used			
The base case analysis does not include pembrolizumab+lenvatinib as a comparator	Unknown	None	No
Treatment effectiveness and extrapolation			
Suitability of RUBY-1 to provide reliable estimate of benefit	+ (and unknown)	Base case (age only)	No

Lack of efficacy in stage III population	+/-	None	No
Overly optimistic PFS extrapolation for dostarlimab	+	Base case	Scenarios - Not satisfactorily
Overly optimistic OS extrapolation for dostarlimab	+	Base case Scenarios	Scenarios - Not satisfactorily
Resource use and cost and Adverse Events			
Insufficient capture of AE cost and monitoring	+	Base Case Scenarios	No
Rate of subsequent treatment use uncertain	+/-	Scenarios	No
Footnotes: Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; '+/-' indicates that the bias introduced by the issue is unclear to the EAG; while '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator and '+and -' indicates the EAG believes the potential bias can be positive or negative depending on the assumptions used.			

5.3 EAG's preferred assumptions

The adjustments made by the EAG to the company's model are summarised below, and the effects of each change are shown in Table 34:

EAG 01: Starting age at baseline is increased from [redacted] to 67.1 years to reflect clinical expert opinion and relevant evidence from the literature.

EAG 02: A different approach to extrapolating PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation, to reflect a more clinically plausible benefit of dostarlimab+CP.

EAG 03: A different approach to the extrapolation of OS. The EAG maintain a log-logistic extrapolation for placebo+CP, as the model fits the data well and a piecewise approach is not necessary.

EAG 04: A different approach to the extrapolation of OS. The EAG applies an exponential model for dostarlimab+CP and converges the hazard rates over a 3-year period from 80 weeks, reflecting the observed trial data and providing a clinically plausible benefit.

EAG 05: Inclusion of a broader range of AE disutilities at grade 3 and above to address underrepresentation of AEs in these treatment classes.

EAG 06: Increased resource use of outpatient visits in the dostarlimab+CP arm from cycle 19+, from 0.13 to 0.23 visits per week to reflect more appropriate monitoring costs due to AEs in this treatment arm and align with EAG clinical expert opinion and recent similar technology appraisals.

Table 34: EAG's preferred model assumptions with individual impact on ICER

Preferred assumption	Section in EAG report	ICER £/QALY (individual impact on company base case ICER)
Company base-case		[redacted]
EAG 01: Starting age at baseline 67.1 years.	*3.2.3*	[redacted]
EAG 02: PFS extrapolation of dostarlimab+CP, using a Weibull plus equal hazard extrapolation.	*3.2.6.2*	[redacted]
EAG 03: OS extrapolation for placebo+CP maintaining a log-logistic extrapolation but without use of a piecewise approach.	*3.2.6.3.1*	[redacted]
EAG 05: OS extrapolation for dostarlimab+CP using an exponential model and converging the hazard rates over a 3-year period from 80 weeks. (The log-logistic extrapolation without piecewise approach is maintained for placebo+CP in this analysis).	*3.2.6.3.2*	[redacted]
EAG 06: Inclusion of a broader range of AE disutilities at grade 3 and above.	*3.2.7*	[redacted]
EAG 07: Alternative estimates of resource use for outpatient visits in the dostarlimab+CP arm (increased to 0.23 outpatient visits per week from cycle 19+).	*3.2.8*	[redacted]

5.4 EAG deterministic base case results

The cumulative results of all changes on the company base case form the EAG's deterministic cost-effectiveness results, presented in Table 35.

Table 35: EAG deterministic base case cost-effectiveness analysis (with PAS price used for dostarlimab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental QALYs (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP (carboplatin paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.50	[redacted]

The main driver of the increased ICER was the OS extrapolation approach for dostarlimab+CP. At a £20,000 WTP threshold dostarlimab + CP return a NHB of -2.33 QALYs and NMB of [redacted] under EAG base case assumptions.

5.5 EAG probabilistic sensitivity analysis results

Probabilistic sensitivity analysis was performed on the EAG base case using 1000 iterations drawn from parametric assumptions in the adapted economic model (Dostarlimab CEM v2 EAG base case with PSA). Incremental costs were £[redacted] and incremental QALYs 1.515 resulting in an ICER of £[redacted].

At a threshold of £30,000/QALY there is a [redacted] probability that dostarlimab + CP is cost effective and a [redacted] probability of cost-effectiveness at £20,000/QALY.

5.6 EAG scenario analysis

Given the sensitivity of the ICER to the OS extrapolation approach, the EAG explores the following scenarios. In all scenarios, the EAG maintains its base case assumption unless otherwise specified in the chosen scenario. Results are presented in Table 36.

Table 36: Impact on ICER of alternative assumptions explored in scenario analyses

Scenario	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base case	[redacted]	[redacted]	1.496	[redacted]
Dostarlimab + CP treatment convergence approach: gradual, starts at 208 weeks, time to reach full effect 3 years, convergence at full effect by week 365	[redacted]	[redacted]	2.312	[redacted]
Dostarlimab + CP treatment convergence approach: gradual, starts at 260 weeks, time to reach full effect 3 years, convergence at full effect by week 417	[redacted]	[redacted]	2.526	[redacted]
Dostarlimab + CP treatment convergence approach: gradual, starts at 80 weeks, time to reach full effect 1 year, convergence at full effect by week 132	[redacted]	[redacted]	1.078	[redacted]
Dostarlimab + CP treatment convergence approach: gradual, starts at 80 weeks, time to reach full effect 5 years, convergence at full effect by week 341	[redacted]	[redacted]	1.804	[redacted]
Dostarlimab + CP treatment convergence approach: gradual, starts at 80 weeks, time to reach full effect 7 years,	[redacted]	[redacted]	2.034	[redacted]

convergence at full effect by week 445				
PFS IA distributions: Dostarlimab + CP = Log-logistic CP = Odds spline	[redacted]	[redacted]	1.504	[redacted]
OS distributions: Dostarlimab + CP = Exponential CP = Exponential	[redacted]	[redacted]	1.162	[redacted]
Starting age at baseline 66.0 years	[redacted]	[redacted]	1.505	[redacted]
Outpatient visit frequency 0.13 per week for dostarlimab + CP cycle 19+	[redacted]	[redacted]	1.496	[redacted]

5.7 Conclusions of the cost effectiveness section

In summary, the EAG accepts the company's model but disagrees with their preferred assumptions. The main driver of the economic model is the extent of the OS benefit associated with dostarlimab+CP. However additional uncertainties around PFS benefit, starting age of population, adverse event monitoring and subsequent treatments should also be considered. The limited follow-up and sample size of the pivotal trial means uncertainty is very high.

6 SEVERITY MODIFIERS

As discussed in section 3.2.9, the company did not submit a case for a 'severity modifier' to be applied. The EAG is in full agreement so nothing further was explored.

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8 Appendices addendum

8.1 ROBIS

Table 37: EAG assessment of risks of bias of the CS systematic review in relation to the scope of the appraisal (modified ROBIS)

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably no**	Eligibility criteria are outlined in Table 5 and Table 6, CS Appendix D. Additional steps to exclude studies were subsequently taken and this was not defined a priori (CS Appendix D.4.5).
1.2 Were the eligibility criteria appropriate for the review question?	**No**	The pre-specified criteria of the SLR were not aligned with the NICE scope and CS decision problem in terms of population and intervention.
1.3 Were eligibility criteria unambiguous?	**Probably yes**	Eligibility criteria were sufficiently detailed in Table 5 and Table 6, CS Appendix D but not aligned with the decision problem and additional steps regarding eligibility were undertaken but not clearly defined.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes**	Restrictions were applied to only include phase II or III RCTs, to include mixed populations where 80% of the population had the condition, and to exclude studies with no results (subsequent criteria) which the EAG considers appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes**	Non-English language studies were excluded. Although no justification for this was provided this is common and is likely to be reasonable.

Concerns regarding specification of study eligibility criteria	**Unclear concern**	Studies that may have been relevant could have been excluded from the review, not all eligibility criteria were specified a priori
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**	Searches were conducted in an appropriate set of bibliographic databases (MEDLINE, Embase, Cochrane Central Register of Controlled Trials, CDSR, ClinicalTrials.gov)
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**	A brief summary of supplementary searches is included (checking references of 12 SRs found via database searches (judged by the company to be the most relevant, recent and comprehensive), checking websites of selected HTA bodies, searching of relevant, recent conference abstracts (if not already indexed in Embase)
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Yes**	Suitable terms, including both thesaurus headings and free-text terms, were combined appropriately. A pragmatic RCT filter was used.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Probably no**	There were no restrictions based on date or publication format (e.g full text). Language was restricted to English therefore there is a potential for publication bias.
2.5 Were efforts made to minimise errors in selection of studies?	**Probably no**	Titles and abstracts and full text articles were screened independently by two reviewers with discrepancies resolved by a third

		reviewer for the primary selection of studies. No details provided as to how the subsequent stage of selection was made.
Concerns regarding methods used to identify and/or select studies	**Unclear concern**	A satisfactory effort has been made to identify as many relevant studies as possible through a variety of search methods. However, language was restricted to studies in English. While steps were taken to minimise bias and errors in the selection of studies for the initial selection, no details were provided for the subsequent stages.
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Data from the included studies were extracted into standardised data extraction tables in Microsoft® Excel by one reviewer and was checked by a second reviewer, with differences resolved through a third reviewer if necessary
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Yes**	Summary study characteristics were presented in the CS and Appendix D. Although full data extractions were not provided there is no synthesis of studies to assess for similarity.
3.3 Were all relevant study results collected for use in the synthesis?	**Yes**	Results from the RUBY-1 trial were reported in tables and figures or provided in the clarification response.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	Quality assessment of included studies was performed using questions from the NICE STA user guide (last updated February 2022).

		The EAG has undertaken assessment using ROB2 and the NICE questions and report differences to the assessment of risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	**No information**	The process for undertaking assessment of quality was not reported.
Concerns regarding methods used to collect data and appraise studies	**Unclear concern**	The assessment of risk of bias may have introduced some bias but there is insufficient information to make a judgement.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	**Yes**	The SLR included all of the relevant studies for the decision problem
4.2 Were all predefined analyses followed or departures explained?	**No information**	No reference to a protocol for the SLR is given
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Not applicable**	No quantitative or narrative synthesis performed
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Not applicable**	No quantitative or narrative synthesis performed
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**Not applicable**	No quantitative or narrative synthesis performed

4.6 Were biases in primary studies minimal or addressed in the synthesis?	**No**	Bias was not explicitly incorporated into the findings/ conclusions of the SLR
Concerns regarding the synthesis and findings	**Unclear concern**	Risk of bias of the included study was undertaken but this was not explicitly incorporated into the findings of the SLR.
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	Unclear	A satisfactory effort was made to identify as many relevant studies in line with the NICE scope as possible, but not all steps were clearly taken.

8.2 ROB

Table 38: EAG assessment of risks of bias of the RUBY-1 trial

	RUBY-1 Company assessment	**RUBY-1 EAG assessment**
Was the randomisation method adequate?	Yes – Participants were assigned to study intervention in ad comparator in 1:1 ratio. • Randomization was stratified by 3 stratification factors: MMR/MSI status: Determined by local IHC, PCR, or next-generation sequencing test, or by central IHC testing when local testing was not	Unclear – randomisation was appropriate for the overall population: the primary publication [19] states randomization was performed in a blinded manner using an interactive Web response system (although this is not stated in CSR or protocol [19]). Randomisation was stratified as described; the relevant subgroup for this appraisal, dMMR/MSI-H was identified by one of the stratification factors. However, there appears to be an imbalance

	available. The MMR/MSI status for randomization was derived from the data entered at the time of randomization. • Prior external pelvic radiotherapy (yes or no): Determined from radiation therapy history provided by investigators at the time of randomization. • Disease status (recurrent, primary Stage III, or primary Stage IV): Derived from the cancer history and disease stage provided by investigators at the time of randomization. Data provided for the most recent FIGO stage and recurrence status were used to assign the participant to the appropriate stratum. If recurrence was selected, participants were assigned to recurrent strata. If no recurrence was selected, then participants were	in the numbers in each arm within the subgroup (dostarlimab+CP n=53 vs placebo+CP n=65, total n=118). The CSR provides an explanation for this [redacted] 2.2.3.3

	assigned to primary Stage III or primary Stage IV based on most recent FIGO stage.	
Was the allocation adequately concealed?	Yes- Randomisation was performed in a 1:1 blinded manner with an interactive Web response system.	Yes – interactive Web response system.
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes- No substantial between-group differences were noted in the demographic and clinical characteristics of patients in the dMMR/MSI-H population or in the overall population.	Unclear – groups in the dMMR/MSI-H subgroup are generally similar, however as the company notes on CS p42 there are some slight differences: • Weight and BMI are slightly higher in the placebo arm • Proportion with ECOG performance status 1 is slightly higher in the intervention arm In addition, the EAG considers that the proportion aged ≥65 years appears slightly higher in the placebo arm (see Table 6 for details of baseline characteristics). The impact of these differences is unclear.
Did the analysis include an intention-to-treat analysis? If so, was this	Yes- The ITT population included all participants who were randomised. Participants were analysed according to the treatment assigned at randomisation	Yes – ITT analysis was performed, although the results in CS are for a pre-specified subgroup. Methods to account for missing data were reported in the study protocol and appear appropriate.

appropriate and were appropriate methods used to account for missing data?	even if no study intervention was received.	
Did the comparison groups receive the same care apart from the intervention(s) studied	Yes- patients received either dostarlimab (500 mg) or placebo intravenously in combination with carboplatin as part of the first six cycles. No differences were seen between the treatment groups with respect to carboplatin or paclitaxel infusion interruptions, infusion delays, missed infusions, or dose reductions.	Yes – it is likely that the groups received the same care apart from the intervention. The EAG agrees there were no differences between groups in the overall population with respect to modifications of carboplatin or paclitaxel treatment [19] as stated by the company here, however data have not been provided for the dMMR/MSI-H so cannot be checked.
Were participants receiving care kept 'blind' to treatment allocation	Yes- [redacted]	Yes – The participant, investigator, study staff, the sponsor study team, and its representatives were blinded to the assigned treatment from the time of randomisation until database lock. The study protocol allowed for unblinding for urgent or non-urgent clinical reasons, [redacted]
Were individuals administering	Yes- The participant, investigator, study staff, the sponsor study team, and its	Yes – as above.

care kept 'blind' to treatment allocation	representatives were blinded to the assigned treatment from the time of randomisation until database lock as described in the protocol. Treatment assignment could be unblinded by the investigator for urgent or non-urgent clinical reasons as described in the protocol.	
Were all groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes- The median duration of follow-up was 24.8 months (range, 19.2 to 36.9) in the dMMR/MSI-H population and 25.4 months (range, 19.2 to 37.8) in the overall population, and was consistent between the arms.	Yes – groups were followed for a similar length of time.
How many participants did not complete treatment in each group?	At the data cut off- 52/241 that started on treatment in the dostarlimab arm and 36/246 that started on treatment were still receiving placebo.	Patient flow was not reported for the relevant subgroup in the initial CS. Clarification response A3 states that 23/52 (44.2%) in the dostarlimab arm and 8/65 (12.3%) in the placebo arm were still receiving treatment at data cut off.
Were there any unexpected imbalances in	Yes- [redacted]	No - Patient flow was not reported for the relevant subgroup in the initial CS, however a CONSORT diagram was provided in

drop-outs between groups? If so, were they explained or adjusted for?	[redacted]	clarification response A3. There were no unexpected imbalances in drop-outs, although the proportion discontinuing treatment was higher in the placebo arm than the dostarlimab arm (87.7% vs 55.8%). The most common reasons for discontinuation were progressive disease, which was higher with placebo (placebo 61.5% vs dostarlimab 25.0%) and adverse events, which were higher with dostarlimab (placebo 10.8% vs dostarlimab 17.3%).
Did the study have an appropriate length of follow-up	Yes- The median duration of follow-up was 24.8 months (range, 19.2 to 36.9) in the dMMR/MSI-H population.	Unclear – results are from an interim analysis. For PFS, the data are more mature in the placebo arm, and the CS states that the OS data is only 26% mature.
Did the study use a precise definition of outcome	Yes- The primary endpoints were progression-free survival as assessed by the investigator according to RECIST, version 1.1. Overall survival was defined as the time from randomisation to the date of death from any cause. Secondary endpoints included progression free survival as determined by blinded independent central review, objective response,	Yes – outcomes were clearly defined.
Was a valid and reliable method was used to determine the outcome		Yes – outcomes were assessed by a valid and reliable method.

	disease control, response duration, time to second progressive disease, patient-reported outcomes (scores on the European Organization for Research and Treatment of Cancer [EORTC] Core Quality of Life Questionnaire [QLQ-C30], the EORTC Quality of Life Questionnaire Endometrial Cancer [QLQ-EN24], and the EuroQoL 5-Dimensions 5-Level [EQ-5D-5L] instruments), and pharmacokinetic and immunogenicity analyses. Safety was assessed through monitoring of adverse events, laboratory testing, measurement of vital signs, and physical examination.	
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were	Yes- The participant, investigator, study staff, the sponsor study team, and its representatives were blinded to the assigned treatment from the time of randomisation until database lock as described in the protocol. Treatment assignment could be	Yes – as above, no anticipated impact on outcomes

not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	unblinded by the investigator for urgent or non-urgent clinical reasons as described in the protocol.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No- all measured outcomes are reported	Yes – of outcomes specified on the clinical trial record (clinicaltrials.gov): DCR by BICR and DOR by BICR were not provided in the CS – p58 of the CS states 'DOR by BICR was similar to the investigator assessed DOR (CSR Table 14.2.1.16 and Figure 15.1.10)', however this table and figure are not in the CSR provided to the EAG. The company provided these data in Clarification response A4. (Section 2.2.3.6). Not all quality of life outcomes were presented and details of changes in clinical laboratory parameters, vital signs, and proportion with ECOG PS scores are not available.
Consider whether the authors of the study	No- all authors listed in supplementary materials of publication.	Yes – full disclosures are provided. Trial supported by GSK.

publication declared any conflicts of interest.		

8.3 IrAEs

Table 39: Summary of Immune-related AEs – Interim Analysis (dMMR/MSI-H population, dostarlimab + carboplatin /paclitaxel [N=52] vs placebo + carboplatin/paclitaxel [N=65])

Adverse event category (Dostarlimab N=52 vs placebo N=65)	Overall	Dostarlimab/ Placebo related	≥Grade 3	Dostarlimab/ Placebo related ≥ Grade 3	SAE	Leading to dostarlimab/ placebo infusion delay	Leading to dostarlimab/ placebo interruption	Leading to dostarlimab/ placebo discontinuation	Leading to death
Any event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any non-hypersensitivity event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated skin adverse reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated endocrinopathies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated musculoskeletal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated hepatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune-mediated pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 Addendum Appendix

The EAG noted disutilities and costs for UTI, lipase increase, and abdominal pain had already been sourced within the CEM, however these inputs were only used to inform AE outputs for subsequent treatments as incidence of UTI, abdominal pain and lipase increase did not exceed the >5% cut off used by the company for inclusion in initial treatments.

The EAG retain the costs and disutilities for these AEs within the model by combining the additional AEs detailed in Table 10 of the EAG report where similar adverse events are assumed to have equal disutility and equal cost:

Abdominal pain and lipase amylase increase both have a disutility of 0.069 and associated management cost of £591.53 (see EAG tables 25 and 28).
Nausea and hyponatremia are assigned the same disutility, 0.045, and management cost, £664.75.

As hypergylcaemia had 0.00 disutility and £0 cost assumed, this was not coded into the model.

The incidence (n) of these AEs were then combined to produce input values for Cells G151:151 and G165:169.

Table 40 (below) is taken from Table 10 including only the additional AEs included by the EAG in the same format as previously reported. Table 41 summarises how this data is entered into the CEM (following the methods described above) to produce the analyses which include EAG preferred AE inputs.

Table 40: Summary of Grade ≥3 TEAEs (adapted from Table 10 of this report)

	dMMR/MSI-H		**Overall population**	
Adverse event category	**Dostarlimab + CP (N=52)**	**Placebo + CP (N=65)**	**Dostarlimab + CP (N=241)**	**Placebo + CP (N=246)**
Selected TEAEs Grade ≥3 occurring in ≥2% of patients in the overall population AND with proportion higher in the dostarlimab + CP arm				
[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]

Table 41: Summary EAG modelling approach to additional AEs

Adverse Event Category	EAG approach	Dostarlimab+CP (n=241) (%)	Placebo+CP (n=246) (%)
[redacted]	Figures from Table 40. entered in pre-existing category in CEM	[redacted]	[redacted]
[redacted]	Figures from Table 40. entered into CEM where [redacted] coded as equal cost/disutility assumed (note there were 0 incidence of abdominal pain for initial treatment so figure here only counts [redacted] and is as per Table 40.)	[redacted]	[redacted]
[redacted]	Figures from Table 40. entered into existing category in CEM	[redacted]	[redacted]
[redacted]	Figures for these two categories in Table 40. combined, as a single category as equal cost/disutilities assumed (Sourced by EAG and added in existing placeholder Cells).	[redacted]	[redacted]
[redacted]	Figures from Table 40. entered (Cost/disutilities sourced by EAG and added in existing placeholder Cells).	[redacted]	[redacted]

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency - ID3968

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 Tuesday 3rd October** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.
x

Section A. Key issue related factually inaccurate statements and clarity of language

Issue 1 Comparison to pembrolizumab plus lenvatinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
No problems identified			

Issue 2 Suitability of RUBY-1 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
No problems identified			

Issue 3 Stage III subgroup

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.3.7 Subgroup analyses page 45 "In the CSR for RUBY 1, the company provided an equivalent plot for the MMRp/MSS population, where the equivalent group had a hazard ratio of [redacted]. For whole ITT population, the hazard ratio is 1.03 (0.56, 1.89; n=92).	The Company request that this sentence is removed.	The statement is an inappropriate representation of the available data. The ITT and MMRp/MSS populations are not relevant to the scope of this appraisal. The ITT and MMRp/MSS efficacy is not expected to be aligned with that of the dMMR/MSI-H population and reporting the ITT and MMRp hazard ratios alongside a critique of the dMMR/MSI-H outcomes is inappropriate. No	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.3.7 Subgroup analyses page 45 "..however for the whole ITT population it was [redacted]."		other efficacy data related to the ITT and MMRp/MSS data has been referenced throughout the EAG report or company submission.	
Section 2.2.3.7 Subgroup analyses page 45 "For OS, no hazard ratio was provided by the company for stage III subgroup of the dMMR population..."	The Company request that this sentence is revised to reflect that it was not possible to estimate a hazard ratio in this subgroup due a low number of events. The Company were not able to provide it, rather than they chose not to provide it.	The statement is inaccurate, and an inappropriate representation of the Company clarification response.	Not a factual error, no response required

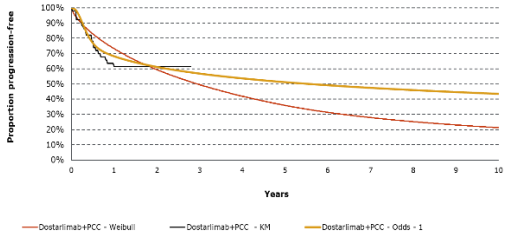
Abbreviations; CSR – Clinical study report; dMMR – DNA mismatch repair deficiency; EAG – External assessment group; ITT – Intention-to-treat; MMRp – Mismatch repair-proficient; MSI-h – microsatellite instability-high; MSS – Microsatellite stable; OS – Overall survival

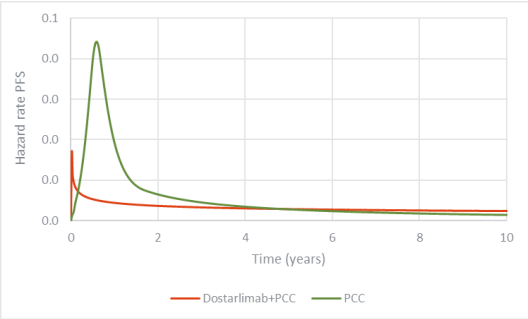
Issue 4 The extent of PFS benefit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.6 page 76-77 Technical error in implementation of equal hazard rates. The EAG's preferred assumption is to use an adjusted Weibull distribution for dostarlimab in combination with PCC. In	The EAG stated that an adjustment to PFS will be made after five years. Within the model the adjustment is incorrectly made after 52 weeks as opposed to five years.	Technical coding error. The Company request that the EAG review and correct their base case PFS curve for dostarlimab in combination with PCC. The Company have returned CEM with amend made (file name 20231003_Dostarlimab_RUBY	Not an error, it only comes into effect at the point where the hazard rates cross. The EAG acknowledge the error in the formula as highlighted. This has been amended accordingly in the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
their updated model, the EAG has suggested "*At the point that the hazard rates cross, the EAG assumes the hazard rate for the dostarlimab population will follow the hazard rate for the chemotherapy population, which occurs at roughly 5 years".*	Secondly, the formula that has been included is incorrect. At 52 weeks, the model uses a "MIN" function in *Extrapolations, Column I* to model the change of hazard rate for dostarlimab in combination with PCC when the hazards cross. In cell *Extrapolations, I62*, which corresponds to week 52, the formula "=MIN(-LN(1-(1-H62/H61)),G62)" is used, where G62 is a blank cell. Instead, this cell should be referring to the PCC arm and therefore no adjustment is being made in the model. This means that the dostarlimab in combination with PCC arm is not adjusted.	IA1_CEM_Update_v6.0_ EAG Report Response_GSK).	updated model, analyses re-run and results amended in the report.
Selection of Weibull curve for dostarlimab in combination with PCC PFS by the EAG is inappropriate**.**	The Company request that the EAG reconsider the basecase PFS curve. The current EAG choice of dostarlimab in combination with PCC curve for PFS does not follow the recommendations in the NICE DSU (DSU TSD 14[1]) guidelines by considering including diagnostic	**1. Diagnostic plots - demonstration of non-monotonic hazard rates** The diagnostic plots for dostarlimab in combination with PCC (Figure 12, Section B3.3.3 of the CS) show that the hazard rate is non-monotonic, which suggests that accelerated failure time models (such as log-	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	plots, visual and statistical fit and clinical opinion. The company propose the Odds (n=1) PFS curve as a more appropriate option considering these recommendations.	logistic, log-normal or generalised gamma) should be used. The Weibull distribution can only be used in case of monotonically increasing, decreasing or constant hazard function over time which is not the case for the PFS hazard rate observed for dostarlimab in combination with PCC. For flexible distributions, the Odds and normal curves are relatives of the log-logistic and log-normal curves. The Odds k=1 was selected for the base case based on the lowest AIC value and provides the most appropriate proportion of patients in the PFS state to align with advisory board external expert estimates. **2. Visual fit and statistical fit** As independent standard parametric curves did not fit the observed RUBY-1 data or clinical expert estimates well, flexible approaches were explored. The Weibull specifically does not fit the observed data from approximately 18 months (Figure 1). The Odds k=1 curve has an improved visual fit with the observed data (Figure 1). Furthermore, the Odds k=1 has a better statistical fit to the data based on an AIC	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		value six points lower than that for the Weibull curve ([redacted] and [redacted] respectively) (CS section B.3.3.2). **Figure 1: Dostarlimab in combination with PCC - PFS curves**  PCC – platinum containing chemotherapy; PFS – progression free survival **3. Implausible extrapolation of hazards** The choice of the Weibull distribution for dostarlimab in combination with PCC PFS leads to an implausible hazard rate beyond five years, where patients in the dostarlimab group have a higher hazard rate for progression compared to the PCC group (see Figure 2).	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Figure 2: Hazard rate for PFS - Weibull for dostarlimab in combination with PCC; Odds k=1 for PCC  PCC – platinum containing chemotherapy; PFS – progression free survival **3. Clinical validity not aligned to available clinical data.** Furthermore, Page 75 of the EAG report notes *"The EAG questions the validity of this implied assumption as comments from the EAG's clinical expert suggested that people who respond well to chemotherapy and remain progression-free will be very similar people with an equivalent response who have received dostarlimab+CP, and there is no reason why these groups would have a different hazard rate."*	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		The data for the RUBY-1 trial demonstrate a clear difference between progression rates, and response rates, for patients treated with dostarlimab in combination with PCC compared with PCC. None of the RUBY-1 results would indicate that short, medium or long-term PFS outcomes for dostarlimab in combination with PCC align with those experienced by patients treated with PCC. Dostarlimab in combination with PCC resulted in a statistically significant and clinically meaningful benefit in PFS (HR: 0.28; 95% CI: 0.16, 0.50; p<0.001). PFS from RUBY-1 has reached its median and is mature enough to draw meaningful conclusions on the efficacy. At 24 months, the estimated probability of PFS was four times higher in the dostarlimab in combination with PCC group compared with the PCC group (61.4% [95% CI: 46.3, 73.4] and 15.7% [95% CI: 7.2, 27.0], respectively[15]. Regarding response, patients in the dostarlimab in combination with PCC group had a higher ORR by investigator assessment compared with the placebo in combination with PCC group (77.6% [95% CI: 63.4, 88.2] versus 69.0% [95% CI: 55.5, 80.5],	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		respectively). This difference was also observed for the 24-month estimated probability of maintaining response (62.1% [95% CI: 44.4, 75.5] for the dostarlimab in combination with PCC group versus 13.2% [95% CI: 4.6, 26.3] for the placebo in combination with PCC group. In both treatment arms, a plateau is observed in both progression and response from approximately 18 months. However, this plateau is observed in a much larger proportion of the patients treated with dostarlimab in combination with PCC. The high overall response rate, including 30.6% of patients with complete responses in the dostarlimab in combination with PCC group is more likely to equate to more durable long-term period of progression-free survival than what is seen with standard of care PCC. In comparison, long-term data on PCC outcomes show that while response rates to chemotherapy are high (50-60% ORR), these responses are not durable[3]. Despite the high proportion of patients who respond, in a real-world cohort of English patients treated	

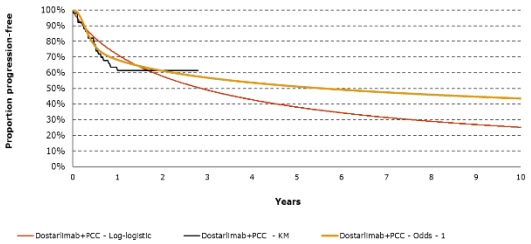
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		with PCC at first line (n=902) only 18% were progression-free at 5 years [4]. Long-term response, and longer progression-free time, has been demonstrated with immunotherapies in the pre-treated, relapsed, advanced or recurrent dMMR/MSI-H endometrial cancer setting (Table 6 below). There is no clinical rationale why the durable impact on response and progression seen on pre-treated patients, treated with immunotherapy monotherapy, would not be seen in the front-line setting. **4. Clinical validity of EAG PFS base case – not aligned with external data** The proportion of patients who are progression-free – years 3-5 – within the EAGs base case are highly pessimistic and not supported by the available clinical data from the RUBY-1 trial (outlined above). Furthermore, Table 1 shows that 30-40% of patients treated with dostarlimab and pembrolizumab monotherapy in the pre-treated, relapsed, advanced or recurrent endometrial cancer setting remained progression-free up to year four[13,7]. The	

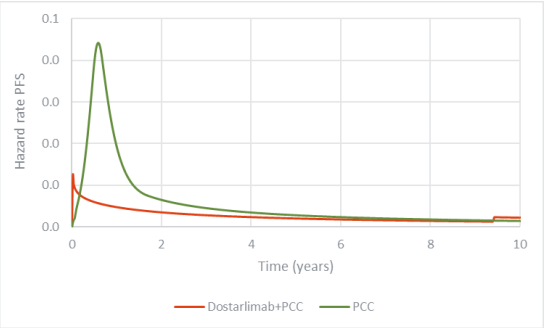
<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td>EAG's base case equates to 36% of patients progression-free at year five, assuming a pessimistic proportion more closely aligned with the outcomes seen in the relapsed setting.

This is not clinically plausible. Health outcomes in the front-line setting are significantly different to those seen by relapsed patients, where median OS for patients treated with standard of care chemotherapy is less than one year, compared with 2-3 years in the front-line setting.

Table 1: PFS landmark percentages – EAG dostarlimab in combination with PCC primary dMMR/MSI-H A/R EC and external evidence relapsed A/R dMMR/MSI-H EC
<table>
<tr><th></th><th>EAG preferred</th><th>GARNET [7]</th><th>KEYNOTE 158[13]</th></tr>
<tr><td>2 years</td><td>60%</td><td>40.1%</td><td>41%</td></tr>
<tr><td>3 years</td><td>50%</td><td>40.1%</td><td>37%</td></tr>
<tr><td>4 years</td><td>-</td><td>35%*</td><td>37%</td></tr>
<tr><td>5 years</td><td>36%</td><td>-</td><td>-</td></tr>
</table>
A/R – advanced recurrent; EC – endometrial cancer *no landmark percentage reported for 48 months, visual estimation of PFS KM curve GARNET: NCT02715284 Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1)</td><td></td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET) KEYNOTE-158: NCT02628067 Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) The Company believe that the average from the advisory board of five external expert estimates are a more accurate representation of the anticipated longer term progression-free survival than the implausible estimates provided by the EAG (Table 2 below). Based on the evidence presented above, the EAG's PFS assumptions do not adhere to the NICE DSU (DSU TSD 14[1]) guidelines, and do not align with the observed RUBY-1 data nor the estimated landmark PFS from the advisor mean. In contrast, the Company's PFS assumptions have considered the NICE DSU (DSU TSD 14[1]), the RUBY-1 trial and better aligned to the advisor estimates.	
Inclusion of log-logistic with equal hazards as an alternative curve for dostarlimab in combination with PCC PFS by the EAG is inappropriate**.**	The choice of dostarlimab in combination with PCC curve for PFS does not follow the recommendations in the NICE DSU (DSU TSD 14[1]) guidelines by considering including diagnostic	**1. Visual fit and statistical fit** As independent standard parametric curves did not fit the observed RUBY-1 data or clinical expert estimates well, flexible approaches were explored. The log-logistic curve specifically does not fit the observed data from approximately 18 months (Figure	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	plots, visual and statistical fit and clinical opinion.	3). The Odds k=1 curve has an improved visual fit with the observed data (Figure 3). Furthermore, the Odds k=1 has a better statistical fit to the data based on an AIC value five points lower than that for the log-logistic curve ([redacted] and [redacted] respectively) (CS section B.3.3.2). **Figure 3: Dostarlimab in combination with PCC - PFS curves (Log-logistic scenario)**  **2. Clinical validity not aligned to available clinical data** As outlined in the previous row, the application of equal hazards at the five-year time point is not supported by what is shown in the available clinical data from RUBY-1 up to 3 years. Furthermore, the choice of the log-logistic curve for dostarlimab in combination with PCC leads to clinically implausible hazard rate within	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		the first year where dostarlimab in combination with PCC hazard rate is greater than that of PCC (Figure 4). The hazard of dostarlimab in combination with PCC also converges on the hazard rate of PCC alone, which based on the evidence present above is deemed clinically implausible. **Figure 4: Hazard rate for PFS - Log-logistic for dostarlimab in combination with PCC; Odds k=1 for PCC**  	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Table 2: Progression-free survival landmark percentages – dostarlimab in combination with PCC and external evidence

Months (years)	EE1	EE2	EE3	EE4	EE5	EE mean (n=5)	EAG Advisor (n=1)	Overall Expert mean (EEs + EAG)	Relapsed setting - GARNET*	Relapsed setting - KEYNOTE-158**	Company Preferred (spline Odds 2 knot)	EAG preferred (Weibull/equal)	EAG alternative (log-logistic/equal)
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60%	60%	60%	40.1%	41%	61%	60%	58%
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56%	40%	53%	40.1%	37%	57%	50%	49%
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46%	20%	42%	35%#	37%#	51%	36%	38%
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36%	15%	33%	-	-	44%	21%	25%
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30%	10%	27%	-	-	36%	10%##	15%

EAG – external assessment group; EE – external expert; PCC – Platinum-containing chemotherapy

*GARNET: NCT02715284 Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET)

**KEYNOTE-158: NCT02628067 Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)

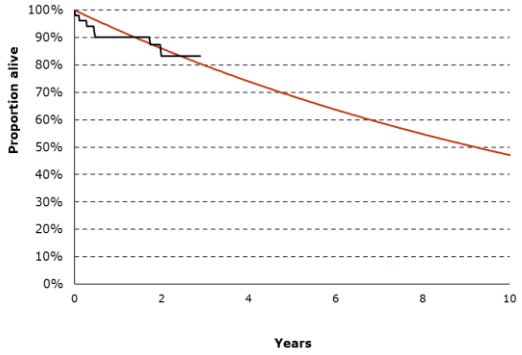
Proportion progression-free at year 4, year 5 not published.

Note this percentage has been updated from Table 18 of the EAG report to reflect the updated cost effectiveness model

Abbreviations: AFT – Accelerated failure time; AIC – Akaike information criterion; CP – Carboplatin plus paclitaxel CS – Company submission; dMMR – DNA mismatch repair deficiency; DSU – Decision support unit; EAG – external assessment group; EE – external expert; HR – Hazard ratio; MSI-H - Microsatellite instability-high; NICE – National institute for health and care excellence; ORR – Objective response rate; OS – Overall survival; PCC – Platinum-containing chemotherapy; PFS – Progression-free survival; TSD – Technical summary document

Issue 5 The extent of OS benefit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Selection of Exponential curve for dostarlimab in combination with PCC for OS, and the risk convergence applied by the EAG, is inappropriate.	The Company request that the EAG reconsider the basecase OS curve and treatment waning application. The current EAG choice of dostarlimab in combination with PCC curve for OS does not follow the recommendations in the NICE DSU (DSU TSD 14[1]) guidelines by considering including diagnostic plots, visual and statistical fit and clinical opinion. Furthermore, the choice of curve and the applied waning approach for OS is not evidence driven and conflicts with the observed evidence from the RUBY-1 trial. The approach taken by the EAG does not align with the NICE Methods Guide[2], which states that there is a strong preference for high-quality randomised control trial evidence in appraisals. The company propose the hazard ratio approach as a more	**1. Diagnostic plots - demonstration of non-monotonic hazard rates** The observed hazard rate plot for dostarlimab in combination with PCC OS is shown to be non-monotonic (Figure 17, Document B of the CS). The Exponential distribution is characterised by a constant hazard,[1] which does not align with the observed hazard rate for dostarlimab in combination with PCC in the RUBY-1 trial. **2. Visual fit** Furthermore, the choice of the Exponential curve for dostarlimab in combination with PCC OS is of **poor visual fit to the observed KM data** (see Figure **5** below), and hence raises concerns with the clinical plausibility of the	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	appropriate option considering these recommendations.	model, as it fails to predict the survival for the observed period well. **Figure 5: Independent Exponential distribution for dostarlimab in combination with PCC OS**  **3. Clinical validity – not aligned with external clinical expert estimates** The clinical estimates provided by the EAG advisor for long-term OS are highly conservative. In the RUBY-1 trial patients in the dostarlimab plus CP group had a 70% reduction in risk of death compared with the placebo plus CP group (HR 0.30; 95% CI: 0.13, 0.70; nominal p=[redacted]), indicating an unprecedented	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		clinically meaningful survival benefit with the dostarlimab plus CP regimen. The estimated probability of survival at 24 months was 83.3% (95% CI: 66.8, 92.0) in the dostarlimab plus CP group 58.7% (95% CI: 43.4, 71.2) respectively, in the placebo plus CP group. Based on the OS data seen with dostarlimab in combination with PCC at the 24-month time point, it is clinically plausible and expected that the proportion of patients surviving following treatment would be higher than those treated with standard of care at the 5- and 10-year time points. Long-term OS data is available for PCC for the treatment of advanced or recurrent endometrial cancer. Table 5 outlines that based on 14 year follow-up from the pivotal RCT in this setting 20% of patients treated with PCC remain alive at ten years post treatment. These results were supported by the available English real-world data, with 18% of patient available at year 5 (as expected less optimistic that survival estimates from an RCT). The EAG advisor estimates are more closely aligned with the current survival seen with PCC alone, and therefore are not clinically plausible	

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td>in consideration of the early OS benefits seen with the addition of dostarlimab in RUBY-1

Table 3: Overall survival landmark percentages - standard of care (PCC) and EAG advisor
<table>
<tr><th>Months (years)</th><th>EAG Advisor (n=1)</th><th>Primary A/R EC SOC – Miller 2020[3]</th><th>Primary A/R EC SOC – NCRAS (n=902) [4]</th></tr>
<tr><td>24 (2)</td><td>80%</td><td>49%</td><td>40%</td></tr>
<tr><td>36 (3)</td><td>50%</td><td>36%</td><td>31%</td></tr>
<tr><td>60 (5)</td><td>20%</td><td>27%</td><td>18%</td></tr>
<tr><td>120 (10)</td><td>10%</td><td>20%</td><td>-</td></tr>
<tr><td>240 (20)</td><td>8%</td><td>-</td><td>-</td></tr>
</table>
A/R – advanced/recurrent; EAG – external assessment group; EC; endometrial cancer; NCRAS – national cancer registry analysis service; PCC - Platinum-containing chemotherapy; SOC – standard of care

Furthermore, the proportion of patients estimated to remain alive at years 10 and years 20 were lower than the proportion of patients estimated to be progression-free at these time points by the EAG clinical advisor (at year 10 - 10% OS versus 15% PFS, and at year 20 - 8% OS versus 10% PFS). These</td><td></td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		represent highly pessimistic and implausible long-term estimates. The choice of the Exponential distribution by the EAG is reliant on the feedback from one clinical expert, and ignores the advice collected by the Company at an advisory board from five UK external clinical experts. To increase sample size thereby reducing uncertainty, the Company have included the percentages from the EAG's clinical expert into an n=6 pooled advisor average (Table 5 below). The Company's base case OS curve for dostarlimab in combination with PCC better aligns with the pooled predictions at 10 and 20 years. **4. Clinical validity – not aligned with external data** The proportion of patients alive at year 5 (and beyond) within the EAGs base case is highly pessimistic and the year 5 estimate specifically is not supported by the available clinical data. As outlined in Company response to EAG clarification question B5 - sustained treatment effect in the relapsed advanced or recurrent dMMR/MSI-H endometrial cancer setting also supports the durability of efficacy in the	

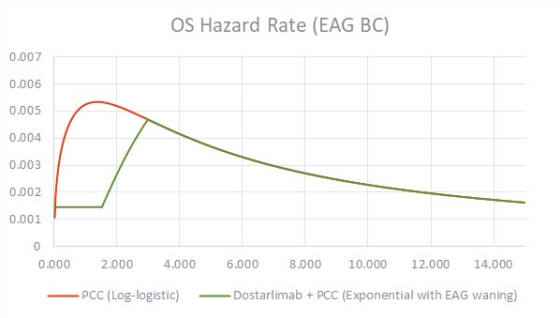
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		primary advanced and recurrent setting, with both the GARNET trial and KEYNOTE-158 trial showing sustained efficacy up to five years[13,7]. Since these populations have poorer prognosis due to pre-treatment and the relapsed nature of the disease, it is reasonable to assume that the outcomes and sustained treatment effect with immunotherapy monotherapy in second-line will be no less prominent for an immunotherapy in combination with chemotherapy in the primary setting. Table 4 shows that 55-60% of patients treated with immunotherapy monotherapy in the pre-treated, relapsed, advanced or recurrent dMMR/MSI-H endometrial cancer setting survive up to year four. The EAG's base case equates to 51% of patients alive at year five, assuming a pessimistic proportion more closely aligned with the outcomes seen in the relapsed setting. This is not clinically plausible. Health outcomes in the front-line setting are significantly different to those seen by relapsed patients, where median OS for patients treated with standard of care chemotherapy is less than one year, compared with 2-3 years in the front-line setting. The survival estimates based on the EAG preferred	

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td>base case at year five and beyond are unsubstantiated considering available data on durable response to immunotherapies in this disease area.

Table 4: Overall survival landmark percentages – relapsed, pre-treated, advanced endometrial cancer with immunotherapy monotherapy versus Company and EAG base case
<table>
<tr><th>Months (years)</th><th>Relapsed setting - GARNET</th><th>Relapsed setting - KEYNOTE -158</th><th>Company Preferred (KM + HR)</th><th>EAG preferred (exponential with convergence)</th></tr>
<tr><td>24 (2)</td><td>60.5%</td><td>64%</td><td>87%</td><td>86%</td></tr>
<tr><td>36 (3)</td><td>58.4%</td><td>60%</td><td>83%</td><td>75%</td></tr>
<tr><td>60 (5)</td><td>55%[#*]</td><td>60%[#]</td><td>72%</td><td>52%</td></tr>
</table>
Proportion survival at year 4, year 5 not published. EAG – external assessment group; HR – hazard ratio; KM – Kaplan-Meier *no landmark percentage reported for 48 months, visual estimation of OS KM curve
GARNET: NCT02715284 Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET) [7] KEYNOTE-</td><td></td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		158: NCT02628067 Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/ KEYNOTE-158) [13] **5. Clinical validity – waning/risk convergence approach not aligned with available clinical data and previous NICE appraisals** The waning approach for OS applied by the EAG is not evidence based and ignores observed RCT evidence form the RUBY-1 trial. The selection of a 80-week waning start point is not evidence based, with the EAG providing no rationale in their report for the choice of this time point. The duration of waning (3 years) by the EAG also lacks justification. The EAG's approach does not appropriately considering the RUBY-1 observed data and hence does not follow the NICE Methods guide.[2] RUBY-1 data is available for 3 years ([redacted] weeks for OS). The EAG's application of waning prior to [redacted] weeks is highly pessimistic and adds uncertainty in the OS by adjusting the observed data from the RUBY-1 trial. In addition, EAG's waning approach allows the continued accrual of treatment acquisition	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		costs while modelling that treatment effect is waning prior to the formal discontinuation rule of three years. At 80-weeks (time of EAG waning initiation) approximately [redacted]% of patients remain on treatment, and hence according to the EAG's base case, the rate of discontinuation will not increase despite a loss of treatment benefit. Furthermore, the EAG's base case curve for dostarlimab in combination with PCC for OS produces a clinically implausible modelled hazard rate (Figure **6**). The EAG's base case assumptions results in a constant hazard for dostarlimab in combination with PCC OS for up to 80 weeks, followed by a sharp linear increase in the hazard over three years, before a decline in the hazard over the rest of the time horizon. Clinical evidence from RUBY-1 supports that treatment with dostarlimab will lead to an early and sustained response and a decline in the risk of death overtime.[5] It is clear that this does not align with the modelled hazard rate for OS by the EAG, indicating that the assumptions imposed by the EAG on OS are inappropriate.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Figure 6: EAG base case OS hazard rate – Exponential for dostarlimab in combination with PCC; Log-logistic for PCC  I Finally, as outlined in Company response to EAG clarification question B5, treatment waning has been discussed by NICE committees recently in the relapsed advanced or recurrent endometrial cancer setting in ID4036 and TA779. Within the recently published final appraisal determination document for pembrolizumab in ID4036, the committee concluded *"that applying treatment waning from 7 to 9 years was a reasonable and potentially conservative assumption based on the data provided for this particular indication."* [16] TA779 also featured	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		discussion by the committee about treatment waning with the preferred assumption that treatment waning did not begin until treatment discontinuation.[6] These appraisals, in the relapsed, pre-treated endometrial cancer setting, applied a treatment waning after the treatment stopping rule and after the available follow-up data. The EAG's preference to apply a treatment waning effect before most patients have discontinued dostarlimab treatment, and before the treatment stopping rule, is unsupported by the data and does not align with previous appraisal methodology in this area. Any treatment waning application is a conservative OS scenario only, and any assumptions more pessimistic than those accepted in within ID4036 would be clinically implausible to apply in the first line setting.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Table 5: Overall survival landmark percentages – dostarlimab in combination with PCC and external evidence

Months (years)	EE1	EE2	EE3	EE4	EE5	EE mean (n=5)	EAG Advisor (n=1)	Overall Advisor mean (EEs +EAG)	Relapsed setting - GARNET *	Relapsed setting - KEYNOTE -158**	Primary A/R EC SOC – Miller	Primary A/R EC SOC – NCRAS (n=902)	Company Preferred (KM + HR)	EAG preferred (exponential with convergence)
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	82%	80%	82%	60.5%	64%	49%	40%	87%	86%
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76%	50%	72%	58.4%	60%	36%	31%	83%	75%
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67%	20%	59%	55%[#]	60%[#]	27%	18%	72%	52%
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53%	10%	46%	-	-	20%	-	57%	24%
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44%	8%	38%	-	-	-	-	39%	10%

EAG – external assessment group; EE – external expert; HR – hazard ratio; KM – Kaplan-Meier; PCC - Platinum-containing chemotherapy

**GARNET: NCT02715284 Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET)[7] **KEYNOTE-158: NCT02628067 Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158*

Abbreviations: AIC – Akaike Information Criterion; AFT – Accelerated failure time; A/R – advanced recurrent CP – Carboplatin plus paclitaxel; CS – Company submission; dMMR – DNA mismatch repair deficiency; DSU – Decision Support Unit; EAG – external assessment group; EC – endometrial cancer; EE – external expert; HR – Hazard ratio; IO – Immunotherapy; KM – Kaplan-Meier; MSI-H – Microsatellite instability-high; NCRAS – National cancer registration and analysis service; NICE – National institute for health and care excellence; OS – Overall survival; PCC – Platinum-containing chemotherapy; PFS - Progression-free survival; RCT – Randomised controlled trial; SOC – Standard of care; TSD - Technical Support Document; UK – United Kingdom

Issue 6 Resource use monitoring costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.8 page 96 "Estimates of resource use monitoring data from company clinical experts stated by the company have not been provided to the EAG despite request during clarification questions, therefore have not been verified." **Section 3.2.8.4 page 98** "This did not include the questionnaire, responses, or summary of responses from the company experts."	The Company requests this section of text is removed.	The Company believe that the insights provided by the external clinical experts are robust, highly credible, and an important validatory resource for this appraisal. The Company have provided comprehensive information regarding the advice seeking activities and the outputs. An additional excel spreadsheet containing individual expert responses on resource use was provided within the EAG clarification questions reference pack, and separately on 7th September via NICE docs. The tables relevant to resource use are 'pre progression HCRU' and 'post progression HCRU'. The questionnaire was previously and will be provided now. The Company will provide an updated external expert advisory board reference pack to ensure all content is collated: minutes to three advisory boards, health care	EAG acknowledge this as a factual error and has removed these sections.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		resource use questionnaire, excel file containing response to health care resource use and subsequent treatment questions, Appendix from the CS outlining the external expert relevant experience.	
Section 3.2.8 page 96, Table 27 "TA904 [15] also used in TA620.[42]"	The Company believe that the use of 0.23 to inform outpatient resource use is does not align with UK HCP feedback and cannot be substantiated within the referenced NICE TA. The Company propose the EAG base case is amended to align with UK external expert insights regarding health care resource use.	The Company note that based on the feedback from external experts, the ongoing monitoring of patients with advanced or recurrent endometrial cancer who are progression-free is undertaken by the multidisciplinary team. Therefore, within the model the Company have included resource use assigned to outpatient consultant time (0.13 units per week/8 weekly/7 visits per year), and in addition included specialist nursing time - 0.07 units per weekly cycle (which equates to one visit every 14 weeks or 4 visits per year). In total the model therefore accounts for approximately 11 appointments to engage with specialist services during their progression-free, long-term	Not a factual error, no response required. The resource use estimate of 0.23 from TA904 and TA620 can be verified as the figure is published non-redacted in the TA904 Committee Papers committee-papers (nice.org.uk) EAG is aware TA908 guidance replaces TA620, however verification of the use and source of this figure in TA620 is available at: https://www.nice.org.uk/guidance/ta908/evidence/ta620-appraisal-consultation-committee-papers-pdf-13075915501 No changes or further discussion of this parameter arose during TA908.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		monitoring period. It is worth noting that these costs can accrue within the model for the entire time progression-free (i.e. costs accruing up to [redacted] progression free LYs post treatment start as per the Company base case). This is in addition to the other health care resource use accounted for within the model (CT scans, blood counts and GP visits). The resource use estimate of 0.23 from TA904 and TA620 cannot be verified as the value does not feature in TA620 and TA904. It should also be noted that TA908 guidance replaces TA620.[9,10] The Company question if this value is appropriate considering its non-endometrial cancer, non-immunotherapy origin, and its application for the entire duration of PFS in the model. As the EAG have retained the specialist nursing time resource use within the model, which equates to 16 annual appointments with specialist services during their progression-	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		free, long-term monitoring period (12 outpatient plus 4 specialist nursing). This does not align with the resource use feedback from UK external experts, specific to advanced or recurrent endometrial cancer, received by the Company. It is important also to note that the Company also accounts for more frequent outpatient visits (3-4 weekly) and specialist nurse visits (8 weekly) during the first 18 weeks of treatment with dostarlimab in combination with PCC.	

Abbreviations: AE – Adverse event; EAG – External Assessment Group; CS – Company submission; CT – Computerised tomography; GP – General practitioner; HCP – Healthcare professional; HCRU – Health care resource utilisation; ICER – Incremental cost-effectiveness ratio; LY – Life year; NICE – National institute for health and care excellence; PCC – platinum-containing chemotherapy; PFS – Progression-free survival; TA – Technology appraisal; UK – United Kingdom

Issue 7 Lack of data on subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2. page 34 "The EAG has checked the RUBY-1 schedule of events, the RUBY-1 protocol and the CSR. Some	The Company request that theses sentences (and any related statements) are revised to reflect that further information on subsequent treatments was	In response to EAG clarification A9, the Company provided detailed information on the source and derivation methods behind the subsequent treatments received in	The EAG acknowledge that further information on subsequent treatments was provided within this section of the report, however, the earlier text which was provided for context could be revised to

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
references are made to there being subsequent treatments." **Section 2.2.2 page 35** "CS section B3.5.5 reports subsequent anti-cancer therapies costed in the economic model post progression and include carboplatin with paclitaxel, doxorubicin, and pembrolizumab with lenvatinib (See Section 3.2.8) but the EAG is unable to fully validate the use of these subsequent treatments." **Section 2.2.3.4 PFS2 page 42** "Details on subsequent treatments are not fully reported and it is not clear whether they can be considered well-balanced across arms."	provided to the EAG by the Company at EAG clarification question stage.	RUBY-1 and modelled in the cost-effectiveness analysis.	reflect this. The following changes have been made: The EAG were unable to establish what subsequent therapies were given from the sources initially available (RUBY-1 schedule of events, the RUBY-1 protocol and the CSR) but was aware that there was the potential for subsequent anti-cancer treatments. The EAG is unable to fully validate the use of these subsequent treatments and no factual error has occurred. For context the EAG are referring to not being able to cross check these data with other sources from the trial or against alternative data sources for UK clinical practice. While the EAG were provided details of subsequent treatments this statement reflects earlier comment in Section 2.2.2 made by the EAG that the subsequent anti-cancer treatment data is immature. This has been added to section 2.2.3.4 for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.2 page 35 "Owing to the short follow-up of RUBY-1 the subsequent anti-cancer treatment data is immature, however, it can be seen that there was imbalance in the proportion receiving an anti-cancer therapy of some sort between the two arms, and that the specific anti-cancer therapies used differed between the two arms."	The Company requests the text be amended to reflect that it is clinically plausible for more patients to have received subsequent treatment in the CP arm of the trial given that more patients have progressed compared to the dostarlimab in combination with CP arm. "Owing to the short follow-up of RUBY-1 the subsequent anti-cancer treatment data is immature, however, it can be seen that there was a higher proportion receiving a subsequent anti-cancer therapy in the PCC in combination with placebo arm, and that the specific anti-cancer therapies used differed between the two arms."	Unclear language.	The EAG acknowledge this is unclear language and has updated the section as suggested.

Abbreviations; CP – Carboplatin plus paclitaxel; CS – Company submission; CSR – Clinical study report; EAG – External assessment group; PCC – Platinum-containing chemotherapy

Issue 8 EAG cost-effectiveness analysis: Adverse event rates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In the EAG's preferred assumptions, they have run exploratory analysis to update the AE inclusion to: *"Inclusion of a broader range of AE disutilities at grade 3 and above to address underrepresentation of AEs in these treatment classes."* The Company has checked the AE rates in the model, and these do not align with the AEs presented in Table 10 (Page 52). The values have been 'hard coded' in Cells E142:169 of the *Data Store* sheet.	The Company proposes that the AE rates should be updated in row G142:169 to align with the AE incidence (n) and corresponding AEs in Table 13.	The AE rates are currently incorrect and are not informed by the RUBY-1 trial. Therefore, the exploratory analysis results presented in Section 5.1, Table 32 are incorrect.	The figures used in the model are the correct, but are not entered into the model in the exact format in which they are presented in Table 10. The EAG acknowledge this is not sufficiently clear and have detailed methodology in addendum appendix 8.4.
In line with the error above, the EAG's base case is incorrect. The EAG have suggested an update to the company's base with *"EAG 05: Inclusion of a broader range of AE disutilities at grade 3 and above to address underrepresentation of AEs in these treatment classes."* Since the AE rates are incorrect (as well as the aforementioned issues	The Company proposes that the AE rates in the EAG's model should be updated to reflect those in Table 10 of the EAG report. In line with these changes, the updated cost-effectiveness results around outlined in Table 12.	The Company proposes that the EAG base case cost-effectiveness results are updated to reflect the model errors (namely the AE rates and implementation of the PFS for both treatment arms)	The EAG have updated AE rates in the model using the AE incidence (n) entered into Cells G142:149 of the Data Store sheet. This produces the same incidence rates as used in our original analysis (explained as discussed above in addendum appendix). Due to hard coding of these Cells, a negligible difference in ICER value of [redacted]

raised in “issue 1”, the EAGs deterministic base case ICER is incorrect.	**Incremental Costs (£)** / **Incremental QALYs** / **Deterministic ICER (£/QALY)** [redacted] / 1.49 / [redacted] Note. This corrected ICER also includes the correct to the PFS hazard rate adjustment		was produced on re-run of this analysis in the EAG amended model. Results have been amended throughout the report.

Abbreviations: AE – Adverse event; EAG – External Assessment Group; ICER – Incremental cost-effectiveness ratio; PCC – Platinum-containing chemotherapy; PFS – Progression-free survival; QALY – Quality adjusted life year

Section B. Non-key issue related factually inaccurate statements and clarity of language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 0.6 page 14 In Table 2 the last column states it includes the ICER (change from Company base case), however the change from Company base case is not reported	Please provide the change from Company base case or update the title of the table.	Incomplete information provided.	The EAG acknowledge this error and has amended the report to remove "change from Company base case"
Section 2.2.2.2 page 33 “In the first 16 weeks of RUBY-1 participants received dostarlimab”	The Company requests the text be amended to: “In the first **18** weeks of RUBY-1 participants received dostarlimab”	The dostarlimab in combination with PCC regimen during the combination phase is three weekly cycles. The final three weekly cycle starts on week 16 and ends on week 18, with the monotherapy phase starting	The EAG acknowledge this error and has amended the report with ‘18’.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		on week 19. For clarity therefore the first 18 weeks are the dostarlimab in combination with PCC regimen (rather than 16 weeks).	
Section 2.2.3.1 Page 37, Table 1	In Table 1, the Company request that for data where the EAG have noted as not reported (NR) updated.	The Company has not provided any additional data beyond the core CSR unless related to the dMMR/MSI-H population. Additional data on ITT population baseline characteristics included in Table 14.	Not a factual error, no response required
Section 2.2.3 page 40 "Whilst again similar, there is a difference in the plateau where BICR PFS levels off at roughly 0.66 and 0.26 for dostarlimab and placebo respectively, whilst IA PFS plateaus at 0.61 and 0.15 respectively."	The Company would like to confirm if the numbers in this sentence relate to survival probabilities. If so, can the data please be related to the appropriate figure or table within the text.	Unclear presentation of data.	Not a factual error, no response required. For context the sentence preceding this refer to the appropriate figures.
Section 2.2.3.4, PFS2 page 41 **"**This outcome was not in the NICE scope and it is unclear whether this outcome was IA or BICR assessed."	The Company request that this statement is updated to reflect that PFS2 is assessed as per investigator assessment	This statement is currently unclear, and the clinical development team have confirmed that PFS2 is assessed by as per investigator assessment (this is the usual assessment method for PFS2).	Thank you for this clarification, however, as this is not a factual error, no response is required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.3 page 43 "People without evaluable disease are unlikely to be eligible for treatment according to the EAG's clinical expert."	The Company request that this statement is removed as it does not align with the RUBY eligibility criteria trial or with the published clinical guidelines. Patients were eligible for inclusion with or without evaluable disease as per the RUBY-1 trial protocol (any patient with first recurrent, stage IV or IIIC disease, or patients with stage III 3 disease with carcinosarcoma, clear cell, serous, or mixed histology). Furthermore, neither the BGCS or ESMO guidelines note presence or absence of evaluable disease as a definitive decision-making factor for the systemic treatment of advanced or recurrent endometrial cancer.[11,12]	This statement is not reflective of available evidence.	Not a factual error, no response required, this is referring to usual practice not the trial characteristics.
Section 3.2.7 page 84 "There is no observed differences in HRQoL between the dostarlimab+CP and placebo+CP arms in either the ITT or dMMR/MSI-H populations at each	Please review the text in these sections and update to reflect that Table 31 and Table 32 of the Company clarification document show numerical differences in the HRQoL in the dostarlimab in combination with PCC and PCC arm in both populations.	Incorrect statements.	Not a factual error. Differences are either statistically significant or not and the figures presented are not. The term 'numerical difference' is ambiguous and lacks scientific meaning. No amendments are made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
treatment cycle/measurement point". **Section 3.2.7 page 91** "Health utility index values for both ITT and dMMR/MSI-H populations show no difference in HRQoL between people in the dostarlimab + CP arm and placebo + CP arm at each equivalent treatment cycle/time point."			
Section 3.2.6.3.1 page 79 "Spline models were not considered due to the suitability of the standard parametric models.	The Company requests the text be amended to: "Spline models were not considered as they are unlikely to converge for OS due to the low number of events."	The justification for not considering flexible spline modelling presented by the EAG is incorrect.	Not a factual error, no response required
Section 3.2.6 page 72 **"**Despite the good fit to the data, the company preferred to use the extrapolation in a piecewise nature and use the Kaplan-Meier estimates of survival for the duration of trial follow-up, and apply the estimated hazard rate beyond this point."	The Company requests the text be amended to: "Despite the good fit to the data, the company preferred to use the extrapolation in a piecewise nature and use the Kaplan-Meier estimates of survival for the duration of trial follow-up, and thereafter extrapolate	Incorrect statement. Only the dostarlimab in combination with PCC arm is extrapolation using a hazard ratio. The Company notes that using the KM directly during the trial follow up period is their preferred approach to best use all available trial data.	The EAG acknowledge this and have updated the report accordingly

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	based on a log-logistic parametric curve."		
Section 3.2.6.2.2 Figures 11 and 14 PFS hazards rates figures	The Company requests that an additional image or inset image is provided in addition to figures 11 and 14. These figures illustrate the long-term hazards well, however the current Y axis, as illustrated in the figure, cuts off the increase in the dostarlimab in combination with PCC figure. This therefore makes the non-monotonic nature of the hazard less clear.	Current figure not representative of the entire hazard rate.	As this relates to the clarity of presentation rather than a factual error, no response is required
Section 3.2.6 page 83, Figure 20 The graph does not overlay the Kaplan-Meier data from the RUBY trial.	The Company requests the Kaplan-Meier data is superimposed on Figure 20.	Interpretation of the OS extrapolation curves is aided. The extrapolations are only used in the model beyond the end of the follow-up period therefore it is beneficial to see the Kaplan-Meier data from baseline until the end of the follow-up period.	Thank you, we have updated this figure

Abbreviations: BGCS - British Gynaecological Cancer Society; BICR – Blinded independent central review; CSR – Clinical study report; CP – Carboplatin plus paclitaxel; dMMR – mismatch repair deficiency; EAG – External Assessment Group; ESMO - European Society for Medical Oncology; HCRU – Health care resource utilisation; HRQoL – Health-related quality of life; IA – Investigator assessed; ICER – Incremental cost-effectiveness ratio; ITT – Intention-to-treat; MSI-H – Microsatellite Stable-high; NR – Not reported; OS – Overall survival; PCC – Platinum-containing chemotherapy; PFS – Progression-free survival; PFS2 - Progression-free survival-2

Section C. Typographical errors

EAG response overall: Any punctuation or grammar preferences that do not affect the meaning, factual accuracy or expression of statements are clear the report has not been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Abbreviations are not used after they have been defined Instances found on pages: 9: bottom of the page (PFS and OS) 10: top of the page (TRAE) 13: Issue 7: second row and column (AE) 14: second to last row (AE) 23: row 2 column 2 Page 33: several mentions of carboplatin and paclitaxel instead of CP 34: first three words carboplatin and paclitaxel instead of CP 42: overall survival in the first sentence of 2.2.3.5 47: first sentence of the second paragraph “company submission” 50: last sentence before table 9 (AE)	Please use abbreviations after they have been defined in the text.	Consistency.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
50: row 6 column 1 of table 9 (AE) 52: start of second paragraph (AE) 57: start of second paragraph (TRAE) Page 62: last sentence of first paragraph (AE and irAE)			
Section 0 page 8 "Sections 0.3 to 0.5 explain the key issues in more detail."	The Company requests the"0.5" should be a cross-reference link instead of text.	Cross-reference link is not included.	Not a factual error, no response required
Section 0.3 page 9 "…either dostarlimab+PC or pembrolizumab + lenvatinib."	The Company requests the text be amended to: "…either dostarlimab+**CP** or pembrolizumab + lenvatinib"	Abbreviation was misspelled.	Updated throughout
Section 0.3 page 9 "This is a likely to be a minority of patients,"	The Company requests the text be amended to: "This is likely to be a minority of patients,"	Typographical error.	Not a factual error, no response required
Throughout the submission The verb conjugation for CS is inconsistent. Sometimes first-person singular is used, and	As CS is defined as Company submission in the abbreviations table, using third person singular is more appropriate.	Consistency.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
other times third person singular is used			
Section 0.4 page 11 "The EAG notes a lack of efficacy in RUBY-1 study among"	The Company requests the text be amended to: "The EAG notes a lack of efficacy in **the** RUBY-1 study among"	Typographical error.	Not a factual error, no response required
Section 0.4 page 11 **"Issue 2: Suitability of RUBY-1 data for estimating benefit of dostarlimab+PC "** And "The true benefit gained from dostarlimab+PC may be very different.."	The Company requests the text be amended to: "**Issue 2: Suitability of RUBY-1 data for estimating benefit of dostarlimab+CP"** And "The true benefit gained from dostarlimab+**CP** may be very different…"	Abbreviation was misspelled.	Updated throughout
Section 0.5 page 12 **"**the long term hazard rate would differ**"**	The Company requests the text be amended to: **"**the **long-term** hazard rate would differ**"**	The word long-term should be hyphenated.	Not a factual error, no response required
Section 0.5 page 13 "The EAG (1) applies AE disutilities for a broader profile of adverse events at grade 3 and above and (2) incorporates	The Company requests the text be amended to: "The EAG (1) applies AE disutilities for a broader profile of adverse events at grade 3 and above and (2) incorporates	Typographical error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
additional monitoring costs into the EAG base"	additional monitoring costs into the EAG base **case.**"		
Section 0.5 page 13 "potential implementation of dostarlimab+PC may"	The Company requests the text be amended to: "potential implementation of dostarlimab+**CP** may"	Abbreviation was misspelled.	Updated
Table 2 section 0.6 page 14 All sentences in the first column are missing a full stop at the end.	Please add in a full stop at the end of every sentence in this table	Sentences should end with a punctuation	Not a factual error, no response required
Section 1.1 page 17 "Quality of life can be affected a reduction in the ability to perform daily activities and in confidence"	The Company requests the text be amended to: "Quality of life can be affected **by** a reduction in the ability to perform daily activities and in confidence"	Missing word.	Not a factual error, no response required
Section 1.1 page 17 "with just over quarter of these being primary advanced or recurrent disease."	The Company requests the text be amended to: "with just over **a** quarter of these being primary advanced or recurrent disease."	Missing word.	Not a factual error, no response required
Section 1.1 page 17 "Further details can be found in the CS sections B1.3-1.4."	The Company requests the text be amended to:	An abbreviation was used before it was defined.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"Further details can be found in the **company submission (**CS**)** sections B1.3-1.4."		
Across multiple sections and pages Company and CS are used interchangeable when they are two different things	Please ensure you align on consistent use of the words CS and the Company when appropriate	Inconsistency of language.	Not a factual error, no response required
Section 1.3 page 19 "The decision problem provided by the company (CS Section B1.1) is broadly consistent with the NICE scope with the EAG main issue relating to the population as described in Table 3."	The Company requests the text be amended to: "The decision problem provided by the Company (CS Section B1.1) is broadly consistent with the NICE scope with the EAG**'s** main issue relating to the population as described in Table 3."	Grammatical error.	Not a factual error, no response required
Across multiple sections and pages The formatting of the tables across the report is inconsistent these issues relate to: Inconsistent line spacing Inconsistent text alignment	Correct formatting.	Inconsistency of formatting.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Across multiple sections and pages There are several instances where a double space is used after punctuation, or in the middle of a sentence. These can be found on pages: 20: top and bottom of the EAG comment column 21 28: Twelve systematic reviews were chosen 29: after – "Table 4 provides a summary of the EAG critique and cross-references to the relevant section in the CS." 30: between all sentences in the first paragraph 30: after the first sentence in the second paragraph 31: after the third sentence 32: after the second sentence in 2.2.2.1 32: before – "This may be relevant in particular for people with Stage III EC."	Correct formatting.	Inconsistency of formatting.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
32: after – “July 2022.’) that some Stage III endometrial cancers are amenable to cure. “ 32: after – “There is not enough detail of these people presented to explore if they would be surgically treated in the real world. “ 32: before – “It is also not clear from the evidence reported if any of these people would be candidates for radiotherapy in the real-world setting.” 32: before – “The EAG clinical expert confirmed that this is considered usual practice in the real-world setting.” 33: after first sentence on this page 33: after - “(see CS Section B2.3.1.3 for further details). “ 33: before last sentence of 2.2.2.1 33: after second sentence of 2.2.2.2 34: Top of the page before “in the CSR for the” 34: before last sentence before section 2.2.2.3			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
34: bottom of the page before "some details of concomitant" 35: before – "Further treatments most commonly" 36: after first and second sentence of the last paragraph 55: before the last sentence of the page 57: before the last sentence on the page 58: in between the two sentences in the second paragraph 58: before the last sentence 59: before "This left 150 results" 59: in between the last 4 sentences of the first paragraph			
Section 1.3 page 20 "The EAG clinical advisor confirmed that there is no objective criteria and that clinical judgement is used"	The Company requests the text be amended to: "The EAG clinical advisor confirmed that there **are** no objective criteria and that clinical judgement is used"	Wrong verb conjugation, should be "are" as criteria is plural	Not a factual error, no response required
Section 1.3 page 23 The bullet point Health-related quality-of-life is missing a bullet point:	The Company requests the text be amended to: • Adverse effects of treatment • Health-related quality-of-life.	Formatting error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Adverse effects of treatment Health-related quality-of-life.			
Section 2.1.1 page 28 "For MEDLINE and Embase, a pragmatic RCT filter from a recognised source (SIGN) was applied (the EAG note that this is not the most sensitive available filter, but it is a reasonable choice for this CS)."	The Company requests the text be amended to: "For MEDLINE and Embase, a pragmatic **randomised control trial (**RCT**)** filter from a recognised source (SIGN) was applied (the EAG note that this is not the most sensitive available filter, but it is a reasonable choice for this CS).""	Abbreviation was used before being defined.	Not a factual error, no response required
Section 2.1.1 page 28 "The same conferences are also listed in CS Appendices Table 4."	The Company requests the text be amended to: "The same conferences are also listed in **the** CS Appendices Table 4."	Typographical error.	Not a factual error, no response required
Section 2.2 page 30 "RUBY-1 was an international multi-centre, double-blind, randomised Phase III trial."	The Company requests the text be amended to: "**RUBY is** an international multi-centre, double-blind, randomised Phase III trial."	Wrong verb tense as this is an ongoing trial this should be 'is', like the sentence before.	Not a factual error, no response required
Section 2.2 page 30 "The study compromised a 16-week period of dostarlimab+CP or placebo+CP"	The Company requests the text be amended to:	Missing word.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"The study compromised **of** a 16-week period of dostarlimab+CP or placebo+CP"		
Section 2.2.1 page 31 "There appears to be some differences between arms in some potential prognostic factors at baseline for the subgroup"	The Company requests the text be amended to: "There appears to be some differences between arms in some potential prognostic factors at baseline for the subgroup"	Grammar: should be 'appear' as differences is plural.	Not a factual error, no response required
Section 2.2.2.1 page 32 "The EAG clinical expert concurs with some of the CS clinical experts discussions"	The Company requests the text be amended to: "The EAG clinical expert concurs with some of the CS clinical **experts'** discussions"	Grammatical error.	Not a factual error, no response required
Across multiple sections and pages There are certain instances where there is a space before and/ or after + or /, which is inconsistent with how these are mostly sued in the document 33: "inclusion criteria of the trials of carboplatin / paclitaxel that"	Correct formatting.	Formatting error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
35: “In the dostarlimab + CP arm” 35: “pembrolizumab + lenvatinib” 49: “placebo+ CP” 50: table 9 row 2 51: table 10 second row 53: table 11 second row 54: “dostarlimab + CP”, “placebo + CP”, “dostarlimab + CP”, “dostarlimab + CP”, “placebo + CP” 54: table 12 second row 55: “(dostarlimab + CP 13.3%, placebo + CP 12.6%).” 57: “protein-1 / programmed death-ligand 1” 57: “dMMR / MSI-H population” 60: “dostarlimab + CP”, “dostarlimab + niraparib” “placebo +CP”, “dostarlimab + CP”			
Section 2.2.2.3 page 34 “Following the 16 week period of dostarlimab+CP”	The Company requests the text be amended to: “Following the **18** week period of dostarlimab+CP”	The dostarlimab in combination with PCC regimen during the combination phase is three weekly cycles. The final three weekly cycle starts on week 16 and ends on week 18, with the monotherapy phase starting on week 19. For clarity therefore the first	Updated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		18 weeks are the dostarlimab in combination with PCC regimen (rather than 16 weeks)	
Section 2.2.3 page 36 "All hypotheses present here assumed one-sided testing, assuming a benefit for dostarlimab."	The Company requests the text be amended to: "All hypotheses **presented** here assumed one-sided testing, assuming a benefit for dostarlimab."	Presented is a verb in this sentence not a noun.	Not a factual error, no response required
Section 2.2.3.6 page 43 "DCR was defined as the number of participants who achieved one of the following response: CR, PR, SD or no disease."	The Company requests the text be amended to: "DCR was defined as the number of participants who achieved one of the following response**s**: CR, PR, SD or no disease."	Clarity.	Not a factual error, no response required
Section 2.2.3.6 page 44 "The EAG also requested the company present DOR for the dMMR-MSI-H subgroup who achieved CR (Figure 6). A plateau is evident for both arms, although the numbers in each arm are small."	The Company requests the text be amended to: "The EAG also requested the Company **to** present DOR for the dMMR**/**MSI-H subgroup who achieved CR (Figure 6). A plateau is evident for both arms, although the numbers in each arm are small."	Typographical error.	Not a factual error, no response required
Section 2.2.3.7 page 45	The Company requests the text be amended to:	Consistency in abbreviations.	Updated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"In the CSR for RUBY 1, the company provided an equivalent plot for the MMRp/MSS"	"In the CSR for **RUBY-1**, the company provided an equivalent plot for the MMRp/MSS"		
The abbreviation QoL is not included in the abbreviation table, and it is not defined in the text but a mix of the abbreviation and the written-out text is used.	Please either use the abbreviation and use this after it is defined and added to the table or always write it out fully	Consistency in abbreviations.	Not a factual error, no response required
Section 2.2.3.9 page 48 "Adverse events from RUBY-1 were reported in CS Section B2.10 and Appendix R. The EAG has summarised key data from the adverse events reported in RUBY-1."	"**AEs** from RUBY-1 were reported in **the** CS Section B2.10 and Appendix R. The EAG has summarised key data from the **AEs** reported in RUBY-1."	Typographical errors.	Not a factual error, no response required
Section 2.2.3.9 page 48 "Duration on treatment and interruption to treatment is summarised in Table 10."	The Company requests the text be amended to: "Duration **of** treatment and interruption to treatment **are** summarised in Table 10."	Incorrect preposition and verb tense used.	Not a factual error, no response required
Section 2.2.3.9.1 page 49	The Company requests the text be amended to:	Minor text alteration for clarity.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"the proportion of participants who at had at least 4 incidents of infusion interruption"	"the proportion of participants who **had at** least 4 incidents of infusion interruption"		
Section 2.2.3.9.5 page 54 "Treatment-related TEAEs related to any study drug are presented in CS Appendix Table 58."	The Company requests the text be amended to: "Treatment-related TEAEs related to any study drug are presented in **the** CS Appendix Table 58."	Minor text alteration for clarity.	Not a factual error, no response required
Section 2.2.3.9.6 page 55 "CS Appendix Tables 69 and 70 report summary irAEs in the dMMR/MSI-H populations for the two RUBY-1 trial arms respectively and the EAG has combined these data as seen in Appendix Table 39."	The Company requests the text be amended to: "**The** CS Appendix Tables 69 and 70 report summary irAEs in the dMMR/MSI-H populations for the two RUBY-1 trial arms respectively and the EAG has combined these data as seen in Appendix Table 39."	Minor text alteration for clarity.	Not a factual error, no response required
Section 2.2.3.9.7 page 57 Reference to table 15 is missing a hyperlink	Please add in an internal reference to Table 15.	Missing hyperlink.	Not a factual error, no response required
Section 2.2.4 page 57 2.2.4 Trial Generalisibility	The Company requests the text be amended to: 2.2.4 Trial **Generalisability**	Word misspelled.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3 page 59 "The EAG undertook update searches for additional studies of relevance on 14th August 2023."	The Company requests the text be amended to: "The EAG undertook update searches for additional studies of relevance on **the** 14th August 2023."	Minor text alteration for clarity.	Not a factual error, no response required
Section 2.3 page 59 "The EAG used the company original search,"	The Company requests the text be amended to: "The EAG used the company**'s** original search,"	Minor text alteration for clarity.	Not a factual error, no response required
Section 2.3.1 page 59 "CS section B2.11 reports"	"Section B2.11 in the CS reports"	Minor text alteration for clarity.	Not a factual error, no response required
Section 2.3.1 page 61 Inclusion criteria part 2 bullet points are inconsistent with the other bullet points used in the documents	Please align bullet point formatting to the rest of the document	Consistent formatting is required.	Not a factual error, no response required
Section 2.4 page 62 "DCR was similar between arms and ORR as slightly higher with dostarlimab."	The Company requests the text be amended to: "DCR was similar between arms and ORR **was** slightly higher with dostarlimab."	Wrong word used.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, page 22, Table 3, column 5, row 3 "The EAG has not been able to identify any real world evidence comparing dostarlimab + carboplatin + paclitaxel with pembrolizumab + lenvatinib (Section 2.3)." **Section 3.2.3, page 70, Table 16, column 4, row 7** "Feedback on mean age of patients in practice emphasising real world population rather than generally younger, fitter trial populations" **Section 3.2.6, page 75** "Hence, the EAG concludes that the magnitude of PFS benefit suggested by the company's approach is an overestimation of the expected benefit in real world use." **Section 3.2.8.4, page 98** "The substantial differences in responses between experts	The Company requests the text be amended to included "**real-world**" in these instances.	The adjective form of "real-world" is hyphenated.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
suggests a high degree of variability in real world practice"			
Section 3.1.1, page 63 "Searches for all three SRs were conducted separately on 10 November 2021 (with an update on 22 February 2023) in a relevant range of databases."	The Company requests the text to be amended to: "Searches for all three **SLRs** were conducted separately on 10 November 2021 (with an update on 22 February 2023) in a relevant range of databases."	The abbreviation for systematic literature review has been mistyped.	Not a factual error, no response required
Section 3.2.3, page 68 "The RUBY-1 trial collected data for both ITT and dMMR/MSI-H populations which was used to inform the economic model."	The Company requests the text be amended to: "The RUBY-1 trial collected data for both ITT and dMMR/MSI-H populations which **were** used to inform the economic model."	Data is plural.	Not a factual error, no response required
Section 3.2.3, page 68 "The clinical expert for the EAG advised this was not unrepresentative of patients seen in clinical in England and Wales,"	The Company requests the text be amended to: "The clinical expert for the EAG advised this was representative of patients seen in clinical in England and Wales,"	The use of double negatives is grammatically incorrect.	This use of a double negative is a nuance of the English language to convey more complexity in the response. This was the advice received by the EAG and reflected appropriately in the report. No response required.
Section 3.2.4, page 71 The text "Table 3" is font size 11.	The Company requests the font size of the text "Table 3" be amended to font size 12.	Correcting inconsistent formatting.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.7 page 85 "…suggesting the utility value for PFS and PD is reasonably consistent across the RUBY trial population.	The Company requests the text be amended to: "…suggesting the utility **values** for PFS and PD **are** reasonably consistent across the RUBY trial population"	Health states have their own utility values therefore this is plural.	Not a factual error, no response required
Section 3.2.7 page 85 "A SLR was conducted…"	The Company request the text be amended to: "**An** SLR was conducted…"	Grammatically correct.	Not a factual error, no response required
Section 3.2.7 page 85 No cross-reference provided: "See section 3.1.1" **Section 3.2.7 page 89** No cross-reference provided "See sections 2.2.3.9.2 and 2.2.3.9.3"	The Company requests this is cross-referenced to the correct section.	Consistency of cross referencing.	Not a factual error, no response required
Section 3.2.7 page 86 "It would be expected that patients who have moved on from front line treatment in RUBY…"	The Company requests the text be amended to hyphenate: "**front-line**".	Grammatically correct hyphenation.	Not a factual error, no response required
Section 3.2.7 page 86	The Company requests the text be amended to:	Correcting typing error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"In the EAG opinion…" **Section 3.2.7 page 90** "The EAG preferred estimates…"	**page 86:** "In the **EAG's** opinion…" **page 90:** "The **EAG's** preferred estimates…"		
Section 3.2.7 page 87 Broken cross-reference for Table 24.	The Company requests this cross-reference is fixed.	Correcting formatting error.	Not a factual error, no response required
Section 3.2.7, page 89, Table 25, column 3, row 6 "TA779[24] and Lloyd (2006) [38]" **Section 3.2.7, page 89, Table 25, column 3, row 8** "EAG assume equal to hand and foot syndrome, Lloyd (2006)[38]"	The Company requests the formatting is consistent: Row 6: "**TA779 [24]** and Lloyd (2006) [38]" Row 8: "EAG assume equal to hand and foot syndrome, **Lloyd (2006) [38]**"	Correcting inconsistent formatting.	Not a factual error, no response required
Section 3.2.8.1 page 94, Table 26, column1, row 2 Text is different font sizes.	The Company requests the font size of the text in the table be amended to font size 12.	Correcting inconsistent formatting.	Not a factual error, no response required
Section 3.2.8.1 page 94, Table 26 Missing abbreviations for CP and HRG.	The Company requests the abbreviations for CP (carboplatin plus paclitaxel) to be added to Table 26, Table 30 and Table 31, and HRG (healthcare resource group) to be added to Table 26.	Adding missing text.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1, page 103, Table 30, Table 31 Missing abbreviations for CP			
Section 3.2.8.2 page 95 "…for their use as a second line treatment for this indication"	The Company requests the text be amended to hyphenate: "**second-line**".	Grammatically correct hyphenation.	Not a factual error, no response required
Section 3.2.8.2, page 95 Repeat word: "…is reflected in in the immune-related TEAEs"	The Company requests the text be amended to: "…is reflected in the immune-related TEAEs"	Correcting typing error.	Not a factual error, no response required
Section 3.2.8.2 page 95 Missing words "The overall profile of these TEAEs is reflected in in the immune-related TEAEs (discussed in detail in section 2.2.3.9.6 and shown in full in Table 13) and impact of these further substantiated by additional trial outcomes."	The Company requests the text be amended to (includes previous typographical correction or repeated word): "The overall profile of these TEAEs is reflected in the immune-related TEAEs (discussed in detail in section 2.2.3.9.6 and shown in full in Table 13) and **the** impact of these **is** further substantiated by additional trial outcomes."	Correcting typing error.	Not a factual error, no response required
Section 3.2.8.2 page 96 "The EAG identified estimates for weekly outpatient visit	The Company requests the text be amended to:	Correcting grammatical error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
frequency in the literature in addition to calculating estimates based upon the EAG clinical expert advice, which are compared in Table 27."	"The EAG identified estimates for weekly outpatient visit frequency in the literature in addition to calculating estimates based **on** the EAG clinical expert advice, which are compared in Table 27."		
Section 3.2.8.2, page 96, Table 27, column 2, row 3 "TA904 [15] also used in TA620.[42]"	The Company requests the text be amended to: "TA904 [15] also used in TA620 [42]"	Correcting inconsistent formatting.	Not a factual error, no response required
Section 3.2.8.2 page 96 "The EAG feel the use of these values in the analysis are more appropriate…"	The Company requests the text be amended to: "The EAG feel the use of these values in the analysis **is** more appropriate…"	Correcting grammatical error as "use" is singular.	Not a factual error, no response required
Section 3.2.8.4 page 98 Use of abbreviation: "1st-line" and "2nd-line"	The Company requests these are typed out as: "**first-line**" and "**second-line**", respectively for consistency.	Correcting inconsistent style.	Not a factual error, no response required
Section 3.2.8.4 page 99 "…determine if this method may under or over-estimate the total costs."	The Company requests the text be amended to: "…determine if this method may **underestimate or overestimate** the total costs."	Correct grammatical error.	Not a factual error, no response required

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2 page 104 "The model was most sensitive to the OS HR, completion rates per cycle associated with dostarlimab+CP arm, and both outpatient visit frequency per cycle for dostarlimab+CP in PF state from cycle 19+ and outpatient visit unit cost."	The Company requests the text be amended to: "The model was most sensitive to the OS HR, completion rates per cycle associated with dostarlimab+CP arm, and both outpatient visit frequency per cycle for dostarlimab+CP in **PFS** state from cycle 19+ and outpatient visit unit cost."	Correcting inconsistent use of abbreviations.	Updated
Section 5.3 page 108 "A different approach to extrapolating PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation, to reflect a more clinically plausible benefit of dostarlimab+CP."	The Company requests amending the text to: "A different approach to **the extrapolation of** PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation, to reflect a more clinically plausible benefit of dostarlimab+CP.	Correcting inconsistent style.	Not a factual error, no response required

Abbreviations: AE – Adverse event; CP – Carboplatin plus paclitaxel; CS – Company submission; CR – Complete response; CSR – Clinical study report; DCR – Disease control rate; DOR – Duration of response; dMMR – mismatch repair deficiency; EAG – Evidence Assessment Group; EC – Endometrial cancer; HR – Hazard rate; irAE – Immune -related adverse event; ITT – Intention-to-treat; MMRp – Mismatch repair proficient; MSI-H – Microsatellite instability high; MSS – Microsatellite stable; NICE – National institute for health and care excellence; OS – Overall survival; ORR – Objective response rate; PD – Progressed disease; PFS – Progression-free survival; PR – Partial response; QoL – quality-of-life; SD – Stable disease; SLR – Systematic literature review; RCT – Randomised controlled trial; SIGN – Scottish Intercollegiate Guidance Network; TEAE – Treatment emergent adverse event; Treatment-related adverse event

Section D. Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 2.2.3.1 page 36 "The study recruited from 164 sites from 19 countries globally, [redacted] of the sites were from the UK although only [redacted] currently have recruited participants (clarification response A14), [redacted] of which were in the dMMR/MSI-H subgroup."	Number of sites and success of recruitment should be marked up as CIC.	Number of sites and success of recruitment remain unpublished.	These data were not marked CIC in the Company response to clarifications. The EAG has marked these as CIC in the updated report, however, the company may want to request these be marked CIC in their response to prevent these being published.
Section 2.2.3.6, page 44, Figure 5	The Kaplan-Meier plot of DOR follow-up for dMMR/MSI-H subgroup of RUBY-1 is available in the Figure S4 (A) of Mirza et al.[13] supplementary materials.	Figure 5: The Kaplan-Meier plot of DOR follow-up for dMMR/MSI-H subgroup of RUBY-1 CIC mark-up can be removed as it is a published figure.	Updated
Section 2.2.3.9.5	All figures in the text should be marked up for CIC.	Figures within this section remain unpublished.	Updated
Section 3.2.3 page 68 **Section 3.2.3, page 69, Table 16, column 2, row 2** **Section 5.3 page 108**	The baseline age in the CEM should be marked up for CIC.	"The mean age of the dMMR/MSI-H population within RUBY-1 was used as the baseline age in the CEM ([redacted])." "EAG 01: Starting age at baseline is increased from [redacted] to 67.1 years to reflect clinical expert opinion and relevant evidence from the literature."	Updated
Section 3.2.7 page 90	dMMR/MSI-H subgroup irAE is CIC as in CS doc B.	"The most common dostarlimab-related irAE was hypothyroidism (overall	Updated

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
"The most common dostarlimab-related irAE was hypothyroidism (overall population 11.2%; dMMR/MSI-H subgroup 15.4%)."		population 11.2%; dMMR/MSI-H subgroup [redacted]%)."	

Abbreviations: CEM – Company economic model; CIC – Commercial-in-confidence; dMMR – mismatch repair deficiency; DOR – Duration of response; HR – Hazard rate; MSI-H – Microsatellite Stable- high; irAE – Immune-related adverse event

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Appendix

Table 6: External expert estimates of the proportion of patients who would be progression-free at landmark time points in dMMR/MSI-H population in the RUBY-1 trial treated with PCC

Months (years)	dMMR/MSI-H						
	Mean (n=6)	EE1	EE2	EE3	EE4	EE5	EAG advisor
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18%
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10%
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8%
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5%
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3%

EE1-5 – External expert 1-5; dMMR – DNA mismatch repair deficiency; EAG – External Assessment Group; MSI-H – Microsatellite instability high; PCC – Platinum-containing chemotherapy. Please note, external expert 4 was from Scotland.

Table 7: External expert estimates of the proportion of patients who would be progression-free at landmark time points in dMMR/MSI-H population in the RUBY-1 trial treated with dostarlimab in combination with PCC

Months (years)	dMMR/MSI-H						
	Mean (n=6)	EE1	EE2	EE3	EE4	EE5	EAG advisor
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60%
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56%
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46%

120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36%
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30%

dMMR – DNA mismatch repair deficiency; EAG – External Assessment Group; EE1-5 – External expert 1-5; MSI-H – Microsatellite instability high; PCC – Platinum-containing chemotherapy. Please note, external expert 4 was from Scotland.

Table 8: External Expert mean estimates and modelled PFS for EAG and Company base case for PCC

Months (years)	External expert' mean (n=6)	PCC PFS	
		EAG base case	Company base case
24 (2)	[redacted]	17%	17%
36 (3)	[redacted]	13%	13%
60 (5)	[redacted]	9%	9%
120 (10)	[redacted]	5%	5%
240 (20)	[redacted]	3%	3%

EAG – External Assessment Group; PCC – Platinum-containing chemotherapy; PFS – Progression-free survival

Table 9: External Expert mean estimates and modelled PFS for EAG and Company base case for dostarlimab in combination with PCC

Months (years)	External expert' mean (n=6)	Dostarlimab in combination with PCC PFS	
		EAG base case	Company base case
24 (2)	[redacted]	60%	61%
36 (3)	[redacted]	50%	57%
60 (5)	[redacted]	36%	51%

120 (10)	[redacted]	21%	44%
240 (20)	[redacted]	10%[#]	36%

EAG – External Assessment Group; PCC – Platinum-containing chemotherapy; PFS – Progression-free survival # - Note this percentage has been updated from Table 18 of the EAG report to reflect the updated cost effectiveness model estimate

Table 10: External expert 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 dostarlimab in combination with PCC

Months (years)	dMMR/MSI-H						
	Mean	EE1	EE2	EE3	EE4	EE5	EAG advisor
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80%
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50%
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20%
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10%
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8%

EE1-5 – External expert 1-5; dMMR – DNA mismatch repair deficiency; EAG – External Assessment Group; MSI-H – Microsatellite instability high; PCC – Platinum-containing chemotherapy. Please note, external expert 4 was from Scotland.

Table 11: External expert mean estimates and modelled OS for EAG and Company base case for dostarlimab in combination with PCC

Months (years)	External Expert mean (n=6)	Dostarlimab in combination with PCC OS	
		EAG base case	Company base case
24 (2)	[redacted]	86%	87%
36 (3)	[redacted]	75%	83%

60 (5)	[redacted]	52%	72%
120 (10)	[redacted]	24%	57%
240 (20)	[redacted]	10%	40%

EAG – External Assessment Group; MSI-H – Microsatellite instability high; OS – Overall survival; PCC – Platinum-containing chemotherapy.

Table 12: Updated EAG cost-effectiveness results

Incremental Costs (£)	Incremental QALYs	Deterministic ICER (£/QALY)
[redacted]	1.49	[redacted]

EAG – External Assessment Group; ICER – Incremental cost-effectiveness ratio; QALY – quality adjusted life year

Table 13: Summary of Grade ≥3 Treatment-Emergent Adverse Events in ≥2% of patients – Interim Analysis (ITT population)

Adverse event category	Dostarlimab in combination with PCC (N=241)	Placebo in combination with PCC (N=246)
Anaemia	36 (14.9%)	40 (16.3%)
Neutropenia	23 (9.5%)	23 (9.3%)
Neutrophil count decreased	20 (8.3%)	34 (13.8%)
Hypertension	17 (7.1%)	8 (3.3%)
White blood cell count decreased	16 (6.6%)	13 (5.3%)
Hypokalemia	12 (5.0%)	9 (3.7%)
Pulmonary embolism	12 (5.0%)	12 (4.9%)
Lymphocyte count decreased	13 (5.4%)	18 (7.3%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ITT – Intention-to-treat; PCC – Platinum-containing chemotherapy

Table 14: Additional ITT baseline characteristics

	ITT population dostarlimab in combination with PCC (N=245)	ITT population placebo in combination with PCC (N=249)	Total (N=494)
Mean (SD)	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Age Group, n (%)			
19-64	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]

BMI – body mass index; CP – Carboplatin plus paclitaxel; ITT – Intention-to-treat; kg – kilogram; m – meter; Q – quarter; SD- standard deviation
Source CSR Table 14.1.1.15

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer ID3968

Clinical expert statement

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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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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 31 October 2023.** 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 Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer

ID3968

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 and University of Manchester
3. Job title or position	Consultant and Honorary Senior Lecturer in Medical Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with endometrial cancer? ☐ A specialist in the clinical evidence base for <<this condition>> 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.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
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? (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. Progression-free survival is often a more important marker of treatment benefit.
10. In your view, is there an unmet need for patients and healthcare professionals in primary advanced or recurrent endometrial cancer ?	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 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, 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. This TA would result in dostarlimab being moved forward in the treatment algorithm so that is given as part of first-line treatment with chemotherapy.
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 a 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 at 24 months was also significantly higher in the dostarlimab arm (83% vs 59%; HR 0.30 in favour of dostarlimab). This improvement was seen despite 38% of participants in the placebo arm receiving immunotherapy after disease progression. The flat tail of the Kaplan-Meier progression-free survival curve 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. The reported benefits are likely to continue to be observed with additional follow-up.
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	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.

acceptability or ease of use or additional tests or monitoring needed)	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 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?	Yes. This is the first novel biomarker-directed therapy to be licensed as part of the first-line treatment of advanced/recurrent endometrial cancer. 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 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 impact of dostarlimab on HRQoL during the chemotherapy phase and also suggests improved quality of life during ongoing maintenance treatment with dostarlimab compared to placebo (Fig S6 Mirza et al 2023).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	It should be noted that in the last 12 months, 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 (LBA40 ESMO 2023 annual meeting- Colombo et al). 125 MMRd cases. HR0.36 median PFS; Atezo- not reached Placebo 6.9months

	Durvalumab- DUO-E (LBA 41 2023 ESMO 2023 annual meeting- Westin et al). MMRd- HR0.42 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.
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 • lead to recommendations that have an adverse impact on disabled people.	Nil specific.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

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

Carboplatin + paclitaxel chemotherapy is 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 reduces the chance of disease progression at 2 years by over 70% compared to placebo (HR 0.28) and increased 2-year overall survival by 24%.
Dostarlimab treatment has manageable adverse effects and was associated with improved quality-of-life.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer ID3968

Clinical expert statement

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Part 1: Treating Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer

ID3968

and current treatment options

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

1. Your name	Laura Tookman
2. Name of organisation	Imperial College Healthcare NHS Trust
3. Job title or position	Medical Oncology Consultant
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 Endometrial cancer? ☐ A specialist in the clinical evidence base for <<this condition>> 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.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for primary advanced or recurrent endometrial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Aim of treatment: The main aim of treatment in the recurrent setting is stop progression, shrink the cancer, improve progression free survival, maintain response, improve symptoms and lengthen the time until next treatment. A proportion of patients with primary advanced endometrial cancer have the potential to be cured with multimodality treatment (surgery, systemic anticancer treatment, radiotherapy). Optimal treatment in the first line setting is most likely to achieve the best long-term outcome and potential cure.
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)	I would consider a clinically significant treatment response in the following: - Radiological response based on RECIST criteria (30% reduction) - Marker response (for example, CA125) in those cancers that express tumour markers - Clinical response – improvement in symptoms, or performance status. - Ongoing stable disease (particularly those who have been previously progressing prior to treatment) can represent a benefit from treatment. - Duration of response, time without disease related symptoms, improvement in quality of life and prolonging time to next treatment also represents a benefit of treatment.
10. In your view, is there an unmet need for patients and healthcare professionals in primary advanced or recurrent endometrial cancer ?	In my opinion, there is an unmet need for patients with primary advanced and recurrent endometrial cancer. This view is based on the following: • Chance of relapse in advanced endometrial cancer is high and overall survival is poor. Stage IV disease has the poorest survival rate with 5-year survival of just 20%. There is a need to improve treatments in the first line setting to prevent relapse and improve overall survival and potential cure.

	• For those that relapse following initial platinum-based chemotherapy treatment, response rates to further cytotoxic treatment is low. This suggests that relapsed endometrial cancer post platinum chemotherapy is refractory to further standard chemotherapy treatments. Progression free survival in this patient population in real-world data has been reported as 7.7 months with survival of less than 12 months (Goulden S, et al. Int J Gynecol Cancer 2023). The chemotherapy control arms of a recent clinical trial in endometrial cancer that has progressed following carboplatin and paclitaxel chemotherapy highlights poor prognosis with chemotherapy treatment (Keynote 775 trial, N Engl J Med 2022; 386:437-448). There is no consensus for the standard second line chemotherapy treatment for recurrent endometrial cancer post platinum-based chemotherapy. • Taken together, in my view, there is an unmet need for new, more effective treatments in recurrent endometrial cancer. There is also a need for biomarker driven therapy. • Immune checkpoint inhibition is now entering the treatment landscape for endometrial cancer. Trials show a benefit of single agent immune checkpoint inhibition particularly in the mismatch repair deficient (dMMR)/ microsatellite instability (MSI)-high group (approximately 25% of endometrial cancers) in the treatment of endometrial cancer at the time of recurrent disease, following platinum-based chemotherapy. There is an unmet need to consider immune check-point inhibitor therapy earlier in the treatment pathway and to combine with standard of care chemotherapy.
11. How is primary advanced or recurrent endometrial cancer 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	<u>Clinical guidelines include:</u> British Gynaecological Cancer Society (BGCS) guidelines British Association of gynaecological pathologists (BAGP) guidance ESMO guidance ESGO-ESTRO-ESP NICE guidance including NICE diagnostics guidance 42

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NCCN Guideline for uterine neoplasms Regional and local guidelines **<u>Summary of current pathway of care in the NHS:</u>** All cases are managed by a multidisciplinary team and discussed at a specialist MDT meeting. <u>Primary advanced disease:</u> In the first line setting, the treatment pathway is determined by multidisciplinary discussion. Potential treatment options are influenced by pathology findings and stage of cancer (FIGO staging, including molecular markers) imaging findings (CT/MRI) along with patient fitness. Surgery is considered with the aim to completely remove all visible disease. In high-risk disease (including primary advanced disease), there a high chance of relapse and surgery should then be followed by chemotherapy +/- radiotherapy. If surgery is not deemed appropriate/not possible (particularly in stage 4 disease/ pattern of disease is not amenable to surgical resection), chemotherapy (carboplatin and paclitaxel) +/- radiotherapy is considered. Alternative treatments include hormone-based treatment in those with ER/PR receptor positive disease, if not candidates for chemotherapy. Following first line treatment, there is currently no maintenance treatment option. Patients would then enter a period of follow up and further treatment would be considered at the time of relapse/progression. <u>Recurrent endometrial cancer:</u> Treatment of relapsed/recurrent disease depends on previous treatments, location of disease, time from previous treatment, pathology of the cancer, molecular markers (MMR IHC, ER/PR receptor status) patient factors (fitness for treatment, other medical co-morbidities, patient preference) - Surgical resection/radiotherapy/ ablative therapy should be considered particularly if local disease or single site recurrent disease.

	- Systemic treatment options include chemotherapy (combination platinum-based chemotherapy, including carboplatin and paclitaxel) if not previously given or >6 months from last chemotherapy. Single agent chemotherapy (including weekly Taxol, doxorubicin) is an alternative particularly in those with likely 'platinum resistant' disease. There is no standard of care option in the second line setting, response rates to single agent regimes is poor (up to 20%, highest reported responses were with weekly Taxol).
	- MMR deficient/MSI high cancers previously treated with platinum- based chemotherapy are potential candidates for single agent Immune checkpoint inhibition:
	  o Dostarlimab (PD-1 inhibitor): Garnet trial. Technology appraisal guidance [TA779],
	  o Pembrolizumab (PD-L1 inhibitor): Keynote 158 trial. Technology appraisal guidance [TA914].
	- The combination of pembrolizumab and lenvatinib: Keynote 775 trial, Technology appraisal guidance [TA904] is an option in those previously treated with platinum-based chemotherapy or patients with MMR deficient and MMR proficient cancers.
	- Endocrine treatment (such as high dose progesterone) – for those with ER/PR disease
	- Palliative surgery/radiotherapy can be considered alone or in conjunction with systemic treatment options
	
	<u>Impact of proposed technology on current pathway of care:</u>
	Dostarlimab is an immune check point inhibitor that targets the PD-1 receptor. Current technology would add dostarlimab to standard of care carboplatin and paclitaxel chemotherapy and then dostarlimab in maintenance (every 6 weeks for 3 years) in newly diagnosed advanced (stage III/IV) dMMR endometrial cancers. In relapsed dMMR endometrial cancer, dostarlimab is added to carbopatin paclitaxel chemotherapy for those who are chemotherapy naïve or

	who have had >6months chemotherapy free interval. This would alter the treatment options in this setting. Addition of dostarlimab would not change the diagnostic pathway or requirement for surgery/chemotherapy (and radiotherapy) and therefore pathway of care would be similar. Dostarlimab would, however, lead to extra treatment as it is also given as maintenance (6 weekly for up to 3 years) in the first line setting. The proposed technology reinforces the requirement of MMR IHC (NICE DG 42).
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)	Chemotherapy and dostarlimab are given by a team trained to administer anticancer treatment in a specialist chemotherapy unit. Immune check point inhibitor therapy is standard of care in many cancers and there is experience using dostarlimab in the NHS for endometrial cancer as single agent. There is, therefore, experience within oncology units in preparation, administration and management of side effects. Further training might be required and patient education around side effect management is important. The addition of dostarlimab to chemotherapy and then in maintenance will require resource and extra hospital visits for the patient. Routine care following chemotherapy for advanced/relapsed endometrial cancer would involve patients entering a period of follow up. Administering dostarlimab in the maintenance setting will require patients to attend a chemotherapy unit every 6 weeks for up to 3 years and have more frequent blood tests/clinical reviews.
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?	I expect the addition of dostarlimab to chemotherapy and then in maintenance to have clinically meaningful benefits compared with current care of chemotherapy treatment. This technology has the potential to increase length of life and health-related quality of life in this group of patients with MMR deficient/MSI-high advanced/relapsed endometrial cancer. This view is based on the evidence reported from the Ruby trial (N Engl J Med 2023;388:2145-68). This phase 3 double-blind randomised, placebo-controlled

	trial randomised patients with advanced (stage III or IV) or first recurrent endometrial cancer to: (a) standard of care carboplatin and paclitaxel chemotherapy (and placebo) for 6 cycles every 3 weeks followed by placebo every 6 weeks or (b) carboplatin paclitaxel and dostarlimab (500mg) for 6 cycles every 3 weeks followed by dostarlimab (1000mg) maintenance treatment iv, 6 weekly for 3 years. 118 patients that underwent randomisation (23.9%) had mismatch repair deficient (dMMR) or MSI-H tumours (the population targeted by this appraisal). In this population 50% had recurrent disease, 20.3% primary stage III and 29.6% had primary IV disease. Majority (>80%) had endometrioid histology, remainder had serous, carcinosarcoma or mixed histology. - Progression free survival in the dMMR group at 24 months was 61.4% (95% CI, 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (HR 0.28 P<0.001). Median PFS in the dMMR group had not been reached. The probability of duration of response (DOR) at 24 months was 62.1 % (44.4–75.5) in the dostarlimab group and 13.2 % (4.6–26.3) in placebo. Quality of life outcomes/patient reported outcomes have also been reported and suggest a benefit with the addition of dostarlimab treatment at end of treatment (ESMO Congress 2023, (Abstract 749P)) and no deterioration with the addition of dostarlimab during chemotherapy. - With 25.4 months of follow-up, a trend was seen showing an improvement in overall survival in the group treated with dostarlimab. Overall survival in the patients with dMMR/MSI-H tumours at 24 months was 83.3% (95% CI 66.8-92) in the dostarlimab group and 58.7% (95%, 43.4 to 71.2) in the placebo group (HR 0.30; 95% CI, 0.13 to 0.70). Updated results are awaited to establish longer-term outcomes particularly to determine overall survival benefit and duration of response and to establish benefits across subgroups, particularly those with stage III disease. Durable benefit of dostarlimab treatment has, however, been demonstrated as second line single-agent therapy in patients with advanced or recurrent dMMR endometrial cancer who have progressed following platinum chemotherapy in the GARNET clinical trial. To my knowledge, at this current time, there is no published randomised trial data comparing combination chemo + immune

	checkpoint inhibitor with chemotherapy free immunotherapy-based regimes in the first line or recurrent disease setting.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on the data to date, treatment appears to have the greatest effect in MSI high/ MMR deficient cancers. This is the population that is targeted by this appraisal. Further research is required to determine whether the pattern of protein loss is important to determine efficacy and whether there are other markers that determine treatment effectiveness particularly in the MMR proficient endometrial cancer group. It is also important to establish the relative benefit in stage III, stage IV and recurrent disease, in those previously treated with chemotherapy, measurable disease and non-measurable disease and the role of radiotherapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The addition of dostarlimab to chemotherapy treatment has a potential impact on service delivery, particularly when given in primary advanced disease where the standard of care would be chemotherapy alone. This would include - Longer chair time at the time of chemotherapy administration (extra 30min infusion) - To administer dostarlimab in maintenance in the first line setting: Increased clinical reviews, Increased visits for treatment administration (requirement of chair time on a chemotherapy unit, need for cannula/vascular access, drug handling by pharmacy, chemotherapy nurse time, need for additional blood tests) - Need to educate healthcare professionals and patients regarding the possible treatment related side effects and how to manage these. However, the addition of dostarlimab could delay/prevent further recurrence in the future and reduce the need for further chemotherapy treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligible patients will be identified according to stage (imaging or pathological stage) and by routine histology and immunohistochemistry for the mismatch repair proteins (NICE diagnostics guidance 42), additional testing is therefore unlikely to be required.

	Treatment response and toxicity is monitored by clinical review, bloods and imaging (CT scans/ MRI). As a result, increased clinical reviews, bloods and scans are likely to be required when comparing dostarlimab maintenance treatment with routine standard of care (standard of care follow up includes clinical reviews every 3-6 months). Dostarlimab is given for 3 years as maintenance treatment. Guidelines exist on the management of toxicity due to immune checkpoint inhibitor therapy and when to stop treatment due to toxicity.
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	
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?	I consider that the addition of immune checkpoint inhibitor therapy represents a step change in the management of MMR deficient primary advanced endometrial cancer. The addition of dostarlimab, guided by biomarkers, addresses an important unmet need in the management of advanced/relapsed endometrial cancer.
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?	Adverse events: There were a higher number of treatment-related adverse events in the dostarlimab arm of the Ruby trial (70.5% vs 59.8%). 17.4% of patients in the dostarlimab group discontinued treatment due to an adverse event compared with 9.3% in the placebo group. The frequency of discontinuation of chemotherapy was similar in both groups, suggesting that the addition of dostarlimab does not compromise the amount of chemotherapy given.

	Management of immune mediated adverse events is well established (supportive care, treatment interruption, use of steroids) and unlikely to affect the management of the condition. In a small proportion of cases, side effects and their management can impact quality of life and require longer term treatment. Quality of life: During the time on chemotherapy the mean change in baseline in EORTC-QLQ-C30 global health status and quality of life scores showed no difference between the chemotherapy +placebo and chemotherapy + dostarlimab group. Further data presented at ESMO Congress 2023, (Abstract 749P) demonstrated that quality of life measures show improvements with dostarlimab versus placebo in the change from baseline to end of treatment.
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?	The control arm of the trial (carboplatin and paclitaxel chemotherapy) reflects current UK practice in the treatment of primary advanced endometrial cancer. Although there is no established standard of care for chemotherapy in recurrent endometrial cancer following platinum-based chemotherapy, the combination of carboplatin and paclitaxel is an option in patients >6months from previous chemotherapy treatment. In this setting, in MMR deficient cancers, other options for treatment include single agent immune checkpoint inhibitor therapy with dostarlimab or pembrolizumab or the combination of pembrolizumab and lenvatinib. At the present time, there are no trial data comparing these options. The demographics of the population within the trial were slightly different to the population that would be expected in a UK setting (for example the median age in the trial was younger than in a real-world population). <u>Outcomes:</u> In my view, the most important end point is overall survival. Progression free survival is important but cannot always be used as a surrogate for overall survival. The primary end point of progression free survival in the Ruby trial was

	met and there is a trend for improved overall survival (further data awaited). Quality of life and patient reported outcomes are also particularly important as patients have advanced cancer and could be receiving treatment for many years; these outcomes were the secondary endpoints in the trial. Adverse events: Immune checkpoint inhibitor therapy is established in the treatment of a variety of cancers and there is longer follow up for other agents. Rare immune mediated adverse events have been reported following longer term follow up with other immune checkpoint inhibitors.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Other than recent data presented at congress (for example ESMO Oct 2023), I am not aware of other evidence not found by systematic review of the trial evidence. Further evidence will also be obtained by the opened EAMS.
22. How do data on real-world experience compare with the trial data?	Data on real world outcomes highlights the poor outcomes of advanced and relapsed endometrial cancer and the poor responses to second line chemotherapy treatment. This is also demonstrated in the control arm of more recent randomised clinical trials including the Ruby trial. Many real-world outcome data sets do not include MMR IHC data and therefore it is difficult to compare real-world data confidently and accurately with the data with the clinical trial data. Real-world experience in a range of cancers, however, supports the finding that immune check-point inhibitor therapy is tolerable and side effects can be managed and there are durable long-term responders. To my knowledge, there is no real-world data evaluating different immune checkpoint inhibitor therapy/ combinations of treatment in advanced 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.	Treatment should be offered to all those eligible based on biomarkers.

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.	

Part 2: Key messages

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

Advanced or recurrent endometrial cancer has a poor prognosis and there is a clear unmet need to improve treatment and outcomes for this population.
Ruby trial demonstrates a clinically meaningful and significant improvement in progression free survival for patients with MMR deficient advanced/recurrent endometrial cancer treated with dostarlimab together with chemotherapy and then in maintenance compared with chemotherapy.
Dostarlimab treatment is well tolerated
Evidence supports the use of dostarlimab in dMMR/MSI-high advanced or recurrent endometrial cancer.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer [ID3968]

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 endometrial cancer or caring for a patient with endometrial cancer. 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).

NICE National Institute for Health and Care Excellence

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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 17 November 2023.** 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, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer [ID3968]

Part 1: Living with this condition or caring for a patient with endometrial cancer

Table 1 About you, endometrial cancer, current treatments and equality

1. Your name	Helen White
2. Are you (please tick all that apply)	☐ A patient with endometrial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with endometrial cancer? ☒ A patient organisation employee or volunteer? ☒ Other (please specify): An individual with previous experience of endometrial cancer
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
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 endometrial cancer? **If you are a carer (for someone with endometrial cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for endometrial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for advanced or recurrent endometrial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of dostarlimab 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 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	
10. If there are disadvantages of dostarlimab over current treatments on the NHS please describe these. For example, are there any risks with dostarlimab? If you are concerned about any potential 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 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	
12. Are there any potential equality issues that should be taken into account when considering endometrial cancer and dostarlimab? 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	

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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:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer [ID3968]

Patient expert statement

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Patient expert statement

Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer [ID3968]

Part 1: Living with this condition or caring for a patient with endometrial cancer

Table 1 About you, endometrial cancer, current treatments and equality

1. Your name	Sue Woodburn
2. Are you (please tick all that apply)	☒ A patient with endometrial cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with endometrial cancer? ☐ 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
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 endometrial cancer? **If you are a carer (for someone with endometrial cancer) please share your experience of caring for them**	I was diagnosed in October 2021 following a traumatic hysteroscopy that led to me having a GA to stop the bleeding. I went on to have an abdominal hysterectomy. This was graded as Grade 3 stage 3a. I had six rounds of chemotherapy (carboplatin and paclitaxel) followed by 25 external beam radiotherapy sessions. This all finished in July 2022. In February I was diagnosed with a recurrence at the top of the vagina. I was initially offered quite extensive and radical surgery. After completing all the associated tests and examinations three days before the planned surgery they discovered the tumour had become inoperable and surgery was cancelled. I was completely devastated and felt I had been handed a death sentence. Further scans showed spread to the lungs. I was then referred back to oncology. At this point I was given a list of possible of options, one of which included my oncologist applying for patient led funding to access Dostarlimab. This gave me some hope but the wait to find out if the application had been successful was horrendous. I was fortunate. This new drug gave me the first glimmer of hope in a long time. Prior to this I didn't expect to see Christmas? I went on to have six rounds of the previous chemo alongside Dostarlimab. I have since had two standalone Dostarlimab treatments. My last two scans have shown a reduction in the size of the tumour in the vagina and the lung nodules are no longer visible. I am due another Dostarlimab on Thursday 23rd. November. The two years since I was diagnosed have been really hard. Hard for family, and for me. They have already lived through my breast cancer diagnosis and I think they knew that this time I wasn't as hopeful. The surgery was harder, the recovery longer. I couldn't do any of my normal activities for months. The radiotherapy was

	longer (every day, a 70mile trip for five weeks), with more intensive side effects, (which are still affecting me). The chemotherapy had a greater impact on me. The side effects were worse and for longer. Psychologically it is harder. The success rate is lower, and we all knew this. The treatments are less well managed and less effective. My elderly parents have really struggled. We are a close family with my sons and their wives and grandchildren all nearby, we ski together, we holiday together, we all have camper vans for weekends away in Southern Scotland and the Lakes, we mountain bike together. This has had a huge impact on all of us. I never saw my husband or sons cry through the breast cancer treatment, but we've all been so much more emotional this time. More needs to be done to raise the profile of endometrial cancer with a message of hope which I believe this new drug could achieve.
7a. What do you think of the current treatments and care available for endometrial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I found it a very different experience to when I had breast cancer in 2014. That was a much joined up service that felt supportive and caring. A one stop shop! With endometrial cancer I felt I was constantly waiting for answers. I was being seen by so many different people in different places, ranging from Kendal, Chorley, Preston and Lancaster with associated travel and long waits. I have an amazing Macmillan Nurse who has actually been considerably better than the breast cancer one. Thank goodness. I don't know what I would have done without her; she has been a valuable link with all the services I've been involved with. The current treatments are brutal, I've had three lots of six chemo now and the last six hit me hard, I had a week when I didn't leave the house I felt so awful. I was a fit and active 64 yr. old with four grandchildren. I ski, mountain bike and play tennis. I'm not used to being still! I found it a lonely experience. Even on social media there is limited UK networking, very unlike breast cancer. I never felt despair when I had breast cancer, I was always assured that there many different treatment options. So very different from endometrial cancer. I was told

	that this time chemo might not be effective as I have had it before ad my recurrence occurred quickly. I lost all hope. I really thought I was going to die in months.
8. If there are disadvantages for patients of current NHS treatments for advanced or recurrent endometrial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The current treatments are brutal; you lose a week of your life every three weeks. A week where it is impossible to be 'normal'. The steroids alter your appearance, you lose your hair and eyebrows and eyelashes, and you lose your identity! You lose your femininity. You are scared, scared to see people because of how you look, scared of infection, scared to hug your grandchildren. Isolated. Unable to travel. I was a successful headteacher for twenty years, I am now on anti-depressants for anxiety, something that I thought would never happen to me, that's what the treatment and lack of hope do to you.
9a. If there are advantages of Dostarlimab 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 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**	Although the negative effects of chemotherapy still apply to this treatment, the Dostarlimab gave me optimism. Now I have finished the chemo part I am nearly back to normal. I am able to travel (just back from Rome), I'm biking again and back to tennis. It's given me a confidence in the future; I've booked a skiing holiday for January, which is amazing as I actually thought I'd be dead by then! **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. My appearance is improving, my hair is growing back. The treatment is 30minutes rather than eight hours! Hope is the most important, an option when other doors are closing. Dostarlimab addresses all the disadvantages of current treatment, the current treatment makes you ill!! Dostarlimab helps your progression free survival!
10. If there are disadvantages of Dostarlimab over current treatments on the NHS please describe these. For example, are there any risks with Dostarlimab? If you are concerned about any potential side affects you have	A slight fear of the unknown. I haven't come across anyone else on this treatment so it can feel a lonely place.

heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Dostarlimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients were radiotherapy for recurrences isn't an option (as in my case). Where surgery isn't possible anymore.
12. Are there any potential equality issues that should be taken into account when considering endometrial cancer and Dostarlimab? 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:

- Hope of a future.
- A treatment that allows you to live a near normal life
- An option when all others have failed.
- Optimism for improved outcomes for women with endometrial cancer.
- Greater treatment choices

Thank you for your time.

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Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Dostarlimab with carboplatin and paclitaxel for treating recurrent or advanced endometrial cancer**
Topic ID: **3968**
Managed Access Lead: **Catrin Austin**
Date of assessment(s): **13/10/2023**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Yes	This appraisal could benefit from additional data collection to resolve uncertainties in long term data. Current OS estimates are immature but are likely to be mature within 2 years. This data can be retrieved from the ongoing RUBY trial that supports the company submission. The trial has a small population and this is making it difficult to assess effectiveness in important subgroups. Further data collection through the trial may address some of this uncertainty by getting more events. Alternatively, SACT could be used to validate some outcomes, such as adverse events, or provide more data on usage, costs and effects of subsequent therapies within UK practice.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	This technology is eligible for the Cancer Drugs Fund
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Yes	Uncertainties around long-term data and generalisability can either be fully resolved or partially resolved with further data collection from the RUBY trial and SACT.
Can data collection be completed without undue burden on patients or the NHS system	Yes	Collecting data on survival outcomes and generalisability would not create a burden on the system or patients.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	No other barriers identified.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	How long would data collection need to be to sufficiently resolve uncertainties?
2	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	This technology is eligible for the Cancer Drugs Fund

IMF* prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	Carboplatin plus paclitaxel currently only option in this line. Unmet need arises from this regimen being poor in delaying or preventing recurrence.
Potential to provide significant clinical benefits to patients	Company submission shows large QALY gain over carboplatin plus paclitaxel, but unknown vs pembrolizumab plus lenvatinib.
represents a step-change in medicine for patients and clinicians	Dostarlimab is an immunotherapy; it would be a step-change from platinum-based chemotherapy.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	Evidence generation could resolve uncertainties.

*** Noting the IMF criteria do not apply to for selection of CDF topic eligibility, they are applied for internal use only by the NICE Managed Access team.**

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Grouo (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	Uncertainties around long-term data can either be fully resolved or partially resolved with further data collection from the RUBY trial and generalisability to UK practice can be somewhat resolved through SACT.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
COMP1	Long term OS efficacy	Current OS within RUBY is relatively immature. An extra 1-2 years of data will provide mature data.	TBC	Unquantified	Longer term OS data	RUBY trial	High	Data maturity is expected within 1-2 years. Data cuts are event driven. Cuts are expected roughly annually but have no definite date and are subject to change.

EAG2	Suitability of RUBY data for estimating benefit of dostarlimab+CP	RUBY trial has small sample size and limited follow-up, randomisation issues, lower average age at recruitment and lack of data to allow exploration of subgroups described in the decision problem.	Increasing the age at baseline to 67.1 years as this was supported by several alternative literature sources and EAG clinical expert opinion. The EAG could not resolve the other limitations.	Medium	Longer follow-up with larger sample size	RUBY trial	Medium	Longer term data could resolve some of the uncertainty but the other limitations in this key issue would need a new trial, or otherwise cannot be resolved through data collection.
EAG3	Lack of efficacy in people with stage III disease	The EAG notes a lack of efficacy in RUBY-1 study among people with stage III disease. This effect is persistent across the dMMR/MSI-H and MMRp subgroups. It is unknown if this a chance finding.	The EAG has not been able to exclude these patients from the clinical or cost-effectiveness analyses.	Unquantified	Longer follow-up and data generation specifically designed to address this issue	RUBY trial	Medium	Novel data generation has not been suggested and therefore only data from the RUBY trial would be available.
EAG4	Uncertain degree of progression-free survival benefit	The company models a substantial benefit of progression-free survival for dostarlimab which is sustained for the duration of the model.	The EAG has selected a different approach to extrapolating PFS of dostarlimab+CP, using a Weibull plus equal hazard extrapolation.	Medium	Longer follow-up	RUBY trial	High	The EAG regard the extrapolations as inconsistent with the current available data. Further data may resolve this uncertainty.
EAG5	Uncertain degree of overall survival benefit	The company models a substantial survival benefit for dostarlimab which is sustained for the duration of the model.	The EAG use a different approach for extrapolation of OS.	High	Longer follow-up	RUBY trial	High	The EAG regard the extrapolations as inconsistent with the current available data. EAG converges the hazard rates over a 3-year period from 80 weeks in the dostarlimab arm. This could be reanalysed within a period of managed access as well as further data be obtained that could reduce the uncertainty by shortening the length of extrapolation.
EAG6	Unknown usage, costs and effects of subsequent therapies	Robust information on subsequent treatment use is not available. RUBY data is immature and may not be generalisable to England.	The EAG explores some scenarios varying the costs of subsequent therapies.	Low	Data from UK practice	SACT	Medium	Data from SACT may provide some data on subsequent therapies within UK practice but within a rare disease it may not fully resolve the uncertainty.

EAG7	Underrepresentation of Adverse Events	The current limited follow-up and sample size mean it is likely that AEs are under-reported and their impact underestimated in the company's base case. The risk of immune related adverse events is associated with additional patient monitoring, which is not captured in the company's base case.	The EAG applies AE disutilities for a broader profile of adverse events at grade 3 and above and incorporates additional monitoring costs into the EAG base	Medium	Longer follow-up and data from UK practice on adverse events	RUBY trial and SACT	High	Data from SACT may provide some data on adverse events within UK practice but within a rare disease it may not fully resolve the uncertainty. Continued monitoring within the trials should further reduce uncertainty.
MAT2	Risk convergence after treatment discontinuation stopping rule	The company have completed scenario analyses exploring a continuing treatment effect after treatment discontinuation. Values are based on clinical expert input.	EAG converges the hazard rates over a 3-year period from 80 weeks in the dostarlimab arm. This could be assessed within a period of managed access.	Low	Long- and very long-term data	RUBY trial	Medium	Longer term data could resolve some of the uncertainty. But if the 3-year assumption is too short, very long term data (5+ years) will not be available to fully resolve this uncertainty.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	RUBY is an ongoing trial relevant to this appraisal.

Clinical trial data	
Anticipated completion date	Dec-26
Link to clinicaltrial.gov	https://classic.clinicaltrials.gov/ct2/show/NCT03981796
Start date	Jul-19
Data cut presented to committee	Sep-22
Link(s) to published data	Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer | NEJM
Description of trial	This is a 2 part, phase 3 study. Part 1 is relevant to this appraisal and is evaluating the efficacy and safety of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus placebo plus carboplatin-paclitaxel followed by placebo. Primary outcomes are PFS and OS.

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	Data collection in clinical practice would be feasible using SACT.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS Digital's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS Digital have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHS Digital have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS Digital have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS Digital's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSD, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	-
Analyses		

How easily could collected data be incorporated into an economic model	High	Individual-level patient data is available for the economic model. Subgroups of interest should be identified at the point of managed access entry so all relevant analyses can be produced.
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	-
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Not applicable	-
Patient consent	Yes	No prior patient consent required
Funding		
Existing funding	Yes	Established partnership between NHS England and NHS Digital
Additional funding required for MA	No	-
If yes, has additional funding been agreed in principle	Not applicable	-
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		

Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	-

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	No barriers identified.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access
	Expected overall additional system burden from data collection?	Low	As above
	Do stakeholders consider any additional burden to be acceptable	Not applicable	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative drugs fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	Dostarlimab for cancer is already available in the NHS
	Will implementation subject the NHS to irrecoverable costs?	No	
	Is there an existing service specification which will cover the new treatment?	Yes	Complex Gynaecology -Specialist Gynaecological Cancers

		Rating	Rationale / comments

Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that the entire eligible patient population, as recommended by NICE, will be able to access the medicine. Detailed blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	-

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	As above
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There is not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access