Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

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 AstraZeneca

2. **Company summary of information for patients (SIP)** from AstraZeneca

3. **Clarification questions and company responses**
   a. Clarification response
   b. Response to additional clarification questions

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

5. **Expert personal perspectives** from:
   a. Dr Gemma Eminowicz – clinical expert, nominated by NICE
   b. Helen White – patient expert, nominated by Peaches Womb Cancer Trust
   c. Grace Teeling – patient expert, nominated by Peaches Womb Cancer Trust

6. **External Assessment Report** prepared by BMJ Technology Assessments Group

7. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for newly diagnosed advanced or recurrent EC [ID6317]

Document B

Company evidence submission

October 2024

File name	Version	Contains confidential information	Date
DUO-E in EC [ID6317]_Document B_2ndOctober24 [REDACTED]	FINAL	**No**	Submitted 2nd October 2024 (confidentiality marking updated 21/02/2025)

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Tables and figures

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Abbreviations

Abbreviation	Definition
ADR	Adverse drug reactions
AE	Adverse event
AEPI	Adverse event of possible interest
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AIHA	Autoimmune haemolytic anaemia
AML	Acute myeloid leukaemia
AUC	Area under the curve
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BMI	Body mass index
BNF	British National Formulary
BRCA1	Breast cancer susceptibility 1
BTC	Biliary tract cancer
CA	Cancer antigen
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPH	Cox proportional hazards
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DCO	Data cut-off
DCO1	Primary data cut-off
dMMR	Mismatch repair deficient
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSU	Decision Support Unit
EBRT	External beam radiation therapy
EC	Endometrial cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module

EQ-5D	European Quality of Life scale-5-Dimensions
EQ-5D-3L	European Quality of Life scale-5-Dimensions-3-Levels
EQ-5D-5L	European Quality of Life scale-5-Dimensions-5-Levels
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FIGO	International Federation of Gynecology and Obstetrics
GFR	Glomerular filtration rate
GP	General practitioner
HCC	Hepatocellular carcinoma
HCRU	Health care resource use
HER2	Receptor tyrosine-protein kinase erbB-2
HR	Hazard ratio
HRQoL	Health-related quality of life
HRRm	Homologous recombination repair mutation
HSE	Health Survey of England
HSU	Health state utility
HSUV	Health state utility values
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IPD	Individual patient data
IQR	Interquartile range
IRP	International recognition procedure
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response
IWRS	Interactive web response
KM	Kaplan–Meier
LYG	Life years gained
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndrome
MHRA	Medicines and Healthcare Products Regulatory Agency
MMR	Mismatch repair
MMRM	Mixed model for repeated measures
MSI	Microsatellite instability
MSS	Microsatellite stable
MTP	Molecular tumour profiling
NGS	Next-generation sequencing
NHSCII	NHS Cost Inflation Indices
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer

NSMP	No specific molecular profile
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PARP	Poly ADP ribose polymerase
PD	Progressed disease
PDL1	Programmed cell death ligand 1
PF	Progression-free disease
PFS	Progression-free survival
PFS2	Second progression-free survival
PGI-TT	Patient Global Impression of Treatment Tolerability
PH	proportional hazards
pMMR	Mismatch repair proficient
PRCA	Pure red cell aplasia
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RMST	Restricted mean survival time
RoW	Rest of the world
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
TA	Technology appraisal
TAP	Cisplatin, doxorubicin and paclitaxel
TCGA	The Cancer Genome Atlas
TDT	Time to study treatment discontinuation or death
TFST	Time to first subsequent therapy
TKI	Tyrosine kinase inhibitor
TNF-alpha	Tumour necrosis factor alpha
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TSST	Time to second subsequent therapy
TTE	Time-to-event
UK	United Kingdom
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening

US	United States
USD	United States Dollars
VAS	Visual analogue scale
WTP	Willingness-to-pay

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

B.1.1 Decision problem

This submission focusses on the use of two separate regimens in two separate target patient populations:

- Durvalumab in combination with platinum-based chemotherapy (carboplatin + paclitaxel), followed by maintenance durvalumab (**SoC + D**) for patients with newly diagnosed advanced or recurrent endometrial cancer (EC) that is mismatch repair (MMR) deficient (**dMMR**); and
- Durvalumab in combination with platinum-based chemotherapy (carboplatin + paclitaxel), followed by maintenance durvalumab with olaparib (**SoC + D + O**) for patients with newly diagnosed advanced or recurrent EC that is MMR proficient (**pMMR**).

The target populations are narrower than the National Institute for Health and Care Excellence (NICE) final scope, to align with the expected full marketing authorisations for durvalumab and olaparib in the EC indication, as detailed below.

- Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:
    - Durvalumab as monotherapy in EC that is dMMR
    - Durvalumab in combination with olaparib in EC that is pMMR
- Olaparib in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

The proposed positioning of each regimen is further supported by the results of subgroup analyses of the pivotal DUO-E trial, as detailed in Section B.2.7, and expected use of each regimen in clinical practice (Section B.1.3.2.6).[1]

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

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission		Rationale if different from the final NICE scope
Population	People with newly diagnosed advanced or recurrent EC	People with newly diagnosed advanced or recurrent EC that is dMMR	People with newly diagnosed advanced or recurrent EC that is pMMR	Aligned with the expected marketing authorisations for durvalumab and olaparib in the EC indication and the expected use of SoC + D and SoC + D + O in United Kingdom (UK) clinical practice.[1]
Intervention(s)	Durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with or without olaparib.	Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab (SoC + D)	Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC + D + O)	Aligned with the expected marketing authorisations for durvalumab and olaparib in the EC indication. Further details are provided in Sections B.1.3.6–B.1.3.7.
Comparator(s)	• Platinum-based chemotherapy (such as paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide) followed by routine surveillance • Hormone therapy (such as medroxyprogesterone acetate and megestrol)	Platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance (standard of care [SoC]) for both dMMR and pMMR populations.		The final NICE scope proposes that hormone therapy is a relevant comparator for patients newly diagnosed with advanced or recurrent EC that is pMMR or dMMR. The Company do not consider that this is a relevant comparator for the following key reasons: • **Hormone therapy in the first-line setting is only considered in a small minority of EC cases**. As stated in section 9.2 of the British Gynaecological Cancer Society (BGCS) guidelines, hormone therapy is only recommended as an alternative option in the palliative setting and is mainly suitable for patients with low grade, hormone sensitive tumours, and for patients where chemotherapy may not be well-tolerated (such as those who are older with multiple comorbidities). Furthermore, these recommendations are supported by Grade C evidence, and it is explicitly stated that there is “no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival (OS)”.

			• **Patients who would receive hormone therapy would not be suitable for SoC + D or SoC + D + O**. Given that hormonal therapy is only usually considered for the minority of patients who are not suitable for chemotherapy, SoC + D and SoC + D + O (which both include chemotherapy) would not be considered an appropriate option for these patients. This is reflected in the DUO-E trial (which represents the primary evidence base for SoC + D and SoC + D + O), which specifically enrolled patients who exhibited good performance status. • **There is no precedent for the consideration of hormone therapy as a relevant comparator in the setting proposed in this submission**. In the recent NICE appraisal of dostarlimab with platinum-based chemotherapy [TA963] in the first-line setting for advanced or recurrent EC that is dMMR, hormone therapy was not listed as a comparator in the final scope. Hormonal therefore should therefore not be considered a comparator in this appraisal within the same setting. In summary, the only appropriate comparator for this appraisal (for both the dMMR and pMMR populations) is platinum-based chemotherapy followed by routine surveillance, which is currently recommended as the first-line SoC in this setting.[2]
Outcomes	• Progression-free survival (PFS) • OS • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life.	As per the NICE final scope	N/A
Subgroups to be considered	• MMR status (MMR-deficient or MMR-proficient) • Level of PD-L1	• Mismatch repair (MMR) status (MMR-deficient or MMR-proficient). • Within the intention-to-treat (ITT)	As detailed above, the focus of this submission will be subgroups by MMR status (pMMR and dMMR), to align with the expected full marketing authorisations for olaparib and durvalumab in the EC indication and the expected use of SoC + D and SoC + D + O in

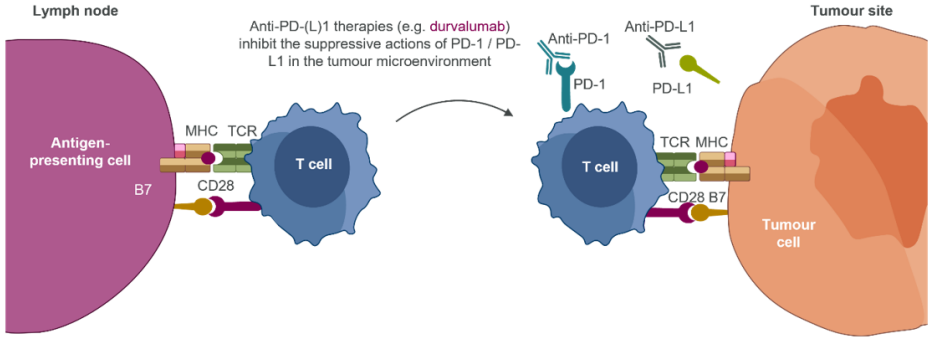
	expression • Local vs. metastatic recurrence • People who have had primary debulking surgery vs. those who have had not had surgery	population, a range of other prespecified subgroups are presented, including analyses by PD-L1 status.	clinical practice. The company have also presented a range of pre-specified subgroup analyses within the ITT, to demonstrate the consistent effect of SoC + D and SoC + D + O irrespective of key demographic and disease-related baseline characteristics. However, the Company do not consider that additional economic analyses which sub-divide the MMR subgroups would aid decision making or reduce uncertainty within this appraisal. This is because the DUO-E trial was not powered to perform these types of analyses, and such 'subgroups-within-subgroups' would have very limited sample sizes. Therefore, the results of such analyses would not be sufficiently robust to inform decision-making. Additionally, these analyses were not stratified, and so would be subject to potential imbalances in baseline characteristics which risks confounding the results. Finally, some of the suggested analyses in the final scope lack appropriate clinical/biological evidence to warrant their implementation. **PD-L1** As part of these pre-specified subgroup analyses in the ITT, the Company will present subgroups according to PD-L1 status (as per the NICE final scope). However, these analyses should not be a core focus of the appraisal for several reasons. Firstly, PD-L1 status was not a stratification factor in the DUO-E trial, and PFS analyses by PD-L1 status were only exploratory (i.e., the DUO-E trial was not powered for this analysis). Secondly, as discussed further in Section B.1.3.2.6, the clinical significance of PD-L1 expression in EC is currently unclear. Specifically, evidence surrounding PD-L1 status as a prognostic marker for survival is inconclusive. There is also inconsistent evidence regarding whether PD-L1 expression is a driver or predictor of response to currently available treatments in EC.[3, 4] It is possible that any observed impact of PD-L1 status could in fact simply represent a high correlation with other biomarkers. The Company therefore consider that MMR status should be the primary focus of the appraisal, given that the implications of MMR status are well-established, and given that this biomarker is already routinely

			measured and used to inform clinical practice in the UK for EC patients. Other subgroups listed in the final scope are not presented in the Company Submission due to the following limitations which affect the feasibility and reliability of such analyses for decision making: **Local vs. metastatic recurrence:** The DUO-E trial enrolled patients with newly diagnosed EC as well as those with recurrent disease (this classification was a stratification factor). Within the newly diagnosed cohort, the Company presents a subgroup analysis according to International Federation of Gynecology and Obstetrics (FIGO) stage, (which provides details on the extent of local or distant metastatic spread of the tumour). However, within the subgroup of patients with recurrent disease, there was no further subgroup analysis conducted to further segment such patients into local or distant sites of recurrence. Eligibility criteria for the DUO-E trial specified that patients with recurrent disease must have a poor potential for cure by surgery alone or in combination. For this reason, such patients were already pre-selected to have a similar baseline prognosis, and further subgroup analyses according to specific site(s) of recurrence will not be informative. **With or without primary debulking:** Across the three treatments arms in the DUO-E trial, only a small proportion (13.4% to 16.2%) received no prior surgery. The reliability of such a subgroup analysis would therefore be limited by small sample sizes. Furthermore, the decision to offer primary debulking surgery is based on multiple clinical tumour characteristics, as well as subjective local and regional clinician preferences. This would confound the results of such an analysis and limit its value for decision-making.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with durvalumab and olaparib are presented in Table 2 and Table 3, respectively.

Table 2: Technology being appraised (durvalumab, relevant for SoC + D and SoC + D + O)

UK approved name and brand name	Durvalumab (Imfinzi®)
Mechanism of action	Durvalumab, an immunotherapy, is an anti-programmed cell death ligand 1 (PDL1) monoclonal antibody.[5, 6] PD-L1 is a protein that disguises cancer cells from the immune system. Durvalumab binds to and blocks PD-L1, enabling the immune system to find and attack cancer cells (Figure 1).[6, 7] **Figure 1. Durvalumab mechanism of action: PD-L1 blockade**  **Source:** Buchbinder 2016.[8]
Marketing authorisation/ CE mark status	A marketing authorisation submission to the Medicines and Healthcare Products Regulatory Agency (MHRA) has been submitted via the international recognition procedure (IRP). MHRA marketing authorisation is expected in October 2024.

Indications and any restriction(s) as described in the SmPC	**Indication(s) of interest to this evaluation:**
	• Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:
	  • Durvalumab as monotherapy in EC that is dMMR.
	  • Durvalumab in combination with olaparib in EC that is pMMR.
	
	Other current indications:[9]
	Non-small cell lung cancer (NSCLC)
	Durvalumab is indicated:
	• as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
	• in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, for the treatment of adults with resectable (tumours ≥4 cm and/or node positive) NSCLC with no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase rearrangements.

	Small cell lung cancer (SCLC) • durvalumab is indicated in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage SCLC. Biliary tract cancer (BTC) • durvalumab is indicated in combination with gemcitabine and cisplatin for the first-line treatment of adults with locally advanced, unresectable or metastatic BTC. Hepatocellular carcinoma (HCC) • durvalumab is indicated in combination with tremelimumab for the first-line treatment of adults with advanced or unresectable HCC. **Contraindications** Contraindications include hypersensitivity to the active substance or to any of the excipients. For full details of the warnings and precautions for use of durvalumab, please refer to the SmPC.
Method of administration and dosage	Durvalumab 1,120 mg administered via an intravenous line with platinum-based chemotherapy (carboplatin + paclitaxel) every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles, followed by maintenance with 1,500 mg every 4 weeks as either a monotherapy or in combination with olaparib.
Additional tests or investigations	Prior to initiation of SoC + D or SoC + D + O, patients must have confirmation of MMR status using a validated test. MMR status is routinely tested in patients diagnosed with advanced or recurrent EC.[1] Initiating treatment with the SoC + D regimen requires patients to have a dMMR tumour status, whereas the SoC + D + O regimen requires patients to have a pMMR tumour status.
List price and average cost of a course of treatment	£592 per 120 mg vial £2,466 per 500 mg vial Total acquisition cost of treatment: • Chemotherapy phase (every 21 days for up to 6 cycles): £5,523.84 • Maintenance phase (every 28 days): £7,398.00
Patient access scheme (if applicable)	A confidential commercial access agreement is in place for durvalumab that provides a discount of [redacted] per 500 mg vial).

Source: Stewart, *et al.* (2015);[7] AstraZeneca (2024);[6] DUO-E Clinical Study Protocol (CSP);[5] Schofield, *et al.* (2021);[10] DUO-E Clinical Study Report (CSR);[11] Buchbinder 2024.[8]

Table 3: Technology being appraised (olaparib; relevant for SoC + D + O)

UK approved name and brand name	Olaparib (Lynparza®)
Mechanism of action	Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. The PARP enzyme repairs accumulated or therapy-induced DNA damage to tumour cells.[12] Olaparib targets PARP to disrupt the DNA-repair process, which ultimately destroys tumour cells.[13] Olaparib in combination with durvalumab has the potential to further promote an anti-tumour immune response. Through inhibition of PARP, olaparib induces DNA damage, which can result in tumour cell death and enhanced immune priming via activation of proinflammatory signalling. This can promote a more robust anti-tumour response than durvalumab alone, particularly in pMMR tumours which are heterogenous with scarce immune cell infiltration. Notably, there is growing evidence for the efficacy of PARP inhibition in combination with immunotherapies.[13]

Marketing authorisation/ CE mark status	A marketing authorisation submission to the MHRA has been submitted via the IRP. MHRA marketing authorisation is expected in October 2024.
Indications and any restriction(s) as described in the SmPC	**Indication of interest to this evaluation** Olaparib in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. **Other current indications:**[14] <u>Ovarian cancer</u> Olaparib is indicated as monotherapy for the: • maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA*1/2 mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. • maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Olaparib in combination with bevacizumab is indicated for the: • maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a *BRCA*1/2mutation and/or genomic instability. <u>Breast cancer</u> Olaparib is indicated as: • monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA*1/2-mutations who have HER2−, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy. • monotherapy for the treatment of adult patients with germline *BRCA*1/2-mutations, who have HER2− locally advanced or metastatic breast cancer (mBC). Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with HR+ breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. <u>Adenocarcinoma of the pancreas</u> • Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA*1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. <u>Prostate cancer</u> Olaparib is indicated: • as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA*1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. • in combination with abiraterone and prednisone or prednisolone for the

	treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. **Contraindications** Contraindications include hypersensitivity to the active substance or to any of the excipients or breastfeeding during treatment and one month after the last dose. For full details of the warnings and precautions for use of olaparib, please refer to the SmPC.
Method of administration and dosage	Olaparib 300 mg (2 x 150 mg tablets) orally administered twice daily (equivalent to a daily dose of 600 mg)
Additional tests or investigations	Prior to initiation of SoC + D + O, patients must have confirmation of pMMR status using a validated test. In UK clinical practice, MMR status is routinely tested in patients diagnosed with advanced or recurrent EC.[1]
List price and average cost of a course of treatment	The list price of olaparib is: £2,317.50 (56 x 150 mg tablets) per 14-day pack. Total acquisition cost of treatment: £4,635.00 per 28 days.
Patient access scheme (if applicable)	A confidential commercial access agreement is in place for olaparib that provides a discount of [redacted] per 14-day pack).

Source: AstraZeneca (2024);[12] Goulooze, *et al.* (2016).[15]

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

Disease overview

- The population of relevance to this appraisal are patients with newly diagnosed advanced (stage III or stage IV) or recurrent EC; advanced disease describes EC that has spread beyond the uterus, while disease recurrence is defined as EC which cannot be detected after primary treatment, but then returns at a later point in time.[16-18]
- In the UK, EC is the fourth most common cancer, with approximately 9,700 new diagnoses each year.[16]
- Patients diagnosed with advanced or recurrent EC face an aggressive disease course with a very poor prognosis and high mortality rates.[19-22]
- Among other methods of classifying EC, molecular subtyping is now widely conducted in the UK to support the selection of treatments that are tailored to the molecular features of a patients' EC, with differential clinical features and responses to immunotherapies and targeted therapies observed in these subgroups:[2, 22, 23]
  - EC that is dMMR is highly immunogenic, displaying enhanced susceptibility to immune checkpoint inhibitors, such as PD-L1 inhibitors.[24]
  - EC that is pMMR is less susceptible to immune checkpoint inhibitors and is therefore considered more difficult to treat.[2, 22, 25-28]
- MMR testing is routinely performed for patients with advanced or recurrent EC and directly informs prescribing decisions in UK clinical practice, whilst testing for other molecular features is more variable, and does not have the same direct impact on prescribing decisions.[1]
- Given that MMR testing is already routinely performed to guide treatment decisions in the UK, and given that the licenses for SoC + D and SoC + D + O are expected to depend on MMR status, this submission will focus on newly diagnosed advanced or recurrent EC that is pMMR or dMMR.

- Based on the budget impact analysis provided as part of this submission, it is estimated that approximately 1,500 patients with pMMR EC would become eligible for treatment with SoC + D + O, whilst approximately 500 patients with dMMR EC would become eligible for treatment with SoC + D.

Treatment pathway for newly diagnosed advanced or recurrent EC

- The treatment pathway for EC is guided by factors including disease stage, molecular classification, and patient choice; however, newly diagnosed advanced or recurrent EC are typically treated via the same treatment pathway.[2, 22, 29]
- Patients with dMMR and pMMR advanced or recurrent EC follow a similar treatment pathway, with similar options available for each group of patients.
- The current SoC for patients with advanced or recurrent EC is first-line platinum-based chemotherapy (carboplatin + paclitaxel), although dostarlimab in combination with platinum-based chemotherapy is also an option for patients with dMMR advanced or recurrent EC via the cancer drugs fund (CDF) [TA963].[2, 22, 30]
- In the second-line setting and beyond, there is no SoC for EC. Patients who have received first-line platinum-based chemotherapy may receive a range of different options, including immunotherapy in combination with targeted treatments [TA904], single agent chemotherapy, hormonal therapies, or single agent immunotherapy for patients with dMMR EC [TA779, TA914].[25, 31, 32]
- Despite the availability of innovative second-line options, fewer than a third of patients are able to tolerate further treatment following first-line therapy.[33] Furthermore, given that immunotherapy rechallenge is not reimbursed in the UK, patients who have received first-line dostarlimab with platinum-based chemotherapy via the CDF are ineligible to receive immunotherapy-based regimens in the second-line setting even if they are able to tolerate these treatments.[1]

Burden of newly diagnosed advanced or recurrent EC

- Endometrial cancer primarily affects postmenopausal women, with an average age at diagnosis of 60 years.
- The poor prognoses and high mortality rates faced by patients with advanced or recurrent EC leads to a significant clinical and humanistic burden.[34] The vast majority of patients will have an expected survival of less than 5 years; only ~15% of patients diagnosed with stage IV EC and 20% of patients with recurrent disease survive beyond 5 years.[21, 22, 34]
- Unlike many other types of cancers, there has been limited advancement in first-line treatment options, with carboplatin + paclitaxel remaining the longstanding SoC in this setting.[2, 22] EC is therefore one of the few types of cancer where survival has not seen any improvement since mid-1970.
- A range of immunotherapy-based regimens are currently available in the second-line setting, but at this stage of the treatment pathway, many patients are either unable to tolerate or are ineligible for these therapies following first-line treatment.[30]
- Patients with advanced or recurrent EC report a significant emotional and psychological burden from living with a life-threatening disease with debilitating symptoms and a poor prognosis.[35]

Unmet need and positioning of SoC + D for dMMR EC

- Current first line treatment options for patients with dMMR EC are limited, and the longstanding carboplatin + paclitaxel SoC comes at a cost of toxicity that may not be outweighed by the clinical benefits for many patients.[2, 22, 36]

- The absence of a maintenance regimen following carboplatin + paclitaxel results in a limited treatment response and therefore the potential need for second-line treatment, of which there are few effective and tolerable options available.
- Recently, dostarlimab with platinum-based chemotherapy was recommended by NICE for use within the CDF in patients with dMMR/microsatellite instability-high (MSI-H) EC following the RUBY-1 trial, which clearly demonstrated the efficacy of combining platinum-based chemotherapy with an immunotherapy (dostarlimab) in the first-line EC setting, and particularly for dMMR tumours.[3]
- Durvalumab has proven efficacious in the DUO-E trial in combination with carboplatin + paclitaxel for treating advanced or recurrent EC that is dMMR.[4]
- There remains an unmet need for innovative therapeutic options in the first-line setting for patients with dMMR EC, to expand the range of effective therapeutic options and to ensure these patients can benefit from immunotherapies when they are most likely to be able to tolerate them.
- Given the compelling evidence for the use of immune checkpoint inhibitors in dMMR EC and the demonstrated efficacy of SoC + D specifically, SoC + D would represent an important additional treatment option for this patient population with a clear unmet need in UK clinical practice.

Unmet need and positioning of SoC + D + O for pMMR EC

- Patients with advanced or recurrent pMMR EC represent the majority (~80%) of the overall advanced and recurrent EC population, and have even more limited treatment options than patients with dMMR EC.[37]
- Platinum-based chemotherapy is currently the only available option for these patients in the frontline setting, but evidence suggests that the benefit of this regimen is short-lived.[38]
- Moreover, SoC is associated with a range of unpleasant side effects and an associated health-related quality of life (HRQoL) detriment, which may not be justified by the poor clinical outcomes observed in patients with advanced or recurrent EC who initiate this treatment.
- Studies have shown that pMMR EC tumours exhibit lower sensitivity to immune checkpoint inhibitors than dMMR EC tumours, making this population more challenging to treat. As such, there is a clear unmet need for a first line regimen with demonstrated efficacy for patients with newly diagnosed advanced or recurrent EC that is pMMR.
- Combining durvalumab-induced immune checkpoint inhibition with the immune priming effects of olaparib can potentiate a more robust anti-tumour response, and has been demonstrated in the DUO-E trial to support a durable benefit in this patient population versus the longstanding SoC.
- The introduction of SoC + D + O would therefore represent a critical addition to the treatment pathway, allowing patients with pMMR EC to equally benefit from the availability of innovative therapies in the first-line setting.[4]

B.1.3.1 Disease overview

EC originates in the lining of the womb (uterus), known as the endometrium. The term EC is frequently used synonymously with uterine cancer, as most (~96%) uterine cancers are EC.[16] However, two types of uterine cancer (EC and uterine sarcoma) exist and are clinically distinct.[16] The focus of this submission is patients with advanced or recurrent EC. EC is classified as advanced (stage III or stage IV) once the cancer has spread beyond the uterus, while disease recurrence is defined by disease which cannot be detected after primary treatment, but then returns at a later point in time (Section B.1.3.2.1, Section B.1.3.2.4).[16, 17, 39]

In the UK, EC is the fourth most common cancer among women, accounting for approximately 9,700 diagnoses each year, including approximately 2,227 patients with newly diagnosed advanced or

recurrent disease who would be eligible for first-line anti-cancer systemic treatment (Section B.1.3.3) [40] Patients diagnosed with advanced or recurrent EC face particularly poor prognoses and high rates of mortality, with five year survival rates of just 15% and 20%, respectively, for patients with Stage IV disease and recurrent disease (Section B.1.3.5).[21, 22, 34]

Newly diagnosed advanced or recurrent EC is also associated with a range of debilitating symptoms, and these have a profound effect on physical functioning and HRQoL.[35] The main symptoms of EC include periodic, continuous, or abnormal vaginal bleeding, which may be extremely heavy for some patients. Additional symptoms include pain in the lower back or pelvic region, blood in the urine, the presence of a mass in the lower abdomen or unintentional weight loss.[41-43] Patients also report abdominal distention, early satiety, changes in bowel or bladder function, and pain during intercourse.[41, 42] These symptoms negatively impact patient HRQoL, interfere with patients' daily lives and contribute to significant psychological burden, as detailed further in Section B.1.3.5.[35, 44-48]

Historically, EC was categorised into two distinct subtypes, based on histological characteristics, grade and hormone sensitivity:

- Type 1 'endometrioid' tumours: these tumours comprise oestrogen-dependent endometrioid adenocarcinomas, and represent approximately 75% of all ECs. They are generally less aggressive and are often cured by surgery when detected at the early stages of the disease. A subset of these patients may present with high grade disease which is associated with a higher chance of metastasis and a poorer prognosis.[16, 49]
- Type 2 tumours 'non-endometrioid' tumours: these tumours include oestrogen independent non-endometrioid 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 1 EC. These tumours also have higher rates of recurrence.[46, 50, 51]

More recently, the classification of EC increasingly adopted a molecular-based approach, with a focus on identifying specific molecular features, including the determination of a patients' MMR status. This classification system was implemented due to increasing understanding about the importance of molecular features in patient prognosis and responses to treatment. Given that this submission proposes that SoC + D and SoC + D + O will be used in distinct subgroups based on MMR status (dMMR and pMMR, respectively), the following sections will particularly focus on the identification and clinical significance of MMR status in EC, as well as the unmet needs in each of these patient populations.

B.1.3.2 Disease classification, progression, and recurrence

The diagnosis of EC is based on clinical examination to assess tumour location, size and spread, radiological examinations of the uterus, and histopathological examinations using a biopsy in order to determine the histological type and grade.[52] According to UK clinical feedback, biopsies are also routinely used to determine a patient's MMR status, as per NICE diagnostic guidance DG42 for Lynch syndrome in people with EC (Section B.1.3.2.6).[23] Other molecular testing (including POLE and p53) may also be performed in some centres, whilst PD-L1, HRD, homologous recombination repair mutation (HRRm) and BRCA testing are not performed routinely in UK clinical practice.[1]

EC is a heterogenous disease which, if diagnosed and treated at an early stage, can be largely curable. However, in patients who are diagnosed with advanced or recurrent EC – the population of relevance to this appraisal − the disease is often aggressive, resulting in poor prognoses and high mortality rates.[19, 20] Contributory factors to the severity of EC include stage at diagnosis, tumour grade, histology and molecular classification;[53] each of these aspects is discussed in further detail below.

B.1.3.2.1. Stage at diagnosis

In NHS clinical practice, disease staging is generally performed at diagnosis according to the FIGO system.[52, 54] This staging system is based on tumour spread from its initial location in the endometrium to other tissues or organs. Stage I describes EC that is localised to the uterus or womb, whilst stage II describes EC where invasion of the cervical stoma is present.

Stage III or IV are considered advanced stages of EC – at this point, the cancer has spread beyond the uterus. Stage III disease involves local and/or regional invasion, whilst for stage IV, the cancer has invaded the bladder, rectum and/or distant organs.

Approximately 80% of patients with EC are diagnosed at an early-stage, with a smaller proportion (approximately 20%) being diagnosed with advanced disease (stage III and IV).[16, 17]

B.1.3.2.2. Tumour histology

EC can be further classified according to histology, of which there are four primary subtypes. The most common tumour histology (70–80%) is endometrioid adenocarcinoma. Other histologies include serous adenocarcinoma, clear cell adenocarcinoma and carcinosarcoma, which are significantly less common but tend to be characterised by a more aggressive disease course compared with endometrioid adenocarcinoma.[49, 55]

B.1.3.2.3. Grade of tumour

For patients with Type I (endometrioid) endometrial tumours, the FIGO grading system is used. The FIGO grading system allows for classification of tumours into the following categories, with higher tumour grades corresponding to an increased likelihood of developing metastases:[56]

- 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)

B.1.3.2.4. Recurrent endometrial cancer

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, can be experienced by any patient with EC, regardless of disease stage.[39] Of the patients who are originally diagnosed with early-stage disease (FIGO stages I–II), a proportion will experience disease recurrence, at which point their prognosis and treatment pathway becomes similar to those patients newly diagnosed with advanced stage disease.[57] Prognosis severely deteriorates in the recurrent setting, as discussed further in Section B.1.3.5.

B.1.3.2.5. Molecular classification

In recent years, the Cancer Genome Atlas (TCGA) Research Network proposed four distinct molecular subgroups based on mutational burden and somatic copy-number variations, including POLE-mutated, dMMR, p53 abnormal, and ‘no specific molecular profile’ (NSMP). Importantly, each of these subgroups have distinct clinical, pathologic and molecular features and have since been integrated into the BGCS, European Society for Medical Oncology (ESMO) clinical practice guidelines 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 EC.[22, 29, 58]

Various techniques can be used for molecular subtyping, including the array- and sequencing-based technologies originally applied by TCGA.[59] However, research has found that immunohistochemical and molecular tests can serve as surrogates for the comparatively complex and expensive TCGA

analyses.[60-62] The importance of MMR status in guiding treatment pathway choice, as well as the association of MMR status and Lynch Syndrome, has established MMR testing as routine in the case of advanced or recurrent EC.[23]

Currently, the only first-line treatment option guided by MMR testing in UK clinical practice is dostarlimab with platinum-based chemotherapy, which is recommended by NICE via the CDF for patients with dMMR primary advanced or recurrent EC.[30] UK clinical feedback and the results from the Lynch Syndrome project have indicated that the most routinely conducted molecular testing for EC in clinical practice is MMR testing, as per NICE diagnostic guidance DG42.[23, 63] Clinical feedback additionally indicates that other molecular testing, such as for p53, POLE, PD-L1, HRD, and HRRm are either not tested or seldomly tested in these patients.[1]

B.1.3.2.6. MMR status, microsatellite stability and PD-L1 status in EC

As indicated above, various factors impact treatment outcomes in EC, including MMR status, which particularly influences clinical decision-making.[2, 22] In EC, MMR status is used to classify tumours as either MMR deficient (dMMR) or MMR proficient (pMMR).[64] Patients can be divided into each of these groups based on the functionality of the MMR system – a multiprotein pathway involved in the recognition and repair of DNA damage in cells. In dMMR EC, the MMR pathway loses functionality, meaning that errors during DNA replication are not properly corrected. Conversely, in tumours that are pMMR, the functionality of the MMR pathway remains intact, such that any mutations are corrected.[65]

Microsatellites are short, repetitive sequences of DNA. MSI and MMR status are closely related concepts in EC and other cancers, as defects in DNA repair mechanisms lead to the accumulation of mutations, which are usually clustered in microsatellites. Tumours with dMMR typically show high levels of MSI as mutations in microsatellites are not corrected; these tumours are referred to as MSI-H.[64, 66] On the other hand, in tumours that are pMMR, the MMR pathway remains intact. Tumours with a functional MMR system show low or no MSI and are referred to as MSI-low (MSI-L) or microsatellite stable (MSS).[67]

As described in Table 2, EC that is dMMR is highly immunogenic and has increased mutational burden, enhancing its susceptibility to immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 therapies.[24] In contrast, pMMR tumours do not exhibit the same immunogenic characteristics, meaning that pMMR EC is less susceptible to immune checkpoint inhibitors, and can be more difficult than dMMR tumours to treat in clinical practice (Section B.1.3.6).

Across all solid tumours, EC is reported to have the highest incidence of dMMR/MSI-H, accounting for approximately 20–30% of EC cases.[68] This is partly attributed to the association between dMMR and Lynch syndrome, a hereditary condition linked to germline mutations in MMR genes (such as MLH1, MSH2, MSH6, PMS2), which results in a predisposition for developing EC. Importantly, as part of the NICE diagnostics guidance DG42, all patients diagnosed with EC are now tested for Lynch syndrome – this relies on MMR testing using immunohistochemistry; a relatively inexpensive technique that is routinely used in cancer diagnostics.[23] In contrast, whilst MSI-H testing is also conducted within the UK in certain cases, it is far less common than MMR testing for EC.[69] Considering this, the testing used in the DUO-E study and the licenses for SoC + D and SoC + D + O, which depend on MMR status (Section B.1.1), the focus of this submission will be on MMR status, rather than MSI.

Beyond MMR and MSI, there has been growing research into the clinical significance of PD-L1 expression in EC. PD-L1 is a biomarker linked with patient response to anti-PD-L1 treatment in other cancers, but studies in EC have proven inconclusive to date, with inconsistent results relating to its prognostic association with survival.[70] Results from different first-line studies investigating immunotherapies in the first-line for advanced or recurrent EC (including NRG-GY018, RUBY II, and DUO-E) demonstrate conflicting results by PD-L1 status and used different methods to capture PD-L1 expression.[3, 4, 71]

Importantly, whilst UK clinical feedback highlighted that MMR testing is routine and has a significant impact on prescribing decisions in current UK clinical practice, PD-L1 is seldomly tested, and does not inform current prescribing decisions, as it has not yet been demonstrated to be a strong driver or predictor of response to currently available treatments in EC. Of particular relevance to this appraisal, clinical experts also highlighted that given the observed data from the DUO-E trial as well as the current evidence base regarding the role of PD-L1 in EC, they would not consider it necessary to use PD-L1 status in addition to MMR status to inform prescribing decisions in either dMMR or pMMR EC. For patients with dMMR EC, this is due to the fact that this subgroup is well-defined and is a distinct group in which immune checkpoint inhibition has demonstrated efficacy. In contrast, the pMMR EC subgroup is less well-defined, and consists of a heterogeneous group with more varied biomarkers. However, as there is no clinical nor biological rationale underpinning PD-L1 as a predictor of PARP inhibitor response, clinicians noted that PD-L1 would also not be of relevance in informing prescribing decisions in this subgroup where SoC + D + O is the only licensed regimen.

B.1.3.3 Epidemiology

In the UK, EC is the fourth most common cancer and the most common gynaecological cancer among women, with approximately 9,700 new diagnoses each year.[40] Whilst recent UK-specific incidence data are not available for EC specifically, uterine cancer (the most common of which is EC [~96% cases][16]) incidence rates increased by 59% in females in the UK (2016–2018). Moreover, over the last decade, uterine cancer incidence rates have increased by 12% in females in the UK.[40] By 2040, it is predicted that there will be ~11,800 new cases of uterine cancer every year in the UK.[40]

EC incidence increases with age, with 27% of all new uterine cancer cases in the UK between 2016–2018 being diagnosed in females aged 75 and over.[40] High body mass index (BMI) is also a common risk factor for EC, with 34% of uterine cancer cases in the UK linked with increased BMI.[72] As such, obesity is now considered the key contributor to the increased incidence of EC.[73] Additionally, prolonged or unopposed exposure to oestrogen is associated with hormonal risk factors that increase the risk of EC development.[72] Differences in risk related to ethnicity have also been identified; in England, incidence rates for uterine cancer are higher in the Black ethnic group, lower in people of mixed or multiple ethnicities, and similar in the Asian ethnic group, compared with the White ethnic group (2013–2017).[16]

In the absence of empirical data, in the UK, it is estimated that there are approximately 2,227 patients with newly diagnosed advanced or recurrent disease who would be eligible for systemic treatment. Approximately 529 of these annual incident patients will present with dMMR EC, whilst the remaining proportion will present with pMMR EC; full details of the size of the eligible patient populations for SoC + D and SoC + D + O are outlined in the budget impact analysis document.

B.1.3.4 Treatment pathway

In the UK, various clinical guidelines are used to inform clinical decision-making, including the BGCS, the European Society of Medical Oncology (ESMO) and the ESGO/ESTRO/ESP guidelines.[2, 22, 29] Whilst there are no published NICE guidelines for EC, there is guidance for specific interventions, such as laparoscopic hysterectomy [IPG356][74], as well as systemic anti-cancer treatments for advanced or recurrent EC, which are detailed below.

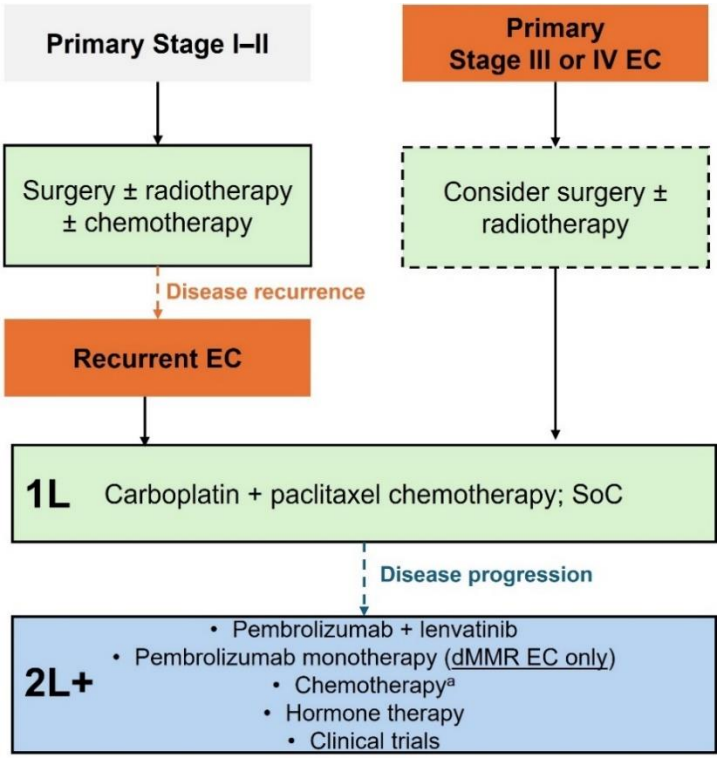
Figure 2 presents an overview of the current treatment pathway for EC in UK clinical practice, which is aligned with clinical expert feedback.[1] The treatment pathway for EC is complex and guided by various factors, including disease stage, tumour grade, tumour type, molecular classification, and patient choice.[2, 22, 29] Clinical feedback also indicated that performance status and comorbidities may influence treatment decisions.[1] Newly diagnosed advanced or recurrent EC (that is unlikely to be cured by surgery alone) are usually treated via the same treatment pathway, as both forms of EC are associated with a poorer prognosis and require more aggressive treatment, compared to early-stage disease.

It should also be noted that in routine UK clinical practice, the treatment pathways for pMMR and dMMR EC are largely aligned. However, there are additional treatment options in both the first- and second-line for patients with dMMR EC; these options are discussed further below.

As shown in Figure 2, initial management of EC usually involves surgical treatment in early-stages.[2, 22] In advanced stages, especially when distant metastases are present, surgery is less commonly used and may be bypassed entirely if the tumour is considered inoperable.[2, 22] Clinical feedback received during TA963 was that when surgery with or without neoadjuvant/adjuvant treatment (usually with carboplatin + paclitaxel) is used, patients are usually monitored following surgery and first-line treatment considered subsequently.[30] In other cases, neoadjuvant chemotherapy may be given, followed by regular interval scanning to check response to treatment and whether the disease has become operable.[30]

Throughout the treatment pathway, radiotherapy may also be used. The most common use of radiotherapy is in patients diagnosed with advanced or recurrent EC that are unfit for surgical management. In cases of high risk EC, external beam radiation therapy (EBRT) with concurrent and adjuvant chemotherapy, or alternatively sequential chemotherapy and radiotherapy, is recommended as per BGCS guidelines.[2] In patients with salvageable recurrent disease or stage III disease, radiation therapy is also used after chemotherapy with curative intent.[22] Importantly, radiotherapy is not used in place of first-line systemic therapy, and is therefore not considered a comparator in this submission.

Figure 2. Treatment pathway for EC in UK clinical practice



Footnotes: Options recommended via the CDF are not presented as these do not represent part of established clinical practice as per the NICE processes and methods.[75] In the first-line setting, these options include dostarlimab with platinum-based chemotherapy for patients with advanced or recurrent EC that is MSI-H or dMMR [TA963]. In the 2L setting, these options include dostarlimab monotherapy [TA779] for previously treated EC that is dMMR or MSI-H or dMMR.
[a]As per BGCS guidelines, further platinum-based is generally only considered for patients who relapse more than 6 months after receiving carboplatin + paclitaxel.
Source: Morrison, *et al.* (2022);[2] Oaknin, *et al.* (2022);[22] NICE (2024).[30]

B.1.3.4.1. First-line treatment for advanced or recurrent EC

Current clinical guidelines recommend the use of platinum-based chemotherapy (carboplatin + paclitaxel) as the first-line treatment for patients with recurrent or advanced EC.[2, 22] This recommendation is based on the Phase III GOG-0209 trial, which evaluated the efficacy of carboplatin in combination with paclitaxel vs. TAP regimen (cisplatin, doxorubicin and paclitaxel) in patients with advanced EC (stage III−IV).[22] Overall, the GOG-0209 trial, which established carboplatin + paclitaxel as the first-line SoC in this indication, demonstrated that carboplatin + paclitaxel was non-inferior to the TAP regimen, but offered an improved safety profile and HRQoL benefit.[38] Specifically, patients treated with carboplatin + paclitaxel achieved a median PFS of 13 months and a median OS of 37 months, compared with 14 months and 41 months for median PFS and OS, respectively, in the TAP arm.[38]

Despite these overall results, it should be noted that the GOG-0209 trial had a much broader inclusion criteria compared with the DUO-E trial that informs this submission, including patients with lower risk, fully resected stage III disease. When restricted to patients with stage III and IV measurable disease and recurrent EC only (n=400), outcomes for carboplatin + paclitaxel were much poorer.[38] The DUO-E trial similarly demonstrates the poor survival outcomes for patients with advanced or recurrent EC receiving carboplatin + paclitaxel in the first-line setting, with a median OS of 25.9 months.[4]

In some cases, carboplatin + paclitaxel may not be a suitable option due to comorbidities, performance status or patient choice. Furthermore, clinical feedback indicated that in particular, patients with disease recurrence may not always be offered systemic therapies on the basis of a risk assessment.[1] In these cases, carboplatin as monotherapy may be used, given its more favourable safety profile.[48] BGCS guidelines also recommend that hormone therapy can be a first choice for these patients where chemotherapy may not be well-tolerated (such as those who are older with multiple comorbidities), as well as in the patients in the palliative setting and for patients with low grade, hormone-sensitive tumours.[2] Of note, patients who would be offered hormonal therapy were excluded from the DUO-E trial and would not be considered suitable candidates for SoC + D or SoC + D + O in clinical practice, supporting the generalisability of patients enrolled in DUO-E trial to those who would receive SoC, SoC + D or SoC + D + O in UK clinical practice.[5] For these reasons, whilst hormonal therapy was included in the final NICE scope (Table 1), it is not an appropriate comparator and is not considered further within this submission.

Recently, dostarlimab with platinum-based chemotherapy (carboplatin + paclitaxel) has also been recommended for use in the first-line setting [TA963]. However, this is only available through the CDF and is only recommended for patients with dMMR (or MSI-H) advanced or recurrent EC. Whilst these options do not represent “established practice” (as per NICE processes and methods) and thus cannot be considered relevant comparators in this appraisal, a large proportion of patients receive this option in clinical practice.[30, 75] Clinical expert opinion was that 80–90% of patients with advanced or recurrent dMMR EC would be offered dostarlimab with platinum-based chemotherapy in a clinical setting. The remaining small minority who are ineligible for this treatment (due to performance status or comorbidities) would be offered SoC platinum-based chemotherapy.[1]

B.1.3.4.2. Second-line treatment for advanced or recurrent EC

There is currently no agreed second-line SoC for EC.[22, 76] As such, patients may receive a range of different options, including re-treatment with chemotherapy, enrolment in a clinical trial or hormonal therapy.

In addition, dostarlimab monotherapy via the CDF [TA779], and pembrolizumab monotherapy [TA914], are recommended in the second-line setting, but only for patients with dMMR or MSI-H EC.[31, 32] Finally, pembrolizumab in combination with lenvatinib has recently been recommended by NICE for routine use for the treatment of previously treated advanced or recurrent EC regardless of MMR status [TA904].[25] UK clinical feedback was that immunotherapy monotherapy tends to be

favoured due to favourable toxicity profiles, whilst pembrolizumab + lenvatinib is usually reserved for patients with pMMR EC as they will not be eligible for immunotherapy monotherapy.[1]

The introduction of pembrolizumab as monotherapy or in combination with lenvatinib represents a significant advancement in the treatment paradigm for EC, allowing patients to benefit from innovative treatment options. However, following disease progression on first-line platinum-based therapy, fewer than one third of patients will be able to tolerate further treatment, underlining the importance of utilising the most effective treatment options as early as possible in the first-line setting.[33]

Furthermore, given the recent introduction and uptake of dostarlimab with platinum-based chemotherapy in the first-line setting for patients with dMMR or MSI-H advanced or recurrent EC via the CDF (Section B.1.3.4.1), many patients who are able to tolerate further treatment will be ineligible to receive immunotherapy-based regimens in the second-line setting. For instance, the Blueteq criteria for pembrolizumab + lenvatinib stipulates that a patient is not eligible for this regimen if they have “received any prior antibody treatment which targets PD-1 or PD-L1”, meaning patients who receive first-line dostarlimab with platinum-based chemotherapy (and potentially those who receive SoC + D and SoC + D + O in the future, if recommended) are ineligible for this treatment.[77] The Blueteq criteria for immunotherapies used as monotherapy are similar, meaning that immunotherapy re-challenge is not reimbursed in UK clinical practice.

As noted by clinical experts, the current reimbursement criteria which preclude the routine use of immunotherapy rechallenge (outside of clinical trials) reflect the insufficient clinical data surrounding the efficacy of this strategy in the EC setting. Clinical expert feedback was also that there is a lack of data regarding which patients could benefit from this approach, with one clinician hypothesising that it may only be suitable for some patients who responded well to their initial immunotherapy, and who had a certain minimum treatment-free interval before relapse. This is supported by studies in other cancer types (such as NSCLC and melanoma), which suggest that immunotherapy rechallenge is only likely to be successful for those who discontinue first-line immunotherapy after achieving a good response and then experience progression after an immunotherapy-free interval, as opposed to patients who progress while receiving first-line immunotherapy.[78, 79]

This ultimately means that patients in the UK typically have only one opportunity to receive innovative immunotherapy-based treatment regimens within the current treatment paradigm. It is therefore pivotal that patients are treated with effective immunotherapy-based regimens as early as possible, in the first-line setting, when patients are likely to be in the best health and have the greatest chance of achieving the most durable response to treatment.

B.1.3.5 Burden of disease

B.1.3.5.1. Clinical burden of advanced or recurrent EC

Compared to early-stage disease, advanced or recurrent EC are associated with particularly poor prognoses and high mortality rates.[34] In the UK, approximately 99% of patients with EC will survive for one year or more when diagnosed at stage I; considering only patients with stage IV EC, fewer than half will survive for one year (47%).[34]

These differences are similarly stark for five-year survival rates: for patients with stage I disease, approximately 75% survive for five years or more, compared to just ~15% for patients diagnosed with stage IV EC.[21, 34] Disease recurrence is associated with a similarly poor prognosis, with only 20% of patients surviving beyond 5 years.[22, 34, 80, 81]

Despite the high mortality rates in newly diagnosed advanced or recurrent EC, there has been limited advancement in the first-line treatment of advanced or recurrent EC, with carboplatin + paclitaxel remaining the longstanding SoC in this setting.[2, 22]

Compared to other advanced or recurrent cancer types, there is a lack of novel first-line treatment options for advanced or recurrent EC - particularly innovative immunotherapies that may prevent or delay recurrence and prolong survival. The treatment paradigm in the UK is starting to change with the recent recommendation of dostarlimab with platinum-based chemotherapy for patients with dMMR (or MSI-H) EC in the first-line setting via the CDF.[30]

All other immunotherapy-based regimens are only recommended in the second-line setting, which limits the proportion of patients that can benefit from these therapies as many are unable to tolerate further treatment after first-line therapy.[25, 32, 33] As highlighted above, some patients may also be ineligible for second-line immunotherapy if they have received dostarlimab with platinum-based chemotherapy in the first-line given the Blueteq criteria surrounding immunotherapy rechallenge.[1, 77] Patient experts involved in TA963 highlighted the importance of introducing additional innovative options in the first-line, rather than the current treatment paradigm, which is “geared towards expecting a recurrence”, where the most effective therapies are available predominantly in the second-line setting.[30]

The importance of introducing additional effective first-line options is underscored by retrospective EC studies which demonstrate that increasing the length time until disease recurrence is independently associated with a prolonged survival post-recurrence.[82, 83] Moreover, when considering other cancer types, the availability of innovative therapies (such as olaparib as a first-line maintenance option for ovarian cancer either with or without bevacizumab following the pivotal SOLO-1 and PAOLA-1 trials, respectively [84, 85]) has had a demonstrable impact on the proportion of patients achieving progression-free intervals, with a subsequent impact on OS.[86] It is expected this same benefit would be observed following the introduction of innovative first line EC therapies, such as SoC + D and SoC + D + O. UK clinical experts also highlighted that there is curative potential for a proportion of patients with advanced or recurrent endometrial cancer in the first-line setting, and that by bringing targeted immunotherapies into the first-line setting, there is potential to increase the proportion of patients who achieve long-term remission or cure.[1]

B.1.3.5.2. Humanistic burden of advanced or recurrent EC

Advanced or recurrent EC is associated with a significant humanistic burden and a profound negative impact on HRQoL, driven by the life-limiting impacts of treatments, as well as the psychological burden of living with a life-threatening disease.[35] In addition, symptoms of EC are often debilitating for patients, and contribute to decreased HRQoL by impacting physical functioning and increasing psychological burden.[35, 44-48] Symptoms include unintended weight loss, abnormal vaginal or uterine bleeding, sexual dysfunction, and, in advanced disease, can include abdominal pain, fatigue, changes to bowel and bladder habits. These symptoms, and their associated impacts on wellbeing, typically increase in severity as the disease progresses.[41-43]

Upon initiating treatment, patients may experience a range of unpleasant side effects from the current first-line SoC (carboplatin + paclitaxel), which risk surpassing the clinical benefits associated with this treatment regimen for patients with advanced or recurrent EC. Side effects of chemotherapy include lymphoedema, neurotoxicity, fatigue, nausea, vomiting, and alopecia, all of which impact patients’ ability to lead normal lives and result in a decline in HRQoL.[46, 87] Furthermore, among those who undergo surgery, the removal of the uterus and surrounding affected tissues can damage sex organs, leading to impaired sexual function, with one cross-sectional study reporting that 68.6% of EC survivors had sexual dysfunction, while a further 55.9% reported that they had no sexual intercourse with their partners after surgery.[48] Lingering side effects after surgery include pain during intercourse, impaired physical function and even impaired mobility, all of which reduce a patient’s ability to participate in their usual daily activities.[48]

Besides the physical impacts of EC symptoms and current treatment options, patients experience a significant psychological burden due to the disease, including increased anxiety and depression

resulting from living with a life-threatening disease.[88] Given that the majority of patients with advanced or recurrent EC are women in their 60s who are likely to be employed, patients may also worry about their inability to work and support their families. Additionally, patients may be concerned about managing their additional responsibilities at home, such as caring for dependents. Even after treatment, patients who achieve remission report long-term physical and psychological effects that include persistent lack of stamina and strength, in addition to fear and worry around their cancer returning.[89] Furthermore, the negative impact of EC on HRQoL extends beyond patients, and can impact caregiver HRQoL.[90] While EC-specific literature is limited, evidence from gynaecological cancers more broadly suggests that caregivers often report a decreased HRQoL.[91, 92]

Importantly, studies indicate that the HRQoL detriment is most pronounced in patients diagnosed with EC that has an aggressive disease course, such as primary advanced or recurrent EC. One prospective study that investigated HRQoL outcomes in woman diagnosed with EC between 2016–2020 reported that EC survivors with more aggressive disease had significantly lower HRQoL (assessed by FACT-G), compared to survivors with less aggressive disease. This difference was driven by lower scores in physical and functional subscales among women with aggressive disease compared to those with less aggressive disease.[35]

B.1.3.6 Unmet need and positioning of SoC + D in dMMR EC

As highlighted above, newly diagnosed advanced or recurrent EC is associated with a significant clinical and humanistic burden, resulting in a profound impact on patient HRQoL. Despite this, current treatment options available through routine commissioning are extremely limited. Moreover, the longstanding first-line SoC (carboplatin + paclitaxel) is associated with a range of unpleasant side effects and an associated HRQoL detriment, which may not be justified by the poor clinical outcomes observed in patients with advanced or recurrent EC who initiate this treatment alone.

Recently, dostarlimab with platinum-based chemotherapy was recommended by NICE for use within the CDF for patients with newly diagnosed advanced or recurrent EC that is MSI-H or dMMR EC, marking a significant advancement in the treatment paradigm for this patient population.[30] This recommendation was supported by the pivotal RUBY-1 trial, a Phase III, randomised, double-blind, multicentre, placebo-controlled study, which clearly demonstrated the efficacy of combining platinum-based chemotherapy with an immunotherapy (dostarlimab) in the first-line EC setting, particularly for dMMR tumours which are known to be highly susceptible to immune checkpoint inhibitors, providing the potential for long-term survival for patients who would otherwise experience an extremely poor prognosis.[3] Durvalumab, which acts via the inhibition of PD-L1, has proven similarly efficacious in the DUO-E trial when used in combination with carboplatin + paclitaxel in the treatment of advanced or recurrent EC that is dMMR (Section B.2.7.3).[4]

Given the compelling evidence for the efficacy of immune checkpoint inhibitors in dMMR EC to date and the resulting potential for long-term survival, and clinically meaningful results in the DUO-E trial for SoC + D specifically, the introduction of SoC + D would represent a further important advancement in the EC treatment paradigm, expanding the available options for this patient population and potentially providing a more hopeful outlook for patients diagnosed with newly diagnosed advanced or recurrent EC that is dMMR.

B.1.3.7 Unmet need and positioning of SoC + D + O in pMMR EC

Patients with newly diagnosed advanced or recurrent EC that is pMMR represent a greater proportion of the overall EC population (~80%) and similarly face an extremely bleak prognosis with limited life expectancy and significant impacts on HRQoL. Despite this, first-line treatment options are even more limited for these patients as there are currently no immunotherapies recommended by NICE for patients with newly diagnosed advanced or recurrent EC that is pMMR. As such, these patients often

rely solely upon the longstanding SoC of platinum-based chemotherapy as first-line therapy, despite the poor outcomes associated with this treatment in newly diagnosed advanced or recurrent disease.

In the second-line, options are similarly limited, given that a substantial proportion are unable to tolerate further treatment. For those who are able to receive further treatment, pembrolizumab + lenvatinib represents an innovative regimen; however, this regimen is associated with considerable toxicity and an associated HRQoL detriment.[25]

EC that is pMMR is biologically heterogenous, and is considered more challenging to treat with immunotherapy as a result of the more diverse genomic drivers and variable immune priming.[28, 93, 94] As such, whilst immunotherapy combined with chemotherapy is emerging as a new first-line SoC for advanced or recurrent EC that is dMMR, previous studies have demonstrated that pMMR EC is less responsive to immunotherapy compared with dMMR tumours. For instance, during TA904, which appraised pembrolizumab + lenvatinib in the second-line EC setting, it was noted that the dMMR population experienced a more extensive response compared to the pMMR population; this was based on data from the KEYNOTE-775 trial where the HR for OS was 0.37 vs. 0.68 in the pMMR group.[25] Additionally, the GARNET trial, a Phase I study of dostarlimab monotherapy for patients with advanced or recurrent solid tumours, revealed a greater response rate among those with dMMR or MSI-H tumours than pMMR tumours.[3, 26] Finally, the RUBY I demonstrated an increased benefit for patients with dMMR EC compared to the ITT. A benefit for patients with pMMR EC when treated with dostarlimab with platinum-based chemotherapy in the first-line setting was also seen. It should be noted, however, that the RUBY I trial was not powered to support this analysis, and the benefit for pMMR EC was not observed to the same extent as that for dMMR EC.[3]

There is a need to improve responses to immunotherapy in patients with challenging-to-treat pMMR advanced or recurrent EC. The combination of durvalumab-induced checkpoint inhibition with the priming effect of olaparib has demonstrated enhanced anti-tumour activity and a more durable benefit for these patients in the DUO-E trial, resulting in clinically meaningful improvements in PFS and OS compared with SoC, and providing a strong rationale for the use of SoC + D + O in pMMR EC.[4] The introduction of SoC + D + O for patients with pMMR EC would therefore represent a critical addition to the treatment pathway for these patients as the first first-line regimen recommended by NICE that combines an immunotherapy with PARP inhibition. This would allow patients with pMMR EC to benefit from the availability of innovative therapies in the first-line setting and provide the potential for long-term survival, for patients who would otherwise face an extremely poor prognosis.

B.1.4 Equality considerations

As highlighted in Section B.1.3.3, incidence rates for uterine cancer are higher in the Black ethnic group, lower in people of mixed or multiple ethnicities, and similar in the Asian ethnic group, compared with the White ethnic group. Data from England and Wales (2012–2019) published by the Office for National Statistics (ONS) also suggest that Black ethnic groups have substantially higher mortality rates than other ethnic groups: in the Black ethnic group, age-standardised mortality rates per 100,000 population were ~15 for Black African, Black Caribbean and Black Other ethnic groups, compared with 6.9 for the White ethnic group.[95] The availability of novel and innovative treatments for late-stage disease may help address the disparities in survival outcomes across different ethnicities.

Additionally, there are documented variations in the incidence of different molecular subtypes of EC (including MMR status) across ethnic groups.[96] Given that patients with pMMR EC currently have access to fewer treatment options in the first-line setting in UK clinical practice, and that these patients have a particularly poor prognosis (as outlined in Section B.1.3.2.5), this is an important equality consideration. Ensuring that innovative treatment options are available across all molecular subtypes would help address this concern.

B.2 Clinical effectiveness

Summary of clinical effectiveness

DUO-E trial design

- The DUO-E trial was a Phase III, randomised, multicentre, double-blind, placebo-controlled trial that explored the efficacy and safety of SoC + D, and SoC + D + O in patients with newly diagnosed advanced (stage III or IV) or recurrent EC in comparison to SoC.[4, 11]
- The DUO-E trial enrolled adult female patients with newly diagnosed EC, or recurrent EC with a low potential for cure by surgery alone or in combination with other EC therapies.[5]
- Trial stratification factors included MMR status, disease status (recurrent vs. newly diagnosed) and geographic region (Asia vs. rest of the world).[4, 11]
- A total of 718 patients underwent randomisation in a 1:1:1 ratio to receive either SoC (241 patients), SoC + D (238 patients), or SoC + D + O (239 patients).[4, 11]

Results in the ITT

- At the time of the primary PFS analysis (primary data cut off [DCO1]: 12 April 2023), with a median follow-up between 12.6 and 15.4 months (depending on treatment arm) and 61% data maturity, the DUO-E trial met its primary endpoint in the ITT, demonstrating a statistically significant Investigator-assessed PFS benefit for both SoC + D vs. SoC (median PFS: 10.2 months vs. 9.6 months, respectively; hazard ration [HR] 0.71; 95% confidence interval [CI] 0.57, 0.89; p=0.003) and SoC + D + O vs. SoC (median PFS: 15.1 months vs. 9.6 months, respectively; HR 0.55; 95% CI 0.43, 0.69; p<0.0001), representing a 29% and 45% reduction in the risk of disease progression or death, respectively.[4, 11]
- Interim OS results were supportive of the primary endpoints for both SoC + D vs. SoC (HR 0.77; 95% CI 0.56, 1.07; p=0.120) and SoC + D + O vs. SoC (HR 0.59; 95% CI 0.42, 0.83; p=0.003).[4, 11]
- In pre-specified subgroup analyses of PFS within the ITT, all HRs were below one and favoured SoC + D and SoC + D + O vs. SoC:[4, 11]
  - The HR for SoC + D vs. SoC in the dMMR population (HR 0.42; 95% CI 0.22, 0.80) was markedly lower compared with ITT (HR 0.71; 95% CI 0.57, 0.89), demonstrating a substantial clinical benefit for SoC + D in the dMMR population.[4, 11]
  - A much greater clinical benefit was observed for SoC + D + O vs. SoC compared with SoC + D arm vs. SoC in the pMMR population, indicating that the addition of olaparib results in an improved clinical benefit for the difficult-to-treat pMMR population.[4, 11]
  - These subgroup results supported the marketing authorisation applications for olaparib and durvalumab in the EC indication and the proposed positioning of SoC + D in the dMMR population and SoC + D + O in the pMMR population within this submission; a summary of key results from these analyses are provided below.

SoC + D vs. SoC in the dMMR population

- In the dMMR population, a clinically meaningful PFS benefit was observed for SoC + D vs. SoC (median PFS: not reached [NR] vs. 7.0 months, respectively; HR 0.42; 95% CI 0.22, 0.80), representing a 58% reduction in the risk of disease progression or death, with 67.9% of patients in the dMMR population remaining progression-free at 18 months compared with 31.7% for patients receiving SoC.[4, 11]
- In support of the PFS results, a substantial improvement in OS was observed for the SoC + D arm compared with the SoC arm in the dMMR population, representing a 66% reduction in the risk of death (HR 0.34; 95% CI 0.13, 0.79), with 86.1% of patients in the dMMR population remaining alive and progression-free at 18 months compared with 65.8% in the SoC-treated population, further demonstrating the clinical benefits associated with durvalumab maintenance therapy in the dMMR population.[97]

- There was a substantial improvement in the objective response rate (ORR) for patients treated with SoC + D compared with the SoC arm (30 patients [71.4%] vs. 17 patients [40.5%]; odds ratio [OR] 3.68; 95% CI 1.51, 9.39), and approximately three-times the proportion of patients in the dMMR population receiving SoC +D achieved a complete response (CR) compared to the SoC arm (28.6% vs. 9.5%, respectively).[97]
- A clinically meaningful improvement in duration of response (DoR) was observed for SoC + D vs. SoC, with 75.2% of the patients who achieved a confirmed response maintaining a response at 18 months, compared to 48.2% in the SoC arm. There was also an improvement across all other key endpoints (second progression-free survival [PFS2], time to first subsequent treatment [TFST], time to second subsequent treatment [TSST] and time to discontinuation or death [TDT]) for SoC + D vs. SoC, consistent with the PFS and OS results.[97]

SoC + D + O vs. SoC in the pMMR population

- In the pMMR population, a clinically meaningful PFS benefit was observed for SoC + D + O arm vs. SoC (median PFS: 15.0 months vs. 9.7 months, respectively; HR 0.57; 95% CI 0.44, 0.73), representing a 43% reduction in the risk of disease progression or death within the pMMR population, with a 42% probability of PFS for patients at 18 months compared with 20% in SoC-treated patients.[4, 11]
- In support of the PFS results, a clinically meaningful improvement in OS was observed for the SoC + D + O arm compared with the SoC arm in the pMMR population (HR 0.69; 95% CI 0.47, 1.00), representing a 31% reduction in the risk of death, with a 76.9% OS rate at 18 months compared with 69.9% in SoC-treated patients.[97]
- ORR was marginally greater in the SoC + D + O arm vs. the SoC arm; however, the proportion of patients with CR was 1.5 times greater in the SoC + D + O arm relative to the rate of CR in the SoC arm (15.6% in the SoC + D + O arm and 9.6% in the SoC arm).
- Notable differences in DoR were observed for SoC + D + O vs. the SoC, with a median DoR of 18.7 months vs. 7.6 months in the SoC + D + O and SoC arm, respectively.[97]
- Additionally, there was consistency with the PFS and OS results across all other key endpoints (PFS2, TFST, TSST and TDT), with SoC + D + O demonstrating an improvement compared to SoC in the pMMR population.[97]

Summary of safety and HRQoL data in the ITT

- Safety data collected within the ITT population (safety analysis set [SAS]) represents the primary source of evidence for the safety of SoC + D and SoC + D + O as there is no expectation that safety would vary depending on MMR status.
- Overall, a similar frequency of adverse events (AEs) were observed in the SoC + D arm and SoC + D + O arm; Grade ≥3 AEs occurred in a greater proportion of patients in the SoC + D + O arm compared to the SoC + D and SoC arms (67.2% vs. 54.9% and 56.4%, respectively).[4, 11]
- Overall, the safety profiles across treatment arms were generally consistent with the known profiles of each agent, and the proportion of patients who discontinued treatment due to AEs was generally consistent across all three treatment arms.[4, 11]
- Analysis of HRQoL data from the ITT population was considered most appropriate to maximise the available sample size, as UK clinical feedback indicated there is no expectation that HRQoL would vary depending on MMR status.[1]
- Within the ITT, there were no clinically meaningful changes or deteriorations in HRQoL or symptoms based on the EORTC-QLQ-C30 nor EORTC-QLQ-EN24 questionnaires for either SoC + D or SoC + D + O vs. SoC.[5]
- Similar results were observed for the European Quality of Life scale-5-Dimensions-5-Levels (EQ-5D-5L) instrument within the ITT, with similar scores between all trial arms and HRQoL remaining most stable over the trial duration.[11]

Conclusions

- SoC + D demonstrated a substantial improvement in PFS, OS, PFS2, TFST and TSST and increased ORR and DoR when compared with SoC within the dMMR population. This treatment regimen was also generally well-tolerated.[4, 11] As such, these data demonstrate that SoC + D represents an important advancement in the treatment of patients with newly diagnosed advanced or recurrent EC that is dMMR, offering a substantial and sustained response, alongside a manageable safety profile.
- In the pMMR population, SoC + D + O was associated with a marked improvement in PFS, OS, PFS2, TFST and TSST and an improved DoR when compared with SoC, with a manageable safety profile.[4, 11] These clinical effectiveness and safety data therefore demonstrate that SoC + D + O addresses the clear unmet need for people with newly diagnosed advanced or recurrent EC that is pMMR, representing an important step-change for the management of EC in this challenging-to-treat population.

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of SoC + D, and SoC + D + O and its comparators for the treatment of newly diagnosed advanced or recurrent EC to support this appraisal. The original SLR was conducted in September 2023 and subsequently updated in May 2024. In total, the SLR and SLR update identified 166 studies meeting the inclusion criteria, of which 93 were unique studies, with evidence generated from 29 randomised controlled trials (RCT) and 64 non-RCTs.

One randomised clinical trial investigating the safety and efficacy of SoC + D, and SoC + D + O in newly diagnosed advanced or recurrent EC was identified in the SLR: the DUO-E trial, which will be presented in detail throughout Section B.2.[4] Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

As detailed above, DUO-E was the only trial identified in the SLR that provides evidence on the clinical efficacy and safety of SoC + D, and SoC + D + O as a treatment for the patient populations of relevance for this submission. DUO-E was a Phase III RCT that enrolled adult female patients with newly diagnosed stage III or IV EC, or recurrent EC with a low potential for cure by surgery alone or in combination with other EC therapies. It investigated the effect of two treatment regimes, SoC + D, and SoC + D + O, in comparison to SoC, on the coprimary outcomes of PFS for patients receiving SoC + D, and SoC + D + O versus SoC alone. DUO-E additionally reported on the key secondary outcome of OS, as well as other secondary outcomes that include ORR, DoR, number of AEs, and patient-reported outcomes. Other outcomes reported in DUO-E but not specified in the decision problem included PFS2, TFST, TSST, and TDT. A summary of the DUO-E trial is provided in Table 4.

Additionally, prespecified subgroup analyses examined the effect of SoC + D, and SoC + D + O, in patients stratified by MMR status, with subgroup analyses performed for the dMMR and pMMR patient populations. Of relevance to decision-making, the SoC + D regimen was clinically efficacious in the dMMR population, whilst SoC + D + O proved to be clinically efficacious in the pMMR population. These results supported the marketing authorisation applications for durvalumab and olaparib, which are expected to stipulate that SoC + D is indicated for the dMMR primary advanced or recurrent EC population, whilst SoC + D + O is indicated for the pMMR primary advanced or recurrent EC population. As such, the subgroup analyses for the relevant treatment arms in the patient populations of relevance to this appraisal are presented in detail in Section B.2.7.

Table 4. Clinical effectiveness evidence

Study	DUO-E (NCT04269200/GOG-3041/ENGOT-EN10)[4]
Study design	Phase III, randomised, multicentre, double-blind, placebo-controlled.
Population	Adult female patients with newly diagnosed stage III or IV EC, or recurrent EC with a low potential for cure by surgery alone or in combination with other EC therapies.
Intervention(s)	Durvalumab in combination with first-line platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (SoC + D) or maintenance durvalumab in combination with olaparib (SoC + D + O).
Comparator(s)	SoC (first-line platinum-based chemotherapy [paclitaxel + carboplatin]).
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Reported outcomes specified in the decision problem	A summary of reported outcomes specified in the decision problem is provided below, with full details in the CSR. Outcomes that have been highlighted in bold are included in the economic model.
	• **PFS**
	• **Overall survival (OS)**
	• Objective response rate (ORR)
	• Duration of response (DoR)
	• Adverse effects of treatment:
	  ○ Incidence of any AEs
	  ○ **Incidence of ≥Grade 3 AEs**
	  ○ Incidence of serious AEs
	  ○ Incidence of adverse events of interest (AESI)
	  ○ Incidence of treatment-emergent adverse events
	• Patient reported outcomes/HRQoL:
	  ○ **EQ-5D-5L**
	  ○ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)
	  ○ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module (EORTC QLQ-EN24)
	  ○ Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
	  ○ Patient Global Impression of Treatment Tolerability (PGI-TT)

Study	DUO-E (NCT04269200/GOG-3041/ENGOT-EN10)[4]
All other reported outcomes	Other reported outcomes are provided below, with full details in the CSR. Outcomes that have been highlighted in bold are included in the economic model. • Progression-free survival 2 (PFS2) • Time to first subsequent therapy or death (TFST) • Time to second subsequent therapy or death (TSST) • **Time to study treatment discontinuation or death (TDT)**

Source: DUO-E CSR.[11] Westin *et al.* (2023).[4]

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

B.2.3.1 Trial design

The DUO-E trial is an ongoing Phase III, international, double-blind, placebo-controlled RCT evaluating the efficacy and safety of SoC + D and SoC + D + O, both compared to SoC alone in patients with newly diagnosed advanced (stage III or IV) or recurrent EC. The overall trial design is summarised in Figure 3.[4, 11]

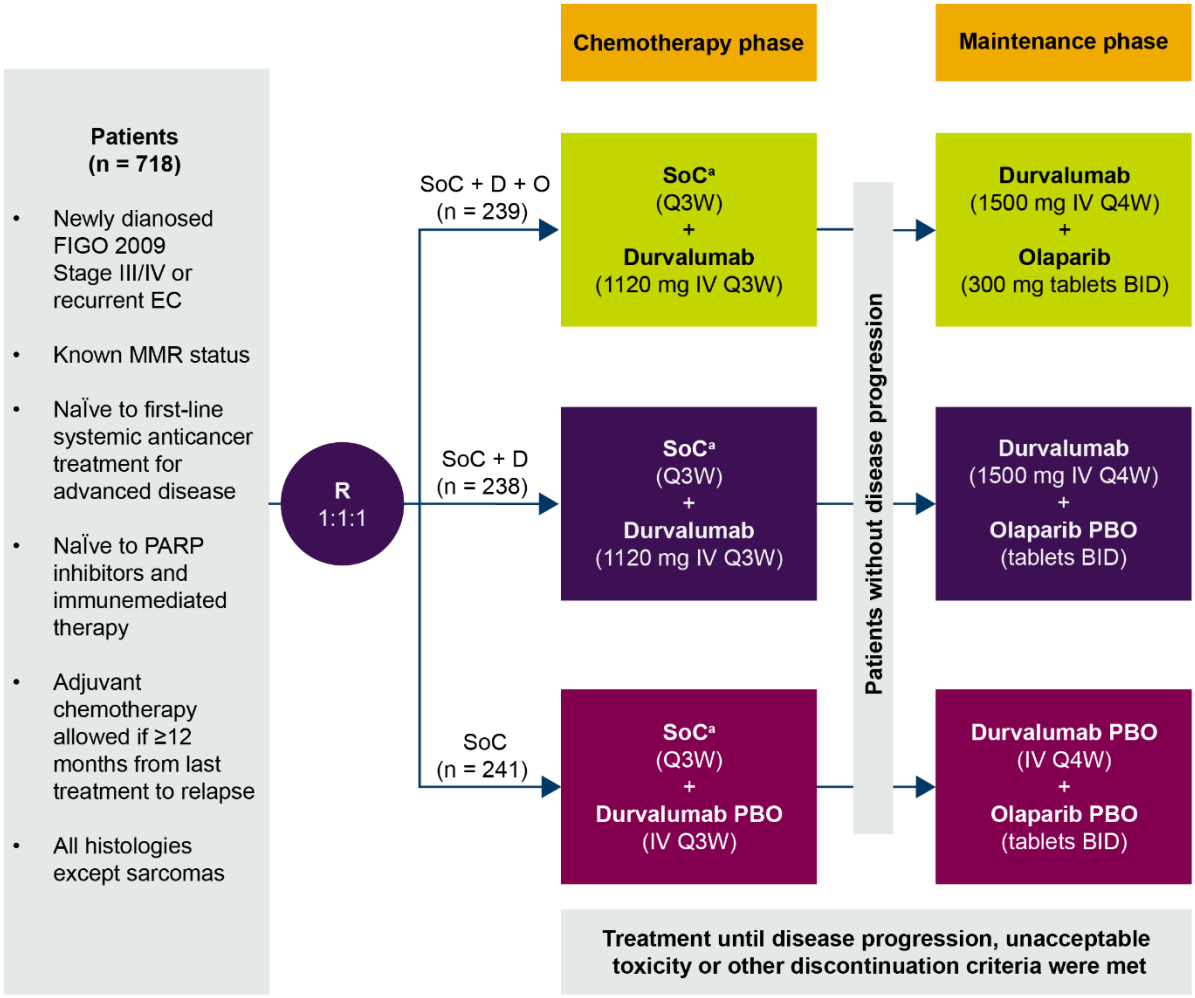
In total, 718 patients were randomised 1:1:1 to three treatment arms (Figure 3), stratified by MMR status (proficient vs. deficient), disease status (newly diagnosed vs. recurrent), and geographic region (Asia vs. rest of world [RoW]). The three treatment arms comprised:

- Platinum-based chemotherapy (carboplatin: area under the time-concentration curve [AUC], 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2) in combination with durvalumab placebo intravenously every three weeks for six cycles, followed by maintenance durvalumab placebo intravenously every four weeks plus olaparib placebo tablets twice daily (**SoC arm**);
- Platinum-based chemotherapy in combination with durvalumab 1,120 mg intravenously every three weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every four weeks plus olaparib placebo tablets twice daily (**SoC + D arm**); or
- Platinum-based chemotherapy plus durvalumab 1,120 mg intravenously every 3 weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every 4 weeks plus olaparib 300 mg tablets twice daily (**SoC + D + O arm**).

The coprimary endpoints of the DUO-E study were investigator-assessed PFS for both the SoC + D and SoC + D + O arms vs. SoC, which were assessed at the primary DCO (DCO1; 12 April 2023). Secondary endpoints included time to second disease progression (PFS2), OS, objective response rate (ORR), DoR, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), and time to study treatment discontinuation or death (TDT).

The median follow-up was 12.6 months in the SoC arm and 15.4 months in the SoC + D and SoC + D + O arms. A second interim OS analysis is planned when there are ~244 deaths across the SoC + D and the SoC arm and ~244 deaths across the SoC + D + O arm. The final OS analysis is planned when there are ~280 deaths across the SoC + D and SoC arms, and ~280 deaths across the SoC + D + O and SoC arms.

Figure 3. DUO-E study design



Footnotes: [a]Six cycles of carboplatin at AUC of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2
Source: ESMO 2023.[98]

B.2.3.2 Trial methodology

The DUO-E trial methodology is summarised in Table 5 and outcome measures and definitions that will be presented in the submission can be found in Appendix M.

Table 5. Summary of trial methodology

Trial name	DUO-E (NCT04269200)
Location	DUO-E was conducted across 22 countries worldwide: Australia, Belgium, Brazil, Canada, China, Columbia, Estonia, Germany, Greece, Hong Kong, Hungary, India, Israel, Japan, Lithuania, Mexico, Poland, Republic of Korea, Russia, Singapore, Spain, and United States
Trial design	The DUO-E trial is an international, Phase III, RCT evaluating the efficacy and safety of durvalumab in combination with carboplatin and paclitaxel followed by maintenance durvalumab with or without olaparib, compared to carboplatin and paclitaxel alone for patients with newly diagnosed advanced or recurrent EC.
Eligibility criteria for participants	Patients were deemed eligible for inclusion in the DUO-E trial if they were: • Female • ≥18 years of age

	• Had a histologically confirmed newly diagnosed or recurrent epithelial endometrial carcinoma (excluding sarcomas)
	• Had EC in one of the following categories:
	  ○ Newly diagnosed stage III disease (measurable disease per RECIST 1.1 following surgery or diagnostic biopsy), as defined by the FIGO criteria
	  ○ Newly diagnosed stage IV disease (with or without disease following surgery or diagnostic biopsy), as defined by the FIGO criteria
	  ○ Recurrence of disease (measurable or non-measurable disease per RECIST 1.1) where the potential for cure by surgery alone or in combination with other EC therapies was poor
	• Naïve to first-line systemic anti-cancer treatment. For patients with recurrent disease only, prior systemic anti-cancer treatment was allowed if it had been ≥12 months from last treatment to relapse
	• Had been able to provide an formalin-fixed paraffin-embedded (FFPE) tumour sample from the locoregional or a metastatic site that was suitable for MMR status evaluation
	• Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	• Had a life expectancy of at least 16 weeks
	Full inclusion and exclusion criteria are available within the CSR.

Interventions	• Platinum-based chemotherapy (carboplatin: AUC, 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2) in combination with durvalumab 1,120 mg intravenously every three weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every four weeks plus olaparib placebo tablets twice daily (SoC + D) • Platinum-based chemotherapy (carboplatin: AUC, 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2) plus durvalumab 1,120 mg intravenously every 3 weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every 4 weeks plus olaparib 300 mg tablets twice daily (SoC + D + O)
Comparator	• Platinum-based chemotherapy (carboplatin: AUC, 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2) in combination with durvalumab placebo intravenously every three weeks for six cycles, followed by maintenance durvalumab placebo intravenously every four weeks plus olaparib placebo tablets twice daily (SoC)
Method of study drug administration	• Carboplatin: administered intravenously • Paclitaxel: administered intravenously • Durvalumab: administered intravenously • Olaparib: administered orally
Permitted and disallowed concomitant medication	The types of concomitant medication used were representative of those commonly prescribed to patients with newly diagnosed or recurrent EC. Other medication considered necessary for the patients' wellbeing could be prescribed by Investigators. All administration of concomitant medications was recorded in detail. Permitted concomitant medications included the following: • Contraception • Anti-emetics/anti-diarrhoeals (after reporting an AE) • Rescue medicine (after reporting an immune-mediated AE [imAE]) Prohibited concomitant medications were specified according to treatment and included:

	• Durvalumab/placebo and olaparib/placebo:
	  ○ Other anticancer therapies: any concurrent chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study; radiotherapy (except palliative); biological therapy mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study
	  ○ Live virus and bacteria vaccines
	  ○ Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)
	• Durvalumab/placebo:
	  ○ Immunosuppressive medications including systemic corticosteroids; corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent; methotrexate; azathioprine; TNF-α blockers
	  ○ Herbal and natural remedies which may have immune-modulating effects
	Restricted concomitant medications were specified according to treatment and include:
	• Durvalumab/placebo and olaparib/placebo
	  ○ Palliative radiotherapy
	  ○ Other anti-cancer agents
	• Olaparib/placebo:
	  ○ Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir
	  ○ Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, dilatiazem, fluconazole, verapamil
	  ○ Strong CYP3A inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifpentine, carbamazepine, nevirapine, enzalutamide, St. John's Wort
	  ○ Moderate CYP3A inducers: bosentan, efavirenz, modafinil
	  ○ CYP3A4 substrates with narrow therapeutic margin, including: cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin
	  ○ Sensitive CYP3A4 substrates, including: buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin
	  ○ CYP2B6 substrates including: bupropion and efavirenz
	  ○ OATP1B1 substrates, including: bosentan, glibenclamide, repaglinide, statins and valsartan
	  ○ OCT, MATE1, and MATE2K substrates including: metformin
	  ○ OCT2 substrates, including: cimetidine and metformin
	  ○ OAT3 substrates, including: furosemide and methotrexate
	  ○ BCRP substrates, including: methotrexate and rosuvastatin
	  ○ P-gb substrates, including: simvastatin, pravastatin, dabigatran, digoxin and colchicine
	  ○ Anticoagulant therapy

Primary outcome(s)	The coprimary endpoints of the DUO-E trial were investigator-assessed PFS in both the SoC + D and SoC + D + O arms vs. SoC (defined in Appendix M).
Secondary endpoints	Secondary and safety outcomes of the DUO-E trial included comparisons of the following endpoints between both SoC + D and SoC + D + O vs. SoC:

	• PFS2 • OS • ORR • DoR • TFST • TSST • TDT • Pharmacokinetic sampling • EORTC QLQ-C30 • EORTC QLQ-EN24 • Safety and tolerability analyses Secondary endpoints are defined in Appendix M.
Exploratory endpoints (relevant to the submission)	Exploratory endpoints included: • PFS for SoC + D + O • s. SoC + D • OS for SoC + D + O vs. SoC + D • EQ-5D-5L
Pre-planned subgroup analyses	Subgroup analyses of PFS were performed to assess the consistency of treatment effect across potential or expected prognostic/predictive factors, including the following subgroups of the ITT: • MMR status (pMMR, dMMR) • Disease status (newly diagnosed EC, recurrent EC) • Region (Asia, RoW) Other baseline variables were also assessed as there was clinical justification to do so or because there were imbalances between treatment arms, including: • Age (<65, ≥65 years) • Race (White, Black or African American, Asian, Other) • HRRm status (HRRm, non-HRRm, unknown) • PD-L1 expression (positive, negative, unknown) • Histology (endometrioid, serous, other) • Histological grade (low grade, high grade) • ECOG performance status (normal activity, restricted activity) • FIGO stage in newly diagnosed patients (stage III, stage IV)
Duration of study and follow-up	Data from the DCO1 (12 April 2023) represent a median duration of follow-up in censored patients of 15.4 months in the SoC + D and SoC + D + O arm, and 12.6 months in the SoC arm.

Source: Westin *et al.* (2023)[4]

B.2.3.3 Baseline characteristics and study participants

The demographic and key baseline characteristics in the ITT were well-balanced across the treatment arms (Table 6). Overall, patients had a median age of 64 years, with 46.9% of patients aged ≥65 years. The majority of patients were White (57.4%) and there were similar proportions of patients with newly diagnosed advanced (47.6%) and recurrent disease (52.4%). Other disease characteristics were also broadly aligned across treatment arms (Table 7); the majority of patients had EC that was pMMR (80.1%) with endometroid histology (60.2%) and had an ECOG score of 0 (66.6%). Stratification factors recorded at randomisation are presented in Appendix M. Details of baseline biomarker characteristics can be found in Table 7.

Overall, UK clinical expert feedback indicated that the population enrolled in the DUO-E trial is broadly generalisable to patients with newly diagnosed advanced or recurrent EC in UK clinical practice and that there were no areas of significant concern which would hinder their ability to interpret and apply the data to UK patients.[1]

With regards to demographic characteristics, clinical feedback was that whilst there was a relatively high proportion of Asian patients in the DUO-E trial, this could be considered a positive aspect of the trial, as these patients are often under-represented in clinical trials (for example, RUBY I). Nevertheless, clinical experts noted that they would not expect the tolerability of either regimen to differ based on ethnic group.[1]

With regards to disease characteristics, clinical experts suggested that the relatively low number of patients enrolled with FIGO stage III disease compared to stage IV may be due to the inclusion criteria in the DUO-E trial, which specified that patients must have measurable disease. However, this was not considered to be of concern, and as such, clinicians indicated that they would still consider SoC + D and SoC + D + O in their licensed populations for patients with stage III EC.[1] Additionally, the proportion of patients who had received surgery for their EC was considered to be broadly aligned to what is seen in UK practice, as it was noted that most patients would receive some type of surgery in clinical practice, consistent with the DUO-E trial population.[1]

Baseline characteristics for the populations of particular relevance to decision-making are further presented in Section B.2.7, with baseline characteristics for the dMMR population found in Section B.2.7.2 and those for the pMMR population in Section B.2.7.4.

Table 6. Baseline patient demographics and characteristics in the ITT

Characteristic	SoC (N=241)	SoC + D (N=238)	SoC + D + O (N=239)	Total (N=718)
Age (years)				
Mean (standard deviation [SD])	62.1 (10.36)	63.3 (9.82)	62.4 (9.90)	62.6 (10.03)
Median (min–max)	64.0 (31–85)	64.0 (22–84)	63.0 (27–86)	64.0 (22–86)
Age group, years, n (%)				
<65	124 (51.5)	122 (51.3)	135 (56.5)	381 (53.1)
≥65	117 (48.5)	116 (48.7)	104 (43.5)	337 (46.9)
Race, n (%)				
White	143 (59.3)	136 (57.1)	133 (55.6)	412 (57.4)
Asian	73 (30.3)	72 (30.3)	70 (29.3)	215 (29.9)
Black or African American	10 (4.1)	11 (4.6)	14 (5.9)	35 (4.9)
Other	10 (4.1)	8 (3.4)	12 (5.0)	30 (4.2)
American Indian or Alaska Native	0	6 (2.5)	6 (2.5)	12 (1.7)
Native Hawaiian or Other Pacific Islander	2 (0.8)	0	1 (0.4)	3 (0.4)
Not reported	3 (1.2)	5 (2.1)	3 (1.3)	11 (1.5)
Time from initial diagnosis to randomisation (weeks) – newly diagnosed patients				
n	114	113	112	339
Mean (SD)	8.8 (4.49)	9.8 (6.11)	10.1 (14.02)	9.6 (9.17)
Median (min–max)	7.7 (3–29)	8.3 (3–35)	7.6 (3–150)	7.9 (3–150)
Time from initial diagnosis to randomisation (weeks) – recurrent patients				
n	127	125	127	379

Mean (SD)	178.8 (149.43)	166.8 (112.17)	161.3 (131.60)	169.0 (131.90)
Median (min–max)	129.1 (8–804)	132.0 (7–556)	120.9 (24–909)	126.1 (7–909)
Time from recent progression to randomisation (weeks) – recurrent patients				
n	127	124	127	378
Mean (SD)	8.3 (9.98)	8.4 (8.10)	8.0 (5.86)	8.2 (8.13)
Median (min–max)	6.3 (0–87)	6.9 (0–59)	6.9 (1–34)	6.7 (0–87)

Source: DUO-E CSR;[11] Westin *et al.* (2023)[4]

Table 7. Disease characteristics in ITT

Characteristic/extent, n (%)	SoC (N=241)	SoC + D (N=238)	SoC + D + O (N=239)	Total (N=718)
ECOG performance status				
(0) Normal activity	156 (64.7)	156 (65.5)	166 (69.5)	478 (66.6)
(1) Restricted activity	85 (35.3)	81 (34.0)	73 (30.5)	239 (33.3)
(2) In bed ≤50% of the time	0	1 (0.4)	0	1 (0.1)
Histology type[a]				
Endometrioid	139 (57.7)	141 (59.2)	152 (63.6)	432 (60.2)
Serous	54 (22.4)	58 (24.4)	42 (17.6)	154 (21.4)
Carcinosarcoma	21 (8.7)	12 (5.0)	18 (7.5)	51 (7.1)
Mixed, epithelial	11 (4.6)	9 (3.8)	9 (3.8)	29 (4.0)
Other	6 (2.5)	9 (3.8)	5 (2.1)	20 (2.8)
Clear cell	7 (2.9)	4 (1.7)	8 (3.3)	19 (2.6)
Undifferentiated	3 (1.2)	4 (1.7)	5 (2.1)	12 (1.7)
Mucinous	0	1 (0.4)	0	1 (0.1)
FIGO stage[a]				
Stage I–II	77 (32)	78 (32.7)	73 (30.5)	228 (31.8)
Stage III	42 (17.4)	50 (21.0)	45 (18.8)	137 (19.1)
Stage IV	120 (49.8)	110 (46.2)	120 (50.2)	350 (48.7)
Missing	2 (0.8)	0	1 (0.4)	3 (0.4)
Recurrence of earlier cancer[b]				
Yes	127 (52.7)	125 (52.5)	127 (53.1)	379 (52.8)
No	114 (47.3)	113 (47.5)	112 (46.9)	339 (47.2)
Baseline overall disease classification				
Metastatic[c]	206 (85.5)	201 (84.5)	193 (80.8)	600 (83.6)
Locally advanced[d]	22 (9.1)	25 (10.5)	29 (12.1)	76 (10.6)
Missing	13 (5.4)	12 (5.0)	17 (7.1)	42 (5.8)
MMR status per central laboratory[b]				
Proficient	192 (79.7)	191 (80.3)	192 (80.3)	575 (80.1)
Deficient	49 (20.3)	46 (19.3)	46 (19.2)	141 (19.6)
Unknown	0	1 (0.4)	1 (0.4)	2 (0.3)
Debulking surgery history				

Yes	202 (83.8)	205 (86.1)	207 (86.6)	614 (85.5)
No	39 (16.2)	33 (13.9)	32 (13.4)	104 (14.5)
Unknown	0	0	0	0
Prior chemotherapy				
Yes	51 (21.2)	51 (21.4)	54 (22.6)	156 (21.7)
No	190 (78.8)	187 (78.6)	185 (77.4)	562 (78.3)
Biomarker, n (%)				
PD-L1[e]				
Positive	163 (67.6)	170 (71.4)	150 (62.8)	483 (67.3)
Negative	75 (31.1)	61 (25.6)	82 (34.3)	218 (30.4)
Unknown	3 (1.2)	7 (2.9)	7 (2.9)	17 (2.4)
HRRm				
HRRm	32 (13.3)	26 (10.9)	39 (16.3)	97 (13.5)
Non-HRRm	132 (54.8)	138 (58.0)	141 (59.0)	411 (57.2)
Unknown[f]	77 (32.0)	74 (31.1)	59 (24.7)	210 (29.2)

Footnotes: [a] Pathology-related disease characteristics were collected at the time of primary diagnosis of disease under investigation; [b] Mismatch repair status (proficient vs. deficient) was per central laboratory result using the FDA-cleared Class II Ventana MMR IHC panel (based on evaluation of tumour cells from a FFPE tumour tissue sample) and disease status (recurrent vs. newly diagnosed) was as collected on the electronic case report form (eCRF). Two patients with "unknown" MMR status per central laboratory were randomised as "deficient" per interactive voice response (IVRS) based on local testing. Two additional patients were mis-stratified in IVRS (one patient: dMMR per central laboratory was randomised as pMMR per IVRS; one patient: pMMR per central laboratory was randomised as dMMR per IVRS). [c] Metastatic disease – patient had any metastatic site of disease; [d] Locally advanced – patient had only locally advanced sites of disease. [e] The Ventana SP263 PD-L1 assay was used: PD-L1 positive samples were samples with PD-L1 expression with a tumour area positivity score ≥ 1%; PD-L1 negative samples were samples with PD-L1 expression with a tumour area positivity score < 1%; and PD-L1 unknown samples were samples with PD-L1 expression not available either due to a test fail (unevaluable sample or assay failure) or sample slide out of cut-slide stability; [f] Retrospective testing of HRRm status was by the FoundationOne® CDx tumour tissue next-generation sequencing (NGS) assay (FoundationOne® CDx-P170019/S017). Per data on file, the unknown samples included 26 patients with a failed FoundationOne® CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China Human Genetic Resources regulations).
Source: DUO-E CSR;[11] Westin *et al.* (2023)[4]

B.2.3.4 Patient disposition

A total of 718 patients underwent randomisation in a 1:1:1 ratio to receive either SoC (241 patients), SoC + D (238 patients), or SoC + D + O (239 patients). Of patients who were randomised, 709 (98.7%) received any study treatment: five patients in the SoC arm, three patients in the SoC + D arm, and one patient in the SoC + D + O arm did not receive any treatment.

In order to be eligible to continue treatment into the maintenance phase of the trial, patients had to have received between 4 and 6 cycles of chemotherapy, and in order to commence olaparib (or olaparib placebo) they must have had adequate organ and bone marrow function (detailed maintenance phase eligibility criteria are outlined in the CSR).[11] In total, 544 (75.8%) of the patients who were randomised met these criteria and continued to receive treatment into the maintenance phase of the study (i.e. received at least one dose of olaparib or olaparib placebo). By arm, the proportion of patients who entered the maintenance phase in the SoC + D and SoC + D + O arms were similar (76.9% and 80.3%, respectively), whilst the proportion who entered the maintenance phase in the SoC arm was lower (70.1%). These data indicate that of those patients who did not continue into the maintenance phase, the majority were randomised into the SoC arm, suggesting

that SoC + D and SoC + D + O are associated with improved clinical outcomes vs. SoC arm.

At the time of the DCO1 (12 April 2023) the number of patients remaining on durvalumab/placebo was 42 (17.8%) in the SoC arm, 71 (30.2%) in the SoC + D + O arm, and 94 (39.5%) in the SoC + D + O arm. The number of patients remaining on olaparib/placebo was 39 (23.1% of those who received at least one dose of olaparib/placebo) in the SoC arm, 70 (38.3%) in the SoC + D arm, and 86 (44.8%) in the SoC + D + O arm.

At the time of DCO1, discontinuations of platinum-based chemotherapy were similar across all treatment arms (~13% in each arm), with cycles of carboplatin and paclitaxel the same across all treatment groups as per protocol. A total of 502 patients had discontinued durvalumab/placebo, consisting of 194 (82.2% of those who had received at least one dose of durvalumab/placebo) in the SoC arm, 164 (69.8%) in the SoC + D arm, and 144 (60.5%) in the SoC + D + O arm, with the most common reason for discontinuation being cited as objective disease progression (SoC: 143 [60.6%], SoC + D: 113 [48.1%], SoC + D + O: 104 [43.7%]). A total of 349 patients had discontinued olaparib/placebo, and these consisted of 130 (76.9% of those who received at least one dose of olaparib/placebo) in the SoC arm, 113 (61.7%) in the SoC + D arm, and 106 (55.2%) in the SoC + D + O arm, with the most common reason for discontinuation of olaparib also being cited as objective disease progression (SoC: 109 [64.5%], SoC + D: 94 [51.4%], SoC + D + O: 73 [38.0%]). Further details on the patient disposition are presented in Appendix D.

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

Efficacy and safety analyses were performed in accordance with a detailed Statistical Analysis Plan.[99] The definitions used for the study populations in the trial are presented in Table 8. All safety and efficacy analyses presented are from the primary DCO (12 April 2023). A summary of the statistical analysis methods used in the trials are presented in Table 9.

Table 8. Trial populations used for the analysis of outcomes in DUO-E of relevance to decision making

Analysis Set or population	Definition	Outcomes analysed
Full analysis set (FAS): ITT (n=718)	The FAS included all randomised patients and compared the treatment groups based on the principles of intent-to-treat i.e. regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomised.	Efficacy and HRQoL
Safety analysis set (SAS; n=709)	All randomised patients who received any amount of study treatment. Safety data were not formally analysed but summarised using the safety analysis set. In order to provide a summary of the underlying safety profile that patients should expect on being initially prescribed treatment, patients who initially received a dose of durvalumab/placebo were summarised according to the arm to which they were randomised.	Safety
dMMR population: SoC and SoC + D treatment arms (n=95)[a]	Tumour MMR status was determined prior to randomisation based on evaluation of MMR status in tumour cells from a FFPE tumour tissue sample, using the Food and Drug Administration-cleared Class II Ventana MMR immunohistochemistry panel. Patients with	Efficacy, HRQoL and safety

	MMR deficient tumours were included in the dMMR population.	
pMMR population: SoC and SoC + D + O treatment arms (n=383)[a]	Tumour MMR status was determined prior to randomisation based on evaluation of MMR status in tumour cells from a FFPE tumour tissue sample, using the Food and Drug Administration-cleared Class II Ventana MMR immunohistochemistry panel. Patients with MMR proficient tumours were included in the pMMR population.	Efficacy, HRQoL and safety

Footnotes: Patient numbers per IVRS.
Source: DUO-E CSR.[11]

Table 9. Statistical methods for the primary analysis

Hypothetical objective	The DUO-E study was designed to test two key hypotheses of interest: • Durvalumab in combination with carboplatin and paclitaxel, followed by maintenance durvalumab (SoC + D) has superior efficacy and acceptable tolerability as compared with carboplatin and paclitaxel alone (SoC) in patients with advanced or recurrent EC, and • Durvalumab in combination with carboplatin and paclitaxel, followed by maintenance durvalumab with olaparib (SoC + D + O) has superior efficacy and acceptable tolerability as compared with carboplatin and paclitaxel alone (SoC) in patients with advanced or recurrent EC
Statistical analysis	• The primary statistical analyses of the efficacy of SoC + D and SoC + D + O included all randomised patients (ITT) and compared treatment groups on the basis of randomised treatment, regardless of treatment actually received (ITT; Table 8) . • Safety data was analysed in the SAS (as defined in Table 8), which included all randomised patients who received at least one dose of investigational treatment (durvalumab/placebo or olaparib/placebo). For the maintenance phase, safety data were summarised in patient who received at least one dose of olaparib/placebo maintenance treatment. **Primary endpoint: PFS** • The primary PFS analysis for each comparison was performed separately using a stratified log-rank test for generation of P values, with HRs and 95% CIs estimated using a stratified Cox proportional hazards (CPH) model. • Kaplan–Meier (KM) plots were presented by treatment arm and were used to estimate the median PFS and the proportion of patients who were progression free at landmark timepoints (6, 12, and 18 months). • The PH assumption was tested by fitting a Cox model with a treatment-by-time interaction. Subgroup analyses were conducted using Cox PH models to determine the consistency of treatment effect across potential or expected prognostic factors. **Key secondary endpoints** • Analyses of secondary time-to-event endpoints used similar methods to PFS. Full details can be found in the CSR and statistical analysis plan (SAP) provided alongside this submission.
Sample size, power calculation	• It was planned that approximately 699 patients were recruited and randomised (1:1:1) into the study, with randomisation stratified according to tumour tissue's MMR status, disease status, and geographic region, in order to achieve approximately 299 PFS events (equating to data maturity of 64%) for the comparison of the SoC + D arm vs. SoC, and approximately 281 PFS events (equating to data maturity of 60%) for the comparison of the SoC + D + O vs. SoC. • Assuming a median PFS of 12 months for the SoC arm and an average true PFS HR of 0.70 for SoC + D vs. SoC and 0.55 for SoC + D + O vs. SoC, the

	study had 80% and >99% power to demonstrate a statistically significant difference for PFS at the overall two-sided significance level of 2.5% for each comparison, respectively. The assumptions included a 27-month period of recruitment, with an approximately 10% uniform dropout rate over the study period. The sample size has been derived on the assumption of a 3-month delay in separation of the PFS curves between SoC + D vs. SoC, and between SoC + D + O vs. SoC.
Data management, patient withdrawals	**Patient withdrawals** • Patients were free to withdraw from the study at any time at their own request without prejudice to further treatment (withdrawal of consent). Such patients were always asked about the reason(s) and the presence of any AEs. These patients were then followed up by the Investigator as medically indicated. • If a patient withdrew consent (i.e., no further assessment or collection of their data) they were specifically asked if they were also withdrawing consent to further participation in the study, including any follow-up (e.g. survival calls), disclosure of future information, and the use of any of their samples taken during the trial. • At the end of the study, AstraZeneca or its delegate requested that Investigators collect information of patients' vital status from publicly available sources, in accordance with local regulations. Knowledge of vital status at study end in all patients was deemed crucial for the integrity of the study. **Data management** • Any genotype data generated in the study was stored at a secure system at AstraZeneca and/or organisations designated to analyse the samples. • AstraZeneca and its designated organisations were able to share summary results from this genetic research with other researchers, which was achieved by placing the results in scientific databases, where they could be combined with the results of similar studies. Researchers were only permitted to use this information for health-related research purposes and could only view summary results rather than any individual patient data or personal identifiers. • It was permitted that some or all of the clinical datasets from the main study could be merged with the genetic data in a suitable secure environment separate from the clinical database.
Multiplicity	• An MTP with a gatekeeping strategy was employed across the key endpoints (PFS and OS) and treatment comparisons of interest (SoC + D vs. SoC, and SoC + D + O vs. SoC) in order to strongly control the Type I error at 5% (2-sided). • OS survival was to be tested at multiple timepoints and the OS tests for the same comparison were to be considered as one test family. • If any interim analysis or primary analysis was statistically significant, the overall alpha (2-sided) was to be allocated to the next level. • If the interim results did not meet the stopping criterion for superiority for a given hypothesis, the follow-up would continue until the final target number of OS events for that comparison had been observed, followed by re-testing of that hypothesis. • If the null hypothesis was then rejected, subsequent testing would continue hierarchically.

Source: DUO-E CSR.[11] DUO-E CSP.[5] Westin *et al.* (2023).[4]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment, can be found in

Company evidence submission template for durvalumab with platinum-based chemotherapy, then with or without olaparib, for newly diagnosed advanced or recurrent EC [ID6317]

Appendix D. A summary of the quality assessments conducted based on the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs for the DUO-E trial is presented in Table 10.

Table 10. Assessment of quality and risk of bias in the DUO-E trial

Criteria	Response	Notes
Was randomisation carried out appropriately?	Yes	Patients were centrally assigned to randomised study treatment in a 1:1:1 ratio. Assignment to treatment group was determined by a computer-generated random sequence using an interactive web response (IWRS). In order to minimise any imbalance in the number of patients assigned to each treatment group, a blocked randomisation was generated, and all centres used the same list.
Was the concealment of treatment allocated adequate?	Yes	Treatment group assignment was determined by computer-generated random sequence using an IWRS. Randomisation codes were assigned strictly sequentially, within each stratum, as patients became eligible for randomisation. The IWRS provided the kit identification number to be allocated to the patient at the randomisation visit and subsequent treatment visits.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	In the ITT, baseline characteristics (Table 6) and disease characteristics (Table 7) were well-balanced between the three treatment arms. Stratification was performed prior to randomisation and details of stratification factors in the ITT can be found in Appendix M.
Were the care providers, participants, and outcomes assessors blind to treatment allocation?	Yes	The actual treatment administered to patients was determined by the randomisation scheme in the IVRS/IWRS. Patients who were not allocated to receive durvalumab/olaparib received placebo forms of durvalumab/olaparib to further ensure effective blinding. The IVRS/IWRS allocated a kit identification number to be allocated to each patient at the dispensing visit, and provided this number to the Investigator(s) or pharmacists. The randomisation code was not to be broken except in medical emergencies, if in the opinion of the Investigator it was in the patient's best interest for the Investigator to know the study treatment. Randomisation codes were not broken for the planned analyses of data until database lock for the primary PFS analysis or interim analysis and all decisions on the evaluability of the data from each individual patient have been made and documented.
Were there any unexpected imbalances in dropouts between groups?	No	The proportion of patients who withdrew or were discontinued from the study were balanced between the groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The reported outcomes aligned with those presented in the clinical study protocol, and study methods provided.

Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Efficacy analysis was ITT and safety analysis were modified ITT (SAS; Table 8). No methods were used to account for missing data.

Source: DUO-E CSP[5], DUO-E CSR[11]

B.2.6 Clinical effectiveness results of the relevant studies

The following sections present the clinical effectiveness results for the DUO-E trial, with a focus on the endpoints specified in the decision problem. Aligning with the coprimary objectives of the DUO-E trial and considering the endpoints of greatest relevance to decision-making, PFS and OS results within the ITT will be presented first in Sections B.2.6.1.1 and B.2.6.1.2, respectively. All other key secondary endpoints are summarised in Table 11 with full details available within the DUO-E CSR provided alongside this submission. . As SoC + D and SoC + D + O are only anticipated to be licensed within subpopulations of the ITT in DUO-E (dMMR and pMMR, respectively), these results are provided only for completeness.

Subsequently, to reflect the subgroups specified in the NICE scope (Section B.1.1), pre-specified subgroup analyses for the DUO-E primary endpoint of Investigator-assessed PFS are presented in Section B.2.7.1, with a focus on the results by MMR status (i.e. the target populations for this appraisal). Finally, to address the decision problem for this appraisal, results for all endpoints specified in the decision problem will be presented for SoC + D in the dMMR population (Section B.2.7.3), followed by results for SoC + D + O for the pMMR population (Section B.2.7.5).

Analyses presented for each target population include pre-specified Investigator-assessed PFS subgroup analyses by MMR status (initially discussed in Section B.2.7.1), as well as *post hoc* analyses for all other endpoints of interest. Baseline characteristics are also presented for both subgroups, with data for the dMMR subgroup presented in Section B.2.7.2 and for the pMMR subgroup in Section B.2.7.4. It should be noted that efficacy results for the dMMR and pMMR subgroups are not controlled for Type I error.

B.2.6.1 Results in the intention-to-treat population (ITT)

Overall, the DUO-E trial met its coprimary objectives, demonstrating a statistically significant and clinically meaningful PFS benefit for both SoC + D vs. SoC and SoC + D + O vs. SoC within the ITT (Section B.2.6.1.1). Statistical and clinically meaningful benefits of SoC + D and SoC + D + O vs. SoC were also demonstrated amongst the secondary efficacy endpoints (Section B.2.6.1.2–B.2.6.1.4).

B.2.6.1.1. Primary efficacy outcome: PFS at DCO1 (12 April 2023)

Achieving improvements in PFS represents a key treatment aim, as prolonging PFS can alleviate the disease burden associated with EC for patients and their families, given the correlation between disease progression and poor HRQoL for patients with advanced or recurrent EC.[11,100] Additionally, PFS functions as a surrogate marker for OS, with a strong positive association between PFS and the probability of future OS in the treatment of advanced or recurrent EC.[101] As highlighted in TA963, first-line systemic treatments that can reduce the chance of disease recurrence, extend PFS, and offer a better quality of life are of paramount importance for patients with advanced or recurrent EC.[101] Additionally, given that fewer than one third of patients will be able to maintain a suitable performance status following first line therapy to benefit from further treatment, it is imperative that improved progression free intervals are achieved in the first-line setting when more patients are able to tolerate these therapies.

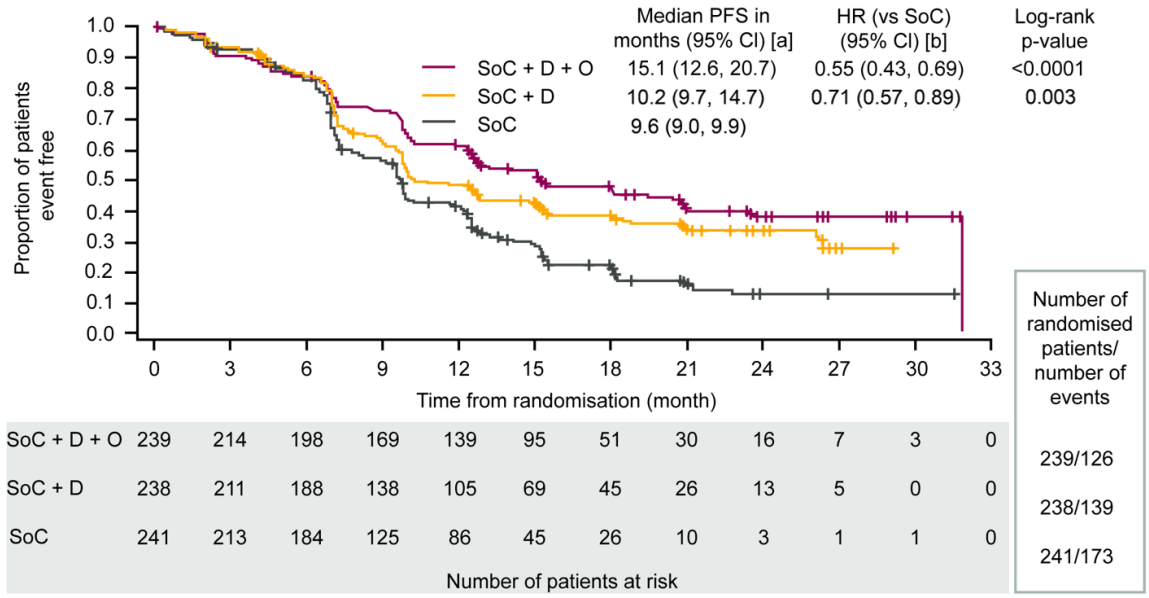
At the time of DCO1 (12 April 2023), both SoC + D and SoC + D + O demonstrated a statistically significant and clinically meaningful improvement in Investigator-assessed PFS compared with SoC in patients with advanced or recurrent EC (Figure 4).

In the SoC + D arm, there was a 29% lower risk of progression or death vs. SoC (median PFS: 10.2 vs. 9.6 months, respectively; HR 0.71; 95% CI 0.57, 0.89; p=0.003). In the SoC + D + O arm, there was a 45% lower risk of progression or death vs. SoC (median PFS: 15.1 vs. 9.6 months, respectively; HR 0.55; 95% CI 0.43, 0.69; p<0.0001).

The KM data for each treatment arm is presented in Figure 4. The curves are similar until approximately 6 months, at which point separation of the three curves is observed. By 18 months, the number of patients who were progression-free was substantially greater both in the SoC + D arm and SoC + D + O arm (37.8% and 46.3%, respectively) compared with the SoC arm (21.7%). The separation of the KM curves upon the addition of maintenance D, and D + O, indicates that these regimens allow patients to continue to maintain their response when they would otherwise have finished receiving treatment with SoC.

A sensitivity analysis demonstrated that PFS results were consistent based on blinded independent central review (BICR) and Investigator assessment for both comparisons (SoC + D vs. SoC: HR 0.74; 95% CI 0.58, 0.94; SoC + D + O vs. SoC: HR 0.55; 95% CI 0.42, 0.70).[11]

Figure 4. Investigator-assessed PFS KM plot in the ITT at DCO1 (12 April 2023)



Footnotes: [a]Calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method. [b]A pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the three treatment arms. The HR and CI were estimated from a CPH model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. [c] The p-value was calculated using a log rank test stratified by variables in (b). + indicates a censored observation.
Source: DUO-E CSR.[11]

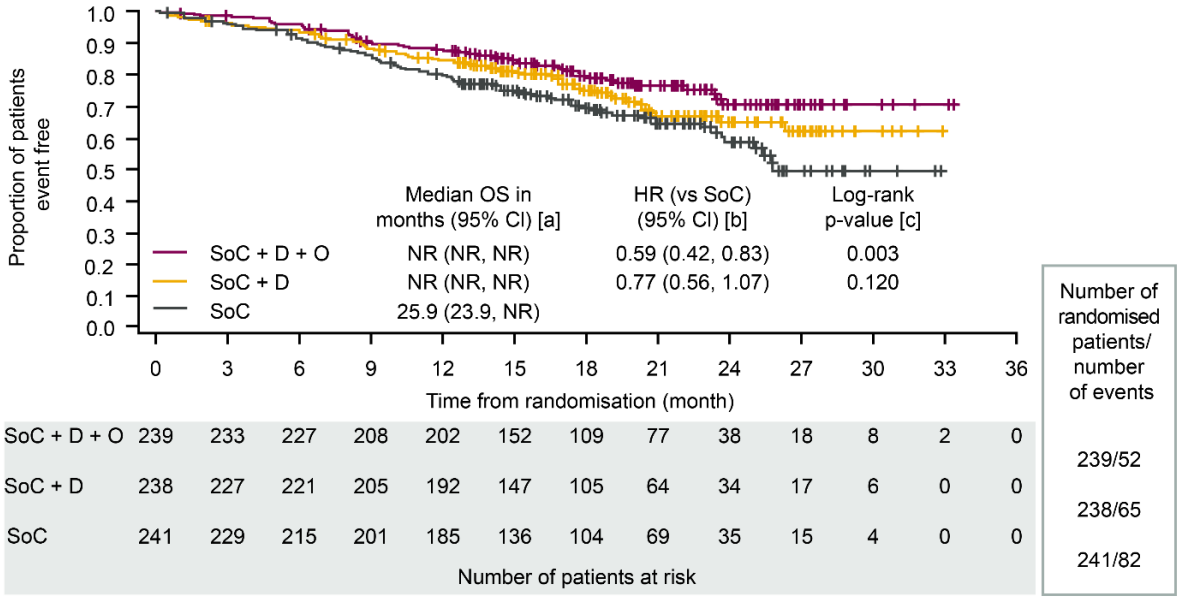
B.2.6.1.2. Key secondary outcome: OS at DCO1 (12 April 2023)

At DCO1 (12 April 2023) in the ITT, 61.0%, 66.8%, and 71.1% of patients in the SoC, SoC + D, and SoC + D + O treatment arms, respectively, were alive and in survival follow-up. The data maturity at the first interim OS analysis in the ITT was 30.7% for the SoC vs SoC + D arms, and 27.9% for the SoC + SoC + D + O arms.[11]

At the first interim analysis of OS, a 2-sided significance level of p<0.0011 was allocated for the comparison of SoC + D vs. SoC and a 2-sided significance level of p<0.0006 was allocated for the comparison of SoC + D + O vs. SoC. The OS HR point estimate showed an improvement for both the SoC + D arm compared with the SoC arm (HR 0.77; 95% CI 0.56, 1.07; p=0.120) and the SoC + D + O arm compared with the SoC arm (HR 0.59; 95% CI 0.42, 0.83; p=0.003), although the results did not reach statistical significance for either comparison (p-value stopping boundary of p<0.0011 and p<0.0006 for SoC + D vs. SoC and SoC + D + O vs. SoC, respectively).

The KM plot for OS is presented in Figure 5, which illustrates the numerical benefit in OS for both SoC + D and SoC + D + O vs. SoC.

Figure 5. OS KM plot in the ITT at DCO1 (12 April 2023)



Footnotes: Calculated using the KM technique. Confidence interval for median OS was derived based on Brookmeyer-Crowley method. [a]Calculated using the KM technique. Confidence interval for median OS was derived based on Brookmeyer-Crowley method. [b]A pooling strategy was applied to the primary comparisons of PFS for SoC + D + O versus SoC and SoC + D versus SoC whereby stratification factors were removed until there were at least 5 events in each stratum of interest across the 3 treatment arms. This analysis was conducted with the same principles. The HR compared to SoC group and CI were estimated from a CPH model with following variables: Unstratified. The CI was calculated using a profile likelihood approach. A HR less than 1 favoured the treatment arm of interest over the reference arm. [c] The p-value was calculated using a log rank test stratified by variables in (b). + indicates a censored observation. 2-sided p-value.
Source: DUO-E CSR.[11]

B.2.6.1.3. Other secondary outcomes

Other secondary outcomes assessed in the ITT included PFS2, TFST, TSST, TDT, ORR, and DoR, which are summarised in Table 11. Overall, the results of these analyses provide further support for the clinical benefits associated with SoC + D and SoC + D + O, with clinically meaningful improvements across all endpoints vs. SoC.

Table 11. Summary of results from other secondary endpoints (ITT)

Endpoint	SoC			SoC + D				SoC + D + O				
	Events, (%)	Median, months	12-month rate, %	Events, (%)	Median, months	12-month rate, %	HR vs. SoC (95% CI)	Events, (%)	Median, months	12-month rate, %	HR vs. SoC (95% CI)	HR vs. SoC + D (95% CI)
PFS2	39.8	19.1	72.2	35.7	22.2	75.3	0.80 (0.59, 1.07)	26.8	NR	83.0	0.55 (0.40, 0.76)	0.69 (0.50, 0.95)
TFST	66.4	11.1	48.0	53.8	14.0	54.6	0.72 (0.57, 0.91)	43.9	21.4	71.8	0.50 (0.39, 0.64)	0.71 (0.54, 0.91)
TSST	38.6	23.9	76.0	31.5	NR	82.3	0.77 (0.57, 1.05)	23.8	NR	85.9	0.57 (0.40, 0.78)	0.73 (0.52, 1.03)
TDT	82.2	8.8	NR	68.5	9.9	NR	0.74 (0.60, 0.91)	58.2	15.1	NR	0.51 (0.41, 0.63)	NR
Endpoint	**Response rate, n (%)**	**Median, months (interquartile range [IQR])**	**12-month rate, %**	**Response rate, n (%)**	**Median, months (IQR)**	**12-month rate, %**	**OR vs. SoC (95% CI)**	**Response rate, n (%)**	**Median, months (IQR)**	**12-month rate, %**	**OR vs. SoC (95% CI**	**OR vs. SoC + D (95% CI**
ORR	109 (55.1)	NA	NA	125 (61.9)	NA	NA	1.32 (0.89, 1.98)	117 (63.6)	NA	NA	1.44 (0.95, 2.18)	NR
DoR	NA	7.7 (5.1–13.5)	32.4	NA	13.1 (6.0–NR)	53.1	NR	NA	21.3 (8.1–29.9)	61.7	NR	NR

Source: DUO-E CSR.[11]

B.2.6.1.4. Health-related quality of life (HRQoL)

Patients with advanced EC often report that EC has a profound negative impact on their HRQoL.[47] Patient reported outcomes included as secondary endpoints in the study were assessed using various instruments that have been reported in the literature to assess the impact of EC on HRQoL. First, the results of the cancer-related tool, EORTC-QLQ-C30 are presented. Second, the results of the EC-specific instrument, EORTC-QLQ-EN24, are presented. Finally, results of the EQ-5D-5L questionnaire are presented.

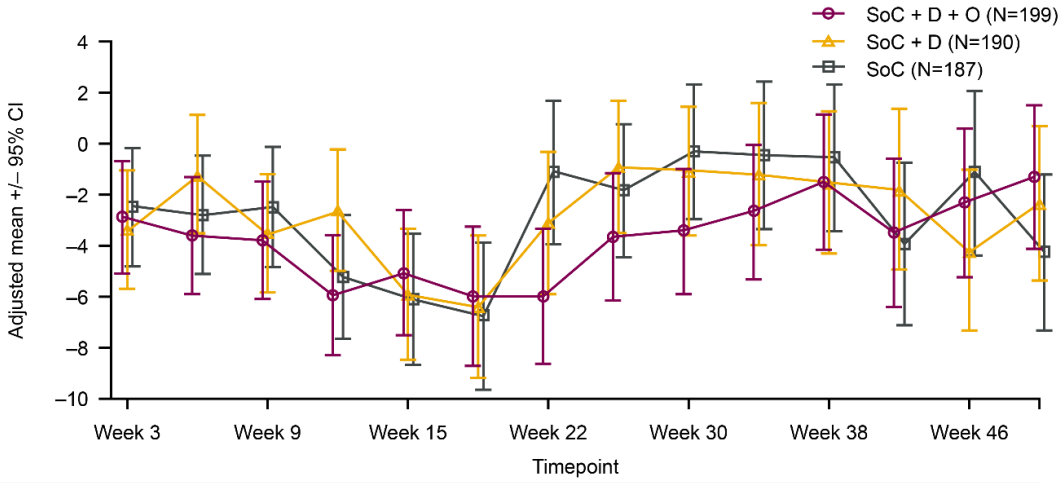
UK clinical expert feedback indicated that HRQoL would not differ based on MMR status.[1]. Therefore, to avoid unduly reducing sample sizes, subgroup analyses of HRQoL data from the DUO-E trial by MMR status were not conducted. HRQoL data for the ITT population of the DUO-E trial presented in the following sections are therefore relevant for both the dMMR and pMMR populations. Furthermore, the EQ-5D-5L data presented below are used in the economic model underpinning this appraisal for both the dMMR and pMMR populations (Section B.1.1).

EORTC-QLQ-C30 at DCO1 (12 April 2023)

The EORTC-QLQ-C30 is an internationally validated HRQoL questionnaire for cancer, and is designed to measure cancer patients' physical, psychological and social functions, comprised of both multi-item scales and single items.[11] Compliance rates with the EORTC-QLQ-C30 were high at baseline (82.1% for the SoC arm, 84.7% for the SoC + D arm, and 87.3% for the SoC + D + O arm), decreasing over time and falling below 60% after Week 30.[11]

For overall HRQoL, the adjusted mean change from baseline averaged across 12 months showed no clinically meaningful deterioration (defined as an absolute change in score of ≥10 points) compared to SoC in either the SoC + D or SoC + D + O arms (−2.8 in the SoC arm, −2.7 in the SoC + D arm and −3.6 in the SoC + D + O arm [lower scores indicate worse HRQoL/functioning]). During the chemotherapy phase, there was an initial decrease in the HRQoL scores compared to baseline in all three treatment arms; however, following completion of the chemotherapy phase there was an increase of functioning, although this improvement was delayed in the SoC + D + O arm when treatment with olaparib started (Figure 6).[11]

Figure 6. EORTC QLQ-C30 change from baseline, plot of adjusted mean in the ITT (±95% CI) at DCO1 (12 April 2023)



SoC + D + O	192	163	156	151	133	126	124
SoC + D	175	164	146	125	126	110	101
SoC	177	158	148	130	118	106	94
				=n:			

Source: DUO-E CSR.[11]

For the physical and role functioning scores, the adjusted mean changes from baseline followed a similar pattern to overall HRQoL, with no deterioration in either SoC + D or SoC + D + O treatment arms compared to SoC from baseline to 12 months.[11]

None of the average changes from baseline over 12 months for the any of the functioning and symptoms scores of the EORTC QLQ-C30 were clinically meaningful (i.e., mean absolute changes were not ≥10 points) in either the SoC + D arm or the SoC arm. Further details are available within the DUO-E CSR.[11]

EORTC-QLQ-EN24 at DCO1 (12 April 2023)

EORTC-QLQ-EN24 is an EC-specific questionnaire, and includes specific questions relating to sexual activity and EC specific symptoms. Compliance rates for the EORTC-QLQ-EN24 were also high at baseline (80.8% in the SoC arm, 80.0% for the SoC + D arm, and 84.8% in the SoC + D + O arm), and decreased over time to fall below 60% by Week 30.[11]

For the EORTC-QLQ-EN24 key symptoms of pain in back and pelvis, gastrointestinal symptoms and urological symptoms, the adjusted mean changes from baseline averaged across 12 months were −4.1, −0.9, and −1.4 in the SoC arm and −4.5, −0.1, and 0.0 in the SoC + D arm and −6.0, −0.4, and −1.1 in the SoC + D + O arm, respectively; none of these adjusted mean changes were clinically meaningful (defined as a mean absolute change of ≥10 points).[11]

Additionally, the overall differences between the SoC and SoC + D treatment arms over 12 months for these key symptoms were not meaningful (estimated difference):

- Pain in back and pelvis: −0.4 (95% CI: −3.8, 3.0)
- Gastrointestinal symptoms: 0.8 (95% CI: −0.9, 2.5)
- Urological symptoms: 1.4 (95% CI: −0.7, 3.5)

For the comparison of SoC + D + O vs. SoC, there were also no clinically meaningful differences (estimated difference):

- Pain in back and pelvis: −2.0; (95% CI: −5.3, 1.4)
- Gastrointestinal symptoms: 0.6; (95% CI: −1.1, 2.2)
- Urological symptom: −0.3; (95% CI: −1.8, 2.3)

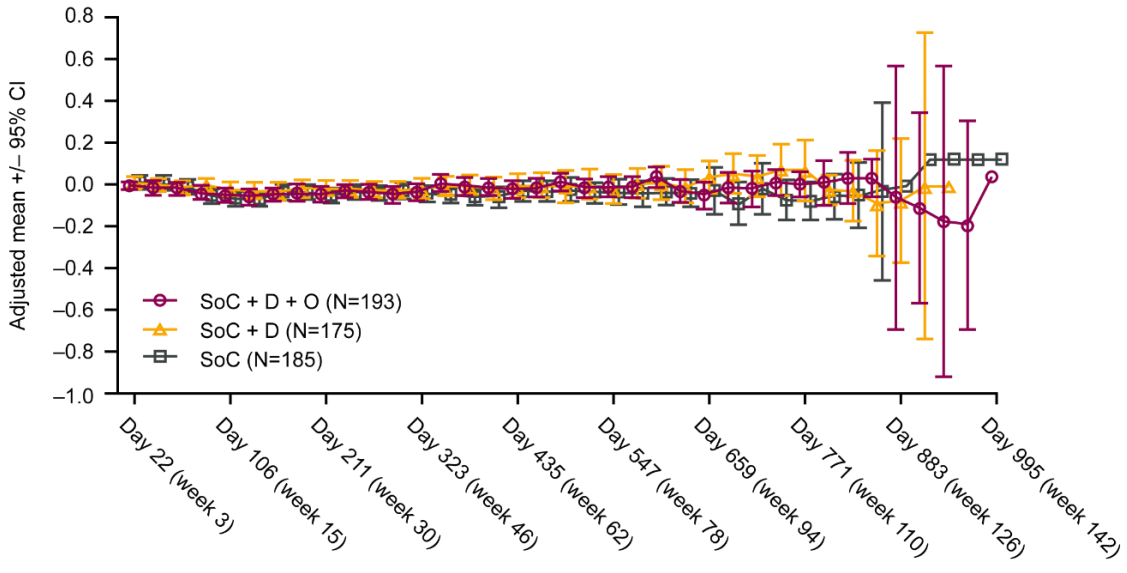
For the EORTC-QLQ-EN24 functioning scores of sexual interest and sexual activity, the adjusted mean changes from baseline averaged across 12 months showed a numerical improvement in the SoC, SoC + D and SoC + D + O treatment arms; however, none of these adjusted mean changes were clinically meaningful.

EQ-5D-5L at DCO1 (12 April 2023)

The EQ-5D-5L, as indicated above, is a generic measure of health status that takes the form of a questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, plus a visual analogue scale (VAS). For the EQ-5D-5L questionnaire, compliance rates were high at baseline and generally similar between arms (80.0% for SoC, 78.7% for SoC + D, and 84.8% for SoC + D + O). Compliance rates decreased over time across the treatment arms and after Week 30 started to fall below 60%.[11]

Baseline EQ-5D-5L scores were comparable for SoC, SoC + D, and SoC + D + O. In all treatment arms, the EQ-5D Index and EQ-VAS were similar between the three treatment arms and remained mostly stable (Figure 7; Table 12).[11]

Figure 7. EQ-5D-5L index score and VAS score, change from baseline in the ITT at DCO1 (12 April 2023)



=n:										
SoC+ D + O	181	148	129	119	84	53	36	16	3	1
SoC + D	160	134	115	93	60	44	26	14	4	0
SoC	170	147	115	92	59	36	12	8	1	1

Footnotes: The y-axis limits are restricted to the range of possible values for EQ-VAS (−100 to 100) and consequently CIs expanding beyond those limits may be truncated.
Source: AstraZeneca. Data on File. 2023.[11]

Table 12: EQ-5D-5L at DCO1 (12 April 2023)

Parameters	SoC	SoC + D	SoC + D + O
EQ-5D-5L VAS Score			
n (Baseline)	192	184	201
Baseline	71.5	71.9	72.0
n (90 weeks)	19	29	47
Change from baseline at 90 weeks	4.3	3.1	−0.1
EQ-5D-5L health state index			
n (Baseline)	192	185	201
Baseline	0.79	0.77	0.78
n (90 weeks)	19	29	47
Change from baseline at 90 weeks	−0.04	−0.00	−0.03

Footnotes: Baseline is defined as last evaluable assessment prior to randomisation.

B.2.7 Subgroup analysis

B.2.7.1 Pre-specified subgroup analyses of Investigator-assessed PFS

As detailed in Table 5, subgroup analyses were explored for the primary endpoint of Investigator-assessed PFS to assess the consistency of treatment effect across potential or expected prognostic/predictive factors. Results of the subgroup analysis by MMR status (the populations of relevance for this appraisal), and other subgroup analyses, are detailed below.

Subgroup analysis by MMR status

In subgroup analysis by MMR status, a global interaction test for the comparison of SoC + D vs. SoC indicated a quantitative interaction involving MMR status, suggesting a numeric difference favouring SoC + D. Specifically, the HR for SoC + D vs. SoC in the dMMR population was notably lower compared with the pMMR population (HR, 0.42; 95% CI 0.22, 0.80 vs. HR, 0.77; 95% CI 0.60, 0.97). These results highlight the substantial clinical benefit for SoC + D in the population with EC that is dMMR, and align with previous reports that pMMR EC are typically more challenging to treat compared with patients with EC that is dMMR (Section B.1.3.7).

Conversely, whilst the global interaction test for SoC + D + O vs. SoC showed no evidence of a difference in treatment effect by MMR subgroup, a much greater numerical clinical benefit was observed for SoC + D + O vs. SoC (HR, 0.57; 95% CI 0.44, 0.73) compared with SoC + D arm vs. SoC in the pMMR population (HR, 0.77; 95% CI 0.60, 0.97). This indicates that the addition of olaparib to durvalumab results in a particular clinical benefit for the pMMR population (HR for SoC + D + O vs. SoC + D, 0.76; 95% CI 0.59, 0.99), who are considered particularly challenging to treat, and suggests that the overall improved results in the SoC + D + O vs SoC + D in the ITT are due to the additional benefit provided by the inclusion of olaparib in the pMMR population.

Importantly, these subgroup analyses demonstrate the clinical benefit associated with SoC + D vs. SoC in the dMMR population and the additional benefits of adding olaparib as part of the SoC + D + O regimen in the pMMR population. As such, these subgroup analysis results strongly support the proposed positioning of these regimens (Section B.1.3.6). Sections B.2.7–B.2.7.5.5 therefore focus on presenting additional evidence to support the clinical benefit of SoC + D in the dMMR population and SoC + D + O in the pMMR population.

Other subgroup analyses

Across all other pre-specified subgroup analyses, HR point estimates were below one and favoured

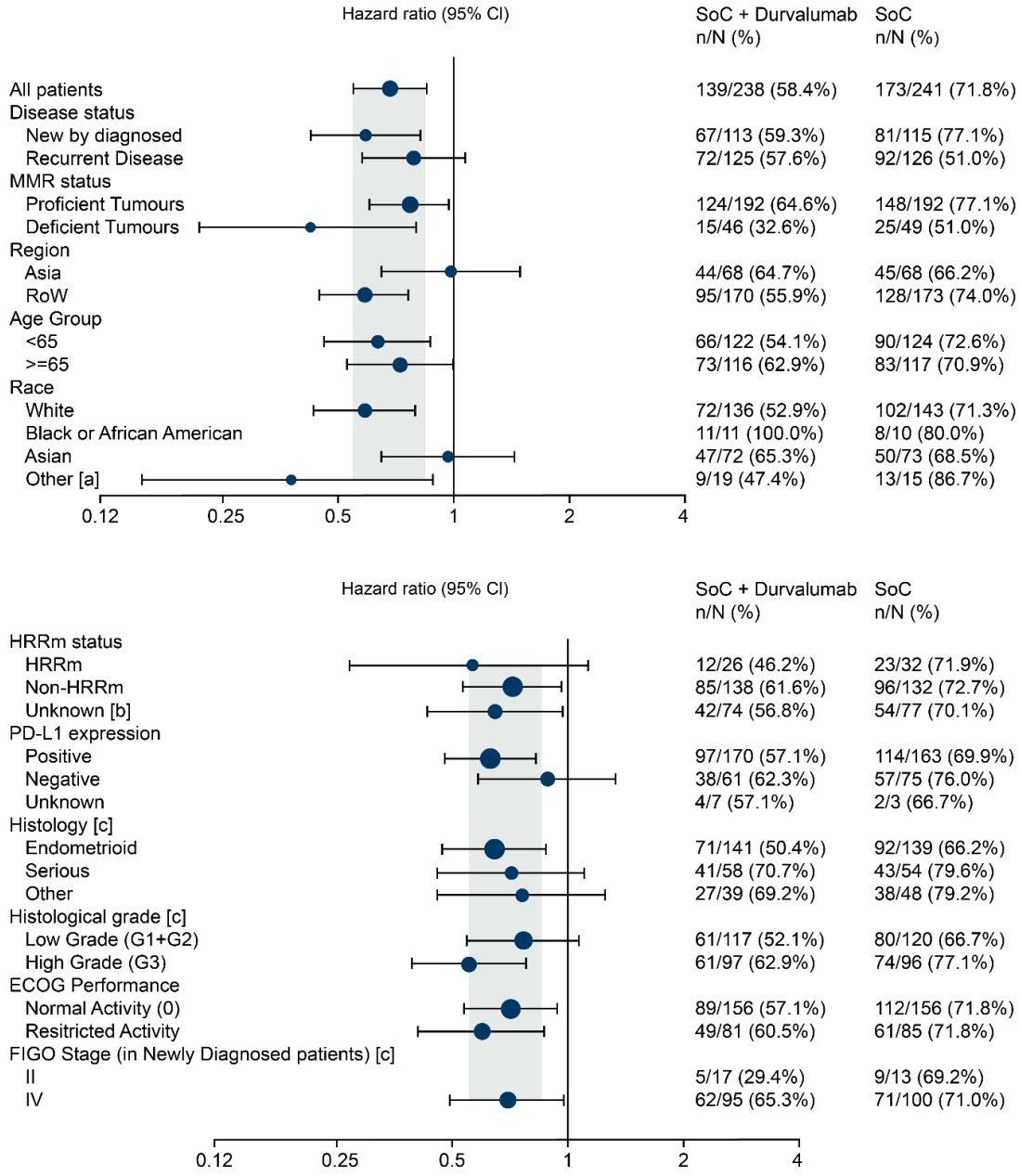
the SoC + D arm for the comparison of SoC + D vs. SoC (Figure 8), consistent with the coprimary endpoint results for the DUO-E trial. This same trend was observed for the comparison of SoC + D + O arm vs. the SoC arm, such that all observed HR point estimates were also below one and favoured the SoC + D + O arm compared to the SoC arm (Figure 9) across all pre-specified subgroups.

For the comparison of SoC + D vs. SoC, the global interaction test indicated (in addition to the MMR status results) a quantitative interaction involving region, suggesting a numeric difference favouring SoC + D. Specifically, there was a greater benefit in PFS for patients in the RoW region compared with the Asia region. However, it should be noted that the clinical relevance of these results is expected to be limited, as it is hypothesised that these results are related to differences in the treatment pathway in Asia vs. RoW rather than any specific demographic characteristics that would be relevant to the eligible population in UK clinical practice.

Across both comparisons (SoC + D vs. SoC and SoC + D + O vs. SoC), a greater PFS benefit was also observed for patients with PD-L1+ expression compared to PD-L1− expression. However, as detailed in Section B.1.3.2.6, PD-L1 does not inform current prescribing decisions, as it has not yet been demonstrated to be a strong driver or predictor of response to currently available treatments in EC. The relevance of these results to clinical practice is therefore limited compared with subgroups based on MMR status when considering the observed data from the DUO-E trial and the current evidence base regarding the role of PD-L1 in EC, particularly given that PD-L1 is seldomly tested in UK clinical practice.[1]

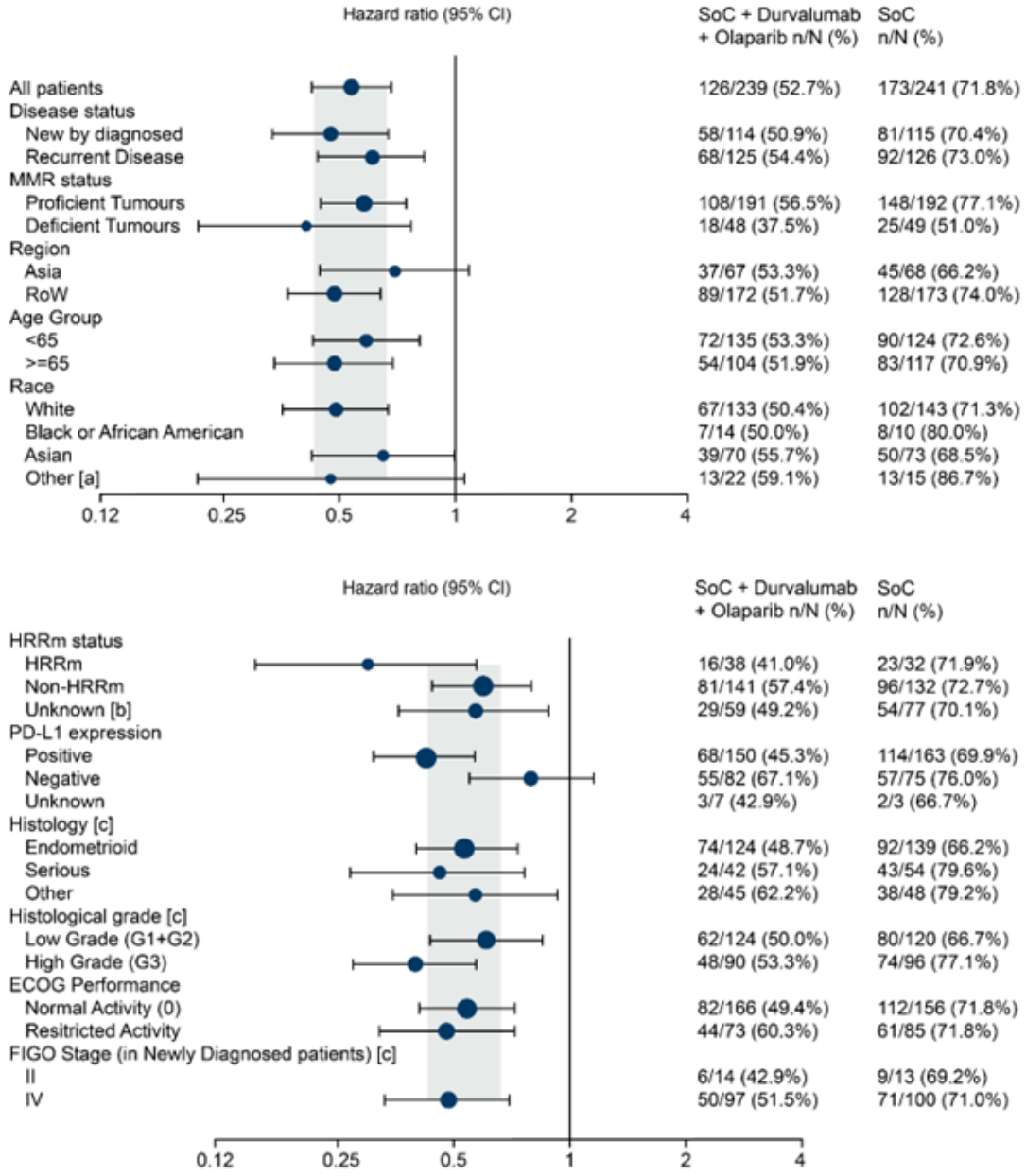
Global interaction tests revealed no further quantitative interactions for either comparison in any other pre-specified subgroup, demonstrating the consistency of the coprimary endpoint results in the DUO-E trial.

Figure 8. PFS forest plot by subgroup (SoC + D vs. SoC)



Footnotes: A HR is not reported for the 'unknown' PD-L1 expression subgroup due to the small number of patients. Size of the circles is proportional to the number of events. The grey band represents the 95% CI for the overall (All patients) HR. [a]Included patients with race "not reported". [b]Retrospective testing of HRRm status was by the FoundationOne® CDx tumour tissue NGS assay. Per data on file, the unknown samples included 26 patients with a failed FoundationOne® CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability. [c]As determined at time of initial diagnosis of disease under investigation. All other subgroups were measured at study baseline. Stratification factors (disease status, MMR status, and region) were based on values entered into IVRS, whereas all other subgroups were based on values recorded on the eCRF or third party vendor data.
Source: DUO-E CSR.[11]

Figure 9. PFS forest plot by subgroup (SoC + D + O vs. SoC)



Footnotes: A HR is not reported for the 'unknown' PD-L1 expression subgroup due to the small number of patients. Size of the circles is proportional to the number of events. The grey band represents the 95% CI for the overall (All patients) HR. [a]Included patients with race "not reported". [b]Retrospective testing of HRRm status was by the FoundationOne® CDx tumour tissue NGS assay. Per data on file, the unknown samples included 26 patients with a failed FoundationOne® CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability. [c]As determined at time of initial diagnosis of disease under investigation. All other subgroups were measured at study baseline. Stratification factors (disease status, MMR status, and region) were based on values entered into IVRS, whereas all other subgroups were based on values recorded on the eCRF or third party vendor data.
Source: DUO-E CSR.[11]

B.2.7.2 Baseline characteristics: SoC + D in the dMMR population

The demographics and key baseline characteristics in the dMMR population (Table 13) were generally comparable to the baseline demographics across treatment arms in the ITT (for characteristics outside the dMMR subgroup definition), with a median age of 64 years and nearly half

of patients aged ≥65.[11, 97] Additionally, there were similar proportions of newly diagnosed advanced patients and recurrent patients to the ITT (approximately 50% of patients in each treatment arm).[11, 97] Disease characteristics are presented in Appendix M.

Table 13. Baseline demographics and patient characteristics in the dMMR population

Characteristic	SoC (N=49)	SoC + D (N=46)
Age (years)		
Mean (SD)	62.4 (10.93)	62.7 (9.04)
Median (min–max)	63.0 (34–85)	63.0 (45–84)
Age group (years), n (%)		
<65	25 (51.0)	25 (54.3)
≥65	24 (49.0)	21 (45.7)
Race, n (%)		
Black or African American	2 (4.1)	0
American Indian or Alaska Native	0	1 (2.2)
Asian	15 (30.6)	14 (30.4)
White	30 (61.2)	29 (63.0)
Other	0	1 (2.2)
Not reported	2 (4.1)	1 (2.2)
Time from initial diagnosis to randomisation (weeks) – newly diagnosed patients		
n	24	20
Mean (SD)	8.7 (4.23)	8.5 (6.13)
Median (min–max)	7.6 (4–22)	6.9 (4–31)
Time from initial diagnosis to randomisation (weeks) – recurrent patients		
n	25	26
Mean (SD)	118.3 (130.35)	147.5 (107.67)
Median (min–max)	78.7 (25–543)	114.6 (7–395)
Time from recent progression to randomisation (weeks) – recurrent patients		
n	25	26
Mean (SD)	7.1 (5.28)	7.1 (4.49)
Median (min–max)	6.1 (2–28)	5.9 (0–18)

Footnote: Disease status (recurrent vs. newly diagnosed) is as collected on the eCRF.
Source: AstraZeneca. Data on File. 2023.[97]

B.2.7.3 Clinical effectiveness results: SoC + D in the dMMR population

As previously detailed in Section B.2.6, this section presents results for each of the key endpoints stipulated within the NICE scope for SoC + D in the dMMR population.

Overall, there was a clinically meaningful improvement in PFS for SoC + D vs. SoC in the dMMR population (Section B.2.7.3.1) alongside clinically meaningful improvements all other key endpoints (Sections B.2.7.3.3–B.2.7.3.4).

B.2.7.3.1. PFS at DCO1 (12 April 2023)

In the dMMR population, SoC + D demonstrated a clinically meaningful improvement in Investigator-assessed PFS when compared to SoC at DCO1 (median PFS: NR vs. 7.0 months, respectively; HR 0.42; 95% CI 0.22, 0.80) with an overall maturity of 40.6%.[97] As summarised in Table 14, there were more PFS events in the SoC arm than the SoC + D arm (25 vs. 15, respectively).

The KM plot for PFS in the dMMR population presented in Figure 10 shows that the SoC and SoC + D arms separate at approximately 4 months from randomisation and separation is maintained in favour of the SoC + D arm throughout the follow up period. Given that SoC is discontinued at 4.5 months, these data suggest that maintenance D beyond 4.5 months in the SoC + D arm is associated with a clear benefit compared to SoC alone, allowing patients to achieve extended PFS compared with those receiving SoC alone and indicating that patients to continue to maintain their response when they would otherwise have finished receiving treatment with SoC. The PFS rate at both 12 and 18 months was also greater in the SoC + D arm vs. the SoC arm, further demonstrating the sustained PFS benefit associated with SoC + D in this population.[97]

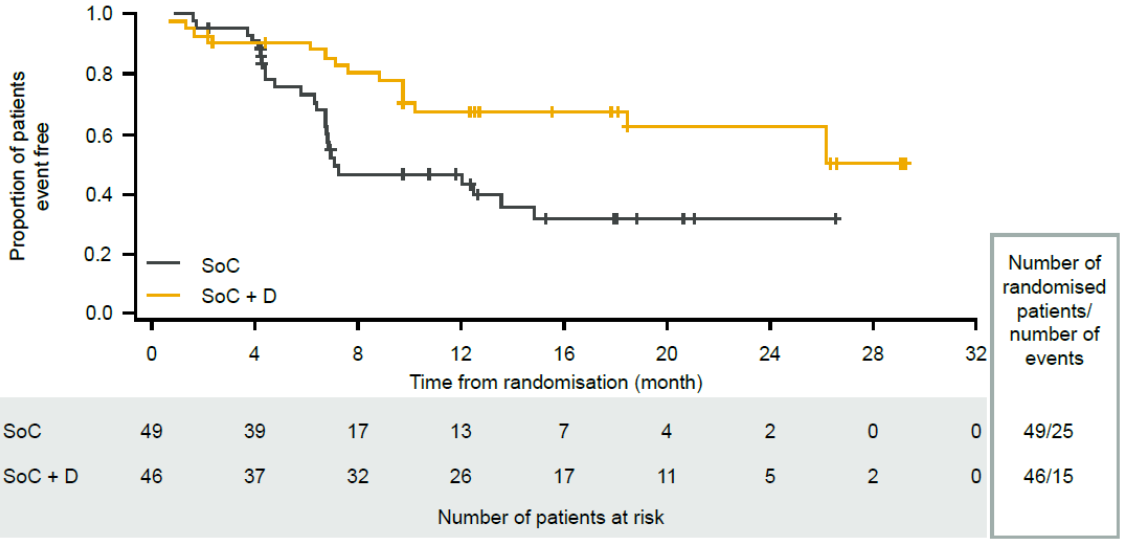
Notably, UK clinicians indicated that the "tail effect" observed in the DUO-E trial is supportive of curative potential, and that this concept supports the use of immunotherapies in the first-line setting to increase the proportion of patients experiencing cure compared with the current SoC.[1]

Table 14. Investigator-assessed PFS in the dMMR population at DCO1 (12 April 2023)

	SoC (N=49)	SoC + D (N=46)
Events, n (%)	25 (51.0)	15 (32.6)
Median, months (95% CI)	7.0 (6.7, 14.8)	NR (NR, NR)
HR (95% CI) vs. SoC	-	0.42 (0.22, 0.80)
PFS rate at 6 months (95% CI)	73.1 (56.6, 84.2)	90.6 (76.9, 96.4)
PFS rate at 12 months (95% CI)	43.3 (27.3, 58.3)	67.9 (51.1, 80.0)
PFS rate at 18 months (95% CI)	31.7 (16.7, 47.9)	67.9 (51.1, 80.0)

Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

Figure 10. KM plot for Investigator-assessed PFS in the dMMR population at DCO1 (12 April 2023)



Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

B.2.7.3.2. OS at DCO1 (12 April 2023)

At DCO1, there were 36.7% of patients in the SoC arm and 15.2% of patients in the SoC + D arm with an OS event; overall, these data had 21.7% maturity.[97] The KM plot for OS in the dMMR population is presented in Figure 11, along with additional details provided in Table 15.

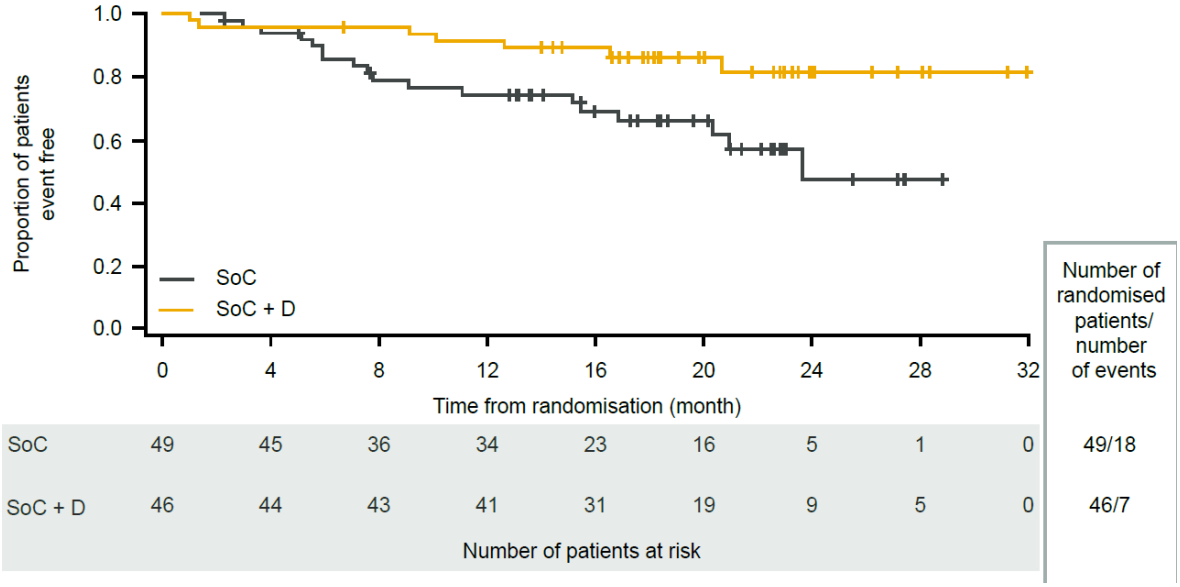
The OS HR point estimate shows a notable improvement for the SoC + D arm compared with the SoC arm (HR 0.34; 95% CI 0.13, 0.79) and suggests a greater OS benefit relative to the PFS benefit (Section B.2.7.3.1). Moreover, the KM curves demonstrate clear signs of separation in favour of SoC + D from ~4 months – approximately the time that maintenance D in the SoC + D arm begins – resulting in an improved OS rate at both 12 and 18 months in the SoC + D arm vs. the SoC arm. These data provide support for the PFS results and clearly demonstrate the OS benefit associated with durvalumab maintenance therapy in the SoC + D arm in the dMMR population.

Table 15. OS in dMMR population at DCO1 (12 April 2023)

	SoC (N=49)	SoC + D (N=46)
Events, n (%)	18 (36.7)	7 (15.2)
Median, months (95% CI)	23.7 (16.9, NR)	NR (NR, NR)
HR (95% CI) vs. SoC	-	0.34 (0.13, 0.79)
OS rate at 6 months (95% CI)	85.3 (71.5, 92.7)	95.7 (83.7, 98.9)
OS rate at 12 months (95% CI)	74.4 (59.4, 84.6)	91.2 (78.2, 96.6)
OS rate at 18 months (95% CI)	65.8 (49.4, 78.0)	86.1 (71.5, 93.6)

Source: AstraZeneca. Data on File. 2023.[97] Baurain, 2024.[103]

Figure 11. KM plot of OS in the dMMR subpopulation at DCO1 (12 April 2023)



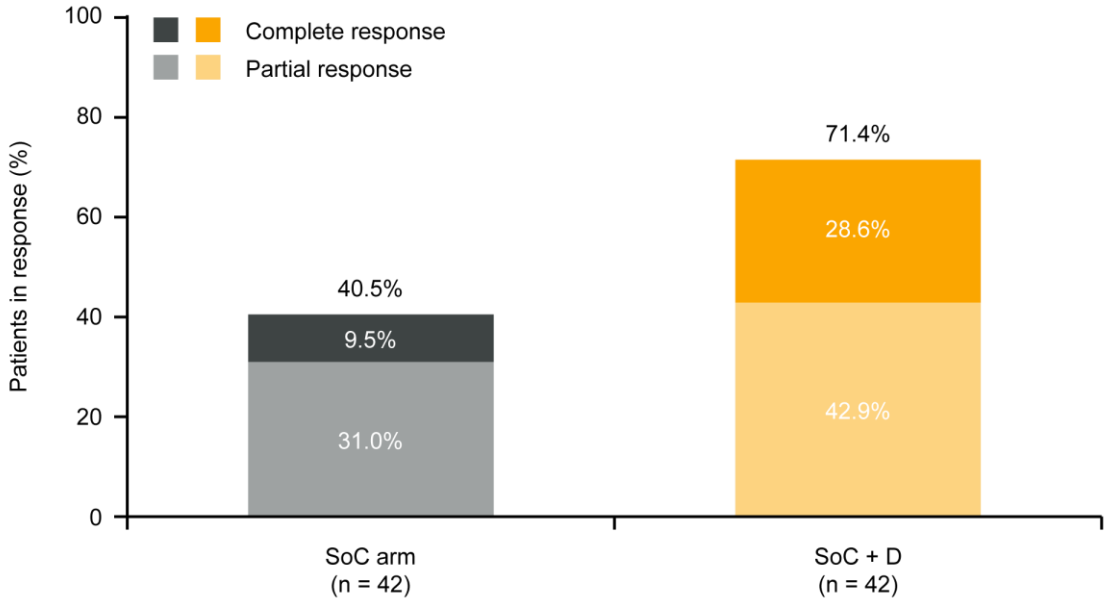
Source: AstraZeneca. Data on File. 2023.[97] Baurain, 2024.[103]

B.2.7.3.3. ORR at DCO1 (12 April 2023)

Overall, a clinically meaningful improvement in ORR was observed for SoC + D (30 patients [71.4%]) when compared with the SoC arm (17 patients [40.5%]) in the dMMR population (OR: 3.68; 95% CI 1.51, 9.39). In the SoC + D arm, 28.6% of patients had a CR compared with 9.5% of patients in the SoC arm (Figure 12). As such, SoC + D was associated with an approximate 3-fold increase in the

proportion of patients achieving CR, whereby patients experienced a complete disappearance of all target lesions.

Figure 12. ORR in the dMMR population at DCO1 (12 April 2023)



Footnotes: n numbers refer to the number of patients with measurable disease at baseline
Source: Chon 2024.[102]

B.2.7.3.4. DoR at DCO1 (12 April 2023)

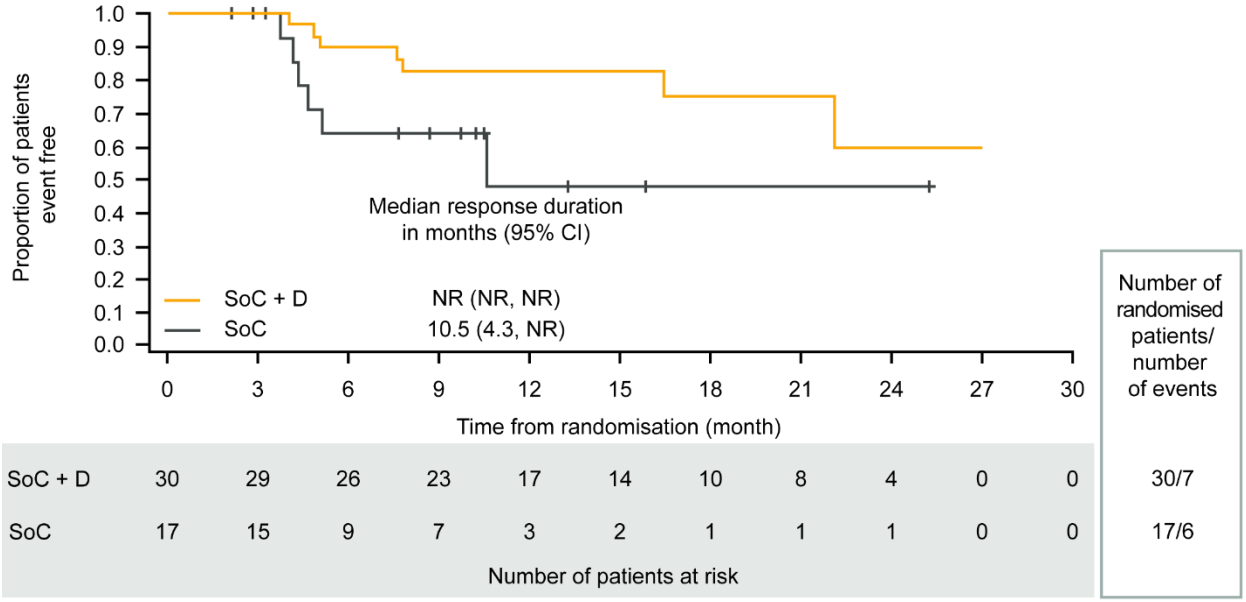
A clinically meaningful improvement in the DoR was observed in the SoC + D treatment arm when compared to SoC (Table 16). Of the patients who achieved a confirmed response, 75.2% in the SoC + D arm maintained a response at 18 months compared with 48.2% in the SoC arm. The KM plot for DoR is shown in Figure 13, which demonstrates a separation in DoR between the arms in favour of SoC + D at approximately ~4 months, the timepoint at which patients discontinue SoC. These data therefore suggest that maintenance D in the SoC + D arm is associated with a clear benefit, allowing patients to maintain their response over a longer duration that those receiving SoC alone.

Table 16. DoR in the dMMR population at DCO1 (12 April 2023)

	SoC (N=49)	SoC + D (N=46)
All patients with confirmed response, n	17	30
Median DoR from onset of response, months (95% CI)	10.5 (4.6, NR)	NR (22.0, NR)
Number remaining in response, %		
18 months	48.2	75.2
24 months	48.2	60.2

Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

Figure 13. DoR KM plot in the dMMR population with confirmed response at DCO1 (12 April 2023)



Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

B.2.7.3.5. Other efficacy endpoints at DCO1 (12 April 2023)

All other secondary outcomes (PFS2, TFST, TSST and TDT) for the comparison of SoC + D with SoC in the dMMR are presented below in Table 17.

A clinically meaningful improvement in PFS2 was observed for the SoC + D arm compared with the SoC arm in the dMMR population (HR 0.32; 95% CI 0.14, 0.68). At DCO1, PFS2 events had occurred for 10 patients (21.7%) in the SoC + D arm compared with 20 patients (40.8%) in the SoC arm. In the dMMR population, SoC + D showed a clinically meaningful improvement compared to SoC for TFST (HR; 0.44; 95% CI 0.23, 0.82) and TSST (HR 0.34; 95% CI 0.15, 0.73). There was a numerical improvement in TDT for the SoC + D arm compared with the SoC arm (HR 0.47; 95% CI 0.27, 0.79).

Notably, whilst SoC + D showed an improvement across all secondary endpoints compared to SoC, the PFS2 and TSST results for SoC + D vs. SoC were marginally better (HR 0.32 and 0.34, respectively) compared with the PFS results (HR 0.42), suggesting that there may be lasting treatment benefits associated with SoC + D even beyond disease progression.

Table 17. Summary of results from other endpoints in the dMMR population at DCO1 (12 April 2023)

Endpoint	SoC			SoC + D			Comparison
	Events, (%)	Median, months (95% CI)	12-month rate, %	Events, (%)	Median, months (95% CI)	12-month rate, %	HR vs. SoC (95% CI)
PFS2	20 (40.8)	15.2 (11.1–NR)	63.7	10 (21.7)	NR (NR–NR)	87.8	0.32 (0.14, 0.68)
TFST	28 (57.1)	8.8 (7.4–NR)	39.9	16 (34.8)	NR (NR–NR)	68.9	0.44 (0.23, 0.82)
TSST	21 (42.9)	16.9 (15.2–NR)	69.1	9 (19.6)	NR (NR–NR)	91.1	0.34 (0.15, 0.73)
TDT	37 (75.5)	6.7 (5.1–7.9)	28.6	22 (47.8)	21.2 (9.3–NR)	58.2	0.47 (0.27, 0.79)

Source: AstraZeneca. Data on File. 2023.

B.2.7.4 Baseline characteristics: SoC + D + O in the pMMR population

The demographics and key baseline characteristics in the pMMR population (Table 18) were generally comparable to the baseline characteristics across treatment arms in the ITT (Section B.2.3.3), with a median age of 64 years across both treatment arms and nearly half of patients aged ≥65.[11, 97] Additionally, there were similar proportions of newly diagnosed advanced patients and recurrent patients to the ITT (approximately half of patients in each group).[11, 97] Disease characteristics are presented in Appendix M.

Table 18. Baseline demographic and patient characteristics in the pMMR population

Characteristic	SoC (n=192)	SoC + D + O (n=191)
Age (years)		
Mean (SD)	62.1 (10.24)	62.7 (10.21)
Median (min–max)	64.0 (31–82)	64.0 (27–86)
Age group (years), n (%)		
<65	99 (51.6)	101 (52.9)
≥65	93 (48.4)	90 (47.1)
Race, n (%)		
Black or African American	8 (4.2)	13 (6.8)
Native Hawaiian or Other Pacific Islander	2 (1.0)	1 (0.5)
American Indian or Alaska Native	0	6 (3.1)
Asian	58 (30.2)	57 (29.8)
White	113 (58.9)	104 (54.5)
Other	10 (5.2)	9 (4.7)
Not reported	1 (0.5)	1 (0.5)
Time from initial diagnosis to randomisation (weeks) – newly diagnosed patients		
n	90	90
Mean (SD)	8.8 (4.58)	8.6 (3.88)

Median (min–max)	7.7 (3–29)	7.5 (3–23)
Time from initial diagnosis to randomisation (weeks) – recurrent patients		
n	102	101
Mean (SD)	193.7 (150.63)	162.8 (133.19)
Median (min–max)	134.9 (8–804)	122.1 (27–909)
Time from recent progression to randomisation (weeks) – recurrent patients		
n	102	101
Mean (SD)	8.6 (10.82)	8.1 (6.28)
Median (min–max)	6.6 (0–87)	7.0 (1–34)

Footnotes: Disease status (recurrent vs. newly diagnosed) is as collected on the eCRF.
Source: AstraZeneca. Data on File. 2023.[97]

B.2.7.5 Clinical effectiveness results: SoC + D + O in the pMMR population

As previously detailed in Section B.2.6, the following sections present the subgroup analysis results for SoC versus SoC + D + O for patients with pMMR EC in the DUO-E trial. In this patient population, a clinically meaningful PFS and OS benefit was observed for SoC + D + O versus SoC, with full results presented below in Sections B.2.7.5.1 and B.2.7.5.2. These results were consistent across all other key endpoints of relevance to this submission, as detailed in Sections B.2.7.5.3–B.2.7.5.5.

B.2.7.5.1. PFS at DCO1 (12 April 2023)

In the pMMR population, SoC + D + O demonstrated a clinically meaningful improvement in Investigator-assessed PFS when compared to SoC (median PFS: 15.0 months vs. 9.7 months, respectively; HR 0.57; 95% CI 0.44, 0.73; Table 19), with an incremental increase in median PFS of 5.3 months in the SoC + D + O arm compared with the SoC arm. Overall, the data maturity was 66.1%.[97]

The KM plot for PFS in the pMMR population is presented in Figure 14, which shows that the SoC + D + O arm separated from the SoC arm at approximately 7 months from randomisation and maintained separation in favour of the SoC + D + O arm throughout the follow up period.[97] The PFS rate at both 12 and 18 months was greater in the SoC + D + O arm vs. the SoC arm (42.0% vs. 20.0%, respectively, at 18 months), further demonstrating the PFS benefit associated with SoC + D + O compared with SoC in this population.[97]

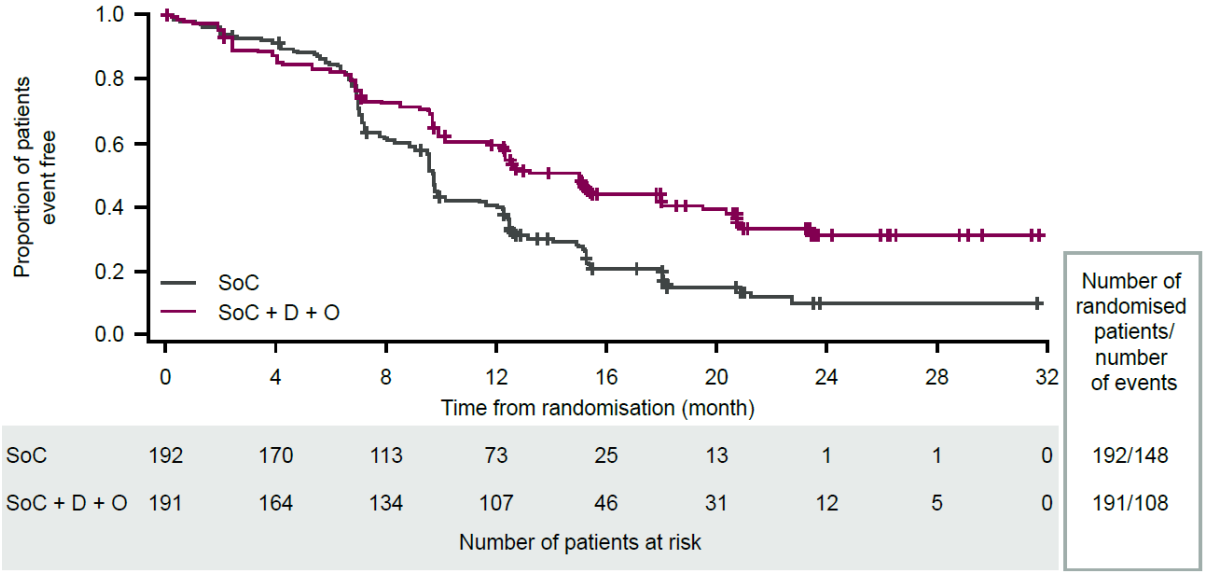
As indicated in Section B.2.7.3.1, UK clinicians indicated that the “tail effect” observed in the DUO-E trial is supportive of curative potential, and that this concept supports the use of immunotherapies in the first-line setting to increase the proportion of patients experiencing cure compared with the current SoC.[1]

Table 19. Investigator-assessed PFS in the pMMR population at DCO1 (12 April 2023)

	SoC (N=192)	SoC + D + O (N=191)
Events, n (%)	148 (77.1)	108 (56.5)
Median, months (95% CI)	9.7 (9.2, 10.1)	15.0 (12.4, 18.0)
HR (95% CI) vs. SoC	-	0.57 (0.44, 0.73)
PFS rate at 6 months (95% CI)	84.4 (78.4, 88.9)	83.1 (77.0, 87.7)
PFS rate at 12 months (95% CI)	40.8 (33.6, 47.8)	59.4 (52.0, 66.0)
PFS rate at 18 months (95% CI)	20.0 (14.1, 26.7)	42.0 (34.1, 49.6)

Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

Figure 14. KM plot for Investigator-assessed PFS in the pMMR population



Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

B.2.7.5.2. OS at DCO1 (12 April 2023)

At DCO1, there were 33.3% of patients in the SoC arm and 24.1% of patients in the SoC + D + O arm with an OS event, where the overall data maturity was 29.2% in the pMMR population.[97]

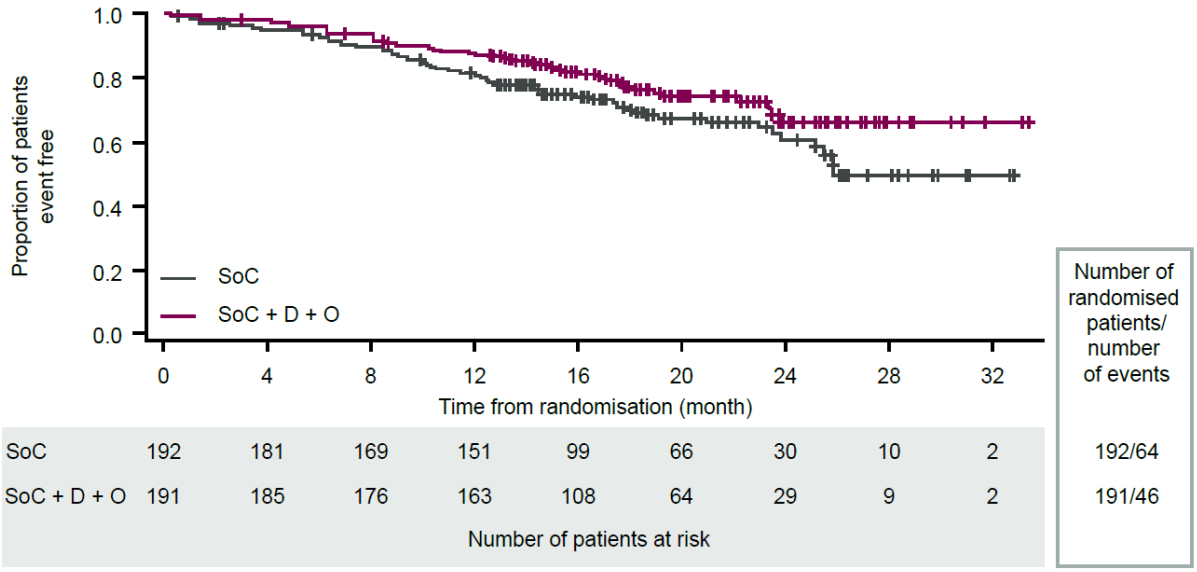
In the pMMR population, SoC + D + O demonstrated a clinically meaningful improvement in OS when compared to SoC (HR 0.69; 95% CI 0.47, 1.00; Table 20). The KM plot for OS in the pMMR population is presented in Figure 15, which shows that the SoC + D + O and SoC arms separate at around 8 months from randomisation and separation is maintained in favour of the SoC + D + O arm, resulting in an improved OS rate for SoC + D + O vs. SoC at both 12 and 18 months.[97]

Table 20. OS in pMMR population at DCO1 (12 April 2023)

	SoC (N=192)	SoC + D + O (N=191)
Events, n (%)	64 (33.3)	46 (24.1)
Median, months (95% CI)	25.9 (25.1, NR)	NR (NR, NR)
HR (95% CI) vs. SoC	-	0.69 (0.47, 1.00)
OS rate at 6 months (95% CI)	92.7 (87.9, 95.6)	95.8 (91.8, 97.9)
OS rate at 12 months (95% CI)	81.0 (74.6, 85.9)	87.3 (81.7, 91.3)
OS rate at 18 months (95% CI)	69.9 (62.3, 76.2)	76.9 (69.5, 82.7)

Source: AstraZeneca. Data on File. 2023.[97] Baurain, 2024.[103]

Figure 15. KM plot of OS in the pMMR subpopulation at DCO1 (12 April 2023)

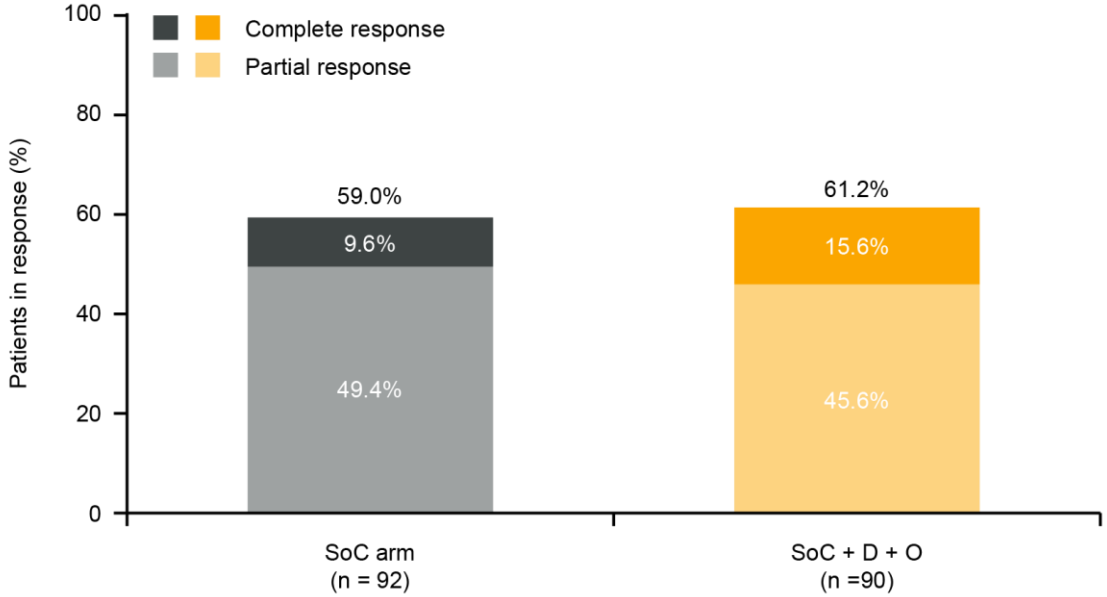


Source: AstraZeneca. Data on File. 2023.[97] Baurain, 2024.[103]

B.2.7.5.3. ORR at DCO1 (12 April 2023)

ORR was marginally greater in the SoC + D + O arm vs. the SoC arm (90 patients [61.2%] in the SoC + D + O arm vs. 92 patients [59.0%] in the SoC arm) with an OR of 1.10; 95% CI 0.69, 1.74). Notably, the proportion of patients that experienced CR, in whom there was a complete disappearance of all target lesions, was 50% greater in the SoC + D + O arm (15.6%, n=23) compared to the SoC arm (9.6%, n=15), presented in Figure 16, further demonstrating the treatment benefit of maintenance D + O in the pMMR population.

Figure 16. ORR in the pMMR population at DCO1 (12 April 2023)



Footnotes: n numbers refer to the number of patients with measurable disease at baseline
Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

B.2.7.5.4. DoR at DCO1 (12 April 2023)

While ORR was broadly similar between the two treatment groups, notable differences were observed in the corresponding DoR, highlighting that the addition of maintenance durvalumab and olaparib has a notable impact on the observed DoRs.

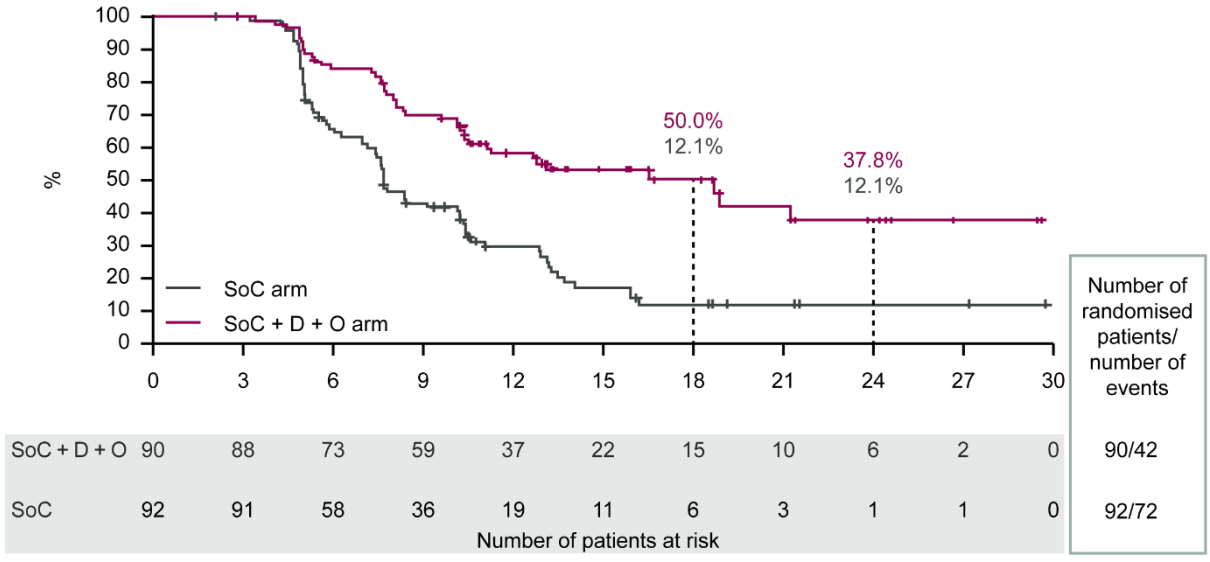
In the SoC + D + O arm median DoR was 18.7 months vs. 7.6 months in the SoC (Table 21), and 50% in the SoC + D + O arm with a confirmed response maintained their response at 18 months compared with 12.1% of patients in the SoC arm. The KM plot (Figure 17), demonstrates a separation in DoR between the arms in favour of SoC + D at ~4 months. Given that SoC was discontinued in DUO-E at approximately 4.5 months, these data suggest that maintenance D + O in the SoC + D + O arm is associated with a clear benefit in the pMMR population, allowing patients to continue to maintain their response when they would otherwise have finished receiving treatment with SoC.

Table 21. DoR in pMMR population at DCO1 (12 April 2023)

	SoC (N=192)	SoC + D + O (N=191)
All patients with confirmed response, n	92	90
Median DoR from onset of response, months (95% CI)	7.6 (5.1, 13.1)	18.7 (8.0, NR)
Number remaining in response, %		
18 months	12.1	50.0
24 months	12.1	37.8

Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

Figure 17. DoR KM plot in the pMMR population with confirmed response at DCO1 (12 April 2023)



Source: AstraZeneca. Data on File. 2023.[97] Chon, *et al.*[102]

B.2.7.5.5. Other efficacy endpoints at DCO1 (12 April 2023)

All other secondary outcomes (PFS2, TFST, TSST and TDT) for the comparison of SoC + D+ O with SoC in the pMMR population are presented below in Table 22.

At DCO1 (12 April 2023), PFS2 events had occurred for 58 patients (30.4%) in the SoC + D + O arm compared with 76 patients (39.6%) in the SoC arm. There was a clinically meaningful improvement in PFS2 for the SoC + D + O arm versus the SoC arm (HR 0.68; 95% CI 0.48, 0.95) in the pMMR

population. A clinically meaningful improvement was also seen in TFST in the comparison of SoC + D + O versus SoC (HR 0.56; 95% CI 0.43, 0.73), and in TSST for the SoC + D + O arm compared with the SoC arm (HR 0.68; 95% CI 0.47, 0.97). There was a numerical improvement in TDT for the SoC + D + O arm compared with the SoC arm (HR 0.54; 95% CI 0.43, 0.69).

Table 22. Summary of results from other endpoints in the pMMR population at DCO1 (12 April 2023)

Endpoint	SoC			SoC + D + O			Comparison
	Events, (%)	Median, months (95% CI)	12-month rate, %	Events, (%)	Median, months (95% CI)	12-month rate, %	HR vs. SoC (95% CI)
PFS2	39.6	19.5 (17.4–23.5)	74.0	30.4	NR (NR–NR)	81.7	0.68 (0.48, 0.95)
TFST	68.8	11.7 (10.4–13.1)	49.9	49.2	19.1 (15.7–24.9)	68.1	0.56 (0.43, 0.73)
TSST	37.5	25.1 (22.5–NR)	77.7	26.7	NR (NR–NR)	85.0	0.68 (0.47, 0.97)
TDT	161 (83.9)	9.3 (8.0–9.9)	33.3	117 (61.3)	13.4 (10.6–15.6)	55.0	0.54 (0.43, 0.69)

Source: AstraZeneca. Data on File. 2023.

B.2.8 Meta-analysis

As only one trial evaluating the efficacy and safety of SoC + D and SoC + D + O in the relevant patient populations and indications was identified, a meta-analysis was not necessary.

B.2.9 Indirect and mixed treatment comparisons

The DUO-E trial is a robust RCT, directly comparing SoC + D and SoC + D + O with SoC (carboplatin + paclitaxel) alone, the comparator of interest specified in the NICE scope. Furthermore, the DUO-E trial provides direct comparative data in both dMMR and pMMR populations with newly diagnosed advanced or recurrent EC, with patient baseline characteristics broadly aligned between comparator arms in each of these populations (Section B.2.7.2; Section B.2.7.4). Therefore, an indirect treatment comparison is not considered necessary to provide indirect evidence to support this submission.

B.2.10 Adverse reactions

The following sections presents safety data within the ITT (safety analysis set) from DCO1 (12 April 2023). The SAS is considered to represent the most relevant source of safety data for SoC, SoC + D and SoC + D + O for this appraisal to maximise the available sample size, as there is no expectation that the safety profile of the intervention would vary depending on MMR status.

For completeness, additional safety data for the ITT, as well as safety data for the dMMR and pMMR populations, are presented in Appendix F; these additional data indicate that safety results in the dMMR and pMMR populations were generally consistent with those in the SAS.

B.2.10.1 Treatment exposure in the ITT at DCO1 (12 April 2023)

At the time of the primary analysis of PFS, the number of patients exposed, and the totality of exposure and follow-up in the study were considered sufficient to characterise the safety profile of SoC, SoC + D and SoC + D + O.

Duration of treatment exposure to SoC, durvalumab/placebo and olaparib/placebo across treatment arms is presented in Table 23. In the study overall, total exposure to SoC was similar in all treatment arms, indicating that treatment with durvalumab did not impact the ability of patients to receive SoC. Moreover, the median duration for actual treatment exposure for durvalumab/placebo was longer for the SoC + D + O arm versus the SoC + D arm, indicating that olaparib did not compromise the ability of patients to receive durvalumab.[11]

Cumulative exposure to durvalumab/placebo was longest in the SoC + D + O treatment arm – in the SoC and SoC + D arms, over half of the patients enrolled in each arm reached 9 months of treatment, whilst in the SoC + D + O arm, over half of the patients reached 13 months of treatment.[11]

In the maintenance phase, the median actual treatment duration was similar to the total treatment duration in all three treatment arms, suggesting that treatment interruptions were minimal.

Table 23. Duration of actual exposure/number of infusions received for SoC, durvalumab/placebo and olaparib/placebo (SAS) at DCO1 (12 April 2023)

	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 169)	SoC + D (N = 183)	SoC + D + O (N = 192)
SoC						
Carboplatin or substitute (number of infusions received)						
n (patients that received an infusion)	236	235	238	NA	NA	NA
Median (min–max)	6.0 (1–6)	6.0 (1–6)	6.0 (1–6)	NA	NA	NA
Paclitaxel or substitute (number of infusions received)						
n	236	235	238	NA	NA	NA
Median (min–max)	6.0 (1–7)	6.0 (1–6)	6.0 (1–7)	NA	NA	NA
Durvalumab/placebo (actual exposure; weeks)[a]						
Median (min–max)	35.3 (0.7–141.3)	41.4 (0.9–130.3)	50.0 (0.7–140.3)	24.0 (3.0–123.6)	31.6 (0.0–114.0)	39.5 (0.0–122.3)
Olaparib/placebo (actual exposure; weeks)[b]						
n	169	183	192	169	183	192
Median (min–max)	24.0 (−0.3–124.3)	32.4 (0.9–113.3)	38.1 (0.3–122.6)	24.0 (−0.3–124.3)	32.4 (0.9–113.3)	38.1 (0.3–122.6)

Footnotes: [a]Actual exposure (weeks) = intended exposure – total duration of dose delays (days), derived as the (sum of [date of the dose – date of previous dose – D days])/7 where D was equal to 21 if it happened during the Chemotherapy Phase and was equal to 28 if it happened during the Maintenance Phase. [b]Actual exposure (weeks) = intended exposure – total duration of dose interruptions. Intended exposure was calculated as above. Dose interruption was defined as any length of time where the patient had not taken any of the planned daily dose (i.e., [sum of (end date of each interruption-start date of the interruption + one)]/7). To calculate actual exposure, dose interruptions included those where a patient forgot to take a dose.
Source: DUO-E CSR[11]

B.2.10.2 Dose interruptions, delays, reductions and discontinuations at DCO1 (12 April 2023)

An overview of dose interruptions, delays, reductions, and discontinuations at DCO1 for durvalumab/placebo and olaparib/placebo are described below and presented in Appendix F. Given that the most common reason for dose delays for durvalumab/placebo, and interruptions and reductions for olaparib was the onset of AEs, these will later be detailed for both maintenance durvalumab in Section B.2.10.3.5, and for olaparib in Section B.2.10.3.6.

Dose interruptions and reductions for olaparib/placebo can be found in Appendix F. In the maintenance phase, there were more interruptions and reductions to olaparib treatment in the SoC + D + O arm (64.6%) compared to olaparib/placebo in the SoC (33.1%) and SoC + D (28.4%) arms; the most common reason for interruptions and reductions to olaparib treatment was due to AEs.

A summary of all dose delays with durvalumab/placebo can be found in Appendix F. Overall, any dose delays for durvalumab/placebo were similar between the three treatment arms (52.5%, 60.9% and 63.0% in the SoC, SoC + D and SoC + D + O treatment arms, respectively); the most common reason for dose delays for durvalumab/placebo in all three treatment arms was due to AEs.[11]

B.2.10.3 Overview of safety and tolerability at DCO1 (12 April 2023)

In the study overall, most patients experienced at least one AE. AEs of maximum Grade 3 or 4 and serious adverse events (SAE) were reported in more than 50% of patients and approximately a third of patients, respectively, across all three treatment arms. The majority of reported deaths due to any cause across all arms were attributed to EC. The number of patients with an AE leading to death was 8 patients (3.4%) in the SoC arm, 4 patients (1.7%) in the SoC + D arm, and 5 patients (2.1%) in the SoC + D + O arm.[11] Notably, discontinuations due to AEs were not significantly increased as a result of additional maintenance D, or D + O, when compared to SoC. The SoC arm saw 18.6% of patients discontinuing on study treatment due to an AE, and this was only moderately increased to 20.9%, and 24.4% for the SoC + D, and the SoC + D + O arms, respectively. This highlights that the majority of discontinuations due to AEs occur due to SoC, and support the tolerability, in addition to demonstrated efficacy, of additional maintenance D and D + O in patients with advanced or recurrent EC.

A summary of AEs reported in the DUO-E trial can be found in Table 24. Overall, a similar frequency of AEs were observed in the SoC + D arm and SoC + D + O arm; however, Grade ≥3 AEs occurred in a greater proportion of patients in the SoC + D + O arm compared to the SoC + D and SoC arms (67.2% vs. 54.9% and 56.4%, respectively). Nevertheless, based on clinical expert opinion, the toxicity profile of the SoC + D + O regimen is considered to be outweighed by the PFS benefit associated with the addition of olaparib in the more difficult-to-treat pMMR population.[1] Furthermore, since clinicians will be familiar with the safety profile of olaparib in the ovarian cancer setting, it is expected that these additional side effects will be considered manageable. Overall, the safety profiles across treatment arms were generally consistent with the known profiles of each agent.

Table 24. Summary of AEs, overall study duration and maintenance phase (SAS) at DCO1 (12 April 2023)

AEs,[a] n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N=236)	SoC + D (N=235)	SoC + D + O (N=238)	SoC (N=169)	SoC + D (N=183)	SoC + D + O (N=192)
Any AEs	236 (100.0)	232 (98.7)	237 (99.6)	143 (84.6)	158 (86.3)	184 (95.8)
Grade ≥3 AEs	133 (56.4)	129 (54.9)	160 (67.2)	28 (16.6)	30 (16.4)	79 (41.1)
Serious AEs	73 (30.9)	73 (31.1)	85 (35.7)	19 (11.2)	22 (12.0)	42 (21.9)
AEs with outcome of death	8 (3.4)	4 (1.7)	5 (2.1)	2 (1.2)	0	3 (1.6)
AESIs to olaparib	4 (1.7)	5 (2.1)	14 (5.9)	2 (1.2)	4 (2.2)	9 (4.7)
myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New primary malignancies[b]	3 (1.3)	1 (0.4)[e]	2 (0.8)	2 (1.2)	1 (0.5)[e]	1 (0.5)
Pneumonitis[c]	1 (0.4)	4 (1.7)	12 (5.0)	0	3 (1.6)	8 (4.2)
Any immune-mediated AEs[d]	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)
AEs leading to discontinuation of study treatment	44 (18.6)	49 (20.9)	58 (24.4)	7 (4.1)	11 (6.0)	27 (14.1)
AEs leading to discontinuation of carboplatin/paclitaxel	32 (13.6)	31 (13.2)	31 (13.0)	NA	NA	NA
AEs leading to discontinuation of durvalumab/placebo	19 (8.1)	26 (11.1)	22 (9.2)	4 (2.4)	9 (4.9)	16 (8.3)
AEs leading to discontinuation of olaparib/placebo	5 (2.1)	11 (4.7)	21 (8.8)	5 (3.0)	10 (5.5)	21 (10.9)
AEs leading to dose interruption/delay of study treatment[f]	118 (50.0)	128 (54.5)	164 (68.9)	37 (21.9)	52 (28.4)	113 (58.9)
AEs leading to dose reduction of olaparib/placebo	5 (2.1)	14 (6.0)	65 (27.3)	4 (2.4)	13 (7.1)	63 (32.8)

Footnote: [a]The data presented here includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). [b]MDS/AML and new primary malignancies include AEs from first dose of investigational product (durvalumab/olaparib/placebo) until the end of the study (includes cases reported beyond the safety follow-up period); [c]Grouped term: includes pneumonitis, bronchiolitis, and interstitial lung disease; [d]As assessed by the Investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related; [e]Excludes one event of basal cell carcinoma; [f]For durvalumab/placebo, this includes dose interruption during infusion as well as doses that were skipped or delayed.
Source: DUO-E CSR.[11] Westin *et al.* (2023)[4]

B.2.10.3.1. Common AEs at DCO1 (12 April 2023)

AEs occurring in ≥20% of patients across the treatment arms are summarised in Table 25 for the overall study duration and the maintenance phase only. The most common AEs were as expected for each treatment arm and, with the exception of arthralgia, are known adverse drug reactions (ADRs) for the study treatments (carboplatin, paclitaxel, durvalumab, or olaparib).[11]

In the study overall, AEs occurring with a ≥5% higher frequency in the SoC + D + O arm compared with the SoC arm were anaemia (61.8% vs. 54.2% [grouped terms: anaemia and haemoglobin decreased]), nausea (54.6% vs. 44.5%), vomiting (25.6% vs. 18.2%), neutropenia (41.6% vs. 41.5%), COVID-19 (20.2% vs. 13.6%), asthenia (19.3% vs. 10.2%), back pain (14.7% vs. 9.3%), thrombocytopenia (29.8% vs. 22.0% [grouped terms: platelet count decreased and thrombocytopenia]), hypothyroidism (13.9% vs. 3.4%), and ALT increased (12.6% vs. 7.6%).[4, 11] These AEs were all known ADRs for durvalumab in combination with chemotherapy, with the exception of arthralgia. These AEs were all known ADR for durvalumab or olaparib, with the exception of COVID-19 and back pain.

AEs occurring with a ≥5% higher frequency in the SoC + D arm compared with the SoC arm in the study overall were arthralgia (30.2% vs. 24.6%), thrombocytopenia (28.1% vs. 22.0% [grouped terms: platelet count decreased and thrombocytopenia]), hypothyroidism (15.7% vs. 3.4%), ALT increased (12.8% vs. 7.6%), and rash (17.4% vs. 11.4%).[11] These were all known ADRs for durvalumab in combination with chemotherapy, with the exception of arthralgia.[4, 11]

During the maintenance phase, AEs occurring with a frequency of ≥5% higher in the SoC + D + O arm than the SoC + D arm were all known ADRs for olaparib with the exception of COVID-19, urinary tract infection, and back pain. Most AEs occurring during the maintenance phase were low-grade.

Table 25. Most common AEs (≥20%) overall study duration and maintenance phase (SAS) at DCO1 (12 April 2023)

AEs,[a] n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N=236)	SoC + D (N=235)	SoC + D + O (N=238)	SoC (N=169)	SoC + D (N=183)	SoC + D + O (N=192)
Anaemia[b]	128 (54.2)	112 (47.7)	147 (61.8)	17 (10.1)	16 (8.7)	70 (36.5)
Alopecia	118 (50.0)	118 (50.2)	121 (50.8)	1 (0.6)	2 (1.1)	5 (2.6)
Fatigue and asthenia	105 (44.5)	101 (43.0)	129 (54.2)	21 (12.4)	19 (10.4)	62 (32.3)
Nausea	105 (44.5)	96 (40.9)	130 (54.6)	25 (14.8)	22 (12.0)	79 (41.1)
Neutropenia[b]	98 (41.5)	84 (35.7)	99 (41.6)	7 (4.1)	13 (7.1)	34 (17.7)
Constipation	81 (34.3)	64 (27.2)	78 (32.8)	9 (5.3)	13 (7.1)	13 (6.8)
Diarrhoea	66 (28.0)	74 (31.5)	67 (28.2)	20 (11.8)	28 (15.3)	34 (17.7)
Thrombocytopenia[b]	52 (22.0)	66 (28.1)	71 (29.8)	9 (5.3)	6 (3.3)	27 (14.1)
Arthralgia	58 (24.6)	71 (30.2)	58 (24.4)	16 (9.5)	34 (18.6)	22 (11.5)
Peripheral neuropathy	66 (28.0)	61 (26.0)	60 (25.2)	5 (3.0)	5 (2.7)	12 (6.3)
Peripheral sensory neuropathy	66 (28.0)	60 (25.5)	60 (25.2)	2 (1.2)	6 (3.3)	3 (1.6)
Vomiting	43 (18.2)	49 (20.9)	61 (25.6)	16 (9.5)	13 (7.1)	39 (20.3)
Decreased appetite	46 (19.5)	42 (17.9)	55 (23.1)	6 (3.6)	9 (4.9)	28 (14.6)
Leukopenia[b]	45 (19.1)	40 (17.0)	48 (20.2)	9 (5.3)	7 (3.8)	19 (9.9)

Urinary tract infection	50 (21.2)	33 (14.0)	48 (20.2)	23 (13.6)	14 (7.7)	25 (13.0)

Footnote: [a]Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. [b]Grouped terms: anaemia includes anaemia and haemoglobin decreased; neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; thrombocytopenia includes platelet count decreased and thrombocytopenia; leukopenia includes leukopenia and white blood cell count decreased.
COVID-19-specific information: In addition to AEs shown, COVID-19 was reported in 32 (14%) patients in the SoC arm, 36 (15%) patients in the SoC + D arm, and 48 (20%) patients in the SoC + D + O arm overall, and in 20 (12%), 21 (12%), and 34 (18%) patients, respectively, during the maintenance phase
Source: Westin *et al.* (2023).[4]

B.2.10.3.2. Serious AEs at DCO1 (12 April 2023)

The most common (≥1% patients in any treatment arm) SAEs including those with an outcome of death are listed in Table 26 and were generally consistent with the known safety profiles of the study treatments.

In the study overall, the percentage of patients with SAEs was similar between all three treatment arms (SoC + D + O: 35.7%; SoC + D: 31.1%; SoC: 30.9%).[11]

In the maintenance phase, although the frequency of SAEs was lower than in the study overall, more patients in the SoC + D + O arm (21.9%) had SAEs compared to either the SoC + D (12.0%) or SoC arms (11.2%). This increase was mostly driven by events of anaemia, which is a known ADR for olaparib.[11]

Table 26. Summary of SAEs with a frequency ≥1% in any treatment arm (SAS) at DCO1 (12 April 2023)

SAEs,[a] n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N=236)	SoC + D (N=235)	SoC + D + O (N=238)	SoC (N=169)	SoC + D (N=183)	SoC + D + O (N=192)
Any SAE	73 (30.9)	73 (31.1)	85 (35.7)	19 (11.2)	22 (12.0)	42 (21.9)
Anaemia	10 (4.2)	1 (0.4)	16 (6.7)	0	0	12 (6.3)
Febrile neutropenia	8 (3.4)	4 (1.7)	7 (2.9)	0	0	2 (1.0)
Urinary tract infection	5 (2.1)	2 (0.9)	6 (2.5)	4 (2.4)	1 (0.5)	3 (1.6)
Neutropenia	3 (1.3)	3 (1.3)	5 (2.1)	0	0	1 (0.5)
Sepsis	3 (1.3)	2 (0.9)	4 (1.7)	1 (0.6)	0	1 (0.5)
COVID-19	3 (1.3)	1 (0.4)	4 (1.7)	1 (0.6)	1 (0.5)	1 (0.5)
COVID-19 pneumonia	0	1 (0.4)	3 (1.3)	0	0	3 (1.6)
Aplasia pure red cell	0	0	3 (1.3)	0	0	3 (1.6)
Deep vein thrombosis	1 (0.4)	2 (0.9)	3 (1.3)	0	0	1 (0.5)
Pneumonitis	0	1 (0.4)	3 (1.3)	0	1 (0.5)	2 (1.0)
Pyrexia	1 (0.4)	1 (0.4)	3 (1.3)	1 (0.6)	0	1 (0.5)
Diarrhoea	4 (1.7)	0	2 (0.8)	0	0	1 (0.5)
Pulmonary embolism	4 (1.7)	0	3 (1.3)	0	0	1 (0.5)
Pneumonia	0	1 (0.4)	2 (0.8)	0	0	2 (1.0)
Vomiting	2 (0.8)	5 (2.1)	1 (0.4)	1 (0.6)	1 (0.5)	0

Nausea	2 (0.8)	3 (1.3)	1 (0.4)	0	1 (0.5)	0
Fall	3 (1.3)	1 (0.4)	1 (0.4)	0	0	1 (0.5)
Infusion-related reaction	3 (1.3)	0	1 (0.4)	0	0	0
Urosepsis	3 (1.3)	1 (0.4)	0	1 (0.6)	0	0
Hyponatremia	4 (1.7)	5 (2.1)	0	0	1 (0.5)	0
Constipation	3 (1.3)	2 (0.9)	0	0	0	0
Hydronephrosis	2 (0.8)	0	0	2 (1.2)	0	0
Neutrophil count decreased	4 (1.7)	1 (0.4)	0	0	0	0

Footnote: [a]Sorted in descending order of incidence in the SoC + D + O arm (overall) and alphabetically for preferred term. Includes AEs with an onset date or worsening on or after the date of first dose of study treatment (overall) or first dose of olaparib/placebo (maintenance phase) up until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib/placebo or 90 days following discontinuation of durvalumab/placebo), whichever occurs first. Patients with multiple serious AEs were counted once for each preferred term. Percentages are based on the total numbers of patients in the treatment group (N).
Source: Westin *et al.* (2023).[4]

B.2.10.3.3. Grade ≥3 AEs at DCO1 (12 April 2023)

Overall, AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 were similar between the SoC + D and SoC arms but reported for more patients in the SoC + D + O arm (Table 24). The most frequently reported AEs (≥5%) in all three treatment arms were anaemia (23.5%, 15.7% and 14.4% in the SoC + D + O, SoC + D and SoC treatment arms, respectively), and neutropenia (26.9%, 21.7% and 23.3%, respectively), consistent with the known safety profiles of the study treatments (carboplatin, paclitaxel, durvalumab, and olaparib; Table 27).

The most frequently reported AEs of maximum Grade 3 or 4 regardless of causality occurring with a ≥5% higher frequency between arms are detailed below:

- SoC + D compared with SoC: no events
- SoC + D + O compared with SoC: anaemia (56 [23.5%] vs. 34 patients [14.4%]), neutropenia (64 [26.9%] vs. 55 patients [23.3%])
- SoC + D + O compared with SoC + D: anaemia (56 [23.5%] vs. 37 patients [15.7%])

In the SoC, SoC + D, and SoC + D + O arms, the overall incidence of Grade ≥3 treatment-emergent AEs was 56.4%, 54.9%, and 67.2%, respectively, and the incidence in the maintenance phase was 16.6%, 16.4%, and 41.1%, respectively.[11]

Table 27. Grade ≥3 AEs (frequency of ≥5% in any treatment arm), overall study duration and maintenance phase only (SAS) at DCO1 (12 April 2023)

AEs,[a] n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N=236)	SoC + D (N=235)	SoC + D + O (N=238)	SoC (N=169)	SoC + D (N=183)	SoC + D + O (N=192)
Grade ≥3 AEs with frequency of ≥5% in any arm						
Neutropenia[b]	55 (23.3)	51 (21.7)	64 (26.9)	1 (0.6)	1 (0.5)	12 (6.3)
Anaemia[b]	34 (14.4)	37 (15.7)	56 (23.5)	1 (0.6)	0	36 (18.8)
Thrombocytopenia[b]	11 (4.7)	16 (6.8)	14 (5.9)	0	1 (0.5)	1 (0.5)

Leukopenia[b]	13 (5.5)	11 (4.7)	15 (6.3)	0	1 (0.5)	2 (1.0)
Fatigue and asthenia	7 (3.0)	8 (3.4)	12 (5.0)	0	1 (0.5)	4 (2.1)
Select other Grade ≥3 AEs						
Pure red cell aplasia	0	0	3 (1.3)	0	0	3 (1.6)
Autoimmune haemolytic anaemia	0	1 (0.4)	2 (0.8)	0	0	2 (1.0)

Footnote: [a]Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). AE leading to death occurred in 17 patients overall, and were acute respiratory failure, cardiac arrest (n=2), COVID-19, death (n=3), general physical health deterioration, multiple organ dysfunction syndrome, myocardial infarction, pneumonia aspiration, pulmonary embolism, renal failure, respiratory failure, sepsis, septic shock, and urosepsis (n=1 for each unless stated otherwise); [b]Grouped terms: anaemia includes anaemia and haemoglobin decreased; neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; thrombocytopenia includes platelet count decreased and thrombocytopenia; leukopenia includes leukopenia and white blood cell count decreased.
Source: Westin *et al.* (2023).[4]

B.2.10.3.4. AESIs at DCO1 (12 April 2023)

The DUO-E trial assessed AESIs, adverse events of possible interest (AEPIs) and immune-mediated adverse events (imAEs). imAEs were defined as AESIs consistent with an immune-mediated mechanism of action requiring the use of systemic steroids or other immunosuppressants and/or endocrine therapy.

Durvalumab AEPIs were defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but were more likely to have occurred due to other pathophysiological mechanisms.[11] Olaparib AESIs are the important identified risk of MDS/AML, the important potential risk of neoplasms (other than MDS/AML), and the potential risk of pneumonitis.

Pure red cell aplasia (PRCA), autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia were considered AESIs in DUO-E. Overall, AEs of PRCA (3 patients [1.3%]), AIHA (two patients [0.8%]) and haemolytic anaemia (one patient [0.4%]) were reported for patients in the SoC + D + O arm either during the maintenance phase or in the follow-up period. No events of MDS/AML were reported within any of the three treatment arms.[11]

In the overall study duration, there was a higher incidence of AESIs (57.9% and 44.9%), AEPIs (54.0% and 50.8%) and imAEs (28.1% and 6.8%) in the SoC + D arm compared with the SoC arm, and a higher incidence of AESIs (57.1% and 44.9%), AEPIs (55.9 % and 50.8%) and imAEs (23.5% and 57.1%) in the SoC + D + O arm compared with the SoC arm, as presented in Appendix F. In the maintenance phase, there was a higher incidence of AESIs (37.7% and 21.9%), AEPIs (34.4% and 27.8%) and imAEs (14.8% and 3.6%) in the SoC + D arm compared with the SoC arm, and a higher incidence of AESIs (37.5% and 21.9%), AEPIs (37.5% and 27.8%) and imAEs (14.1% and 3.6%) in the SoC + D + O arm compared with the SoC arm, as presented in Appendix F.[11]

New primary malignancies were reported for three patients (1.3%) in the SoC arm, one patient (0.4%) in the SoC + D arm, and two patients (0.8%) in the SoC + D + O arm. There was only one event that occurred in the maintenance phase in the SoC + D + O arm; the overall incidence was <1.5% and balanced across all treatment arms.[11]

B.2.10.3.5. Dose interruptions, delays, reductions, and discontinuations due to AEs for durvalumab/placebo

In the DUO-E study, AEs were usually managed by dose modification (interruption or reduction) rather than discontinuation.

Discontinuation of any study treatment due to AEs occurred in 18.6% of patients in the SoC arm, 20.9% of patients in the SoC + D arm in the study overall, and 24.4% of patients in the SoC + D + O arm.

The most common AEs leading to discontinuation of any study treatment (reported in ≥2% patients) in the study overall were peripheral neuropathy (6 patients [2.6%]), anaemia (5 patients [2.1%]) and infusion related reactions (5 patients [2.1%]) for SoC + D. In the study overall, the most common AEs leading to discontinuation of any study treatment (reported in ≥2% patients) were anaemia (24.4%), peripheral neuropathy (3.4%), infusion related reaction (2.5%), neutropenia (2.1%), and pneumonitis (2.1%) for SoC + D + O. No AEs leading to discontinuation of any study treatment occurred at a ≥5% difference between the treatment arms.[11]

In the study overall, AEs leading to dose interruptions of durvalumab/placebo were similar in the SoC + D and SoC + D + O arms and higher compared to the SoC arm (Appendix F).

B.2.10.3.6. Dose interruptions, delays, reductions, and discontinuations due to AEs for olaparib/placebo

The most common AEs leading to dose interruption of olaparib/placebo (reported in ≥5% patients) were anaemia, COVID-19 and nausea for SoC + D + O. No AEs occurred at a frequency ≥ 5% in the SoC or SoC + D arms. As presented in Appendix F, the only AEs occurring at a ≥5% difference between treatment arms were anaemia and COVID-19; however, events of COVID-19 were generally low-grade and event rates of COVID-19 across the treatment arms were consistent.[11]

B.2.10.3.7. Deaths at DCO1 (12 April 2023)

A summary of patients who died in the study overall in the ITT is presented in Table 28. The majority of reported deaths were due to EC across all three treatment arms.

Overall, 82 (34%) patients treated with SoC, 65 (27.3%) patients treated with SoC + D, and 52 (21.8%) patients in the SoC + D + O arm had died at DCO1.[11]

The number of AEs with outcome of death only was similar across all three treatment arms. AEs with an outcome of death were all isolated events with no consistent pattern across the three treatment arms.[11]

Table 28. All deaths in the ITT at DCO1 (12 April 2023)

Category, n (%)	SoC (N=241)	SoC + D (N=238)	SoC + D + O (N=239)
Total number of deaths	82 (34.0)	65 (27.3)	52 (21.8)
Death related to disease under investigation only[a]	60 (24.9)	51 (21.4)	37 (15.5)
Death related to disease under investigation[a] and an AE with outcome of death[b]	1 (0.4)	0	1 (0.4)
AE onset prior to subsequent therapy[c]	1 (0.4)	0	1 (0.4)
AE onset after start of subsequent therapy[d]	0	0	0
AE with outcome of death only[b]	7 (2.9)	4 (1.7)	7 (2.9)
AE onset prior to subsequent therapy[c]	7 (2.9)	4 (1.7)	4 (1.7)

AE onset after start of subsequent therapy[d]	0	0	3 (1.3)
Death after end of safety follow-up period and not due to disease under investigation[e]	11 (4.6)	8 (3.4)	7 (2.9)
Death with unknown reason	1 (0.4)	2 (0.8)	0
Other deaths[f]	2 (0.8)	0	0

Footnote: [a]Death related to disease under investigation was determined by the Investigator; [b]Included AEs with outcome death if they started, or worsened, on or after the date of first dose of any of the investigational study treatments, including durvalumab/placebo or olaparib/placebo, throughout the treatment period and including the safety follow-up period until the later date of 30 days after the last dose of olaparib/placebo and 90 days after last dose of durvalumab/placebo; [c]Included AEs with an onset date or that worsened on or after the date of first dose of durvalumab/placebo or olaparib/placebo up until the initiation of the first subsequent anti-cancer therapy following last dose of study treatment or until the end of safety follow-up period (latest of either 30 days following last dose of olaparib/ placebo or 90 days following last dose of durvalumab/placebo), whichever occurred first; [d]Adverse event start date prior to the end of safety follow-up period (latest of either 30 days following last dose of olaparib/placebo or 90 days following last dose of durvalumab/placebo) and AE start date after the date of initiation of the first subsequent anticancer therapy; [e]Death not due to disease progression; [f]Patients who died and were not captured in the earlier categories.
Source: DUO-E CSR.[11]

B.2.11 Ongoing Studies

DCOs in DUO-E are event-driven, and therefore there remains some uncertainty around the exact timing of the next DCO. However, it is currently estimated that the final OS DCO will be in 2026.

B.2.12 Interpretation of clinical effectiveness and safety evidence

As highlighted in Section B.1, there is a clear unmet need for novel, innovative treatment options in the first-line setting for patients diagnosed with advanced or recurrent EC. Although patients with newly diagnosed advanced or recurrent EC face a particularly poor prognosis and high mortality rates compared with early-stage EC,[19-22] there is currently a paucity of treatment options available for these patients in the first-line setting, particularly for those diagnosed with pMMR EC. As such, carboplatin + paclitaxel remains the current first-line SoC for patients with advanced or recurrent EC, despite this treatment being associated with notably poorer clinical outcomes in this patient population versus those with early-stage disease.[2, 22]

The recent approval of dostarlimab with platinum-based chemotherapy for the first-line treatment of patients diagnosed with EC that is dMMR or MSI-H represents an important paradigm shift in the EC treatment pathway, allowing these patients to benefit from an innovative therapy in the first-line setting via the CDF.[30] However, the majority of innovative therapies remain in the second-line setting, which means that many patients may not maintain a suitable performance status following first line therapy to benefit from these options or are ineligible for these treatments. Furthermore, no immunotherapy-based regimens are currently available for patients with pMMR EC in the first-line, despite the fact these patients are considered more difficult to treat and that they comprise the majority of the overall newly diagnosed advanced or recurrent EC population.

In this context, it is paramount that additional effective immunotherapy-based regimens are introduced in the first-line setting, when patients are able to best tolerate these treatments and are likely to achieve the best outcomes. As supported both by UK clinicians and retrospective EC studies, providing innovative options in the first-line has the potential to notably increase the overall proportion of patients who achieve long-term remission or even cure.[1, 82, 83]

For patients with dMMR EC specifically, introducing an additional therapy would expand the available options, representing a further important advancement in the EC treatment paradigm. For patients with pMMR EC, the availability of a regimen combining PARP inhibition with immunotherapy in the first-line would represent a crucial addition to the treatment pathway, allowing these difficult-to-treat

patients the opportunity to equally benefit from innovative first-line therapies that offer a potentially more hopeful disease outlook.

B.2.12.1 Principal results from the clinical evidence base

B.2.12.1.1. Efficacy

DUO-E is the first Phase III RCT to demonstrate the clinical efficacy of SoC + D and SoC + D and O in patients with newly diagnosed advanced or recurrent EC.[4]

ITT

Within the broader population of patients with newly advanced or recurrent EC (the ITT), DUO-E met its primary objectives, demonstrating a statistically significant and clinically meaningful improvement in PFS for both SoC + D compared with SoC (median PFS: 10.2 months vs. 9.6 months, respectively; HR 0.71; 95% CI 0.57, 0.89; p=0.003) and SoC + D + O compared with SoC (HR 0.55; 95% CI 0.43, 0.69; p<0.0001). In support of the primary endpoints, the first interim analysis (12 April 2023) of OS favoured both the SoC + D (HR 0.77; 95% CI 0.56, 1.07; p=0.120) and SoC + D + O (HR 0.59; 95% CI 0.42, 0.83; p=0.003) arms compared with SoC.[11]

In subgroup analyses of PFS within the ITT, analyses by MMR status demonstrated the HR for SoC + D vs. SoC in the dMMR population (HR 0.42; 95% CI 0.22, 0.80) was markedly lower compared with ITT (HR 0.71; 95% CI 0.57, 0.89), demonstrating a substantial clinical benefit for SoC + D in the dMMR population. Conversely, a much greater clinical benefit was observed for SoC + D + O vs. SoC compared with SoC + D vs. SoC in the pMMR population, indicating that the addition of olaparib results in a particular clinical benefit for the challenging-to-treat population of patients with pMMR EC, and suggests that the overall improved results in the SoC + D + O vs SoC + D in the ITT are driven by the additional benefit provided by the inclusion of olaparib in the pMMR population.[11, 97]

Importantly, these subgroup results supported the marketing authorisation applications for olaparib and durvalumab in the EC indication and provide robust evidence to support the proposed positioning for SoC + D (for patients with dMMR EC) and SoC + D + O (for patients with pMMR EC) in this submission. The principal efficacy results from the DUO-E trial for SoC + D in the dMMR population and SoC + D + O in the pMMR population are provided in the following sections.

SoC + D in the dMMR population

As noted above, pre-specified PFS analyses in the dMMR subgroup demonstrated a clinically meaningful PFS benefit for SoC + D vs. SoC at DCO1 (12 April 2024), with a 58% reduction in the risk of progression or death among those receiving durvalumab maintenance therapy (median PFS: not reached [NR] vs. 7.0 months, respectively; HR 0.42; 95% CI, 0.22 to 0.80).[11] Importantly, more than double the number of patients receiving SoC + D remained progression-free at 18 months vs. SoC in the dMMR population (67.9% vs. 31.7%, respectively).[11, 97] At DCO1 (12 April 2023), PFS results from pre-specified subgroup analyses translated into a notable improvement in OS for the SoC + D arm compared with the SoC arm (HR 0.34; 95% CI 0.13, 0.79), further demonstrating the treatment benefit associated with durvalumab maintenance therapy in the dMMR population.[97]

These PFS and OS results were underpinned by the deep and durable responses associated with durvalumab; there was a clinically meaningful improvement in the ORR for patients treated with SoC + D compared with the SoC arm (71.4% vs. 40.5%; OR 3.68; 95% CI 1.51, 9.39), and approximately triple the proportion of patients in the SoC + D arm experienced CR compared to the SoC arm (28.6% vs. 9.5%, respectively).[97] This depth of response would have a significant impact on how people perceive their future prospects, with patients achieving deeper responses likely to be more hopeful about their future prognosis. DoR was similarly markedly improved in the SoC + D arm compared with SoC arm, with a notable separation in the KM curves at ~4 months – approximately the time at which

maintenance durvalumab was initiated. These results demonstrate that without maintenance durvalumab, a substantial number of patients experience disease progression after discontinuation of SoC, whereas SoC + D regimen offers patients an improved potential to experience a maintained response.

Furthermore, there was an improvement across all other key secondary endpoints (PFS2, TFST, TSST, TDT) for SoC + D vs. SoC.[97] In fact, the post-progression results (PFS2/TSST) suggest a slightly higher magnitude of benefit versus PFS, indicating that SoC + D confers benefits to patients even following first-line disease progression.

Overall, DUO-E is the first Phase III study to demonstrate the efficacy of SoC + D for patients with newly diagnosed advanced or recurrent EC that is dMMR. The apparent and sustained PFS benefit observed for the dMMR population aligns with similar reports for immunotherapy in combination with platinum-based chemotherapy in EC (RUBY Part I with dostarlimab and platinum-based chemotherapy versus platinum-based chemotherapy alone; NRG-GY018 with pembrolizumab and platinum-based chemotherapy versus platinum-based chemotherapy alone), thereby confirming the benefit of integrating immunotherapy into first-line chemotherapy in the treatment of advanced or recurrent EC that is dMMR.[104, 105] Additionally, clinical experts noted that the introduction of an immunotherapy into the first-line setting would be expected to increase the overall proportion of patients who can achieve long-term remission or cure, with a particularly pronounced effect for patients with dMMR EC.[1]

SoC + D + O in the pMMR population

In the pMMR population, pre-specified analyses by MMR status demonstrated a clinically meaningful benefit in the SoC + D + O arm vs. SoC (median PFS: 15.0 months vs. 9.7 months, respectively; HR 0.57; 95% CI 0.44, 0.73), with a 43% reduction in the risk of progression or death compared with the SoC arm.[11] In addition, SoC + D + O demonstrated a clinically meaningful improvement in OS vs. SoC at DCO1 (12 April 2023), providing support for the PFS results (HR 0.69; 95% CI 0.47, 1.00) and demonstrating the survival benefit associated with this regimen in the pMMR population.[97]

In this difficult-to-treat population, SoC + D + O marginally increased ORR; however, for patients that did respond, the addition of maintenance D + O supported deeper responses. Specifically, the proportion of patients with CR was 50% greater in the SoC + D + O arm compared to the SoC arm (15.6% in the SoC + D + O arm and 9.6% in the SoC arm), and notably yielded responses that were more durable. In the SoC arm, the median DoR was 7.6 months, whilst the inclusion of maintenance D + O in the SoC + D + O arm increased this to 18.7 months, with 50% of patients in the SoC + D + O arm maintaining their response at 18 months, compared with only 12.1% in the SoC arm. This demonstrates that the addition of maintenance D + O to SoC can result in a response to treatment that extends beyond the approximate 4.5-month mark where patients would otherwise have finished treatment with SoC and where many patients would subsequently experience disease progression. Furthermore, there were improvements seen with SoC + D + O compared with SoC across all other key secondary endpoints (PFS2, TFST, TSST, TDT), demonstrating the robustness of the PFS and OS results.[97]

Overall, DUO-E is the first Phase III trial to demonstrate that SoC + D + O is associated with a marked PFS and OS benefit in patients with newly diagnosed advanced or recurrent EC that is pMMR.[97] As such, these data confirm the clinical benefit of integrating immunotherapy into first-line chemotherapy and are the first to indicate that the addition of a PARP inhibitor may offer further benefit in this setting and consequently address a significant unmet need. SoC + D + O may therefore represent a step change in the treatment paradigm for first-line treatment for pMMR newly diagnosed or recurrent EC.

B.2.12.1.2. Safety

The safety profiles of the treatment arms were largely consistent with the known profiles of the individual components of the regimens. Notably, the frequency of AEs leading to discontinuation of any treatment for the SoC alone arm was 18.6%, with the addition of D or D + O producing only a marginal increase in the proportion of patients discontinuing any study treatment (20.9%, and 24.4% in each arm, respectively). This indicates that SoC + D and SoC + D + O yield substantial clinical benefit without resulting in meaningful additional toxicity. AEs of special or potential interest related to durvalumab were consistent with the known safety profile of durvalumab. For AEs related to olaparib, there were no cases of MDS or AML. In line with the known safety profile of maintenance olaparib, events of anaemia contributed to a higher rate of Grade 3 or higher AEs in the SoC + D + O arm.[11]

Within the pMMR and dMMR populations, safety results were broadly aligned with the ITT; therefore, the ITT was considered to represent the most relevant source of safety data for this appraisal to maximise sample size, and were subsequently used in the economic model underpinning this submission (Section B.1.1). These data may also be considered to support the use of SoC + D and SoC + D + O in MMR-based subgroups, given that the marginal increase in AEs associated with the addition of D or D + O is likely to be most justified in the dMMR and pMMR populations, respectively, where these regimens confer particular clinical benefits. As highlighted by clinical experts, the additional olaparib-related AEs are also expected to be acceptable given that they are likely to be outweighed by the benefit associated with SoC + D + O.[1] Additionally, clinicians will be familiar with the safety profile of olaparib given its routine use in clinical practice for ovarian cancers.

B.2.12.1.3. HRQoL

Patient HRQoL was also assessed across all three treatment arms using the EORTC-QLQ-C30, EORTC-QLQ-EN24, and EQ-5D-5L. For EORTC-QLQ-C30-assesed overall HRQoL, no clinically meaningful deterioration was observed in either treatment arm compared to SoC, and physical and role functioning scores followed a similar pattern to overall HRQoL. There were also no clinically meaningful changes observed in assessments using the EORTC-QLQ-EN24, demonstrating that maintenance D and D + O does not have a negative impact on symptoms of pain in the back and pelvis, gastrointestinal symptoms, and urological symptoms, as well as sexual interest and sexual activity, when compared to SoC. Baseline EQ-5D-5L scores were also comparable across treatment arms. Overall, this demonstrates that the clinical benefits associated with SoC + D and SoC + D + O do not occur at the detriment of patient wellbeing. Importantly, clinical expert opinion indicated that they would not expect HRQoL to differ based on MMR status.[1] These results, which indicate no clinically meaningful decline in HRQoL, should therefore be considered relevant to the pMMR and dMMR populations.

B.2.12.2 Strengths and limitations of the clinical evidence base

In total, the DUO-E trial enrolled 718 patients who underwent randomisation (1:1:1) to receive SoC, SoC + D and SoC + D + O. These randomised patients were generally balanced across the treatment arms within the ITT. Baseline demographics across the relevant trial arms for the dMMR and pMMR populations were also well-balanced and aligned with the ITT, demonstrating the robustness of the study to derive conclusions in these populations. Other notable strengths include the fact that DUO-E is a randomised, double-blind trial, thus providing good quality and robust evidence for the efficacy and safety of SoC + D and SoC + D + O as a treatment for patients with advanced or recurrent EC. Additionally, DUO-E provides direct head-to-head evidence for SoC + D and SoC + D + O versus the relevant comparator in UK clinical practice (platinum-based chemotherapy; carboplatin + paclitaxel), avoiding any uncertainty introduced from indirect evidence. It should also be noted that DUO-E was specifically designed and adequately powered to demonstrate that both SoC + D and SoC + D + O provide a PFS benefit for patients with newly diagnosed advanced or recurrent EC compared with SoC. The three-arm trial design also enabled both regimens to be compared with the same control

group, reducing the risk of selection bias and allowing more robust comparisons between the interventions.

Importantly, the quality of the trial design is supported by a quality assessment (summarised in Table 10), which identified the risk of bias in DUO-E as low, with features including appropriate randomisation (1:1:1 ratio), appropriate concealment of treatment, a balanced population at baseline, and the use of precise measure of outcome (PFS by Investigator RECIST v 1.1 criteria). All efficacy data was reviewed in a blinded manner with PFS being assessed by both Investigator and BICR to prevent bias. Finally, the endpoints investigated in DUO-E are clinically relevant and important to the population of relevance for this appraisal, as well as their carers and family.

Limitations of the evidence base include the fact that results within the pMMR and dMMR population were mainly *post-hoc* in nature, with the exception of pre-specified PFS subgroup analyses. As such, these analyses were not specifically controlled for Type I error and were therefore not powered to detect statistical differences in efficacy between interventions. Nevertheless, MMR status was a stratification factor, which ensured that patients were balanced between arms and within each subgroup. Additionally, results within the pMMR/dMMR populations were largely consistent with the pre-specified primary and secondary endpoint results within the ITT, and were consistent across endpoints within populations, supporting the robustness of the results. As data from the DUO-E trial are only available from DCO1 (12 April 2023), it is also important to note that there remains some uncertainty around the long-term benefits of SoC + D and SoC + D + O. Nevertheless, data maturity represents a common challenge in oncology trials in the first-line setting, and data collected at the next DCO will provide more mature data to further support long-term extrapolations.

Although DUO-E trial was an international trial, there were also no trial sites in the UK. There was also a large proportion of participants enrolled from Asia compared with the proportion of people of Asian family background in UK clinical practice. However, the large proportion of Asian participants was highlighted by clinicians as an advantage of the DUO-E trial given that these patients are commonly underrepresented in other trials, and it was noted that ethnicity would not be expected to have an effect on tolerability.[1] Moreover, whilst there were some observed differences in PFS results for the Asia region versus RoW, this is likely to be related to differences in the treatment pathway in Asia versus RoW rather than any specific demographic characteristic that would be relevant to consider in UK clinical practice (Section B.2.7.1). Finally, although clinical expert feedback indicated that the DUO-E trial population was considered generalisable to UK clinical practice, there were a relatively small proportion of patients enrolled with FIGO stage III disease. Nevertheless, expert clinical opinion was that this may be due to the inclusion criteria specifying that patients must have measurable disease, and as such, that this would not preclude them from considering SoC + D/SoC + D + O for such patients.[1]

B.2.12.3 Overall conclusions

In summary, SoC + D demonstrated clinically meaningful improvements in PFS, ORR, DoR, PFS2, TFST and TSST, notable improved OS, and showed a numerical improvement in TDT when compared with SoC within the dMMR population. Importantly, the clinical benefit observed in the DUO-E trial was not achieved at the detriment of patient HRQoL. SoC + D was also generally well-tolerated, with safety profiles that were consistent with the known safety profiles of each agent. As such, these data demonstrate that SoC + D represents an important advancement in the treatment of patients with newly diagnosed advanced or recurrent EC that is dMMR, addressing a substantial unmet need and offering patients a deep and durable response, alongside a tolerable safety profile.

SoC + D + O demonstrated clinically meaningful improvements in PFS, OS, PFS2, TFST and TSST, notably improved DoR, marginally improved ORR, and resulted in a numerical improvement in TDT when compared with SoC within the pMMR population. As with SoC + D in the dMMR population, the clinical benefit observed in the DUO-E trial was not achieved at the detriment of patient HRQoL. SoC

+ D + O was also generally well-tolerated, similarly with safety profiles that were consistent with the known safety profiles of each agent. These clinical effectiveness and safety data therefore demonstrate that SoC + D + O addresses the clear unmet need for people with newly diagnosed advanced or recurrent EC that is pMMR, representing a potential step-change for the management of EC in this challenging-to-treat population where there are currently no NICE-recommended treatment options in the first-line setting.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

Model overview

- A *de novo* partitioned survival model (PSM) with three health states (PFS, progressed disease [PD] and death) was developed to evaluate the cost-effectiveness of SoC + D vs. SoC in primary advanced or recurrent EC that is dMMR and SoC + D + O vs. SoC in primary advanced or recurrent EC that is pMMR.
- The use of a PSM structure is aligned with recent NICE appraisals in EC, and reflects the progressive nature of the disease.[30]
- Consistent with the NICE reference case,[106] a cost-utility analysis with an NHS and PSS perspective was considered. Costs and benefits were discounted at a rate of 3.5% and a lifetime time horizon was adopted.
- Clinical outcomes (PFS, OS and TDT) were based on the specific subgroups of interest (dMMR and pMMR) from the DUO-E trial, at the time of the DCO1 (12 April 2023). Given the distinct mechanisms of actions of SoC + D and SoC + D + O compared to SoC, independent models were fitted to both treatment arms.
- The most appropriate extrapolations for each treatment and endpoint were selected in line with NICE TSD 14 and 21.[107] Alongside statistical and visual fit to the observed data from the DUO-E trial, particular consideration was given to the long-term plausibility of the chosen extrapolations. This was considered important, given the potential for long-term remission for those patients who experience the best responses to treatment. Selection of the base case extrapolations was therefore informed based on extensive discussion with clinical experts experienced in treating patients with recurrent or advanced EC in current UK clinical practice.
- For TDT, patients who remained on treatment beyond the trial follow-up were assumed to discontinue after three years. This was applied in order to reflect clinician feedback, which indicated that patients who achieve long-term remission would not remain on treatment indefinitely. Clinicians highlighted that they would discuss continuation of treatment between year one and three, as the full benefits of treatment would likely be realised within this finite treatment duration. The clinicians also highlighted the patient burden and cumulative toxicity concerns associated with prolonged treatment.
- Health state utilities for PFS and PD were informed by EQ-5D-5L data collected in the ITT population of the DUO-E study cross-walked to European Quality of Life scale-5-Dimensions-3-Levels (EQ-5D-3L).
- Costs and healthcare resource use considered in the analysis included treatment acquisition and administration costs, monitoring costs, AE costs, subsequent treatment costs, and end-of-life care costs.
- [redacted]

Summary of cost-effectiveness results (dMMR)

- The cost-effectiveness results are presented using the commercial agreement (confidential discount of [redacted]) for durvalumab as part of SoC + D.
- In the deterministic base-case analysis, SoC + D was associated with [redacted] incremental costs and 5.37 incremental quality-adjusted life years (QALY) compared to SoC, which corresponds to an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained.
- The probabilistic results were consistent with the deterministic results and demonstrate that at a willingness-to-pay (WTP) threshold of £30,000–£20,000, SoC + D has a [redacted] and [redacted] chance of being cost effective, respectively.
- The results from the deterministic sensitivity analysis demonstrate that the cost-effectiveness results are robust to changes in the model structure and inputs, with ICERs remaining below £30,000 per QALY gained for SoC + D vs. SoC in all scenarios considered.

Summary of cost-effectiveness results (pMMR)

- The cost-effectiveness results are presented using the commercial agreement of durvalumab and olaparib (confidential discounts of [redacted] and [redacted], respectively) as part of SoC + D + O.
- In the deterministic base case economic analysis, SoC + D + O was associated with [redacted] incremental costs and 0.67 incremental QALYs compared to SoC, which corresponds to an ICER of [redacted] per QALY gained. The probabilistic results were consistent with the deterministic results.
- Deterministic sensitivity analysis demonstrate that the cost-effectiveness results are robust to changes in the model structure and inputs, given that the majority of the scenarios considered were within 15% of the base case ICER.
- Notably, alternative clinically plausible scenarios suggest that the base case results may be conservative. In particular, an alternative scenario with a maximum treatment duration of two years produced an ICER of [redacted] per QALY. Clinicians highlighted that the risk of AML means that prolonged treatment with olaparib is a particular concern, and previous trials of olaparib in other indications have used a fixed two-year duration of treatment. As such, assuming a three-year maximum treatment duration for olaparib in the base case may be conservative.

Conclusion

- There is a critical unmet need for novel and effective therapies to be made available for patients with newly diagnosed advanced or recurrent EC. These patients experience a significant physical and psychological burden and face a bleak prognosis, with a median OS of approximately two years for current SoC.
- For patients with dMMR, modelling estimates suggest that SoC + D could result in an increase of 7.65 LYG and 5.37 QALYs gained, respectively. The introduction of SoC + D would therefore address the current unmet medical and patient need for a novel and effective treatment option which can result in deep and durable responses, improvements in HRQoL and prolonged survival.
- For the more difficult-to-treat population of patients with pMMR EC, modelling estimates suggest that the introduction of SoC + D + O could result in an increase of 0.89 LYG and 0.67 QALYs gained, respectively. For a patient population who cannot currently access any innovative treatment options in the first-line setting, the introduction of SoC + D + O would represent a step-change in current UK clinical practice. SoC + D + O would also address the current disparity in treatment options between patients with dMMR and pMMR EC, and will provide patients with more time with their loved ones at the end of their lives.

B.3.1 *Published cost-effectiveness studies*

An economic SLR was conducted in December 2023 (with an update in May 2024) 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.

Of the 39 studies identified, the majority were published between 2021 and 2024 (only one study was published in 2019). Most of the identified studies were in North America (n=22), followed by Europe (n=9) and Australasia (n=5). Most studies evaluated anti-PD(L)-1 treatments (pembrolizumab or dostarlimab) (n=38) as either a monotherapy or combination therapy. All the economic evaluation studies identified presented CEMs. Approximately half the included evaluations (n=18) implemented a partitioned survival model (PSM) structure; 14 presented a Markov model; five studies did not explicitly state or describe the model structure, and one was described as an “AE cost model”. Finally, one study used a Bayesian hierarchical modelling approach for PFS and OS in the base-case analysis to combine data from five different tumour sites, and PSMs for tumour sites were evaluated separately in scenario analyses.[108]

B.3.2 *Economic analysis*

No previous or existing economic evaluations of SoC + D or SoC + D + O were identified in the economic evaluations SLR. Therefore, a *de novo* cost-effectiveness model (CEM) was developed in Excel version 2406 Build16.0.17726.20078 (Microsoft 365).

B.3.2.1 Patient population

This submission focusses on the use of SoC + D in the dMMR population and SoC + D + O in the pMMR to align with the expected marketing authorisations for durvalumab and olaparib in the EC indication (Section B.1.1).

Given that this submission focusses on the use of two separate regimens in two separate populations, the economic model includes a switch to toggle between the populations of relevance to this appraisal (dMMR and pMMR).

Baseline characteristics for the dMMR and pMMR populations in the model are presented in Section B.3.3.1.

B.3.2.2 Model structure

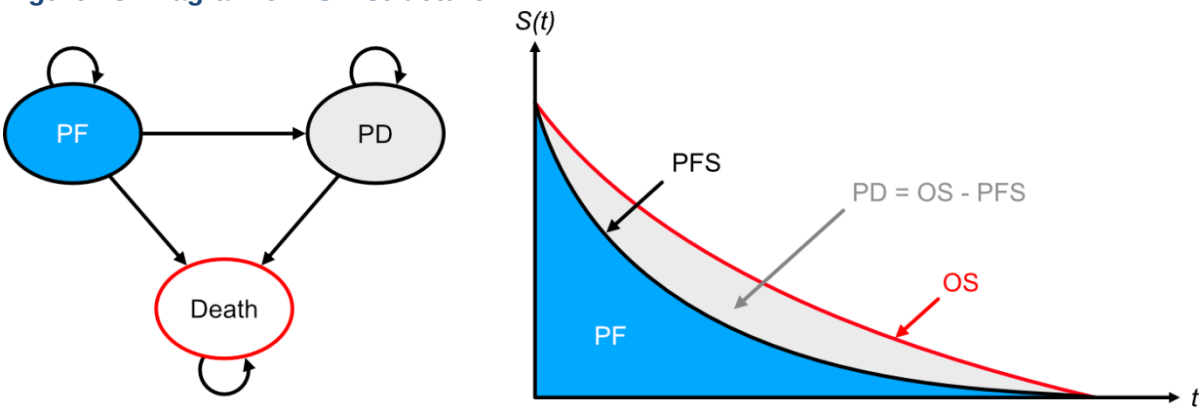
Overview of model structure

The developed model consisted of three exhaustive and mutually exclusive health states: (i) progression-free (PF), (ii) progressed disease (PD), and (iii) death, as shown in Figure 18. In the base case analysis, the occupancy of health states over time was derived from the DUO-E Investigator-assessed PFS and OS KM data in the dMMR and pMMR populations (the main source of clinical evidence in this submission, presented in Sections B.2.7.3 and B.2.7.5, respectively), which were subsequently extrapolated using parametric survival curves (presented in Sections B.3.3.3 and B.3.3.4). The model uses Investigator-assessed PFS rather than BICR-assessed PFS as Investigator-assessed better represents how progression would be assessed in clinical practice (i.e., by the treating physician), and is aligned to the primary endpoint in DUO-E.[4] Furthermore, as mentioned in Section B.2.6.1.1, consistent results are demonstrated between Investigator-assessed PFS and BICR PFS analyses.

The proportion of patients in each health state for any given cycle was calculated as the following:

- PF: Proportion of patients who are progression-free, based on the PFS curve (as described in Section B.3.3.3).
- PD: Proportion of patients alive based on the OS curve minus the proportion of patients who are in the PF health state (OS – PFS as described in Section B.3.3.3 and Section B.3.3.4, respectively).
- Death: 1 - the proportion of alive patients based on the OS curve

Figure 18. Diagram of PSM structure



Upon entering the model, all patients are assumed to initiate first-line treatment for primary advanced or recurrent EC that is dMMR/pMMR. As advanced and recurrent EC is a progressive disease, patients cannot improve their health state (e.g., move from PD to PFS). The death health state is absorbing.

The costs associated with advanced or recurrent EC throughout a patient's journey from treatment initiation to death are accrued within PF and PD health states, whereby each health state is associated with different costs. The PF health state captures treatment acquisition, administration, monitoring, and AEs, whilst the PD health state captures subsequent treatment, monitoring, and end-of-life care.

Alongside the different costs associated with each health state, the model also captures the differential impact that each health state has on HRQoL through assigning health state-specific utilities values. Given that the PF health state reflects a period of disease remission, this health state is associated with greater utility compared with the PD health state, where patients have experienced disease progression and a worsening of their symptoms.

In each model cycle, patients accrue costs, life years (LYs), and QALYs based on their health state membership. The model assesses the incremental cost-effectiveness ratio (ICER) for SoC + D (dMMR) and SoC + D + O (pMMR) versus SoC based on the total costs accrued and the total QALYs gained.

Adjustments for clinical plausibility

To ensure clinical plausibility in the model outputs the following adjustments are applied:

- The mortality risk at each model cycle cannot fall below the age-matched general population mortality risk, sourced from the ONS life tables. In the base case analysis, life tables from 2017–2019 were used as the more recent life tables were likely to be impacted by COVID-19 excess mortality. However, the most recent life tables (2020–2022) were also considered in scenario analyses (Section B.3.11.3), which demonstrate the choice of life tables have a very minor impact on the economic results.[109]

- A limit was built into the model to ensure that OS curves do not fall below the PFS curves to ensure clinical plausibility.
- TDT data were modelled directly to inform the proportion of patients on treatment as described in Section B.3.3.5. A limit was also added to make sure that the TDT curve cannot exceed the PFS curve; if TDT is estimated to be greater than PFS at any time in any model arm, TDT is set equal to PFS. Furthermore, all patients are assumed to discontinue treatment with durvalumab and olaparib after three years, based on clinician feedback. Clinicians highlighted that the benefits of treatment likely would be fully realised within a shorter treatment duration, and longer-term treatment is associated with cumulative toxicity concerns (Section B.3.3.5).

Justification for choice of model structure

A partitioned survival model (PSM) approach was deemed the most appropriate model structure to inform the cost-effectiveness of SoC + D and SoC + D + O versus SoC, as the modelled health states accurately reflect the natural disease course of patients with newly diagnosed recurrent or advanced EC. The key outcomes in this setting, PFS and OS, are time-to-event outcomes, and the PSM approach allows for the observed data from the DUO-E trial to be directly and intuitively replicated within the economic model. This means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with SoC + D, SoC + D + O or SoC.

As noted above, advanced or recurrent EC is a chronic, progressive disease, meaning that there is no requirement for functionality to move backwards between health states, thus further supporting the use of a PSM for the cost-effectiveness analysis.

Finally, the choice of model structure is aligned with extensive precedent for the use and acceptance of PSMs in previous NICE appraisals and across the studies identified in the economic SLR (Section B.3.1). Of particular relevance to this appraisal, the use of a PSM is aligned with the model structure used in previous NICE appraisals in the EC setting, including:

- Dostarlimab for the treatment of patients with primary advanced or recurrent dMMR/MSI-H EC [TA963];[30]
- Dostarlimab for the treatment of patients with recurrent or advanced dMMR/MSI-H EC that has progressed following prior treatment with platinum-based chemotherapy [TA779];[31]
- Pembrolizumab + lenvatinib for the treatment of patients with advanced or recurrent endometrial carcinoma that has progressed following platinum-based treatment [TA904];[25]
- Pembrolizumab for previously treated dMMR/MSI-H endometrial, biliary, colorectal, gastric or small intestine cancer [TA914].[32]

In each of these appraisals, the Committee concluded that a PSM structure was appropriate for decision making.

B.3.2.3 Model characteristics

The *de novo* economic analysis was performed from the perspective of the UK NHS and Personal Social Services (PSS) in England over a lifetime time horizon. In accordance with the NICE reference case[106], an annual discount rate of 3.5% was applied to both costs and effects within the model.

For the *de novo* analysis, a 1-month cycle length (30.44 days) was chosen, to capture all relevant costs and utilities of typical EC progression. This cycle length balances computational efficiency with clinical relevance and the need to accurately reflect the progression and treatment effects over a lifetime time

horizon. To correct for the longer cycle length, the model applies a half-cycle correction using a lifetable approach,[110] with the exception of the following costs:

- Drug acquisition and administration costs, as these were separately calculated based on a weekly cycle length
- AE costs, as these costs were applied as one-off costs in the first model cycle, and
- Subsequent treatment costs, as these were applied as one-off costs in the first model cycle after disease progression.

As the treatments in the model are administered differently in the chemotherapy and maintenance phases (Section B.2.3.1), the model applies a weekly cycle length solely for the purpose of calculating treatment acquisition and administration costs. These are based on the TDT extrapolations for each treatment. This is sufficiently granular to account for the differing administration schedules between chemotherapy and maintenance phases of treatment, which a monthly cycle may not adequately capture.

The components of HRQoL considered in the cost-effectiveness analysis included age-adjusted health state utilities and AE disutilities. Relevant utility values for the UK perspective were derived from the EQ-5D-5L data within the ITT population of the DUO-E trial, which were mapped to the EQ-5D-3L value set in line with the NICE reference case.[111] Disutilities due to AEs were sourced from the published literature.[112-114] A comprehensive description of the utility mapping methodology and the AE disutilities applied in the economic model is provided in Section B.3.4.3.

All relevant clinical outcomes were obtained from subgroup analyses (dMMR, pMMR) of the DUO-E trial. A complete description of the DUO-E trial methodology is provided in Section B.2.3, and a detailed list of the other assumptions made in the cost-effectiveness analysis can be found in Section B.1.1.

Cost categories and health care resource use (HCRU) components used in the economic model included drug acquisition costs, drug administration costs, drug monitoring costs, AE management costs, disease management costs, subsequent therapy costs, and terminal care costs. Full methodology and data sources are provided in Section B.3.5.

A summary of the key features from previously submitted NICE technology appraisals (TAs) and respective *de novo* models are presented in Table 29. Parameters were selected to align with the NICE reference case[106] and were aligned with clinical expert input from five UK-based medical oncologists with direct experience treating advanced and recurrent EC, conducted between August and September 2024 (Section B.3.14).[115]

Table 29. Features of the economic analysis

	Previous appraisals				Current appraisal	
	Dostarlimab [TA779][31]	**Dostarlimab [TA963][30]**	**Pembrolizumab [TA914][108]**	**Pembrolizumab + lenvatinib [TA904][25]**	**Chosen values**	**Justification**
Population	Adult patients with advanced or recurrent EC with dMMR/MSI-H that has progressed on or following prior treatment with a platinum-containing regimen	Adult patients with advanced or recurrent EC with dMMR/MSI-H who are candidates for systemic therapy	Adult patients with dMMR/MSI-H advanced or recurrent EC, 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 advanced or recurrent EC 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 in first-line treatment of primary advanced or recurrent EC who are candidates for systemic therapy and includes both pMMR and dMMR	Aligns with the NICE Decision problem (Section B.1.1)
Time horizon	Lifetime (40 years)	Lifetime (100 – mean age)	Lifetime (40 years)	Lifetime (40 years)	Lifetime (38 years, based on mean starting age of 62.60 years)	Sufficient to capture the long-term clinical and economic impacts of EC on the targeted population with a mean starting age of 62.60 years.
Perspective	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	UK NHS and PSS	Aligned to the NICE reference case[106]
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	3.5% per annum for costs and outcomes	3.5% per annum for costs and outcomes	Aligned to the NICE reference case[106]
Cycle length	3-week	1-week	1-week	1-week	1-month for patient tracking (1-week for drug	A one-month cycle length is chosen to balance computational efficiency

	Previous appraisals				Current appraisal	
	Dostarlimab [TA779][31]	**Dostarlimab [TA963][30]**	**Pembrolizumab [TA914][108]**	**Pembrolizumab + lenvatinib [TA904][25]**	**Chosen values**	**Justification**
					acquisition and administration)	whilst remaining clinically relevant and being able to accurately capture disease progression. A one-week cycle is chosen for drug acquisition and administration to align with drug administration frequencies.
Treatment waning effect	Not considered	Not included in the model	Not considered	Not considered	Not included in the model	Whilst there is some uncertainty surrounding the long-term treatment effect of SoC + D and SoC + D + O, clinical expert input indicated that there would be no or negligible treatment waning with immunotherapies in this setting.[1] Therefore, to reflect clinical input and the precedent in the most recent appraisal in this indication [TA963], treatment waning was not included in the model for any intervention.
Health states	PFS, PD and death	PFS, PD and death	PFS, PD and death	PFS, PD and death	PF, PD and death	Aligned with the PSM health states previously accepted in NICE appraisals in this indication. These health states accurately reflect the natural disease course of patients with newly diagnosed advanced or

	Previous appraisals				Current appraisal	
	Dostarlimab [TA779][31]	**Dostarlimab [TA963][30]**	**Pembrolizumab [TA914][108]**	**Pembrolizumab + lenvatinib [TA904][25]**	**Chosen values**	**Justification**
						recurrent dMMR/pMMR EC (Section B.3.2.2).
Source of utilities[a]	GARNET[26]	RUBY-1[3]	KEYNOTE-158[116]	KEYNOTE-775[27]	DUO-E[4]	Aligned with NICE methods, which stipulates that the preferred source of utility data is EQ-5D data collected from the relevant clinical trial. As such, EQ-5D data from the DUO-E trial is the most appropriate source of utility data per NICE methods, and is also aligned with past appraisals in EC where utility data from the pivotal trial(s) informed the economic model.
Source of costs[b]	UK standard data sources	UK standard data sources	UK standard data sources	UK standard data sources	UK standard data sources	Aligned to the NICE reference case[106], costs were obtained from UK national resources to reflect the NHS and PSS perspective. Where applicable, costs were inflated to 2023/24.[117]

Footnotes: [a] EQ-5D-5L data from each study was cross walked to 3L; [b] UK standard data sources included British National Formulary (BNF), NHS reference costs and the personal social services research unit (PSSRU) 2023
Source: NICE [TA779][31], NICE [TA963][30], [TA914][108], [TA904][25]

B.3.2.4 Intervention technology and comparators

B.3.2.4.1. Intervention (dMMR): SoC + D

Durvalumab is administered intravenously. The dose of durvalumab incorporated into the economic model is aligned with the SmPC (Appendix C) and the DUO-E trial.[4] In the intervention arm of the DUO-E trial[4444] for dMMR, patients received 1,120 mg of durvalumab (equivalent to 15 mg/kg every three weeks for a patient weighing 75 kg) plus carboplatin: AUC, 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2 every three weeks for up to six cycles (i.e., weeks 1, 4, 7, 10, 13, 16) followed by (i.e. from week 18 onwards) maintenance durvalumab 1,500 mg (equivalent to 20 mg/kg) every four weeks.

The base-case analysis assumes that all patients receive carboplatin AUC 6 mg/mL/min. A scenario analysis is included where all patients receive carboplatin AUC 5 mg/mL/min (Section B.3.11.3), which has a negligible impact on the ICER. This is expected, as carboplatin is received by patients across all treatment arms, and is associated with low costs.

B.3.2.4.2. Intervention (pMMR): SoC + D + O

Durvalumab and platinum-based chemotherapy are administered as outlined above in Section B.3.2.4.1. As per SoC + D, the base-case analysis assumes that all patients receive carboplatin AUC 6 mg/mL/min, with a scenario where all patients receive carboplatin AUC 5 mg/mL/min.

Olaparib is administered orally; the dose of olaparib incorporated into the economic model is aligned with the SmPC (Appendix C) and the DUO-E trial. In the intervention arm of the DUO-E trial for pMMR, from week 18 onwards, patients received olaparib 300 mg tablets twice daily with maintenance durvalumab 1,500 mg (equivalent to 20 mg/kg) every four weeks until disease progression or unacceptably toxicity.[4]

B.3.2.4.3. Comparators: SoC

In line with the decision problem outlined in Section B.1.1, the only comparator considered in the economic model is platinum-based therapy, aligned with the comparator in the DUO-E trial and the current standard of care for newly diagnosed advanced or recurrent endometrial cancer in UK clinical practice (Section B.1.3.4).[4] The economic model reflects the administration of platinum-based chemotherapy in the DUO-E trial: carboplatin: AUC, 6 (base case) or 5 (scenario) mg/mL/min and paclitaxel: 175 mg/m^2 every three weeks for six cycles.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics considered as CEM inputs are presented in Table 30. The baseline characteristics for the dMMR and pMMR populations were based on the FAS for the ITT population in the DUO-E trial.[4] The ITT population was considered appropriate to use given the larger sample size. Additionally, no meaningful differences were reported in the baseline characteristics for the dMMR and pMMR subgroups, as presented in Sections B.2.7.2 and B.2.7.4 respectively.[4]

Table 30. Patient baseline characteristics for the base-case economic analysis

Parameter	Value	Reference
Mean age (years)	62.60	DUO-E trial (ITT)[4]
Mean weight (kg)	73.80	DUO-E trial (ITT)[4]

Parameter	Value	Reference
Mean height (cm)	159.4	DUO-E trial (ITT)[4]
Mean body surface area (m^2) (SD)	1.77	Calculated based on DUO-E ITT baseline characteristics for weight and height using DuBois and DuBois method used in Sacco *et al.* (2010)[118,a]
Glomerular Filtration Rate (GRF) (ml/min)	125.00	Maximum taken from the DUO-E trial[4]

Footnotes: [a]body surface area (m^2)=Weight (kg) 0.425×Height (cm)0.725×0.007184
Source: DUO-E CSR;[11]

Scenario analyses

Several scenarios were considered to explore the impact of applying alternative baseline ages on the model results. The first scenarios used a baseline age of 67.1 years in both dMMR and pMMR populations. This was based on Pennington *et al.* (2016),[119] a prospective cohort study nested within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) that enrolled 39 women diagnosed with advanced stage III and IV EC. Whilst this source informed the baseline age in the economic analysis in TA963,[30] Pennington *et al.* was excluded from the base case in this appraisal for several key reasons:

- The DUO-E study represents a more recent source of evidence compared with Pennington *et al.*, given that data reported in Pennington *et al.* was collected from women diagnosed with EC more than two decades ago (between 2001–2005), who are unlikely to reflect current UK clinical practice.
- The DUO-E study also included a substantially greater number of patients compared with Pennington *et al.* (718 vs. 39, respectively). The mean baseline age in the DUO-E trial is therefore less likely to be impacted by outliers and should be considered a more robust source of evidence.
- Notably, of the 39 patents in Pennington *et al.,* only 5 had Stage IV EC. This is substantially lower than the DUO-E trial, where approximately 50% of patients had Stage IV EC across all three treatment arms. Clinicians highlighted that DUO-E was generalisable to UK clinical practice, raising substantial generalisability concerns regarding the appropriateness of Pennington *et al.*
- The study population within Pennington *et al.* also included a substantial proportion of patients with a Charlson score of 1 or higher (between 20–43% depending on Stage), indicating that the enrolled population had a high burden of comorbidities. Since the frequency and severity of comorbidities generally increase with age, this may suggest that Pennington *et al.* included a higher proportion of patients in the older age group than may be expected in UK clinical practice.

These scenarios slightly increased the ICERs in both the dMMR and pMMR populations (Section B.3.11.3). However, for the reasons detailed above, these scenarios are associated with substantial uncertainty. In comparison, clinical experts considered that the baseline characteristics of patients enrolled in the DUO-E trial were generalisable to patients in UK clinical practice.[1] Given this, and that all other baseline characteristics are informed by the DUO-E trial, DUO-E represents a more robust source to inform the baseline age in the economic model.

Two additional scenarios were explored where the baseline age was informed by MMR subgroup data from the DUO-E trial:[4] 62.5 years in the dMMR population and 62.4 years in the pMMR population. As highlighted above, data within the ITT was used in the base case to maximise the sample size, given that the baseline age for the dMMR and pMMR populations were largely aligned with the ITT population. These scenarios had a negligible impact on the ICER (Section B.3.11.3).

B.3.3.2 Survival analyses

Overview of survival analysis methodology

Survival analysis was conducted on TTE outcomes (OS, PFS and TDT) from the DUO-E trial using data from DCO1 (12 April 2023), to generate appropriate TTE model inputs across the lifetime horizon using the subgroup data presented in Section B.2.7.

For all TTE outcomes (OS, PFS, TDT), the DUO-E study follow-up time was less than the model lifetime horizon, necessitating long-term extrapolation. Recommendations in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[107] were considered when selecting survival models for the base-case analysis for each model population (dMMR and pMMR) and across treatment and comparator arms (SoC, SoC + D and SoC + D + O) (Appendix N). Survival analyses were conducted in months to align with the model cycle length.

The standard parametric survival analysis investigated seven distributions: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma. Flexible parametric survival models using splines (with hazard knots [k] = 1, 2, 3) were also considered if the standard parametric distributions fit the data poorly (e.g., due to a complex hazard function), and if data availability was sufficient.

Selection of most appropriate extrapolations

Survival analyses were conducted separately for each target population, given that disease progression and long-term prognosis differ between patients with pMMR and dMMR EC.[24-27] However, consistent with the NICE DSU TSD 14[120], the same type of extrapolation was selected for both relevant trial arms in each population (i.e. SoC + D and SoC in dMMR and SoC + D + O and SoC in pMMR).

SoC + D and SoC + D + O are associated with clearly distinct mechanisms of action compared to SoC alone. As such, the use of the independent models was preferred in the base case analysis, rather than joint models which rely on the PH assumption and a constant treatment effect over time. Further consideration of PH plots is provided in the following sections.

The selection of the most appropriate distribution for each outcome was based on a comprehensive set of criteria, in line with NICE TSD 14:[107]

- Statistical goodness-of-fit as measured by Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC);
- Visual fit of the modelled extrapolations to the KM plots from the DUO-E trial;
- Clinical plausibility of model extrapolations based on clinician predictions of long-term survival provided as part of NICE TA963, as well as previously published long-term survival outcomes in EC published by Chase *et al.* (2023)[121] and Miller *et al.* (2020)[38], where relevant data were available
- Feedback from clinicians experienced in the treatment of patients with advanced and recurrent EC in UK clinical practice collected as part of this appraisal (Section B.3.14).[115]

Clinical outcomes for dMMR in the DUO-E[4] study (Section B.2.7.3) indicate that a proportion of patients may experience long-term remission following treatment with SoC + D and SoC + D + O, given the observed “tail effect” for PFS in the dMMR and pMMR population, respectively. This potential for ‘cure’ was also highlighted by clinicians.[1] As such, the long-term clinical plausibility of the chosen extrapolations informed a particularly key component of the model selection process.

B.3.3.3 Progression-free survival (PFS)

As detailed in Section B.2.6, Investigator-assessed PFS of SoC + D and SoC + D + O versus SoC were the coprimary trial endpoints in the DUO-E trial, and pre-specified subgroup analyses were conducted for this primary endpoint by (dMMR and pMMR) and by treatment arms of the trial.

B.3.3.3.1. dMMR

A summary of the non-parametric results for Investigator-assessed PFS in the dMMR subgroup of the DUO-E trial are presented in Table 31 (previously presented in Section B.2.7.3.1). The median follow up was 10.2 months in the SoC arm and 15.5 months in the SoC + D arm. The median PFS was not reached for the SoC + D arm and was 7.0 months in the SoC arm. Patients in the SoC + D arm had a 58% lower risk of a progression or death event than patients in the SoC arm (HR 0.42; 95% CI 0.22, 0.80).

Table 31. Non-parametric results for PFS for dMMR

Treatment arm (N)	SoC (N=49)	SoC + D (N=46)
Maturity (%) – n/N	51% (25/49)	32.6% (15/46)
Duration of follow up (months) – median (range)	10.2 (0.0, 26.4)	15.5 (0.0, 29.1)
Median (95% CI) (months)	7.0 (6.7, 14.8)	NR (NR, NR)
Restricted mean survival time (RMST) (months) (95% CI)	13.2 (10.1, 16.3)	19.5 (16.6, 22.5)

Diagnostic assessment

Several statistical tests were conducted to assess the proportional hazards (PH) assumption and whether it would hold between the SoC and SoC + D treatment arms within the dMMR subgroup. The results of these tests are presented in Appendix N and demonstrate that the PH assumption may be rejected. This supports the use of independent model in the base case analysis.

Visual and statistical fit

Standard parametric models fitted to PFS for SoC and SoC + D are shown in Figure 19 and Figure 20, respectively. Table 32 summarises the AIC and BIC values for each extrapolation, with the lowest three scores for each shaded in blue. Lower AIC and BIC scores indicate an improved goodness-of-fit.

For the SoC arm, the log-normal, log-logistic and generalised gamma extrapolations had the lowest AIC/BIC values; in comparison, the exponential, log-normal and log-logistic extrapolations had the lowest AIC/BIC in the SoC + D arm.

The exponential extrapolation assumes that there is a constant hazard of disease progression or death over time. In contrast, the observed hazards presented in Appendix N are shown to be decreasing over time. The exponential extrapolation was therefore excluded from further consideration as it was considered clinically implausible.

Figure 19. Standard parametric survival analysis for PFS in the dMMR SoC arm

Source: Survival analysis conducted on DUO-E trial data.

Figure 20. Standard parametric survival analysis for PFS in the dMMR in the SoC + D arm

Source: Survival analysis conducted on DUO-E trial data.

Table 32. Summary of goodness-of-fit data for SoC and SoC + D for PFS (standard parametric independent models)

Distribution	SoC				SoC + D			
	AIC	AIC Rank	BIC	BIC Rank	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	5	[redacted]	4	[redacted]	1	[redacted]	1
Weibull	[redacted]	6	[redacted]	6	[redacted]	5	[redacted]	5
Log-normal	[redacted]	2	[redacted]	1	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	3	[redacted]	3	[redacted]	3	[redacted]	3

Gompertz	[redacted]	7	[redacted]	7	[redacted]	4	[redacted]	4
Generalised Gamma	[redacted]	1	[redacted]	2	[redacted]	7	[redacted]	7
Gamma	[redacted]	4	[redacted]	5	[redacted]	5	[redacted]	6

Source: Survival analysis conducted on DUO-E trial data.

Landmark and external validation

Extrapolated PFS data from the standard parametric models were compared to the landmark survival probabilities (taken from advisor estimated landmarks in TA963[30], which was the only identified source reporting PFS data for the dMMR population), as shown in Table 33 and Table 34, respectively.

Compared to the clinical advisor in TA963, the parametric models consistently underestimate the expected PFS at five and ten years for the SoC arm, with the exception of the Generalised Gamma extrapolation at 5 years.

For SoC + D, the survival expected for the intervention arm (of RUBY) was substantially higher than the estimates predicted by parametric models fitted to SoC + D arm of the DUO-E trial. This suggests that the parametric models may not adequately capture the expected potential for long-term PFS for those patients who experience the most durable responses to treatment.

Table 33. Comparison of parametric models with advisor landmarks of the proportion of patients who would be progression free in the dMMR population in the SoC arm

Distribution	Median PFS (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Year PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1; SoC Arm]	-	-	23.00%	15.00%	9.00%	7.00%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Table 34. Comparison of parametric models with advisor landmarks of the proportion of patients who would be progression free in the dMMR population in the SoC + D arm

Distribution	Median PFS (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Year PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1; SoC + Dostarlimab Arm]	-	-	60.00%	56.00%	46.00%	36.00%

Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

As the standard parametric models aligned poorly with the TA963 advisor predictions of PFS at landmark timepoints, flexible spline approaches were explored (k = 1, 2, 3). NICE TSD 21 recommends spline models as a flexible model type which may be appropriate for complex hazard functions which cannot be captured using standard parametric models.[107] TSD 21 highlights that the advent of immuno-therapy treatments for oncology has resulted in an increase in the use of complex survival models, given the potential for long-term survivors and a resulting complex hazard function.

Flexible models may facilitate an improved fit to the observed trial data from DUO-E, whilst simultaneously providing long-term estimates of survival that are more aligned with the clinician's expectations. Splines allow the consideration of a more complex hazard function which changes over time, where patients who experience the best responses to treatment will achieve long-term remission and extended PFS.

The use of splines is also consistent with the Committee-preferred approach for PFS extrapolation in TA963.[30] Since the empirical hazards observed in the DUO-E trial demonstrated a decrease in hazard over time, with the best-fitting parametric model being the log-normal model (Table 32), the normal scale for flexible splines was considered the most suitable approach. Table 35 summarises the goodness of fit for various flexible spline models.

Based on an analysis of the spline hazard functions versus the empirical hazard functions, the model with three knots appeared to overfit the data in both trial arms, as presented in Figure 21 and Figure 22. This is because the three knot splines predict that the proportion of patients who are progression-free increases over certain time periods (e.g., from months 3 to 6). By definition, the survival probabilities must remain equal or decreasing over time. Therefore, the 3 knot splines were considered implausible and excluded from further consideration.

Figure 21. Flexible spline model fits in the SoC arm (dMMR)

Source: Survival analysis conducted on DUO-E trial data.

Figure 22. Flexible spline model fits in the SoC + D arm (dMMR)

Source: Survival analysis conducted on DUO-E trial data.

Table 35. Summary of goodness of fit for flexible spline methods (dMMR)

Knots	SoC				SoC + D			
	AIC	AIC Rank	BIC	BIC Rank	AIC	AIC Rank	BIC	BIC Rank
1 knot (normal)	[redacted]	3	[redacted]	2	[redacted]	2	[redacted]	1
2 knots (normal)	[redacted]	1	[redacted]	1	[redacted]	3	[redacted]	3
3 knots (normal)	[redacted]	2	[redacted]	3	[redacted]	1	[redacted]	2

Source: Survival analysis conducted on DUO-E trial data.

As demonstrated in Table 35, the models with two knots for SoC and three knots for SoC + D provided

the best statistical fit based on AIC and BIC. However, the models with one knot for SoC and two knots for SoC + D provided a very similar statistical fit, but more closely matched the predicted estimates of long-term survival from TA963[30] (Table 36 and Table 37).

Table 36. Comparison of flexible spline models with advisor landmarks in SoC arm

	Median (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Yar PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1[30]; SoC Arm]	-	-	23.00%	15.00%	9.00%	7.00%
1 knot (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knots (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knots (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Table 37. Comparison of flexible spline models with advisor landmarks in SoC + D arm

	Median (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Year PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1[30]; SoC + Dostarlimab Arm]	-	-	60.00%	56.00%	46.00%	36.00%
1 knot (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knots (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knots (normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Clinical validation

Clinical expert opinion was also sought from five clinicians to assess the clinical plausibility of long-term survival data for PFS in SoC and SoC + D derived from both the standard and flexible survival analyses at landmark survival endpoints.[115] All clinicians agreed they would expect a proportion of patients to achieve long-term remission post-treatment. They considered that models such as Weibull (with PFS reaching <1% at 20 years) would be clinically implausible.

Several of the clinicians also highlighted that the PFS curves in both arms would begin to plateau at approximately five years, with most progression events occurring before that time point. They noted that they would expect very few EC-related events to occur between 10–20 years. All clinicians agreed that the flexible spline models were most appropriate for modelling PFS in dMMR patients. Most clinicians agreed that the two-knot and one-knot flexible spline models were the most representative models for the SoC + D and SoC treatment arms, respectively. However, three clinicians highlighted that even the two-knot extrapolation does not have a sufficient plateau in the tail, and that they would expect the proportion PFS at year 20 to be more aligned to that at year five (~44%). As such, even the best fitting spline models may underestimate the true long-term PFS that would be associated with SoC + D.

Conclusions

Standard parametric models were explored, but were not considered to be clinically plausible when compared to long-term expert predictions of PFS, and as such, were excluded from further consideration. As such, flexible spline approaches were explored, to provide a more flexible fit to the observed trial data and to offer an approach that potentially better reflected clinical opinion, whereby it was highlighted that a proportion of patients would experience long-term periods of PFS.

Based on exploration of these flexible spline models, the three knot splines appeared to overfit the PFS for SoC. Whilst the two knots for SoC and three knots for SoC + D provided the best statistical fit to the observed trial data, there were also limitations associated with these extrapolations, given they did not align with the predicted estimates of long-term survival from TA963, nor clinical expert opinion sought as part of this appraisal.[30, 115]

Therefore, the two-knot and one-knot flexible spline models were selected for the SoC + D and SoC treatment arms in the base case, respectively, since these were associated with a very similar statistical fit, but greater clinical plausibility in the long term. The fitted curves (adjusted for background mortality) are shown in Figure 23.

Figure 23. dMMR PFS base case fitted curves (flexible spline method) in SoC and SoC + D treatment arms

Source: Survival analysis conducted on DUO-E trial data.

As part of the scenario analyses (Section B.3.11.3), the following were explored to demonstrate the impact on the results:

- The two-knot spline model was used to model PFS for both SoC (where it represents the best fitting curve based on AIC/BIC) and SoC + D (where the two-knot spline is the current base case)
- The one-knot spline model was used to model PFS for SoC + D (best fitting curve based on AIC/BIC but underestimates clinical landmark) as well as SoC (were the one-knot spline is the current base case)

These alternative scenarios had a minimal impact on the ICER for SoC + D vs. SoC in patients with dMMR newly diagnosed advanced or recurrent EC, indicating that the choice of PFS extrapolation should not be considered to represent a source of uncertainty in this submission (Section B.3.11.3).

B.3.3.3.2. pMMR

A summary of the non-parametric results from the Investigator-assessed PFS for pMMR are presented in Table 38 (previously presented in Section B.2.7.5.1). PFS data for the pMMR population was more mature in the SoC arm (77.1%) compared with that in the SoC + D + O arm (56.5%) over the follow-up period, with a median follow up of 12.8 months in the SoC arm and 15.2 months in the SoC + D + O arm. Overall, the median PFS was 9.7 months in the SoC arm and 15.0 months in the SoC + D + O arm, with a 43% lower risk of a progression or death event than patients in the SoC arm (HR: 0.57; 95% CI: 0.44, 0.73).

Table 38. Non-parametric results for PFS for pMMR

Treatment arm (N)	SoC (N=192)	SoC + D + O (N=191)
Maturity (%) – n/N	77.1% (148/192)	56.5% (108/191)
Duration of follow up (months) – median (range)	12.8 (0.0, 31.6)	15.2 (0.0, 31.7)
Median (95% CI) (months)	9.7 (9.2, 10.1)	15.0 (12.4, 18.0)
RMST (months) (95% CI)	11.9 (10.7, 13.0)	16.2 (14.7, 17.8)

Diagnostic assessment

The output of the statistical tests to assess PH assumptions are presented in Appendix N and imply that the PH assumption may be rejected, given that the two curves cross in the log cumulative hazard plot and that the Schoenfeld residuals show that beta(t) is not constant over time.

Visual and statistical fit

Standard parametric models fitted to PFS for SoC and SoC + D + O are shown in Figure 24 and Figure 25. Table 39 summarises the AIC and BIC values for each extrapolation, with the lowest three scores shaded in blue. For the SoC arm, the Weibull and log-logistic extrapolations provided the best statistical fit, based on AIC/BIC. However, the Weibull extrapolation was not considered appropriate as the hazard increases monotonically over time, which does not align with the observed (decreasing) hazards for PFS. Accordingly, the Weibull curve was expected to overestimate the rate of progression and underestimate the PFS benefit post-treatment (Appendix N). For the SoC + D + O arm, the log-logistic and gamma extrapolations provided the best statistical fit based on AIC/BIC.

Figure 24. Standard parametric survival analysis for PFS in the pMMR SoC arm

Source: Survival analysis conducted on DUO-E trial data.

Figure 25. Standard parametric survival analysis for PFS in the pMMR in the SoC + D + O arm

Source: Survival analysis conducted on DUO-E trial data.

Table 39. Summary of goodness-of-fit data for SoC and SoC + D + O for PFS pMMR (standard parametric independent models)

Distribution	SoC				SoC + D + O			
	AIC	AIC Rank	BIC	BIC Rank	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	7	[redacted]	7	[redacted]	4	[redacted]	1
Weibull	[redacted]	1	[redacted]	1	[redacted]	3	[redacted]	4
Log-normal	[redacted]	6	[redacted]	6	[redacted]	7	[redacted]	7
Log-logistic	[redacted]	3	[redacted]	2	[redacted]	1	[redacted]	2
Gompertz	[redacted]	5	[redacted]	5	[redacted]	6	[redacted]	5

Generalised Gamma	[redacted]	2	[redacted]	4	[redacted]	5	[redacted]	6
Gamma	[redacted]	4	[redacted]	3	[redacted]	2	[redacted]	3

Source: Survival analysis conducted on DUO-E trial data.

Landmark and external validation

The percentage of PF patients at landmark timepoints for each of the standard parametric models is presented in Table 40 (SoC) and Table 41 (SoC + D + O). There are no landmark survival probabilities available from the literature for PFS in patients with newly diagnosed advanced or recurrent EC that is pMMR; therefore, it was not possible to compare the standard parametric models with landmark timepoints from other sources as per the dMMR population. Selection of clinically plausible extrapolations was therefore supported by clinical expert opinion, as detailed further below.

Table 40. Comparison of parametric models of the proportion of patients who would be progression free at landmark timepoints in the pMMR population in the SoC arm

Distribution	Median PFS (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Year PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Table 41. Comparison of parametric models of the proportion of patients who would be progression free at landmark timepoints in the pMMR population in the SoC + D + O arm

Distribution	Median PFS (months)	1 Year PFS	2 Year PFS	3 Year PFS	5 Year PFS	10 Year PFS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Consistent with the approach taken for the dMMR population, spline models were also explored in the pMMR population but have not been presented here. Whilst there may be some patients who achieve long term remission, there remains uncertainty over the long-term outcomes in the pMMR population. Furthermore, standard parametric models provided a reasonable fit to the trial data, so this more conservative approach was taken.

Clinical validation

As with the dMMR population, clinical input was also sought from five clinicians to assess the long-term survival data for PFS in SoC and SoC + D + O derived from the standard survival analyses.[115] In the SoC arm, clinicians stated that the log-normal and log-logistic extrapolations were most plausible. While the Weibull extrapolation provided a good statistical fit to the data, the clinicians did not consider the Weibull to be clinically plausible. With a predicted PFS of 0% at 5 years, the Weibull was considered to be too pessimistic, with the clinicians expecting at least some patients to achieve long-term remission.

In the SoC + D + O arm, many clinicians felt that the log-logistic extrapolation was most plausible, whilst the remaining clinicians preferred either the log-normal or Weibull extrapolation. Aligned with clinician input received for the dMMR group, clinicians highlighted that they would expect that a proportion of patients (ranging from 0-10%) would experience long-term remission, and that EC-related events would be rare after 10 years.

Conclusions

Given that there was no significant plateau in survival in the DUO-E trial for SoC + D + O in the pMMR population, there was limited justification for the use of a more flexible modelling approach such as spline models. Therefore, simpler, standard parametric models were deemed suitable for the extrapolation of PFS in the pMMR population. Of these parametric models, the Weibull extrapolation provided the best statistical fit to the observed data; however, clinicians indicated that the Weibull was too pessimistic with respect to long-term estimates of PFS. The clinicians considered that the log-normal and log-logistic extrapolations were more plausible, when considering the proportion of patients who would be expected to experience long-term remission.

Of these two models, the log-normal was associated with improved statistical fit compared to the log-logistic, however, the log-logistic model was selected as the base case extrapolation in the economic model for both treatment arms based on clinical expert opinion. The fitted curves (adjusted for background mortality) are shown in Figure 26.

Figure 26. pMMR PFS base case fitted curves for SoC and SoC + D + O treatment arms

Source: Survival analysis conducted on DUO-E trial data.

In a scenario analysis, the log-normal extrapolation (which was considered an alternative, clinically plausible option by clinicians) was used to model PFS for both SoC and SoC + D + O. As detailed in Section B.3.11.3, this scenario had a minimal impact on the overall ICER, indicating that the choice of PFS extrapolation for the pMMR population should not be considered to represent a major source of uncertainty in this submission.

B.3.3.4 Overall survival

B.3.3.4.1. dMMR

A summary of the non-parametric results from the OS are presented in Table 42 (previously presented in Section B.2.7.3.2). OS data for the dMMR population was more mature in the SoC arm (36.7%) than in the SoC + D arm (15.2%) over the follow-up period, with a median follow up of 18.4 months in the SoC arm and 19.1 months in the SoC + D arm. The median OS was not reached in the SoC + D arm and was 23.7 months in the SoC arm. Although the OS data were relatively immature, at DCO1, there was a numerical improvement in OS for SoC + D versus SoC (HR 0.34; 95% CI, 0.13, 0.79).

Table 42. Non-parametric results for OS for dMMR

Treatment arm (N)	SoC (N=49)	SoC + D (N=46)
Maturity (%) – n/N	36.7% (18/49)	15.2% (7/46)
Duration of follow up (months) – median (range)	18.4 (2.4, 28.8)	19.1 (6.7, 31.9)
Median (95% CI) (months)	23.7 (16.9, NR)	NR
RMST (months) (95% CI)	20.7 (17.8, 23.7)	25.7 (23.5, 27.9)

Diagnostic assessment

An assessment of whether the PH assumption would hold between the SoC and SoC + D treatment arms within the dMMR subgroup is presented in Appendix N. The results imply that the PH assumption may be rejected, supporting the use of independent models for both treatment arms.

Visual and statistical fit

Standard parametric models fitted to OS for SoC and SoC + D are shown in Figure 27 and Figure 28. Table 43 summarises the AIC and BIC values for each extrapolation, with the lowest three scores shaded in blue. Based on these results, it was observed that the AIC and BIC values for all curves were within two and five points of each other, indicating that statistical fit alone could not be used to determine the best fitting curve. Nevertheless, the exponential extrapolation was rejected, as this model (which assumed constant hazards over time) did not reflect the decreasing hazards over time in the observed data from the DUO-E trial (Appendix N).

Figure 27. Standard parametric survival analysis for OS in the dMMR SoC arm

Source: Survival analysis conducted on DUO-E trial data.

Figure 28. Standard parametric survival analysis for OS in the dMMR in the SoC + D arm

Source: Survival analysis conducted on DUO-E trial data.

Table 43. Summary of goodness-of-fit data for SoC and SoC + D for OS (standard parametric independent models)

Distribution	SoC				SoC + D			
	AIC	AIC Rank	BIC	BIC Rank	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	2	[redacted]	1	[redacted]	1	[redacted]	1
Weibull	[redacted]	6	[redacted]	5	[redacted]	2	[redacted]	2
Log-normal	[redacted]	1	[redacted]	2	[redacted]	5	[redacted]	6
Log-logistic	[redacted]	4	[redacted]	3	[redacted]	2	[redacted]	4
Gompertz	[redacted]	7	[redacted]	6	[redacted]	5	[redacted]	4
Generalised Gamma	[redacted]	3	[redacted]	7	[redacted]	7	[redacted]	7
Gamma	[redacted]	5	[redacted]	4	[redacted]	2	[redacted]	2

Landmark and external validation

Extrapolated OS data from the standard parametric models were compared to advisor-estimated landmark survival probabilities for both SoC and SoC + D, provided as part of TA963,[30] as presented in Table 44 and Table 45, respectively.

Additionally, the extrapolated OS data for SoC was compared to the findings of the Phase 3 NRG Oncology/GOG0209 trial (Miller *et al.*[38]) for front-line therapy in advanced or recurrent EC patients (Table 44). From this trial, the carboplatin + paclitaxel trial arm was deemed the most suitable proxy to the DUO-E trial SoC comparator. The GOG0209 trial reported OS projections over ~14 years, with a median follow up of 124 months (~10 years).

Finally, extrapolated OS data for the SoC arm was compared to landmark OS outcomes reported by Chase *et al.* (2023).[121] This study documented the outcomes of primary advanced or recurrent EC patients by MMR status in the United States (US), including OS. However, it should be noted that there is some uncertainty regarding the appropriateness of this source as a proxy for the SoC arm in this

submission, given that the study does not specify the distributions of treatments that were received beyond reporting that carboplatin + paclitaxel was the most frequently used therapy.

Based on the comparison of the parametric models with landmark estimates, the generalised gamma overestimated survival at all timepoints for SoC. The log-normal and log-logistic generally aligned with the published estimates of survival, but marginally underestimated OS at 10 years. All other models underestimated OS for SoC at 5 and 10 years. For SoC + D, the log-normal and log-logistic appeared to align most closely with the expert estimates at all timepoints, particularly at 10 years.

Table 44. Comparison of OS parametric models with landmark estimates of the proportion of patients who would be alive in the dMMR population in the SoC arm

Distribution	Median OS (months)	1 Year OS	2 Year OS	3 Year OS	5 Year OS	10 Year OS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1[30]; SoC Arm]	-	-	58.0%	46.0%	30.0%	17.0%
Miller *et al.* (2020)[38]	20.4	71.3%	46.1%	35.3%	26.4%	19.5%
Chase *et al.* (2023)[121]	40.5	75.0%	58.0%	52.0%	NR	NR
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Table 45. Comparison of OS parametric models with landmark estimates of the proportion of patients who would be alive in the dMMR population in the SoC + D arm

Distribution	Median OS (months)	1 Year OS	2 Year OS	3 Year OS	5 Year OS	10 Year OS
KM	NR	[redacted]	[redacted]	-	-	-
Advisor [NICE TA963; RUBY-1[30]; SoC + Dostarlimab Arm]	-	-	82.0%	76.0%	67.0%	53.0%
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Flexible splines were not considered in the analysis for OS, due an insufficient number of events to inform the analysis and the declining risk of death over 3 to 5 years.

Clinical validation

Clinical expert opinion was sought from five clinicians to assess the long-term survival data for OS in SoC and SoC + D derived from the standard survival analyses. Of the clinicians consulted, several considered that a log-normal extrapolation would be most appropriate for both the SoC and SoC + D arms. However, there were two clinicians who felt that the exponential extrapolation was most plausible for the SoC arm rather than the log-normal extrapolation (although this was challenged by another clinician, given the steep decline in OS between years 10 and 20). Meanwhile, there were two clinicians who expressed uncertainty about the most appropriate extrapolation for the SoC + D arm, and in fact suggested that a mid-point between the log-normal and exponential extrapolations at the 20-year timepoint would be more appropriate.

Conclusions

Overall, all models were associated with a broadly similar statistical fits. Therefore, the selection of OS extrapolations was primarily driven by clinical experts, who indicated that the log-normal extrapolation would be the most appropriate and clinically plausible option for both arms. The log-normal also broadly aligned with the advisor estimates of long-term survival as part of TA963. Whilst the clinicians also indicated that the exponential model would be a viable alternative, the exponential was rejected based on the clinically implausible assumption of a constant hazard of death over time. The final models (adjusted for background mortality) are presented in Figure 29.

Figure 29. dMMR OS base case fitted curves for SoC and SoC + D treatment arms

Source: Survival analysis conducted on DUO-E trial[4] data and adjusted for background mortality (National life tables: UK, 2024).[109]

As part of the scenario analyses, the use of gamma and log-logistic extrapolations to model OS for both SoC and SoC + D were explored for patients with newly diagnosed advanced or recurrent EC that is

dMMR. Overall, these scenarios had a minimal impact on the overall ICER as presented in Section B.3.11.3.

B.3.3.4.2. pMMR

A summary of the non-parametric results for OS in the pMMR population are presented in Table 46 (previously presented in Section B.2.7.5.2). OS data for the pMMR population was more mature in the SoC arm (33.3%) than in the SoC + D + O arm (24.1%) over the follow-up period, with a median follow up of 18.6 months in the SoC arm and 18.4 months in the SoC + D + O arm. The median OS was not reached in the SoC + D + O arm and was 25.9 months in the SoC arm. Whilst the OS data were relatively immature, there was a numerical improvement in OS for SoC + D + O versus SoC in the pMMR population (HR; 0.69; 95% CI, 0.47, 1.00).

Table 46. Non-parametric results for OS for pMMR

Treatment arm (N)	SoC (N=192)	SoC + D + O (N=191)
Maturity (%) – n/N	33.3% (64/192)	24.1% (46/191)
Duration of follow up (months) – median (range)	18.6 (0.5, 32.9)	18.4 (3.0, 33.4)
Median (95% CI) (months)	25.9 (24.1, NR)	NR
RMST (months) (95% CI)	24.0 (22.3, 25.7)	26.6 (25.0, 28.1)

Diagnostic assessment

An assessment of whether the PH assumption would hold between the SoC and SoC + D + O treatment arms within the pMMR subgroup is presented in Appendix N. The output of these tests imply that the PH assumption may hold; however, as discussed previously, based on the distinct mechanisms of actions between SoC + D + O and SoC, the use of independent extrapolations was considered to be the most appropriate approach for the base case analysis.

Visual and statistical fit

Standard parametric models fitted to OS for SoC and SoC + D are shown in Figure 30 and Figure 31. Table 47 summarises the AIC and BIC values for each extrapolation, with the lowest three scores shaded in blue. Given that the exponential model assumed a constant hazard of death over time, it was excluded from further consideration. All other curves had similar statistical fits apart from the log-normal extrapolation, meaning that statistical fit alone did not support the selection of the most appropriate extrapolation.

Figure 30. Standard parametric survival analysis for OS in the pMMR SoC arm

Source: Survival analysis conducted on DUO-E trial data.

Figure 31. Standard parametric survival analysis for OS in the pMMR in the SoC + D + O arm

Source: Survival analysis conducted on DUO-E trial data.

Table 47. Summary of goodness-of-fit data for SoC and SoC + D + O for OS (standard parametric independent models)

Distribution	SoC				SoC + D + O			
	AIC	AIC Rank	BIC	BIC Rank	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	3	[redacted]	1	[redacted]	5	[redacted]	1
Weibull	[redacted]	2	[redacted]	3	[redacted]	1	[redacted]	2
Log-normal	[redacted]	7	[redacted]	7	[redacted]	7	[redacted]	6

Log-logistic	[redacted]	6	[redacted]	5	[redacted]	2	[redacted]	3
Gompertz	[redacted]	1	[redacted]	2	[redacted]	4	[redacted]	5
Generalised Gamma	[redacted]	5	[redacted]	6	[redacted]	6	[redacted]	7
Gamma	[redacted]	3	[redacted]	4	[redacted]	2	[redacted]	3

Source: Survival analysis conducted on DUO-E trial data.

Landmark and external validation

Extrapolated OS data from the standard parametric models were compared to the landmark OS outcomes for SoC from the Phase 3 NRG Oncology/GOG0209 trial (Miller *et al.*)[38] and OS outcomes reported by Chase *et al.* (2023)[121] (Table 48).

As previously noted, the goodness-of-fit statistics are similar for several parametric models. However, the log-logistic model provided the most clinically plausible long-term survival projections, given they were consistent with the external evidence from the Miller *et al.* study, which showed that a proportion of patients could achieve long-term survival, with OS curves extending to 10 years of follow-up. The log-logistic model was also associated with a plausible hazards profile over time and provided a good statistical fit based on AIC/BIC. For SoC + D + O, there is no available literature to support a comparison of the extrapolations with landmark OS outcomes, but the projections from the standard parametric curves at the landmark timepoints are presented in Table 49 for completeness.

Table 48. Comparison of parametric models with landmarks and NRG Oncology/GOG0209 of the proportion of patients who would be alive in the pMMR population in the SoC arm

Distribution	Median OS (months)	1 Year OS	2 Year OS	3 Year OS	5 Year OS	10 Year OS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Miller *et al.* (2020)[38]	20.4	71.3%	46.1%	35.3%	26.4%	19.5%
Chase *et al.* (2023)[121]	29.5	78.0%	57.0%	43.0%	NR	NR
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Table 49. Comparison of parametric models with landmarks of the proportion of patients who would be alive in the pMMR population in the SoC + D + O arm

Distribution	Median OS (months)	1 Year OS	2 Year OS	3 Year OS	5 Year OS	10 Year OS
KM	[redacted]	[redacted]	[redacted]	-	-	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Flexible spline models were not considered in the analysis for OS due an insufficient number of events to inform the analysis and the declining risk of death over 3 to 5 years.

Clinical validation

Clinical expert opinion was sought from five clinicians to assess the long-term survival data for OS for patients receiving SoC or SoC + D + O derived from the standard survival analyses and landmark survival endpoints. In both treatment arms, most clinicians favoured the log-logistic curve, whilst the remaining clinicians favoured Weibull or log-normal. Most clinicians considered that at least some patients would remain alive at 20 years, and therefore that the Weibull curve was too pessimistic.

Conclusions

Overall, the log-logistic model was chosen for the base case analysis for both SoC and SoC + D + O. As highlighted above, this is because this model not only fits well according to AIC statistics, but also aligns with the clinical expectation of reducing hazards over time. Finally, the log-logistic model provides a more clinically plausible long-term survival projection according to clinical experts consulted and evidence from the Miller *et al.* study, which showed that a proportion of patients could achieve long-term survival, with OS curves extending to 10 years of follow-up. The final models (adjusted for background mortality) are shown in Figure 32.

Figure 32. pMMR OS base case fitted curves for SoC and SoC + D + O treatment arms

Source: Survival analysis conducted on DUO-E trial data.

As part of the scenario analyses, the following alternative approaches were explored to assess the impact on the cost-effectiveness results for SoC + D + O versus SoC in patients with newly diagnosed advanced or recurrent EC that is pMMR:

- The use of the gamma extrapolation to model OS for both SoC and SoC + D + O (based on goodness-of-fit statistics)
- The use of the log-normal extrapolation to model OS for both SoC and SoC + D + O (based on goodness-of-fit statistics, comparison to landmark survival timepoints and clinical validation)

Overall, these scenarios both resulted in a lower ICERs compared with the base case analysis (Section B.3.11.3), implying the OS extrapolation for SoC + D + O selected in the base case is more conservative than alternative, clinically plausible, survival models.

B.3.3.5 Time to discontinuation of treatment (TDT)

TDT from the DUO-E trial (DCO1 12 April 2023) was used to calculate treatment acquisition costs of SoC (for the first six cycles) and SoC + D and SoC + D + O across the model time horizon. This approach was applied to ensure the model accurately captures both the initial costs of SoC from the observed trial data and the long-term acquisition cost of durvalumab and olaparib, as predicted by the respective parametric extrapolations.

For SoC, a simplified approach was considered to estimate the treatment duration by utilising the observed DUO-E trial data based on the frequency and distribution of SoC cycles administered to patients across all three trial arms. To estimate the average SoC treatment duration per patient, the total number of patients treated, as well as the individual number of treatment cycles received and reported per patient were considered. The observed data were aggregated to calculate the mean number of cycles of SoC administered for each treatment arm (the mean number of weekly carboplatin and paclitaxel cycles across treatment arms in the dMMR population and pMMR population are presented in Table 66 and Table 67, respectively). This provides a measure of the average treatment duration per patient to reflect the typical exposure to SoC.

For durvalumab and olaparib, extrapolation of TDT data was required as patients remained on treatment at the latest DCO in DUO-E. Selection of the most appropriate extrapolations is detailed below. A cap is applied to all extrapolations to ensure TDT does not exceed PFS at any given point (Section B.3.3.5).

Notably, the DUO-E trial did not impose a maximum duration of treatment with durvalumab or olaparib. However, clinician feedback indicates patients would be expected to discontinue treatment within five years, and for those who experience durable responses to treatment, clinicians would start to have discussions with them after one to three years about the potential discontinuation of treatment.[115]

Clinicians and patients are motivated to discontinue treatment for a number of reasons. There is a growing body of evidence and clinical experience suggesting that the benefits of immunotherapy and PARP inhibitors are fully realised within a shorter treatment duration, and prolonged treatment does not result in additional clinical benefit. Johnson *et al.* (2022) highlight that patients who develop durable responses to immune checkpoint inhibitors seem to develop “immunological memory”, potentially explaining why the extended therapeutic effects of immune checkpoint inhibitors far surpass their pharmacokinetic half-life.[122]

While there is a paucity of evidence in EC specifically, the optimum duration of immune checkpoint inhibitor treatment has been extensively discussed more broadly in the published literature. One of the largest studies was conducted by Bogoni *et al.* (2023).[123] This meta-analysis included 57 studies and 22,977 patients, investigating the differences in PFS and OS for patients treated with immune checkpoint

inhibitors for two years, or until disease progression. Across a range of indications including NSCLC, RCC, HNSCC, UC and SCLC, the study found no evidence to suggest that prolonged ICI treatment resulted in improved PFS or OS, compared to 2-year ICI treatment. The only indication where extended treatment resulted in additional benefits was melanoma. Similarly, Yin *et al.* (2022)[124] recommend that discontinuation of immune checkpoint inhibitors should be considered after two years across a range of solid tumour types, including NSCLC, renal and colorectal cancer.

Considering EC specifically, as previously detailed throughout Section B.3.3.2, clinicians highlighted that they would expect a proportion of patients to achieve long-term remission post-treatment. The clinicians suggested that PFS curves in both the SoC + D and SoC + D + O arms would begin to plateau at five years. They indicated most progression events would occur before that time point and subsequent EC-related PFS events would be unlikely. This suggests further treatment beyond 5 years would be associated with limited clinical benefit.[115]

There are also concerns about the cumulative toxicity associated with long-term treatment with immuno-therapies and PARP inhibitors, as well as the burden that continued treatment has on patients. Clinicians particularly highlighted a reluctance towards long-term treatment with olaparib, due to concerns about AML associated with prolonged exposure. The clinicians estimated most patients would discontinue olaparib after two to three years, and all patients would discontinue treatment by five years.[115]

Based on this feedback, it is clinically implausible to assume that patients who achieve long-term remission will remain on treatment for the entirety of the modelled time horizon. Therefore, it is necessary to consider a timepoint at which all patients will be assumed to discontinue treatment with durvalumab and olaparib. Assuming a fixed duration of treatment is aligned with the trials for previous first-line advanced or recurrent EC studies for immunotherapies, including RUBY-I for dostarlimab with platinum-based chemotherapy[26] (maximum three year treatment duration) and NRG-GY018 for pembrolizumab (maximum two year treatment duration).[125]

As a conservative assumption, any patients remaining on treatment with durvalumab and olaparib after three years are assumed to discontinue treatment. This aligns with the DUO-E trial, where, at the time of the latest DCO (12 April 2023), no patients had received treatment for longer than three years. Similarly, an assumption of three years of treatment is aligned with the RUBY-I trial for dostarlimab, and the economic model which was accepted as part of NICE TA963. Based on the clinician feedback, this may potentially represent a conservative assumption, given that it is likely that most patients would discontinue treatment with durvalumab and olaparib before this timepoint.

The uncertainty surrounding treatment duration has been explored further through scenario analyses of maximum treatment duration of two years and five years, as presented in Section B.3.11.3. In the dMMR patient population, these scenarios have a limited impact on the ICER, indicating that this assumption does not represent a major driver of the economic results. The impact of this assumption is more notable in the pMMR patient population. However, it is likely that the assumption of three years of treatment is particularly conservative in the pMMR patient population, due to the additional toxicity concerns related to olaparib, and the risk of AML. For example, in the PAOLA-1 trial for olaparib as a first-line maintenance treatment for ovarian cancer, patients were given olaparib for a maximum treatment duration of 24 months.[84] Many patients are likely to discontinue treatment with olaparib after two years, suggesting that the maximum treatment duration with durvalumab and olaparib is likely to lie between two and three years, and that the base case may be conservative.

B.3.3.5.1. dMMR

The non-parametric results from the TDT are presented in Table 50. TDT data for the dMMR population was [redacted] mature in the SoC + D arm over the follow-up period, with a median time on treatment of [redacted] months in the SoC + D arm.

Table 50. Non-parametric results for TDT for dMMR

Treatment arm (N)	SoC + D (N=46)
Maturity (%) – n/N	[redacted]
Median (95% CI) (months)	[redacted]
RMST (months) (95% CI)	[redacted]

Diagnostic assessment

Several statistical tests were conducted, as presented in Appendix N. The log cumulative hazards plot implies a constant increase in the hazard for treatment discontinuation for durvalumab as part of the SoC + D regimen for patients with dMMR EC over time.

Visual and statistical fit

Table 51 summarises the AIC and BIC values for each extrapolation, with the lowest three scores shaded in blue. The gamma extrapolation had the lowest AIC and BIC values, with Weibull and log-logistic having a similarly low AIC/BIC within one point of the gamma extrapolation. The log-normal and generalised gamma extrapolations all had AIC/BIC values within two and five points[126, 127] of the gamma extrapolations, suggesting that all of the best fitting extrapolations provide a similar fit to the observed data from the DUO-E trial.

The visual fit of the standard parametric models fitted to TDT for SoC + D is presented in Figure 33. As previously detailed, the model assumes that all patients remaining on treatment after three years will discontinue treatment, in line with clinical expert feedback. Therefore, while lifetime extrapolations are provided in Figure 33 for completeness, the proportion of patients remaining on treatment is set to 0% for each of the extrapolations in the economic model.

Figure 33. Standard parametric survival analysis for TDT in the dMMR in the SoC + D arm

Source: Survival analysis conducted on DUO-E trial data.

Table 51. Summary of goodness-of-fit data for SoC + D for TDT (standard parametric independent models) in dMMR

Distribution	SoC + D			
	AIC	AIC Rank	BIC	BIC rank
Exponential	[redacted]	7	[redacted]	7
Weibull	[redacted]	2	[redacted]	2
Log-normal	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	3	[redacted]	3
Gompertz	[redacted]	6	[redacted]	6
Generalised Gamma	[redacted]	4	[redacted]	5
Gamma	[redacted]	1	[redacted]	1

Source: Survival analysis conducted on DUO-E trial data.

Landmark timepoints

Table 52 presents extrapolated TDT data for durvalumab in SoC + D at landmark timepoints up to three years. After three years, all patients were assumed to discontinue treatment.

Table 52. Comparison of parametric models with landmarks of the proportion of patients who remain on SoC + D in dMMR population

Distribution	Median (months)	1 Year TDT	2 Year TDT	3 Year TDT
KM	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Flexible splines were not considered in the analysis for TDT, as standard parametric models capture the more accurately the trend in discontinuation where a plateau is not anticipated as all patients will eventually discontinue treatment before the model horizon.

Clinical validation

An external validation was conducted with five clinicians to assess the plausibility of the TDT curves for SoC + D. Most clinicians stated that patients would begin to discontinue treatment between years one and three, and that the vast majority of patients would be off treatment by five years (estimates ranged from 0% to 5% remaining on treatment at that time point). The clinicians highlighted that the benefits of treatment would likely be fully realised within a shorter treatment duration, while longer-term treatment is associated with cumulative toxicity concerns.

Conclusions

As the economic model assumes that after three years all patients discontinue treatment with SoC + D, statistical fit to the observed TDT KM data from DUO-E represents the most important consideration. As such, the gamma extrapolation, which provides the best statistical fit, was chosen as the base case model for SoC + D, as shown in Figure 34. Compared to the extrapolation presented in Figure 34, all patients remaining on treatment after three years are assumed to discontinue treatment.

Figure 34. dMMR TDT base case fitted standard parametric curve for SoC + D arm

Source: Survival analysis conducted on DUO-E trial data.

As part of the scenario analyses, the following were explored to assess the impact on the results (Section B.3.11.3):

- Assuming a maximum treatment duration of two years and using a gamma curve (base case selection) to model TDT until year two. The choice of three years as a maximum treatment duration may be conservative, as many patients are likely to discontinue treatment before this timepoint – for example, the NRG-GY018 trial assumes a maximum treatment duration of two years for treatment with pembrolizumab. This scenario explores the impact of that assumption.
- Assuming a maximum treatment duration of five years and using a gamma curve (base case selection) to model TDT until year three. Thereafter, an exponential curve is used to model a drop-off between years three and five, until 0% of patients remain on treatment at Year 5. Based on clinical expert feedback, this is likely to represent an extreme scenario, with most patients discontinuing treatment between one and three years due to concerns around patient burden and cumulative toxicity for limited additional clinical benefit

These scenarios had a minimal impact on the overall ICER as presented in Section B.3.11.3, suggesting that the model is relatively insensitive to the maximum treatment duration for durvalumab for patients receiving SoC + D. A larger difference was observed when changing the maximum treatment duration from three to two years; as the majority of patients are expected to discontinue treatment by two years, then there is rationale to suggest that the base case economic analysis may be conservative, and the true ICER may lie closer to the results of the 2-year treatment duration scenario.

B.3.3.5.2. pMMR

Patients in the pMMR population can discontinue either olaparib or durvalumab, whilst continuing the other. The TDT analysis for each is presented below.

pMMR – durvalumab in SoC + D + O

The non-parametric results from the TDT are presented in Table 53. TDT data for durvalumab in the pMMR population was [redacted] mature in the SoC + D + O arm over the follow-up period. The median time on treatment in the SoC + D + O arm was [redacted].

Table 53. Non-parametric results for TDT for durvalumab in pMMR

Treatment arm (N)	SoC + D + O (N=191)
Maturity (%) – n/N	[redacted]
Median (95% CI) (months)	[redacted]
RMST (months) (95% CI)	[redacted]

Diagnostic assessment

Several statistical tests were conducted, as presented in Appendix N. The log cumulative hazards plot implies a constant increase in hazards for treatment discontinuation for durvalumab as part of SoC + D + O for patients with pMMR EC over time.

Visual and statistical fit

Figure 35 presents the standard parametric models fitted to TDT data for durvalumab in SoC + D + O, whilst Table 54 summarises the AIC and BIC values for each extrapolation, with the lowest three scores shaded in blue.

As the exponential assumes that the hazard of treatment discontinuation remains constant over time, it was excluded from consideration as clinically implausible when compared to the log-cumulative hazards plot presented in Appendix N. Of the remaining extrapolations, the log-logistic and Gompertz provided the best fit to the observed data.

The model considers a maximum treatment duration of three years in the base case, after which time all patients are assumed to discontinue treatment. Therefore, while lifetime extrapolations are shown in Figure 35 for completeness, parametric curves are only applied until Year 3 of the model in the base case economic analysis.

Figure 35. Standard parametric survival analysis for TDT of durvalumab in SoC + D + O arm (pMMR)

Source: Survival analysis conducted on DUO-E trial data.

Table 54. Summary of goodness-of-fit data for durvalumab TDT in SoC + D + O (standard parametric independent models) in pMMR

Distribution	SoC + D + O			
	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	4	[redacted]	4
Log-normal	[redacted]	7	[redacted]	7
Log-logistic	[redacted]	2	[redacted]	2
Gompertz	[redacted]	3	[redacted]	3
Generalised Gamma	[redacted]	6	[redacted]	6
Gamma	[redacted]	4	[redacted]	4

Source: Survival analysis conducted on DUO-E trial data.

Landmark timepoints

Table 55 presents extrapolated TDT for durvalumab in SoC + D + O from the standard parametric curves at landmark timepoints.

Table 55. Comparison of parametric models with landmarks of the proportion of patients who remain on SoC + D + O in pMMR population

Distribution	Median (months)	1 Year TDT	2 Year TDT	3 Year TDT
KM	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Flexible splines were not considered in the analysis for TDT, as standard parametric models capture the trend in discontinuation where a plateau is not anticipated as all patients will eventually discontinue treatment over the model horizon.

Clinical validation

As previously detailed above, clinicians highlighted that patients would begin to discontinue treatment between years one and three, and that the vast majority of patients would be off treatment by five years (estimates ranged from 0% to 5% remaining on treatment at that time point). The clinicians highlighted that the benefits of treatment would likely be fully realised within a shorter treatment duration, while longer-term treatment is associated with cumulative toxicity concerns.

pMMR – olaparib in SoC + D + O

The non-parametric results from the TDT are presented in Table 56. TDT data for olaparib in the pMMR population reached [redacted] maturity in the SoC + D + O arm over the follow-up period. Overall, patients remained on treatment with olaparib for [redacted] months. The median time from randomisation to the initiation of olaparib was 137 days (19.6 weeks), and the maintenance phase begins at 18 weeks in the model (where olaparib is initiated in [redacted] of patients and durvalumab is administered every 4 weeks).

Table 56. Non-parametric results for TDT for olaparib in pMMR

Treatment arm (N)	SoC + D + O (N=151)
Maturity (%) – n/N	[redacted]
Median (95% CI) (months)	[redacted]
RMST (months) (95% CI)	[redacted]

Source: TDT reported on DUO-E trial data.

The TDT curve for olaparib was estimated from the point of olaparib initiation at week 18 of the model horizon (which is the earliest opportunity for maintenance in the DUO-E trial for patients completing six cycles of chemotherapy) and was multiplied by the proportion of patients receiving olaparib to accurately depict the proportion of the modelled cohort on olaparib. TDT was defined as time since initiation until discontinuation (or censoring discontinuation).

Diagnostic assessment

Several statistical tests were conducted, as presented in Appendix N. The log cumulative hazards plot suggests an increase in hazard of treatment discontinuation over time for olaparib as part of the SoC + D + O for patients with pMMR EC.

Visual and statistical fit

Figure 36 presents the standard parametric models fitted to TDT data for olaparib in SoC + D + O, whilst Table 57 summarises the AIC and BIC values for each extrapolation, with the lowest three values shaded in blue. The log-normal, log-logistic and generalised gamma had the lowest AIC/BIC values; both the log-normal and log-logistic models provided a good fit to the empirical hazards of discontinuation for olaparib.

The model considers a maximum treatment duration of three years in the base case, after which time all patients are assumed to discontinue treatment. Therefore, while lifetime extrapolations are shown in Figure 36 for completeness, parametric curves are only applied until Year 3 of the model in the base case economic analysis.

Figure 36. Standard parametric survival analysis for TDT of olaparib in SoC + D + O arm (pMMR)

Source: Survival analysis conducted on DUO-E trial data.

Table 57. Summary of goodness-of-fit data for olaparib TDT in SoC + D + O (standard parametric independent models) in pMMR

Distribution	SoC + D + O			
	AIC	AIC Rank	BIC	BIC Rank
Exponential	[redacted]	5	[redacted]	4

Weibull	[redacted]	7	[redacted]	7
Log-normal	[redacted]	1	[redacted]	1
Log-logistic	[redacted]	3	[redacted]	2
Gompertz	[redacted]	4	[redacted]	5
Generalised Gamma	[redacted]	2	[redacted]	3
Gamma	[redacted]	6	[redacted]	6

Source: Survival analysis conducted on DUO-E trial data.

Landmark timepoints

Table 58 presents the extrapolated TDT for olaparib in SoC + D + O from the standard parametric curves at landmark timepoints.

Table 58. Comparison of parametric models with landmarks of the proportion of patients who remain on olaparib in SoC + D + O in the pMMR population

Distribution	Median (months)	1 Year TDT	2 Year TDT	3 Year TDT
KM	[redacted]	[redacted]	[redacted]	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: Survival analysis conducted on DUO-E trial data.

Alternative survival models

Flexible splines were not considered in the analysis for TDT as all patients will eventually discontinue treatment over the model horizon and a plateau is not anticipated.

Clinical validation

As previously detailed above, clinicians highlighted that patients would begin to discontinue treatment between years one and three, and that the vast majority of patients would be off treatment by five years (estimates ranged from 0% to 5% remaining on treatment at that time point). The clinicians highlighted that the benefits of treatment would likely be fully realised within a shorter treatment duration, while longer-term treatment is associated with cumulative toxicity concerns.

The clinicians also highlighted that there would be a particular reluctance about long-term treatment with olaparib specifically, as prolonged exposure is associated with a risk of developing acute myeloid leukaemia. As such, they highlighted that most clinicians would discontinue treatment with olaparib between two to three years, and all patients would have discontinued treatment by year 5.

Conclusions

When considering the goodness-of-fit statistics and visual fit of the extrapolations for TDT for both durvalumab and olaparib, the log-logistic model was determined to provide the best fit for both of these endpoints. As such, the log-logistic model was selected for the base case economic analysis.

The resulting curves are presented in Figure 37, which demonstrates that the proportion of patients remaining on treatment over time is reasonably aligned, with marginally more patients receiving durvalumab than olaparib at each time points. As previously detailed, the model includes an adjustment such that all patients remaining on treatment after three years are assumed to discontinue treatment.

Figure 37. pMMR TDT base case fitted standard parametric curve for durvalumab and olaparib in SoC + D + O arm

Source: Survival analysis conducted on DUO-E trial data.

The following scenario analyses were explored to assed the impact on the results (Section B.3.11.3):

- Assuming a maximum treatment duration of two years and using a log-logistic curve (base case selection) to model TDT until year two. As with dMMR, the choice of three years as a maximum treatment duration may be conservative – this scenario explores the impact of a reduced maximum treatment duration
- Assuming a maximum treatment duration of five years and using a log-logistic curve (base case selection) to model TDT until year three. Thereafter, an exponential curve is used to model a drop-off between years three and five, until 0% of patients remain on treatment at Year 5.

These scenarios had minimal impact on the overall ICER as presented in Section B.3.11.3.

B.3.4 *Measurement and valuation of health effects*

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

The EQ-5D-5L data collected within the ITT in the DUO-E trial were analysed to estimate health state utility values. The EQ-5D-5L questionnaire was applied at baseline (day one of treatment) and then, every three weeks for the first 18 weeks (± 3 days). Following this, the questionnaire was applied every four weeks (± 3 days) until patients experienced a second disease progression (PFS2). Patients were also assessed at the discontinuation visit, unless they had completed within three days prior to the visit. Finally, for those who discontinued for reasons other than progressive disease, the questionnaire was applied at the progressive disease visit (+2 days), unless the questionnaire was completed within three days prior to the visit.

To explore the statistical relationship between EQ-5D utility scores, treatment, and health status, a regression analysis using a mixed model for repeated measures (MMRM) was performed. The MMRM analysis provides valid estimates of the mean and standard error of repeated measures data and considers the correlation that exists between the repeated measurements of utility by subject. It provides valid results under the assumption that missing data are missing at random.

The MMRM analysis was performed using several different covariates, to identify which model provided the best fit to the data available. Covariates were incorporated as fixed effects, including treatment, progression status (pre-and post-progression), and their interactions. The following four models were evaluated:

- Model 1: Utility ~ Treatment arm
- Model 2: Utility ~ progression state
- Model 3: Utility ~ treatment arm + progression state
- Model 4: Utility ~ treatment arm + progression state + treatment arm x progression state (interaction term)

The best fitting model (according to AIC statistics) was the model which included only progression as a covariate (Model 2), providing utility values specific to the progression-free and progressed disease health states, independent of the treatment received. The results of the MMRM model reported a mean progression-free health state utility (HSU) score of [redacted] and a progressed disease HSU score of [redacted], which are used directly in the economic model (Table 59).

The MMRM analyses reported were performed for the full DUO-E trial[4] population, since there was no evidence to suggest that utility would differ based on the MMR biomarker status. These MMRM analyses were also performed separately for the dMMR and pMMR populations within the DUO-E study. For both populations, the same model (model 2, with utility values for pre- and post-progression health states) remained the best fitting model. There was little difference in the utility values observed by MMR status, and therefore the values for the full DUO-E trial population were used for both dMMR and pMMR populations to maximise the sample size.

Table 59. Utility model including progression status as predictors

Predictor	Coefficient (95% CI)	Source
PF	[redacted]	DUO-E utility analysis – ITT population
PD	[redacted]	

B.3.4.2 Mapping

In line with the NICE reference case[106], utility values were estimated by mapping EQ-5D-5L responses to the EQ-5D-3L value set using the DSU mapping function (Hernández Alava *et al.* [2017] and Hernández Alava *et al.* [2020]).[128, 129]

B.3.4.3 Health-related quality-of-life studies

An economic SLR was carried out on 1st December 2023 (with an update on 24th May 2024) to identify existing HRQoL evidence relevant to the decision problem. Full details of the methodology used to identify all relevant studies and results of the identified studies are presented in Appendix H.

The HRQoL SLR identified 19 publications reporting on 19 unique studies that comprised of HRQoL or utility outcomes. Of these, six studies were health technology assessment (HTA) submissions. Geographically, most of the studies were based in North America (n=7), followed closely by Europe (n=5); however, a number of studies with a single country perspective adapted data from international trials, including KEYNOTE-775.

Most studies included in the SLR reported HRQoL/utility outcomes from clinical trials or utilised information from trials to inform population-specific utility values. Only two included studies were original studies focusing on collecting HRQoL/utility data; one had broad eligibility criteria (female patients receiving treatment in the field of mastology and gynaecological oncology) and therefore a small sample size for patients with advanced endometrial cancer (N=12),[130] and the other investigated HRQoL specifically in advanced/recurrent EC.[131] The most frequently used HRQoL instruments were the general cancer EORTC-QLQ C30 scale (n=11),[132-142] EQ-5D (n=9)[25, 30, 130, 134-137, 140, 143] and the endometrial-cancer EORTC QLQ-EN24 instrument (n=4).

Utility values were reported in eight studies, all of which used the EQ-5D to elicit utility values.[108, 130, 135, 136, 140, 142, 143] Values ranged from 0.721–0.817 for PF disease, 0.667–0.752 for PD and 0.750–0.800 for utility values not specific to a health state. Despite utility values being identified in the literature, utility values for the model were derived from the DUO-E EQ-5D trial data (Section B.3.4.5), which is in line with NICE guidance.[106]

B.3.4.4 Adverse reactions

Section B.2.10.3 includes full details of the AE data from the DUO-E trial. The model includes the rate of CTCAE grade ≥3 AEs for each treatment arm, to capture the impact that these have on HRQoL and costs.

Any AEs of grade ≥3 occurring in ≥5% of patients in at least one of the comparator treatments of the DUO-E trial were considered in the model (Table 60). This inclusion rule (i.e., ≥5%) was considered sufficient to capture the key AE costs. Only the grade ≥3 AEs were considered since they reflect the events that are likely to have the greatest burden on medical resource use and QoL. Lower grade AEs were assumed to have a negligible impact on patients' HRQoL and costs.

The AE profile included in the model was derived from the FAS of the DUO-E trial population, which provides the most robust analysis of AEs. The frequency of AEs did not differ by MMR status in the model, since there was little difference observed in the proportion of AEs reported by MMR status.

Table 60. Percentage of patients experiencing grade ≥3 AE by treatment arm (sourced from the FAS set of DUO-E)

Treatment	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 236)
Anaemia	15.7%	23.50%	14.4%
Neutropenia	8.5%	11.3%	5.9%
Neutrophil Count Decreased	11.5%	13.4%	15.3%
Lymphocyte Count Decreased	2.1%	1.3%	2.1%
White Cell Count Decreased	3.8%	4.2%	4.7%
Hypertension	3.8%	4.2%	3.0%
Pulmonary Embolism	2.1%	2.5%	1.3%
Hypokalaemia	2.6%	2.9%	0.8%

The potential impact of AEs on utility was considered for each treatment in the economic model. Utility decrements associated with AEs were not explicitly collected in the DUO-E study, therefore these utility decrement values were sourced from previous NICE appraisals in EC and the published literature (Table 61). The duration of AEs was also derived from the same data sources wherever available. AEs were not considered for subsequent treatments. The total AE-related utility decrement for each treatment arm (Table 62) was calculated by summing the products of incidence per treatment arm, duration, and associated disutility for each AE. The total AE-related utility decrement for each treatment arm was applied once at the start of the model, reflecting the assumption that AEs would occur within the early period of treatment.

Table 61. Utility decrements by AE

AE	Disutility	Source or assumption	Duration (days)	Source or assumption
Anaemia	-0.119	Swinburn *et al.* (2010)[114]	7	NICE TA411[144] (Published: 2016, Accessed: March 2024)
Neutropenia	-0.090	Nafees *et al.* (2008)[113]	7	NICE TA411[144] (Published: 2016, Accessed: March 2024)
Neutrophil count decreased	0.000	Assumed to have no utility impact	7	NICE TA411[144] (Published: 2016, Accessed: March 2024)
Lymphocyte count decreased	0.000	Assumed to have same utility impact as neutrophil count decreased	7	Assumed same as neutrophil count decreased
White cell count decreased	0.000	Assumed to have no utility impact	7	Assumed same as neutrophil count decreased

Hypertension	-0.020	NICE TA673[112] (Published Feb 2021, Accessed: March 2024)	7	Assumption (considered same as other AEs)
Pulmonary embolism	-0.320	Locadia *et al.* (2004)[145]	30.44	NICE TA411[144] (Published: 2016, Accessed: March 2024)
Hypokalaemia	-0.074	Nafees *et al.* (2008)[113]	7	NICE TA411[144] (Published: 2016, Accessed: March 2024)

Table 62. Total AE-related utility decrement per treatment arm

Treatment arm	Total utility decrement due to AE
SoC + D	−0.0135
SoC + D + O	−0.0175
SoC	−0.0095

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 63 summarises the HSU values used in the base case analysis, derived from DUO-E trial data (as described in Section B.3.4.5), and therefore measured directly by patients, as per NICE guidance.[106]

There is no expectation or plausible rationale for utility values to differ by MMR status, therefore data from the ITT population was used regardless of the population chosen in the model. This assumption was also validated by clinical expert opinion.[1] As a scenario analysis, HSU values identified in the SLR were used. From the publications which reported HSU values, NICE TA914[108] was deemed most appropriate for use in the model given that it is a recent NICE submission and that the utility values were derived using EQ-5D-3L trial data, which is in line with NICE guidance[106]. However, it should be noted that these utilities are from a later line of therapy, which may account for why they are lower than those derived from DUO-E trial data.

Utilities were adjusted over the time horizon of the model, to reflect decline in HRQoL seen in the general population and to ensure that utilities did not exceed general population values at a given age. Age-related disutility was based on Health Survey of England (HSE) 2014 estimates (female cohort) modelled by Hernández Alava *et al.* (2022).[146] Following International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidance[147], general population age-related disutilities were applied as a 'multiplier' to the HSU values. The model also has the option to adjust HSU values according to age using use a regression model reported by Ara and Brazier (2010).[148]

Table 63. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	95% CI	Reference in submission (section and page number)	Justification
PF	Base case (ITT): [redacted] Scenario analysis: 0.721	[redacted]	Section B.3.4.1 Page 130	Base case: EQ-5D-5L data from the DUO-E trial[4] were mapped to EQ-5D-3L which is aligned with NICE

PD	Base case (ITT): [redacted] Scenario analysis: 0.667	[redacted]		guidelines. Data from the full DUO-E trial[4] population was used, since there was no evidence to suggest that utility would differ based on the MMR biomarker status. Scenario: Sourced from a recent NICE submission, TA914[108] which derived utility values using EQ-5D-3L trial data.
Age-adjusted utilities:	Base case: included Scenario analysis: excluded		Section B.3.4.3 Page 131	Age-adjusted utilities aligned with NICE guidelines
Adverse events				
Adverse events	Base case: included Scenario analysis: excluded		Section B.3.4.4 Page 131	Applied to first cycle of the model

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

An economic SLR was carried out on 1st December 2023 (with an update on 24th May 2024) to identify existing HCRU evidence relevant to the decision problem. Full details of the methodology used to identify all relevant studies and results of the identified studies are presented in Appendix I.

The economic SLR identified 19 articles from 19 unique studies reporting on HCRU that met the inclusion criteria. All studies enrolled adult women with either advanced or recurrent EC. All of these studies were conducted in Europe or North America, except one in Argentina, and the majority of these were published in 2022.

Direct costs were reported by 13 studies, and none of the studies reported indirect costs. The total costs were reported by five studies,[119, 143, 149-151] three of which were UK based. Pennington *et al.* (2016)[119] reported total costs for patients in England during the two-year and five-year period following diagnosis with stage III/IV EC. The total cost included the costs of diagnosis/surgery, adjuvant therapy and further treatment, as well as other components which were not specified. The Scottish Medicines Consortium (SMC) 2022 study[152] was an economic evaluation, with a healthcare payer perspective, which reported total costs for patients with advanced or recurrent EC who progressed on or following prior treatment with a platinum-containing therapy. Monthly costs were reported for the progression-free and progressed health states which included the costs of outpatient visits, computed tomography (CT) scans, blood tests and patient medication. The SMC 2024[153] study was an economic evaluation in patients with dMMR/MSI-H advanced or recurrent endometrial cancer, with a healthcare payer perspective, which reported total costs per cycle and per year for dostarlimab with carboplatin-paclitaxel. The fourth study, a US-based economic evaluation by Thurgar *et al.* (2021),[143] included patients with dMMR/MSI-H unresectable or metastatic EC who had received prior chemotherapy. This study reported a weekly cost for disease management associated with the progression-free or progressed health state. The total weekly

management cost assumed that patients require one monthly outpatient visit, and one CT scan every quarter. The final study by Prabhu *et al.* (2024)[151] investigated recurrence status in high-risk endometrial cancer patients receiving adjuvant chemotherapy using patients from the SEER-Medicare US database. The study reported annual all-cause costs and endometrial cancer-related costs.

Out of the 19 studies, seven studies reported costs for specific drugs, with the 6-month cost of lenvatinib in the US reported to be 1,312,760,659 US Dollars (USD), whilst two Canadian economic evaluations reported a daily cost of 419.05 Canadian Dollars per patient, and a 28-day cost of 11,733 Canadian Dollars per patient. Overall endometrial cancer-related treatments costs were 1,081 USD per-patient per-month in the US. The costs of treating AEs were reported by two studies, whilst two reported on the cost associated with diagnosis and testing.

Treatment patterns were reported by four studies, with chemotherapy, particularly platinum-based, consistently reported to be the most common therapy. Inpatient and outpatient resource use were reported by three studies, with 69% of patients initiating first-line in a US-based study having outpatient visits. The proportion of patients making inpatient and emergency department visits was considerably lower (13% and 5%, respectively).

The HCRU inputs of the current economic model were based on one of the studies identified in the economic SLR, TA963[30] for dostarlimab with platinum-based chemotherapy for treating advanced or recurrent EC with MSI-H or mismatch repair deficiency. None of the other studies reporting resource use and costs were used in the economic model due to being Canadian or US based, or due to more appropriate UK sources being available such as publicly available UK databases.

The CEM included the following cost components:

- Treatment acquisition (including active and subsequent treatments)
- Treatment administration (including active and subsequent treatments)
- HCRU
- AEs
- End-of-life

In line with the NICE reference case,[106] the CEM was built from the perspective of the NHS and personal social service (PSS) and therefore where possible, HCRU cost inputs were sourced from the NHS Schedule of Reference Costs 2022/2023[154] and PSSRU 2023.[117] Treatment costs were sourced from the BNF.[155] Where necessary, costs were inflated to the 2022/2023 cost year using the NHS Cost Inflation Indices (NHSCII) published by the PSSRU (2023).[117]

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition and administration costs were sustained throughout the active treatment phase and were determined by dosing schedules and treatment duration estimates.

B.3.5.1.1. Drug acquisition costs

The dosing regimen used in the model for each treatment option is reported in

Table **64** and the relevant clinical trials. Dosing information was derived from the DUO-E trial. Dose regimens were used in the model to calculate the cost of treatment. The pack prices of generic drugs were sourced from the Electronic market information tool (eMIT) whilst branded drugs were sourced from the BNF[155] (Table 65).

Table 64. Dosing regimen

Treatment	Dosing regimen	Source
Carboplatin + paclitaxel (SoC)	Patients received carboplatin (AUC 6 mg/mL/min) and paclitaxel (175 mg/m^2) every 3 weeks for 6 cycles.	DUO-E[4]
Durvalumab	Durvalumab 1,120 mg intravenously (IV) every 3 weeks for 6 cycles (chemotherapy phase), followed by maintenance durvalumab 1,500 mg IV every 4 weeks thereafter (maintenance phase).	DUO-E[4]
Olaparib	Olaparib 300 mg tablets taken twice daily (maintenance phase only, assumed from 18 weeks onwards).	DUO-E[4]

Table 65. Drug pack prices

Treatment	Administration route	Available formulation (mg)	Unit	Pack/vial size	Unit cost	Source
Durvalumab	IV	120	mg per vial	2.4 ml	£592.00	BNF[155]
		500	mg per vial	10 ml	£2,466.00	
Olaparib	Oral	100	mg per tablet	56 tablets	£2,317.50	BNF[155]
		150	mg per tablet	56 tablets	£2,317.50	
Carboplatin	IV	50	mg per vial	5 ml	£9.28	eMIT[156]
		150	mg per vial	15 ml	£20.22	
		450	mg per vial	45 ml	£48.09	
		600	mg per vial	60 ml	£71.44	
Paclitaxel	IV	30	mg per vial	5 ml	£3.88	eMIT[156]
		100	mg per vial	16.7 ml	£9.13	
		150	mg per vial	25 ml	£16.92	
		300	mg per vial	50 ml	£24.43	

A confidential commercial access agreement is in place for durvalumab and olaparib that provides a discount of [redacted] ([redacted] per 500mg vial and [redacted] per 120mg vial) and [redacted] ([redacted] per 56 tablets), respectively. The commercial agreement for durvalumab and olaparib were used in the economic model and all results are reported according to these discounts.

A micro-costing approach was used to estimate the cost of carboplatin and paclitaxel chemotherapy (SoC) for each treatment arm. This involved analysing the treatment duration of chemotherapies based on the observed data from the DUO-E trial, as detailed in Section B.3.5.1. The method accounted for the frequency and distribution of chemotherapy cycles, specifically carboplatin and paclitaxel, administered to patients across three treatment arms: SoC, SoC + D, and SoC + D + O. This was performed separately for the dMMR population (Table 66) and pMMR population (Table 67).

For both chemotherapy components used as part of SoC, the total number of patients treated and the individual number of treatment cycles received per patient were recorded. These data were aggregated to calculate the total number of cycles administered across the patient cohort, from which the average number of weekly cycles per patient was derived. The weekly cost of carboplatin was then multiplied by

the average number of cycles per patient to estimate the chemotherapy cost per arm, which is presented in Table 68.

Table 66. Proportion of patients on chemotherapy in the dMMR population

dMMR total patients	Carboplatin (source DUO-E[4])		Paclitaxel (source DUO-E[4])	
Number of cycles	SoC (N = 46)	SoC + D (N = 44)	SoC (N=46)	SoC + D (N=44)
	Number of patients			
0	0	0	0	0
1	1	3	1	3
2	1	2	1	2
3	4	1	4	1
4	2	0	2	0
5	3	3	3	3
6	35	35	35	35
Total cycles	248	235	248	235
Mean number of cycles	5.39	5.34	5.39	5.34

Table 67. Proportion of patients on chemotherapy in the pMMR population

pMMR total patients	Carboplatin (source DUO-E[4])			Paclitaxel (source DUO-E[4])		
Number of cycles	SoC (N = 190)	SoC + D (N = 191)	SoC + D + O (N = 191)	SoC (N=190)	SoC + D (N = 191)	SoC + D + O (N = 191)
	Number of patients					
0	0	0	0	0	0	0
1	8	5	4	8	5	4
2	3	4	3	3	4	3
3	5	5	10	6	5	10
4	6	5	7	7	5	7
5	7	13	10	11	13	10
6	161	159	157	155	159	157
Total cycles	1054	1067	1060	1045	1067	1060
Mean number of cycles	5.55	5.59	5.55	5.50	5.59	5.55

Table 68. Drug acquisition cost associated with SoC

	One-off cost for Chemotherapy	Drug acquisition cost
dMMR	SoC	£654.53
	SoC in SoC + D	£648.41
pMMR	SoC	£672.28

	SoC in SoC + D	£678.21
	SoC in SoC + D + O	£673.76

The base-case analysis excludes drug wastage for IV drugs, assuming perfect vial sharing. This means that the exact dose required for each patient is multiplied by the lowest per mg cost of the drug from the pack sizes available. This approach reflects how NHS resources are used in clinical practice, whereby vial sharing for high-cost oncology drugs is common to minimise wastage.[157] As a scenario analysis, the model assumes full wastage for intravenous drugs. Under this scenario, the dose per administration was rounded up to the closest integer number of vials.

Based on the dosing regimens described in

Table **64**, all the active treatments included in the model were fixed dose-based, except for carboplatin and paclitaxel that were dependent on AUC and BSA, respectively. Therefore, a normal distribution with mean weight, BSA and GFR from DUO-E[4] (reported in Table 30) were utilised for calculating the acquisition cost.

The model also considers the relative dose intensity (RDI) in the drug cost calculation since patients may not receive the full dose of their assigned treatment. RDI was calculated as the actual dose received divided by the standard calculated dose during the trial period. Applying this factor in the calculation of drug cost ensures that the drug exposure was consistent with the efficacy data from the trials. The median RDIs are reported Table 69 and further indicate that durvalumab in SoC + D, and olaparib and durvalumab in SoC + D + O were generally well tolerated.

Table 69. Relative dose intensities

Treatment	Relative dose intensity (median)	Source
Durvalumab in SoC + D	[redacted]	DUO-E CSR[4]
Durvalumab in SoC + D + O	[redacted]	DUO-E CSR[4]
Olaparib in SoC + D + O	[redacted]	DUO-E CSR[4]

Based on the dosing regimen, package price, wastage assumption and RDI, the drug acquisition cost per administration was estimated for durvalumab and olaparib during both chemotherapy phase and maintenance phase (Table 70).

Table 70. Drug acquisition cost per administration

Treatment	Drug acquisition cost per administration	
	Chemotherapy phase	Maintenance phase
Durvalumab	[redacted]	[redacted]
Olaparib	N/A	[redacted]

B.3.5.1.2. Drug administration costs

Administration costs were applied to IV drugs, and these costs differ by administration visit (initial vs. subsequent attendance), as well as the complexity of the administration. No administration cost was assumed for drugs that are orally administered. Unit costs for all categories of administration were sourced from the PSSRU[117] and are presented in Table 71.

At the first attendance visit, SoC regimens (carboplatin and paclitaxel) were assumed to incur a simple administration cost, whilst immunotherapy regimens incurred a complex administration cost. All subsequent administrations were then assigned the same unit cost (IV subsequent administration). For SoC, the administration cost was applied as a one-off cost based on the average number of cycles for the dMMR and pMMR populations (previously reported in Table 66 and Table 67).

Table 71. Drug administration costs

Administration type	Unit cost	Source
IV Simple administration – First attendance	£411.99	NHS reference costs 2022/23[154]; Summary: HRG (SB12Z) Deliver simple parenteral chemotherapy at first attendance
IV Complex Administration – First attendance	£486.10	NHS reference costs 2022/23[154]; Summary: HRG (SB13Z) Deliver more complex parenteral chemotherapy at first attendance
IV Subsequent administration	£393.16	NHS reference costs 2022/23[154]; Summary: HRG (SB15Z) Deliver subsequent elements of a chemotherapy cycle

B.3.5.1.3. Subsequent treatment costs

The cost of subsequent treatments was included in the model, as most patients are likely to receive further lines of treatment following disease progression. Table 72 and Table 73 present the percentage of dMMR and pMMR patients, respectively, treated with each subsequent treatment, which was based on DUO-E[4] trial data and UK clinical expert opinion. As DUO-E is a multinational trial with no UK sites, UK clinical expert opinion was sought to ensure the subsequent treatment model inputs accurately reflect the clinical practice in England and Wales. It is also not possible to determine from DUO-E trial data whether subsequent treatments were used in combination or as a monotherapy. In England, lenvatinib is only available in combination with pembrolizumab, further highlighting the need for clinical expert opinion to verify the applicability of these inputs. Note that as patients may receive a combination of subsequent therapies, proportions in the model calculations may sum to more than 100%. Varying the composition of subsequent treatment only impacts treatment costs, an approach that is consistent with other HTA submissions to NICE in EC.[30, 158]

Immunotherapy re-challenge is not currently permitted under current UK guidelines for high-cost drugs (Blueteq criteria) and have been set to 0% in the intervention arms but is permitted in other countries, including some of the trial sites included within the DUO-E trial.

Table 72. Subsequent treatment proportions (amongst patients receiving at least one subsequent therapy) – dMMR population

Treatment	SoC	SoC + D	Source
Carboplatin	[redacted]	[redacted]	UK clinical expert opinion/DUO-E
Paclitaxel	[redacted]	[redacted]	
Doxorubicin/Doxorubicin Hydrochloride	[redacted]	[redacted]	
Cisplatin	[redacted]	[redacted]	
Pembrolizumab	[redacted]	[redacted]	
Dostarlimab	[redacted]	[redacted]	

Lenvatinib/Lenvatinib Mesylate	[redacted]	[redacted]	
Radiotherapy	[redacted]	[redacted]	

Table 73. Subsequent treatment proportions (amongst patients receiving at least one subsequent therapy) – pMMR population

Treatment	SoC	SoC + D + O	Source
Carboplatin	[redacted]	[redacted]	UK clinical expert opinion/ DUO-E
Paclitaxel	[redacted]	[redacted]	
Doxorubicin/Doxorubicin Hydrochloride	[redacted]	[redacted]	
Cisplatin	[redacted]	[redacted]	
Pembrolizumab	[redacted]	[redacted]	
Dostarlimab	[redacted]	[redacted]	
Lenvatinib/Lenvatinib Mesylate	[redacted]	[redacted]	
Radiotherapy	[redacted]	[redacted]	

The model assumes that, regardless of the treatment arm and MMR status, [redacted] of patients who experience a non-fatal progression event will receive a subsequent treatment. This was validated during interviews with clinicians and is based on the DUO-E[4] trial, where a total of 404 patients experienced a non-fatal progression event, of which [redacted] received at least one subsequent therapy. The assumption that the percentage of patients receiving a subsequent treatment is the same regardless of MMR status was validated by interviews with five clinicians.

For each subsequent therapy, the dosing schedule was derived from either the SmPC, or the relevant clinical trial (Table 74). These were combined with drug pack prices (Table 75) and the estimated duration of treatment (Table 76). Due to a lack of available data, the average treatment durations for pembrolizumab, lenvatinib and dostarlimab were assumed to be equal to the median PFS outcomes from their respective trials.[26, 27] The average duration of chemotherapy was estimated from an observation study.[159]

Table 74. Subsequent treatment dosing regimens

Treatment	Dosing	Number of administrations per cycle	Source
Carboplatin	Patients received carboplatin (AUC 6 mg/mL/min) every 3 weeks.	1.45	SmPC[160]
Paclitaxel	Patients received paclitaxel (175 mg/m^2) every 3 weeks.	1.45	SmPC[161]
Doxorubicin/Doxorubicin Hydrochloride	The recommended dose is 60-75 mg/m^2 i.e. as a single dose or in divided doses on 2-3 consecutive days administered with 21 day's intervals.	1.45	SmPC[162]
Cisplatin	Single dose of 50 to 120 mg/m^2 every 3 to 4 weeks	1.45	SmPC[163]

Pembrolizumab	Pembrolizumab (200 mg) was administered intravenously every 3 weeks	1.45	Makker *et al.* (2022) [KEYNOTE-775][27]
Dostarlimab	Dostarlimab (500 mg) was administered intravenously every 3 weeks for four cycles followed by 1000 mg every 6 weeks for all cycles thereafter	1.45	Oaknin *et al.* (2020) [GARNET][26]
Lenvatinib/Lenvatinib Mesylate	The recommended dosage is 20 mg orally once daily.	30.44	Makker *et al.* (2022) [KEYNOTE-775][27]

Table 75. Subsequent treatment drug pack prices

Treatment	Vial size (mg)/ Tablets per pack	Unit price	Price per mg	Administration cost	Adjusted dosage per month (mg)	Source
Carboplatin	150	£20.22	£0.13	£399.92	1087.05	eMIT[156]
Paclitaxel	100	£9.13	£0.09	£399.92	454.03	eMIT[156]
Doxorubicin/ Doxorubicin hydrochloride	10	£3.91	£0.39	£399.92	155.67	eMIT[156]
Cisplatin	100	£29.27	£0.29	£399.92	130.45	eMIT[156]
Pembrolizumab	100	£2,630.00	£26.30	£399.92	579.76	BNF[155]
Dostarlimab	500	£5,887.33	£11.77	£399.92	724.70	BNF[155]
Lenvatinib /Lenvatinib mesylate	300	£1,437	£4.79	£0.00	608.75	BNF[155]
Radiotherapy	-	-	-	**Base case:** £3,672.00 **Scenario:** £763.00	-	**Base case:** National costs and resource requirements of radiotherapy (2024)[164] **Scenario:** NHS reference costs 2022/23[154]

Table 76. Subsequent treatment durations

Treatment	Duration (months)	Source
Carboplatin	3.20	Coleman, 2023[159]
Paclitaxel	3.20	

Doxorubicin/Doxorubicin hydrochloride	3.20	
Cisplatin	3.20	
Pembrolizumab	7.20	Makker, 2022[27]
Dostarlimab	8.10	Oaknin, 2020[26]
Lenvatinib/Lenvatinib mesylate	7.20	Makker, 2022[27]
Radiotherapy	N/A – applied as a one-off cost	N/A

To estimate the number of non-fatal progression events in each model cycle, the number of total progression events (i.e. death or disease progression events) was multiplied by the proportion of progression events that were non-fatal (92.2%, as derived from the DUO-E trial[4]). It was assumed that this proportion would remain constant over time. Only those patients experiencing a non-fatal progression were eligible to receive subsequent therapies.

The average cost for subsequent therapies, per treatment arm, for a patient experiencing a non-fatal progression event is reported in Table 77 and Table 78 for the dMMR and pMMR population, respectively.

Table 77. Subsequent treatment costs - dMMR population

Treatment arm	Drug acquisition cost (one-off)	Drug administration cost (one-off)	Total cost (one-off)
SoC + D	£48,925.77	£3,173.56	£52,099.34
SoC	£42,933.76	£3,667.00	£46,600.76

Table 78. Subsequent treatment costs - pMMR population

Treatment arm	Drug acquisition cost (one-off)	Drug administration cost (one-off)	Total cost (one-off)
SoC + D + O	£37,629.69	£3,330.81	£40,960.49
SoC	£47,280.00	£3,009.98	£50,289.97

B.3.5.2 Health-state unit costs and resource use

Health-state unit costs were calculated using a micro-costing approach, with resource use differing by treatment arm, health state (PF and PD), and treatment phase (chemotherapy phase [six cycles of chemotherapy] versus maintenance phase [post-six cycles of chemotherapy]).

The resources considered in the model include outpatient visits, computed tomography (CT) scan, complete blood counts, specialist nurse visits, general practitioner (GP) visits, cancer antigen 125 tests, and thyroid function tests. The total costs for each health state were calculated by multiplying the average monthly use of each resource by its respective unit cost. The average monthly use of resources in the PF health state (chemotherapy phase) and PD health state were informed by a NICE submission for dostarlimab with platinum-based chemotherapy [TA963], whilst resource use in the PF health state (maintenance phase) was derived from routine resource use data from the DUO-E trial.[4] In TA963, weekly rates of resource use were reported, therefore these were converted to monthly rates by multiplying 4.34 (average number of weeks in a month).

Unit costs were sourced from the NHS Schedule of Reference Costs 2022/2023.[154] The HCRU and unit costs for each health state and treatment arm are presented in Table 79. The initial chemotherapy phase PF costs were applied for 4.14 months which aligns with the average length of chemotherapy cycle from the DUO-E.[4] The following assumptions were made based on clinical validation:

- Resource use does not differ by MMR status
- Patients in long-term remission (i.e., in the PFS health state for ≥ treatment duration) are discharged from care and incur lower resource use thereafter

As shown by the total health state cost per treatment arm presented in Table 80, SoC + D and SoC + D + O do not add any additional resource use strain on the health care system compared to SoC alone.

Table 79. HCRU and unit costs (per monthly cycle), by treatment arm and health state

Treatment arm	Health state	Resource use per monthly cycle						
		Outpatient visit	CT scan	Complete blood count	Specialist nurse visit	GP visit	Cancer antigen (CA)-125*	Thyroid function tests (TSH, T3 and T4)
SoC + D	PF: Chemotherapy phase	1.30	0.57	1.43	0.48	0.00	1.43	1.43
	PF: Maintenance phase	0.57	0.26	0.96	0.30	0.04	0.96	0.96
	PD	0.52	0.30	0.39	0.43	0.04	0.39	0.39
SoC + D + O	PF: Chemotherapy phase	1.30	0.57	1.43	0.48	0.00	1.43	1.43
	PF: Maintenance phase	0.57	0.26	0.96	0.30	0.04	0.96	0.96
	PD	0.52	0.30	0.39	0.43	0.04	0.39	0.39
SoC	PF: Chemotherapy phase	1.30	0.57	1.43	0.48	0.00	1.43	1.43
	PF: Maintenance phase	0.35	0.22	0.26	0.43	0.04	0.39	0.39
	PD	0.52	0.30	0.39	0.43	0.04	0.39	0.39
Unit cost		£175.17	£141.52	£2.75	£118.51	£49.00	£30.40	£4.96
Source for unit cost		NHS reference costs 2022/23[154]; Outpatient Care 503	NHS reference costs 2022/23[154]; Summary: HRG (RD20A, B,C, RD21A, B, C, RD22-27Z) weighted average	NHS reference costs 2022/23[154]: DAPS05	NHS reference costs 2022/23[154]: N10AF and N10AN (weighted average)	PSSRU - Unit Costs of Health and Social Care 2023[117]: GP per surgery consultation lasting 10 mins including direct costs and qualification costs	NICE CG122[165] Table A1.10 (Inflated 2010 to 2023 using PSSRU 2023[117] inflation indices)	NICE NG145[166] (Inflated 2019 to 2023 using PSSRU 2023[117] inflation indices)

Table 80. Total health state cost per monthly cycle, by treatment arm

Treatment arm	Health state		
	PF (Chemotherapy phase)	PF (Maintenance phase)	PD
SoC + D	£419.87	£210.60	£203.05
SoC + D + O	£419.87	£210.60	£203.05
SoC	£419.87	£159.92	£203.05

B.3.5.3 Adverse reaction unit costs and resource use

The costs of managing treatment-related AEs were calculated based on the frequency of AEs incurred for each of the primary therapies included in the model (described in Section B.3.4.4), multiplied by the corresponding aggregated cost of each event. The unit costs associated with the management of AEs were derived from the NHS Schedule of Reference Costs 2022/2023[154], and are presented in Table 81. The total AE cost per treatment arm (Table 82) were applied as a one-off cost in the first model cycle.

Table 81. Adverse event costs

AE	Unit cost	Source
Anaemia	£855.09	NHS reference costs 2022/23; Summary: HRG (SA04G, H, J, K, L): Weighted average of Iron Deficiency Anaemia with CC Score 0-14+
Neutropenia	£1,400.20	NHS reference costs 2022/23; Summary: HRG (SA08G, H, J): Weighted average of other haematological or splenic disorders with CC Score 0-6+
Neutrophil Count Decreased	£941.25	Assumed equal to white cell count decreased
Lymphocyte Count Decreased	£941.25	Assumed equal to neutrophil count decreased
White Cell Count Decreased	£941.25	NHS reference costs 2022/23; Summary: HRG (RN13Z) nuclear medicine infection scan or white cell scan
Hypertension	£720.94	NHS reference costs 2022/23; Summary: HRG (EB04Z) Hypertension
Pulmonary Embolism	£1,110.87	NHS reference costs 2022/23; Summary: HRG (YQ51A, B, C,D, E) : Weighted average of Deep Vein Thrombosis with CC Score 0-12+
Hypokalaemia	£1,845.37	NHS reference costs 2022/23; Summary: HRG (KC05G, H, J, K, L, M): Weighted average of Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-10+

Table 82. Total AE cost per treatment arm

Treatment arm	Total AE cost (applied as a one-off in first model cycle)
SoC + D	£516.38
SoC + D + O	£650.58
SoC	£464.79

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1. End-of-life costs

The model includes terminal care costs which capture the increase in resource use that typically occurs towards the end of a patient's life. These costs are applied as a one-off to the proportion of patients transitioning to the Dead health state in each model cycle. The cost of end-of-life care was sourced from the PSSRU (2023).[117] Direct costs borne by the healthcare (£8,051.00) and social care (£4,676.00) sectors are considered, in line with the perspective recommended in the NICE reference case.[106] The total terminal care cost per person transitioning to the Dead health state was £12,727.00.

B.3.5.4.2. Diagnostic test costs

According to BGCS guidelines[2] and NICE diagnostics guidance DG42[23], it is recommended that all patients with EC are tested at diagnosis using immunohistochemistry to identify tumours that are for dMMR/MSI-H. As such, the cost of MMR testing was not included in the base-case model. This was also supported by UK clinician feedback[1] which confirmed that MMR tests are conducted as standard practice for EC patients.

B.3.6 *Severity*

In line with the NICE 2022 manual,[107] the absolute and proportional QALY shortfall associated with established clinical management without durvalumab or olaparib was calculated. Within the updated framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within specified cut-off ranges (Table 83).

Table 83. QALY weightings for severity as per the NICE health technology evaluations manual

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

To estimate the shortfall, the Schneider *et al.* (2021)[167] estimator was used, which was cited by NICE as a potential option for calculating applicability of a severity modifier. This tool uses ONS data from England to generate the general population survival with various sources of data to inform utility estimates. The NICE DSU guidance indicates that directly collected EQ-5D-3L using the Health Survey for England (HSE) 2014 dataset is a preferred method of capturing utility values, therefore the reference case data source in the Schneider *et al.* (2021)[167] tool which uses directly collected EQ-5D-3L from the HSE 2014 dataset was used to represent the most recent and robust source for the base case QALY shortfall calculations.

General population QALY estimates were derived using the patient characteristics considered in this economic evaluation (Table 84). The expected total QALYs for the general population were calculated using the Schneider *et al.* (2021)[167] tool reference case for general population utilities (MVH value set + HSE 2014 ALDVMM model [Hernández Alava *et al.*]).[128, 129] The total expected QALYs for adult female patients with primary advanced or recurrent dMMR and pMMR EC treated with SoC was based on the modelled SoC arm of the Company base case. The total QALYs for the dMMR and pMMR populations were then compared to the general population QALYs to calculate the absolute and proportional shortfall for each population. Summary features of the QALY shortfall analysis are provided in Table 84. QALY shortfall estimates from TA963[30] are presented in Table 85. Utility data are outlined in Table 86.

Table 84. 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	Aligned with the licensed population
Starting age	63	DUO-E trial[4] results for the ITT population - Section B.3.3.1

Table 85. Summary of QALY shortfall from TA963[30]

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TA963	11.82	3.21	Absolute: 8.61 Proportional: 72.83%

Table 86. Summary of health state benefits and utility values for QALY shortfall analysis

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

Based on the above, the absolute QALY shortfall is estimated to be 9.10 and 8.55 for the dMMR and pMMR subgroups, respectively, and the proportional shortfall is estimated to be 76.98% and 72.33%, respectively (Table 87). The results show that this appraisal does not meet the threshold of a QALY weight of 1.2 for both absolute and proportional QALY shortfall under the current NICE cut-off threshold criteria for the dMMR or pMMR populations (Table 87) and therefore no adjustments to the QALYs in the CEM were made.

Table 87. Summary of QALY shortfall analysis

General population QALY source	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Reference case: MVH value set + HSE 2014 ALDVMM [Hernández Alava M, *et al.*][128, 129]	11.82	**dMMR:** 2.72 **pMMR:** 3.27	**dMMR:** Absolute: 9.10 Proportional: 76.98% **pMMR:** Absolute: 8.55 Proportional: 72.33%

Footnotes: *All calculations based on the tool developed by Schneider *et al.* 2021[167]

B.3.7 *Uncertainty*

There are several key sources of uncertainty to consider in this appraisal. Firstly, OS data from the DUO-E trial were relatively immature, although uncertainty introduced due to the maturity of OS data is a common challenge faced in NICE appraisal for oncology products, including those that have been recommended for EC. In addition, whilst the DUO-E study[4] was adequately powered to detect differences in OS between the treatment arms in the ITT population (see Section B.2.4), OS KM data for the dMMR and pMMR populations are based on a small number of OS events. Because of this, only independent standard parametric approaches could be considered for OS instead of flexible models. Flexible models were shown to be more appropriate for the extrapolation of PFS, and therefore the use of standard parametric models for OS may underestimate the long-term survival benefits associated with SoC + D and SoC + D + O.

Despite the challenges with the relative immaturity of the OS data, a range of steps were taken to ensure that the OS extrapolations were clinically plausible, including comparing the modelled outcomes with advisor landmarks from TA963, other published literature where available (Miller *et al.*; Chase *et al.)* as well as to clinical expert opinion sought as part of the current appraisal. However, it is important to note that there is no published literature to support comparisons of extrapolations with landmark OS timepoints for SoC + D + O, nor any previous submissions in the pMMR population that could be considered. Therefore, conservative assumptions were made to avoid potentially overestimating the treatment effect, although further data from a future DCO could further support the selection of appropriate OS extrapolations in the pMMR population. An array of scenario analyses have also been performed to further explore this uncertainty, with results presented in Section B.3.11.3.

Finally, it is worth noting that there is some uncertainty surrounding the modelled duration of durvalumab and olaparib treatment. Whilst other trials for EC have implemented a stopping rule as part of the trial design, DUO-E did not impose a maximum duration of treatment. This means that without adjustment, TDT extrapolations from the trial would predict some patients to remain progression-free and on-treatment for an extended period of time.

Expert opinion was sought from UK clinicians who confirmed that in real-world UK clinical practice, patients who remain progression-free for a prolonged period whilst receiving the DUO-E regimen are unlikely to continue therapy indefinitely. The full benefits of treatment are likely to be realised within a finite duration of treatment, and prolonged treatment is associated with cumulative toxicity concerns. Therefore, in the base case a three-year maximum treatment duration was assumed for SoC + D and SoC + D + O, with alternative treatment durations explored via scenario analyses (Section B.3.11.3).

B.3.8 *Managed access proposal*

SoC + D and SoC + D + O are associated with clear clinical benefits versus SoC in the dMMR and the pMMR populations, respectively, in the DUO-E trial (Section B.2). As such, the Company's preference would be to enter routine commissioning for both populations. However, the Company acknowledge that it may become relevant for SoC + D and/or SoC + D + O to be considered as candidates for the Cancer Drugs Fund (CDF), should NICE wish to reduce any perceived uncertainty in the economic modelling underpinning this appraisal.

To this end, the Company wish to re-iterate that the final OS analysis from the DUO-E trial is expected in 2026.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of the base-case analysis inputs is presented in Table 88.

Table 88. Summary of variables applied in the base-case economic model

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Settings							
Time horizon	37.40	Years	-	-	-	-	Section B.3.2.3 Page 91
Discount rate – outcomes	0.035	Proportion	-	-	-	-	Section B.3.2.3 Page 91
Discount rate – costs	0.035	Proportion	-	-	-	-	Section B.3.2.3 Page 91
Model cycle length	1.00	Months	-	-	-	-	Section B.3.2.3 Page 91
Mean age at baseline	62.60	Years	-	-	-	-	Section B.3.3.1 Page 96
Mean body surface area at baseline	1.77	m^2	-	-	-	-	Section B.3.3.1 Page 96
Mean GFR at baseline	125.00	Months	-	-	-	-	Section B.3.3.1 Page 96
Maximum Treatment Duration: SoC + D	36.00	Months	-	-	-	-	Section B.3.3.5 Page 119
Maximum Treatment Duration: D in SoC + D + O	36.00	Months	-	-	-	-	Section B.3.3.5 Page 119
Maximum Treatment Duration: Olaparib in SoC + D + O	36.00	Months	-	-	-	-	Section B.3.3.5 Page 119
Time to initiation of maintenance (in weeks)	18.00	Weeks	-	-	-	-	Section B.3.5.1.1 Page 135
Proportion of patients initiating Olaparib	0.79	Proportion	-	0.73	0.85	Beta	Section B.3.5.1.1

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
							Page 137
Drug administration costs							
Drug administration cost: IV first attendance simple	411.99	£	82.40	279.46	607.38	Lognormal	Section B.3.5.2 Page 142
Drug administration cost: IV first attendance complex	486.10	£	97.22	329.73	716.64	Lognormal	Section B.3.5.2 Page 142
Drug administration cost: IV subsequent attendance	393.16	£	78.63	266.69	579.63	Lognormal	Section B.3.5.2 Page 142
Healthcare resource unit costs							
Outpatient Visit	175.17	£	35.03	113.36	250.22	Gamma	Section B.3.5.3 Page 145
CT	141.52	£	28.30	91.58	202.15	Gamma	Section B.3.5.3 Page 145
Complete Blood Count	2.75	£	0.55	1.78	3.92	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit	118.51	£	23.70	76.69	169.28	Gamma	Section B.3.5.3 Page 145
GP Visit	49.00	£	9.80	31.71	69.99	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) – 125	30.40	£	6.08	19.68	43.43	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4)	4.96	£	0.99	3.21	7.09	Gamma	Section B.3.5.3 Page 145
Healthcare resource units per month in initial chemotherapy PF Health State							

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Number of months for which initial chemotherapy PF health state costs are applied	4.14	Months	0.83	2.68	5.91	-	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in initial chemotherapy PF Health State: SoC + D	1.30	Frequency	0.26	0.84	1.86	Gamma	Section B.3.5.3 Page 145
CT resource units per month in initial chemotherapy PF Health State: SoC + D	0.57	Frequency	0.11	0.37	0.81	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in initial chemotherapy PF Health State: SoC + D	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in initial chemotherapy PF Health State: SoC + D	0.48	Frequency	0.10	0.31	0.68	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in initial chemotherapy PF Health State: SoC + D	0.00	Frequency	0.00	0.00	0.00	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in initial chemotherapy PF Health State: SoC + D	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in initial chemotherapy PF Health State: SoC + D	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in initial chemotherapy PF Health State: SoC + D + O	1.30	Frequency	0.26	0.84	1.86	Gamma	Section B.3.5.3 Page 145
CT resource units per month in initial chemotherapy PF Health State: SoC + D + O	0.57	Frequency	0.11	0.37	0.81	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Complete Blood Count resource units per month in initial chemotherapy PF Health State: SoC + D + O	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in initial chemotherapy PF Health State: SoC + D + O	0.48	Frequency	0.10	0.31	0.68	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in initial chemotherapy PF Health State: SoC + D + O	0.00	Frequency	0.00	0.00	0.00	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in initial chemotherapy PF Health State: SoC + D + O	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in initial chemotherapy PF Health State: SoC + D + O	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in initial chemotherapy PF Health State: SoC	1.30	Frequency	0.26	0.84	1.86	Gamma	Section B.3.5.3 Page 145
CT resource units per month in initial chemotherapy PF Health State: SoC	0.57	Frequency	0.11	0.37	0.81	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in initial chemotherapy PF Health State: SoC	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in initial chemotherapy PF Health State: SoC	0.48	Frequency	0.10	0.31	0.68	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in initial chemotherapy PF Health State: SoC	0.00	Frequency	0.00	0.00	0.00	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Cancer Antigen (CA) - 125 resource units per month in initial chemotherapy PF Health State: SoC	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in initial chemotherapy PF Health State: SoC	1.43	Frequency	0.29	0.93	2.05	Gamma	Section B.3.5.3 Page 145
Healthcare resource units per month in post chemotherapy PF Health State							
Outpatient Visit resource units per month in post chemotherapy PF Health State: SoC + D	0.57	Frequency	0.11	0.37	0.81	Gamma	Section B.3.5.3 Page 145
CT resource units per month in post chemotherapy PF Health State: SoC + D	0.26	Frequency	0.05	0.17	0.37	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in post chemotherapy PF Health State: SoC + D	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in post chemotherapy PF Health State: SoC + D	0.30	Frequency	0.06	0.20	0.43	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in post chemotherapy PF Health State: SoC + D	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in post chemotherapy PF Health State: SoC + D	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in post chemotherapy PF Health State: SoC + D	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in post chemotherapy PF Health State: SoC + D + O	0.57	Frequency	0.11	0.37	0.81	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
CT resource units per month in post chemotherapy PF Health State: SoC + D + O	0.26	Frequency	0.05	0.17	0.37	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in post chemotherapy PF Health State: SoC + D + O	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in post chemotherapy PF Health State: SoC + D + O	0.30	Frequency	0.06	0.20	0.43	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in post chemotherapy PF Health State: SoC + D+ O	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in post chemotherapy PF Health State: SoC + D + O	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in post chemotherapy PF Health State: SoC + D + O	0.96	Frequency	0.19	0.62	1.37	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in post chemotherapy PF Health State: SoC	0.35	Frequency	0.07	0.23	0.50	Gamma	Section B.3.5.3 Page 145
CT resource units per month in post chemotherapy PF Health State: SoC	0.22	Frequency	0.04	0.14	0.31	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in post chemotherapy PF Health State: SoC	0.26	Frequency	0.05	0.17	0.37	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in post chemotherapy PF Health State: SoC	0.43	Frequency	0.09	0.28	0.62	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in post chemotherapy PF Health State: SoC	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Cancer Antigen (CA) - 125 resource units per month in post chemotherapy PF Health State: SoC	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in post chemotherapy PF Health State: SoC	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Healthcare resource units per month in PD Health State							
Outpatient Visit resource units per month in PD Health State: SoC + D	0.52	Frequency	0.10	0.34	0.75	Gamma	Section B.3.5.3 Page 145
CT resource units per month in PD Health State: SoC + D	0.30	Frequency	0.06	0.20	0.43	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in PD Health State: SoC + D	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in PD Health State: SoC + D	0.43	Frequency	0.09	0.28	0.62	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in PD Health State: SoC + D	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in PD Health State: SoC + D	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in PD Health State: SoC + D	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in PD Health State: SoC + D + O	0.52	Frequency	0.10	0.34	0.75	Gamma	Section B.3.5.3 Page 145
CT resource units per month in PD Health State: SoC + D + O	0.30	Frequency	0.06	0.20	0.43	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Complete Blood Count resource units per month in PD Health State: SoC + D + O	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in PD Health State: SoC + D + O	0.43	Frequency	0.09	0.28	0.62	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in PD Health State: SoC + D + O	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in PD Health State: SoC + D + O	0.39	Frequency	00.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in PD Health State: SoC + D + O	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Outpatient Visit resource units per month in PD Health State: SoC	0.52	Frequency	0.10	0.34	0.75	Gamma	Section B.3.5.3 Page 145
CT resource units per month in PD Health State: SoC	0.30	Frequency	0.06	0.20	0.43	Gamma	Section B.3.5.3 Page 145
Complete Blood Count resource units per month in PD Health State: SoC	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Specialist Nurse Visit resource units per month in PD Health State: SoC	0.43	Frequency	0.09	0.28	0.62	Gamma	Section B.3.5.3 Page 145
GP Visit resource units per month in PD Health State: SoC	0.04	Frequency	0.01	0.03	0.06	Gamma	Section B.3.5.3 Page 145
Cancer Antigen (CA) - 125 resource units per month in PD Health State: SoC	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145
Thyroid function tests (TSH, T3 and T4) resource units per month in PD Health State: SoC	0.39	Frequency	0.08	0.25	0.56	Gamma	Section B.3.5.3 Page 145

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Cost per AE							
Anaemia	855.09	£	171.02	553.37	1221.42	Gamma	Section B.3.5.4 Page 146
Neutropenia	1400.20	£	280.04	906.13	2000.05	Gamma	Section B.3.5.4 Page 146
Neutrophil count decreased	941.25	£	188.25	609.13	1344.49	Gamma	Section B.3.5.4 Page 146
Lymphocyte count decreased	941.25	£	188.25	609.13	1344.49	Gamma	Section B.3.5.4 Page 146
White cells count decreased	941.25	£	188.25	609.13	1344.49	Gamma	Section B.3.5.4 Page 146
Hypertension	720.94	£	144.19	466.55	1029.79	Gamma	Section B.3.5.4 Page 146
Pulmonary embolism	1110.87	£	222.17	718.90	1586.78	Gamma	Section B.3.5.4 Page 146
Hypokalaemia	1845.37	£	369.07	1194.22	2635.93	Gamma	Section B.3.5.4 Page 146
Subsequent therapy costs							
Proportion of progressed patients receiving subsequent therapy in each cycle: SoC + D	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Proportion of progressed patients receiving subsequent therapy in each cycle: SoC + D + O	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Proportion of progressed patients receiving subsequent therapy in each cycle: SoC	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Pembrolizumab proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Dostarlimab proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Carboplatin proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion	-	[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Paclitaxel proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Doxorubicin/Doxorubicin hydrochloride proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Cisplatin proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Lenvatinib/Lenvatinib mesylate proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Radiotherapy proportion as a subsequent therapy in: SoC + D	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Pembrolizumab proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Dostarlimab proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Carboplatin proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Paclitaxel proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Doxorubicin/Doxorubicin hydrochloride proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Cisplatin proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Lenvatinib/Lenvatinib mesylate proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Radiotherapy Proportion as a subsequent therapy in: SoC + D + O	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Pembrolizumab proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Dostarlimab proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Carboplatin proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Paclitaxel proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Doxorubicin/Doxorubicin hydrochloride proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Cisplatin proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Lenvatinib/Lenvatinib mesylate proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142
Radiotherapy proportion as a subsequent therapy in: SoC	[redacted]	Proportion		[redacted]	[redacted]	Beta	Section B.3.5.2 Page 142

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Price per mg: Pembrolizumab	26.30	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Dostarlimab	11.77	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Carboplatin	0.13	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Paclitaxel	0.09	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Doxorubicin/Doxorubicin hydrochloride	0.39	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Cisplatin	0.29	£	-	-	-	-	Section B.3.5.2 Page 142
Price per mg: Lenvatinib/Lenvatinib mesylate	4.79	£	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Pembrolizumab	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Dostarlimab	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Carboplatin	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Paclitaxel	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Doxorubicin/Doxorubicin hydrochloride	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142
No of administrations per cycle: Cisplatin	1.45	Frequency	-	-	-	-	Section B.3.5.2 Page 142

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
No of administrations per cycle: Lenvatinib/Lenvatinib mesylate	30.44	Frequency	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Pembrolizumab	579.76	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Dostarlimab	724.70	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Carboplatin	1,087.05	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Paclitaxel	454.03	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Doxorubicin/Doxorubicin hydrochloride	155.67	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Cisplatin	130.45	Mg	-	-	-	-	Section B.3.5.2 Page 142
Adjusted dosage in mg per month: Lenvatinib/Lenvatinib mesylate	608.75	Mg	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Pembrolizumab	7.20	Months	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Dostarlimab	8.10	Months	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Carboplatin	3.20	Months	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Paclitaxel	3.20	Months	-	-	-	-	Section B.3.5.2 Page 142

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Mean treatment duration for subsequent therapy: Doxorubicin/Doxorubicin hydrochloride	3.20	Months	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Cisplatin	3.20	Months	-	-	-	-	Section B.3.5.2 Page 142
Mean treatment duration for subsequent therapy: Lenvatinib/Lenvatinib mesylate	7.20	Months	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Pembrolizumab	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Dostarlimab	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Carboplatin	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Paclitaxel	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Doxorubicin/Doxorubicin hydrochloride	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Cisplatin	399.92	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Lenvatinib/Lenvatinib mesylate	0.00	£	-	-	-	-	Section B.3.5.2 Page 142
Administration cost: Radiotherapy	3,672.00	£	-	-	-	-	Section B.3.5.2 Page 142
Proportion of non-fatal PFS events per monthly cycle	0.92	Proportion	-	0.90	0.95	Beta	Section B.3.5.2 Page 142
End-of-life costs							

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Total cost of end-of-life care	12,727.00	£	2545.40	8236.24	18179.30	Gamma	Section B.3.5.4.1 Page 146
Health state utilities							
Utility for PF state	[redacted]	Health status	0.01	[redacted]	[redacted]	Beta	Section B.3.4.1 Page 130
Utility for PD state	[redacted]	Health status	0.01	[redacted]	[redacted]	Beta	Section B.3.4.1 Page 130
Age-based disutility Coefficients (Ara *et al.* [2010][148] disutility method)							
Disutility co-efficient (scenario only): Age	0.00	Estimate	0.00	0.00	0.00	Normal	Section B.3.4.5 Page 133
Disutility co-efficient (scenario only): Age^2	0.00	Estimate	0.00	0.00	0.00	Normal	Section B.3.4.5 Page 133
Disutility co-efficient (scenario only): Male	0.03	Estimate	0.01	0.02	0.04	Normal	Section B.3.4.5 Page 133
Disutility co-efficient (scenario only): Intercept	0.95	Estimate	0.19	0.57	1.32	Normal	Section B.3.4.5 Page 133
AE-related utility decrements							
Anaemia	−0.12	Health status	0.02	0.08	0.17	Beta	Section B.3.4.4 Page 131
Neutropenia	−0.09	Health status	0.02	0.06	0.13	Beta	Section B.3.4.4 Page 131
Neutrophil count decreased	0.00	Health status	0.00	0.00	0.00	Beta	Section B.3.4.4 Page 131
Lymphocyte count decreased	0.00	Health status	0.00	0.00	0.00	Beta	Section B.3.4.4 Page 131

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
White cells count decreased	0.00	Health status	0.00	0.00	0.00	Beta	Section B.3.4.4 Page 131
Hypertension	−0.02	Health status	0.00	0.01	0.03	Beta	Section B.3.4.4 Page 131
Pulmonary embolism	−0.32	Health status	0.06	0.20	0.45	Beta	Section B.3.4.4 Page 131
Hypokalaemia	−0.07	Health status	0.01	0.05	0.11	Beta	Section B.3.4.4 Page 131
Duration of AE, days							
Anaemia	7.00	Days	0.02	6.96	7.04	Lognormal	Section B.3.4.4 Page 131
Anaemia	7.00	Days	0.02	6.97	7.03	Lognormal	Section B.3.4.4 Page 131
Neutropenia	7.00	Days	0.00	7.00	7.00	Lognormal	Section B.3.4.4 Page 131
Neutrophil count decreased	7.00	Days	0.00	7.00	7.00	Lognormal	Section B.3.4.4 Page 131
Lymphocyte count decreased	7.00	Days	0.00	7.00	7.00	Lognormal	Section B.3.4.4 Page 131
White cells count decreased	7.00	Days	0.00	7.00	7.00	Lognormal	Section B.3.4.4 Page 131
Hypertension	30.44	Days	0.12	30.21	30.67	Lognormal	Section B.3.4.4 Page 131
Pulmonary embolism	7.00	Days	0.02	6.96	7.04	Lognormal	Section B.3.4.4 Page 131

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Incidence of AEs							
Incidence (%) for Anaemia - SoC + Durvalumab	0.16	Proportion	-	0.11	0.21	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutropenia - SoC + Durvalumab	0.09	Proportion	-	0.05	0.12	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutrophil count decreased - SoC + Durvalumab	0.11	Proportion	-	0.08	0.16	Beta	Section B.3.4.4 Page 131
Incidence (%) for Lymphocyte count decreased - SoC + Durvalumab	0.02	Proportion	-	0.01	0.04	Beta	Section B.3.4.4 Page 131
Incidence (%) for White cell count decreased - SoC + Durvalumab	0.04	Proportion	-	0.02	0.07	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypertension - SoC + Durvalumab	0.04	Proportion	-	0.02	0.07	Beta	Section B.3.4.4 Page 131
Incidence (%) for Pulmonary embolism - SoC + Durvalumab	0.02	Proportion	-	0.01	0.04	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypokalaemia - SoC + Durvalumab	0.03	Proportion	-	0.01	0.05	Beta	Section B.3.4.4 Page 131
Incidence (%) for Anaemia - SoC + Durvalumab + Olaparib	0.24	Proportion	-	0.18	0.29	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutropenia - SoC + Durvalumab + Olaparib	0.11	Proportion	-	0.08	0.16	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutrophil count decreased - SoC + Durvalumab + Olaparib	0.13	Proportion	-	0.09	0.18	Beta	Section B.3.4.4 Page 131
Incidence (%) for Lymphocyte count decreased - SoC + Durvalumab + Olaparib	0.01	Proportion	-	0.00	0.03	Beta	Section B.3.4.4 Page 131

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
Incidence (%) for White cell count decreased - SoC + Durvalumab + Olaparib	0.04	Proportion	-	0.02	0.07	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypertension - SoC + Durvalumab + Olaparib	0.04	Proportion	-	0.02	0.07	Beta	Section B.3.4.4 Page 131
Incidence (%) for Pulmonary embolism - SoC + Durvalumab + Olaparib	0.03	Proportion	-	0.01	0.05	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypokalaemia - SoC + Durvalumab + Olaparib	0.03	Proportion	-	0.01	0.05	Beta	Section B.3.4.4 Page 131
Incidence (%) for Anaemia - SoC	0.14	Proportion	-	0.10	0.19	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutropenia - SoC	0.06	Proportion	-	0.03	0.09	Beta	Section B.3.4.4 Page 131
Incidence (%) for Neutrophil count decreased - SoC	0.15	Proportion	-	0.11	0.20	Beta	Section B.3.4.4 Page 131
Incidence (%) for Lymphocyte count decreased - SoC	0.02	Proportion	-	0.01	0.04	Beta	Section B.3.4.4 Page 131
Incidence (%) for White cell count decreased - SoC	0.05	Proportion	-	0.02	0.08	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypertension - SoC	0.03	Proportion	-	0.01	0.05	Beta	Section B.3.4.4 Page 131
Incidence (%) for Pulmonary embolism - SoC	0.01	Proportion	-	0.00	0.03	Beta	Section B.3.4.4 Page 131
Incidence (%) for Hypokalaemia - SoC	0.01	Proportion	-	0.00	0.02	Beta	Section B.3.4.4 Page 131
AE-related utility decrements							

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
AE-related utility decrement: SoC + D	[redacted]	Health status	-	-	-	-	Section B.3.4.4 Page 131
AE-related utility decrement: SoC + D + O	[redacted]	Health status	-	-	-	-	Section B.3.4.4 Page 131
AE-related utility decrement: SoC	[redacted]	Health status	-	-	-	-	Section B.3.4.4 Page 131
Clinical inputs							
pMMR: PFS (SoC + D + O)	Log-logistic	-	-	-	-	-	Section B.3.3.3.2 Page 106
pMMR: PFS (SoC)	Log-logistic	-	-	-	-	-	Section B.3.3.3.2 Page 106
pMMR: OS (SoC + D + O)	Log-logistic	-	-	-	-	-	Section B.3.3.4.2 Page 115
pMMR: OS (SoC)	Log-logistic	-	-	-	-	-	Section B.3.3.4.2 Page 115
pMMR: TDT (D in SoC + D + O)	Log-logistic	-	-	-	-	-	Section B.3.3.5.2 Page 124
pMMR: TDT (O in SoC + D + O)	Log-logistic	-	-	-	-	-	Section B.3.3.5.2 Page 124
dMMR: PFS (SoC + D)	PFS, flexible normal k = 2	-	-	-	-	-	Section B.3.3.3.1 Page 99
dMMR: PFS (SoC)	PFS, flexible normal k = 1	-	-	-	-	-	Section B.3.3.3.1 Page 99

Variable	Value	Unit	SE	Lower bound	Upper bound	Within PSA varied by	Reference in submission (section and page number)
dMMR: OS (SoC + D)	Log-normal	-	-	-	-	-	Section B.3.3.4.1 Page 110
dMMR: OS (SoC)	Log-normal	-	-	-	-	-	Section B.3.3.4.1 Page 110
dMMR: TDT (SoC + D)	Gamma	-	-	-	-	-	Section B.3.3.5.1 Page 121

B.3.9.2 Assumptions

Table 89 details the assumptions that underpin the CEM.

Table 89. Assumptions underpinning the CEM

Category	Assumption	Justification
Population	Adult women in first-line treatment of primary advanced or recurrent EC who are candidates for systemic therapy: dMMR population: adult women with dMMR status confirmed by a validated test. pMMR population: adult women with pMMR status confirmed by a validated test.	Aligned with the decision problem for this appraisal.
Comparators	dMMR population: SoC is an appropriate comparator for SoC + D pMMR population: SoC is an appropriate comparator for SoC + D + O	Aligned with the decision problem for this appraisal.
Model structure and settings	UK NHS and PSS perspective.	In line with the NICE reference case.[106]
	Lifetime horizon.	A 37.4-year time horizon was chosen as the mean age of patients in the ITT population of DUO-E[4] was 62.60 years. A lifetime horizon assuming no patients survive beyond a mean age of 100 years is sufficient to capture the long-term clinical and economic impacts of EC.
	The important costs and outcomes associated with primary or recurrent EC can be captured by PFS and PD health states.	A PSM model structure captures the progressive nature of recurrent and advanced EC and is considered standard practice for oncology HTA assessments in the UK.
Quality of life inputs	Utilities were derived from DUO-E[4] EQ-5D data for treatments. EQ-5D-5L data from DUO-E[4] mapped to EQ-5D-3L.	In line with the NICE reference case[106] and described in Section B.3.4.
	Utilities do not differ by MMR status.	In line with clinical expert opinion and the analysis of utilities by treatment arm using EQ-5D trial data.
Clinical parameters	PFS, OS and TDT data were sourced from the DUO-E[4] trial.	In line with the NICE reference case[106] and described in Section B.3.3.
	Disease progression and long-term prognosis are anticipated to differ by MMR status therefore survival analysis was conducted separately for dMMR and pMMR.	There is an increase in understanding about the importance of molecular features, such as MMR status, on baseline prognosis.

Category	Assumption	Justification
	Any patients remaining on treatment after three years were assumed to discontinue treatment.	UK clinicians highlighted that patients who remain progression-free for an extended period of time would not receive treatment with durvalumab and/or olaparib indefinitely. The clinicians highlighted that the full benefits of treatment would likely be realised within a finite treatment duration, while prolonged treatment would be associated with cumulative toxicity concerns. Based on clinician feedback, all patients were assumed to discontinue treatment after three years, with alternative durations considered in scenario analyses (Section B.3.3.5; Section B.3.11.3)[115]
Subsequent treatments	The percentage of patients receiving a subsequent treatment is the same regardless of MMR status.	Validated by UK clinical experts.
	Immunotherapy re-challenge is not modelled.	Immunotherapy re-challenge is not currently permitted under current UK guidelines for high-cost drugs (Blueteq criteria), and this was validated by all five clinicians during clinician interviews.
Cost inputs – wastage	Drug wastage excluded for IV drugs, assuming perfect vial sharing.	Excessive wastage is not expected in clinical practice – vial sharing for high-cost oncology drugs is expected to be common to minimise wastage.[157]
Cost inputs - End-of-life	End-of-life costs are sourced from PSSRU (2023)[117] which reports the costs to the NHS in the last 12 months of a patients' life.	The PSSRU is used as the source as it most accurately captures costs from a NHS and PSS perspective.
HCRU	HCRU does not differ by MMR status.	Validated by UK clinical experts.
	Following treatment discontinuation at 3 years (maximum treatment duration), SoC HCRU costs are applied in the SoC + D + O and SoC + D treatment arms in the PF health state.	Patients that are not receiving active treatment, and who remain PF for a prolonged period, are expected to require reduced HCRU. Validated by UK clinical experts.

B.3.10 *Base-case results*

B.3.10.1 Base-case incremental cost-effectiveness analysis results

B.3.10.1.1. dMMR

The base-case results for the dMMR subgroup are presented using the commercial agreement (confidential discount of [redacted] described in Section B.3.5.1) for durvalumab in SoC + D.

Total costs, LYs, QALYs, and the ICER for SoC + D versus SoC in the dMMR subgroup are

presented in Table 90. In the deterministic base-case analysis, SoC + D was associated with [redacted] incremental costs and 5.37 incremental QALYs compared to SoC, resulting in an ICER of [redacted] per QALY gained over a lifetime horizon. Disaggregated base-case results are presented in Appendix J.

Table 90. Base-case results in the dMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10	-	-	-	-
SoC	73,935.99	3.69	2.72	[redacted]	7.65	5.37	[redacted]

B.3.10.1.2. pMMR

As described in Section B.3.5.1, durvalumab and olaparib have confidential discounts of [redacted] and [redacted] respectively. The base-case results for the pMMR subgroup are presented using the commercial agreement for durvalumab and olaparib in SoC + D + O.

Total costs, LYs, QALYs, and the ICER for SoC + D + O versus SoC in the pMMR subgroup are presented in Table 91. In the deterministic base-case analysis, SoC + D + O was associated with [redacted] incremental costs and 0.67 incremental QALYs compared to SoC, resulting in an ICER of [redacted] per QALY gained over a lifetime horizon. Disaggregated base-case results are presented in Appendix J.

Table 91. Base-case results in the pMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94	-	-	-	-
SoC	72,158.61	4.57	3.27	[redacted]	0.89	0.67	[redacted]

B.3.11 *Exploring uncertainty*

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

B.3.11.1 Probabilistic sensitivity analysis

Uncertainty in the model was explored through PSA, where each parameter is assigned an uncertainty distribution, and a value is drawn from these distributions (see Table 88). This is performed for each parameter simultaneously and the resulting incremental results are recorded, constituting one 'iteration'. A total of 5,000 iterations were performed, which gave a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. If variance in any inputs was not available, a simplifying assumption was made, whereby it was assumed that the standard error was 20% of the mean value.

For costs and resource use estimates, a gamma distribution was fitted to prevent any sampling of values below zero. For utilities and probabilities, a beta distribution was used, to ensure values remained between 0 and 1. Treatment costs for newly diagnosed advanced or recurrent EC remained fixed, but treatment costs for subsequent treatments were varied by varying the proportion of patients receiving each subsequent treatment.

The results of the PSA are presented separately for the dMMR and pMMR population. Results include mean total costs, LYs, QALYs, and the ICER for SoC + D versus SoC (dMMR) or SoC + D + O versus SoC (pMMR). Results are also presented through an incremental cost-effectiveness plane (ICEP) scatter plot, cost-effectiveness acceptability curve (CEAC), and cost-effectiveness acceptability frontier (CEAF).

B.3.11.1.1. dMMR probabilistic results

In the probabilistic base-case analysis for the dMMR population, SoC + D was associated with [redacted] incremental costs and 4.89 incremental QALYs compared to SoC alone, which corresponds to an ICER of [redacted] per QALY gained (Table 92).

The ICEP, CEAC and CEAF for the dMMR population are presented in Figure 38 to Figure 40, respectively. 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, SoC + D has a [redacted] chance of being cost-effective and at a WTP threshold of £20,000 per QALY, SoC + D has a [redacted] chance of being cost-effective.

Table 92. PSA base-case results – dMMR

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.2	8.0	-	-	-	-
SoC	74,136.20	4.2	3.1	[redacted]	6.95	4.89	[redacted]

Figure 38. Incremental cost-effectiveness plane (ICEP) – dMMR

[redacted]

Figure 39. Cost-effectiveness acceptability curve (CEAC) – dMMR

Figure 40. Cost-effectiveness acceptability frontier (CEAF) – dMMR

B.3.11.1.2. pMMR probabilistic results

In the probabilistic base-case analysis for the pMMR population, SoC + D + O was associated with [redacted] incremental costs and 0.66 incremental QALYs compared to SoC alone, corresponding to an ICER or [redacted] per QALY gained (Table 93).

The ICEP, CEAC and CEAF for the pMMR population are presented in Figure 41 to Figure 43, respectively. 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, SoC + D + O has a [redacted] chance of being cost-effective and at a WTP threshold of £20,000 per QALY, SoC + D + O has a [redacted] chance of being cost-effective.

Table 93. PSA base-case results – pMMR

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.47	3.95	-	-	-	-
SoC	72,458.17	4.59	3.28	[redacted]	0.88	0.66	[redacted]

Figure 41. Incremental cost-effectiveness plane (ICEP) – pMMR

Figure 42. Cost-effectiveness acceptability curve (CEAC) – pMMR

Figure 43. Cost-effectiveness acceptability frontier (CEAF) – pMMR

B.3.11.2 Deterministic sensitivity analysis

OWSA was conducted to test parameter uncertainty; individual parameters were set to their upper and lower limits, whilst all other parameters were maintained at their base case setting. Upper and lower values were determined by the 95% CI of the pre-specified appropriate distribution assigned to each parameter.

In the absence of CI data, a standard error of +/- 20% of the mean for each parameter was assumed and the lower and upper bounds were estimated by applying the appropriate distribution. Table 88

presents the mean, standard error, upper bound and lower bound values for each variable.

The OWSA was run separately for the dMMR and pMMR populations. For each, a tornado diagram was developed to highlight the parameters which have the greatest effect on the ICER.

B.3.11.2.1. dMMR OWSA results

The top ten most sensitive parameters for SoC + D versus SoC are presented in Figure 44, with the tabulated results presented in Table 94. The model was most sensitive to the pembrolizumab and dostarlimab proportions as a subsequent therapy for SoC.

Figure 44. OWSA tornado diagram – dMMR

Table 94. Tabulated OWSA results – dMMR

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Pembrolizumab proportion as a subsequent therapy in: SoC	[redacted]	[redacted]	[redacted]
Dostarlimab proportion as a subsequent therapy in: SoC	[redacted]	[redacted]	[redacted]
Drug administration cost: IV subsequent attendance	[redacted]	[redacted]	[redacted]
Outpatient Visit: unit cost	[redacted]	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy in each cycle: SoC	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month: PD Health State: SoC + Durvalumab	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit: unit cost	[redacted]	[redacted]	[redacted]
Total cost of end-of-life care	[redacted]	[redacted]	[redacted]
CT scan: unit cost	[redacted]	[redacted]	[redacted]
Proportion of non-fatal PFS events per monthly cycle	[redacted]	[redacted]	[redacted]

B.3.11.2.2. pMMR OWSA results

The top ten most sensitive parameters for SoC + D + O versus SoC are presented in Figure 45, with the tabulated results presented in Table 95. The model was most sensitive to the pembrolizumab

proportion as subsequent therapy for SoC followed by drug administration cost for IV subsequent attendance.

Figure 45. OWSA tornado diagram – pMMR

Table 95. Tabulated OWSA results – pMMR

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Pembrolizumab proportion as a subsequent therapy in: SoC	[redacted]	[redacted]	[redacted]
Drug administration cost: IV subsequent attendance	[redacted]	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy in each cycle: SoC	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month: PD Health State : SoC	[redacted]	[redacted]	[redacted]
Lenvatinib/Lenvatinib mesylate proportion as a subsequent therapy in: SoC	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month: PD Health State: SoC + Durvalumab + Olaparib	[redacted]	[redacted]	[redacted]
Utility for PF state	[redacted]	[redacted]	[redacted]
Proportion of non-fatal PFS events per monthly cycle	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit resource units per month: PD Health State: SoC	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit resource units per month: PD Health State: SoC + Durvalumab + Olaparib	[redacted]	[redacted]	[redacted]

B.3.11.3 Scenario analysis

Scenario analyses were conducted to test structural and parametric uncertainty and have been outlined throughout Section B.3. The results of these scenarios are summarised below for the dMMR and pMMR populations.

B.3.11.3.1. dMMR scenario analyses results

The results from the scenario analyses presented in Table 96 show that the cost-effectiveness results are robust to changes in model structure and inputs, with all ICERs remaining significantly below the WTP threshold of £30,000/QALY gained for SoC + D compared to SoC. The scenarios with the greatest impact on incremental results are the survival model selected for PFS and OS, and maximum time on treatment. This demonstrates limited structural and parameter uncertainty in the cost-effectiveness results in the dMMR population.

Table 96. Results for scenario analyses explored in the cost-effectiveness analysis – dMMR

No.	Category	Base-case value	Scenario value	Inc. costs	Inc. QALYs	ICER (£/QALY)
Base case	-	--	-	[redacted]	5.37	[redacted]
1	Time horizon	Lifetime	25 years	[redacted]	4.96	[redacted]
2	Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	[redacted]	6.86	[redacted]
3	PFS: SoC + D and SoC	SoC + D: Spline, k = 2 SoC: Spline, k = 1	Spline, k = 1	[redacted]	5.28	[redacted]
4			Spline, k = 2	[redacted]	5.14	[redacted]
5	OS: SoC + D and SoC	Log-normal	Gamma	[redacted]	4.12	[redacted]
6			Log-logistic	[redacted]	4.60	[redacted]
7	TDT (applies to all treatments)	Treatment duration 3 years, **parametric curve** approach for 1-3 years. Drop to zero at year 3.	Treatment duration **2 years**, **parametric curve** approach for 1–2 years. Drop to zero at year 2.	[redacted]	5.37	[redacted]
8			Treatment duration **5 years**, **parametric curve** approach for 1–3 years, **exponential** drop-off 3–5 years	[redacted]	5.37	[redacted]
9			Treatment duration 3 years, **Weibull distribution** for 1–3 years	[redacted]	5.37	[redacted]
10	Half cycle correction	Included	Excluded	[redacted]	5.36	[redacted]
11	Source for age-adjusting utilities	Alava *et al.* (2022)	Ara and Brazier (2010)	[redacted]	5.42	[redacted]
12	Wastage	Excluded	Included	[redacted]	5.37	[redacted]
13	Source for health state utility values (HSUV)	DUO-E ITT	NICE TA914[32]	[redacted]	4.93	[redacted]
14	AE disutilities	Included	Excluded	[redacted]	5.38	[redacted]
15	Baseline age	62.6	67.1 (TA963)[30]	[redacted]	4.89	[redacted]
16			[redacted]	[redacted]	5.39	[redacted]
17	End-of-life care cost	Included	Excluded	[redacted]	5.37	[redacted]
18	Life tables	2017-19	2020–22	[redacted]	5.35	[redacted]

19	Radiotherapy unit cost	£3,672.00	£763.00	[redacted]	5.37	[redacted]
20	Carboplatin AUC units	100% AUC 6 units	100% AUC 5 units	[redacted]	5.37	[redacted]

B.3.11.3.2. pMMR scenario analyses results

The results from the scenario analyses presented in Table 97 show that the cost-effectiveness results are robust to changes in model structure and inputs, with all ICERs remaining within 15% of the base case results, and 15/21 ICERs remaining within 5% of the base case results. The majority of input variation does not cause impactful changes to model results. As with dMMR, the scenarios with the greatest impact on incremental results are the survival models selected for PFS and OS, and maximum time on treatment. This demonstrates limited structural and parameter uncertainty in the cost-effectiveness results in the pMMR population.

Table 97. Results for scenario analyses explored in the cost-effectiveness analysis – pMMR

No.	Category	Base-case value	Scenario value	Inc. costs	Inc. QALYs	ICER (£/QALY)
Base case	-	-	-	[redacted]	0.67	[redacted]
1	Time horizon	Lifetime	25 years	[redacted]	0.65	[redacted]
2	Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	[redacted]	0.78	[redacted]
3	PFS: SoC + D + O and SoC	Log-logistic	Log-normal	[redacted]	0.67	[redacted]
4	OS: SoC + D + O and SoC	Log-logistic	Log-normal	[redacted]	0.96	[redacted]
5			Gamma	[redacted]	0.69	[redacted]
6	TDT (applies to all treatments)	Treatment duration 3 years, **parametric curve** approach for 1-3 years. Drop to zero at year 3.	Treatment duration **2 years**, **parametric curve** approach for 1–2 years. Drop to zero at year 2.	[redacted]	0.67	[redacted]
7			Treatment duration **5 years**, **parametric curve** approach for 1–3 years, **exponential** drop-off 3–5 years	[redacted]	0.67	[redacted]
8			Treatment duration 3 years, **Exponential distribution** for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
9			Treatment duration 3 years, **Gompertz distribution** for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
10	Half cycle correction	Included	Excluded	[redacted]	0.67	[redacted]
11	Source for age-adjusting utilities	Alava *et al.* (2022)	Ara and Brazier (2010)	[redacted]	0.67	[redacted]
12	Wastage	Excluded	Included	[redacted]	0.67	[redacted]

13	Source for HSUV	DUO-E ITT	NICE TA914[121]	[redacted]	0.62	[redacted]
14	AE disutilities	Included	Excluded	[redacted]	0.68	[redacted]
15	Baseline age	62.6	67.1 (TA963)[30]	[redacted]	0.65	[redacted]
			[redacted]	[redacted]	0.67	[redacted]
17	End-of-life care cost	Included	Excluded	[redacted]	0.67	[redacted]
19	Life tables	2017-19	2020–22	[redacted]	0.67	[redacted]
20	Radiotherapy unit cost	3672	763	[redacted]	0.67	[redacted]
21	Carboplatin AUC units	100% AUC 6 units	100% AUC 5 units	[redacted]	0.67	[redacted]

B.3.12 *Subgroup analysis*

Other than the dMMR and pMMR populations detailed in this submission, no other subgroup analyses are relevant to this appraisal.

B.3.13 *Benefits not captured in the QALY calculation*

Advanced or recurrent EC is associated with a devasting physical and psychological burden. As treatments with the potential for long-term remission, the introduction of SoC + D and SoC + D + O are likely to result in substantial benefits to patients HRQoL, which cannot be fully captured in the economic analysis

Advanced or recurrent EC has a devastating impact on patients' quality of life, and is associated with a substantial physical and psychological burden.[30] The Peaches Womb Cancer trust describes how many women experience *'diagnosis-induced feelings of terror and fear at having to face one's own mortality'*, as well as *'ongoing worry and anxiety about how their diagnosis would impact family members and children, and how they would cope'*. Alongside this, patients face debilitating physical symptoms, which have a significant impact on every aspect of women's lives.

As treatments which offer patients the potential to achieve deep and durable responses, and ultimately, long-term remission, SoC + D and SoC + D + O have the potential to result in significant improvements in HRQoL compared to SoC alone. However, as a conservative assumption, the economic model assumes that patients experience the same HRQoL in each of the model health states, regardless of the treatment that they receive (with the exception of adjustments for AE disutilities). Further, the EQ-5D-3L data from the DUO-E trial only suggests a small difference in utility values of [redacted] between the progression-free and the progressed disease health states. This is unlikely to reflect clinical reality, given the worsened symptoms associated with disease progression, as well as the paucity of effective treatment options following progression.

This therefore means that additional HRQoL benefits associated with the introduction of SoC + D and SoC + D + O are unlikely to be fully captured in the economic analysis.

The value of hope associated with the introduction of an effective treatment is likely to be particularly pronounced for patients with pMMR EC, who currently face a critical unmet need for more effective treatment options

As mentioned in Section B.1.3.6, the RUBY[26] and NRG-GY018 trials[125] indicated that bringing immunotherapies into the earlier stages of treatment could delay disease progression. This led to the approval of the immunotherapy dostarlimab with platinum-based chemotherapy followed by dostarlimab alone for patients with dMMR or MSI-H disease, and patients in the UK are now able to access dostarlimab via the Cancer Drugs Fund.

However, there is still a critical unmet need for novel treatment options beyond chemotherapy for those that are newly diagnosed with pMMR tumours, who constitute for the majority of EC patients. There are currently no immunotherapy or PARP inhibitors reimbursed for use in the first-line setting for pMMR patients. The DUO-E trial[4] demonstrates the efficacy of the immunotherapy durvalumab in combination with platinum-based chemotherapy followed by durvalumab with or without the PARP inhibitor olaparib, in both the dMMR and pMMR populations. The importance of introducing additional effective first-line treatments is demonstrated by retrospective EC studies which show that delaying disease progression is associated with prolonged survival post-recurrence.[82, 83]

The introduction of SoC + D + O as novel, effective and tolerable treatment option, is therefore likely to give patients a sense of hope for their future and to lessen the devastating impact of being diagnosed with a disease with no effective treatment options for patients with pMMR EC. This

represents a key element of value in this appraisal which cannot be captured in the economic model.

The quality of life benefits associated with SoC + D and SoC + D + O will likely extend to caregivers and family members, and are also expected to result in a wider societal benefit in terms of patient and caregiver productivity and presenteeism

Furthermore, the negative impact to HRQoL often extends beyond patients and can impact carer HRQoL.[90] Whilst EC-specific literature on this is limited, evidence from gynaecological cancers more broadly suggests that caregivers often report a decline in HRQoL.[91, 92] These issues are also highlighted by patient stories from the Peaches womb cancer trust which show that EC patients worry about their inability to work and the subsequent impact this may have on their finances, as well as the emotional burden that the disease and treatment has on their friends and family. Being able to delay or prevent the progression of disease allows patients to continue with their normal daily activities for longer. Furthermore, offering efficacious alternative treatment options with manageable side effects will also improve on patients' ability to maintain a normal daily routine. These wider benefits to patients' productivity and the quality of life of informal caregivers are not captured in the current economic model.

B.3.14 *Validation*

B.3.14.1 Clinical validation of clinical assumptions

One-to-one clinical interviews were conducted in August and September 2024 to seek UK clinical expert opinion on the clinical assumptions and inputs used in the model. In total, five clinicians based in England took part; all five were consultant medical oncologists with direct experience treating patients with advanced or recurrent EC in UK clinical practice. Questionnaires were completed during a 75-minute teleconference with each clinician. A report of the questions and responses has been included as part of the reference pack accompanying this submission.[115]

B.3.14.2 Independent technical CEM validation

The CEM was quality assured by an independent health economist who reviewed the model codes, expressions, order of calculations and numbers inputted. The model was also subject to stress testing of extreme scenarios to test the plausibility of results and identify any technical modelling errors. The TECH-VER checklist was utilised for validation to ensure the correctness of all programming and logic related to input parameters, calculations, equations and patient flow.[168]

B.3.14.3 Face validation

A face validity check on model results was conducted to ensure the results accurately reflect clinical practice. Results were compared with results from TA963[30] (dostarlimab with platinum-based chemotherapy for dMMR EC) to understand any discrepancies in the results for the dMMR population.

An extreme-value sensitivity analysis was carried out on all relevant model inputs. During this process, the validator observed the direction and extent of changes for each extreme value tested, ensuring that this aligned with expected outcomes. The validation process revealed only minor discrepancies and no significant calculation errors. Feedback from the validation was incorporated into the model, and the updated post-validation model was used to produce the results presented in this submission.

B.3.14.4 Internal and external validation

In accordance with established guidelines for good modelling practices, a comprehensive validation process was implemented whereby PFS, OS and TDT KM data from the DUO-E trial[4] were compared

with the PFS, OS and TDT outputs of the model (see Appendix J). The results show that the model survival projections are consistent with the observed trial data for all outcomes (OS, PFS and TDT), ensuring the model's applicability. In addition, extrapolation of TTE data were compared to landmark survival outcomes from other EC trials.

B.3.15 Interpretation and conclusions of economic evidence

[redacted]

B.3.15.1 Results summary

B.3.15.1.1. dMMR

In the dMMR population, the results from the deterministic base-case analysis show that, over a lifetime time horizon, SoC + D is associated with higher incremental average costs of [redacted] per patient and a QALY gain of 5.37 QALYs per patient, resulting in an ICER of [redacted] QALY. The sensitivity analyses demonstrated the robustness of the base-case model inputs and assumptions; in the base-case PSA, SoC + D was associated with an estimated [redacted] and [redacted] probability of being cost-effective versus SoC alone at WTP thresholds of £30,000/QALY and £20,000/QALY, respectively. In the scenario analyses, all scenarios resulted in ICERs under the WTP threshold of £30,000/QALY.

Overall, this economic analysis shows that SoC + D may be considered an effective use of NHS resources for patients with adult patients with newly diagnosed advanced or recurrent dMMR EC.

B.3.15.1.2. pMMR

In the pMMR population, the results from the deterministic base-case analysis show that, over a lifetime time horizon, SoC + D + O is associated with higher incremental average costs of [redacted] per patient and a QALY gain of 0.67 QALYs per patient, resulting in an ICER of [redacted] /QALY. The sensitivity analyses demonstrated the robustness of the base-case model inputs and assumptions; in the base-case PSA, SoC + D + O was associated with an estimated [redacted] % and [redacted] % probability of being cost-effective versus SoC alone at WTP thresholds of £30,000/QALY and £20,000/QALY, respectively. In the scenario analyses, 15/21 scenarios resulted in an ICER that was within 15% of the base case, demonstrating that the economic analysis was robust to uncertainty.

Overall, this economic analysis shows that SoC + D + O may be considered an effective use of NHS resources for patients with adult patients with newly diagnosed advanced or recurrent pMMR EC (a bigger EC population affected and higher unmet need in terms of first-line treatment options).

B.3.15.2 Strengths of the cost-effectiveness analysis

There are several strengths associated with this cost-effectiveness analysis. Primarily, the economic analysis is underpinned by data from the DUO-E trial, which is representative of patients with newly diagnosed advanced or recurrent dMMR/pMMR EC in UK clinical practice. DUO-E is a Phase III randomised controlled trial which directly addresses the decision problem of relevance to this submission. DUO-E therefore provides directly relevant evidence for the efficacy and safety of SoC + D and SoC + D + O in patients with newly diagnosed advanced or recurrent EC.

Another key strength of the economic analysis is the extensive clinical validation conducted to ensure

that the model is truly reflective of UK clinical practice. All of the clinical assumptions and inputs used in the model, including the long-term survival predictions, have been validated with five leading UK clinical experts in two separate rounds of clinical validation exercises. As such, the model is reflective of UK clinical practice.

Further strengths include the fact that the cost-effectiveness analysis adheres to the NICE reference case.[106] The analysis is conducted from the perspective of the NHS and PSS, costs and outcomes are discounted at 3.5% and efficacy data are sourced from the pivotal trial (DUO-E). Furthermore, methods used for the extrapolation of TTE outcomes, estimation of HSUVs and source of cost inputs align to the NICE guidance.

Finally, the model has undergone an extensive technical review and quality control process, which has included a validation using the TECH-VER checklist, stress testing of extreme scenarios, and face validity checks through comparisons with previous appraisals, published literature, as well as the extensive clinical validation. The results of the model have been extensively tested through a range of probabilistic and deterministic sensitivity and scenario analyses, the results of which showed that the model is robust to parameter uncertainty. In some cases, for pMMR in particular, a number of plausible scenario analyses resulted in notable decreases to the base case ICER, suggesting that the base case results may be conservative – particularly with regard to long-term OS and the maximum duration of treatment.

B.3.15.3 Limitations of the cost-effectiveness analysis

As the median follow-up of the DUO-E trial was shorter than the modelled time horizon, long-term extrapolation of PFS, OS and TDT data was required, which is inevitably associated with uncertainty. This represents a common limitation in oncology appraisals, where the choice of the most appropriate extrapolations for each endpoint may be challenging.

To mitigate this uncertainty, an extensive range of extrapolations were explored, including standard parametric models as well as flexible spline models where there was rationale to suggest that these may be more appropriate. The selection of the most appropriate survival functions followed the recommendations outlined by the NICE TSD 14 and 21.[107] In particular, careful consideration was given to clinician feedback and published estimates of long-term survival to ensure the clinical plausibility of the chosen extrapolation. For each extrapolation, a range of alternative plausible scenario analyses were considered which demonstrated that the ICERs were relatively insensitive to these changes, and in some cases, suggested that the base case results may be conservative.

Similarly, the limited follow-up in the DUO-E trial means that the maximum treatment duration of durvalumab and olaparib is associated with some uncertainty. The DUO-E study did not impose a maximum duration of treatment, meaning that the modelled extrapolations would predict some patients to remain progression-free and on-treatment for several years. This would likely overestimate the costs associated with SoC + D + O and SoC + D, as clinicians highlighted that patients would not receive treatment with durvalumab and olaparib indefinitely in clinical practice.

To overcome this limitation, a maximum treatment duration of three years was considered in the base case economic analysis, based on clinician feedback, with alternative scenario analyses exploring considering durations of two and five years. In the dMMR population, these scenario analyses showed that the maximum duration of treatment had a limited impact on the ICER, suggesting that this does not represent a major source of uncertainty. While the impact of this assumption was greater in the pMMR population, the clinicians highlighted that prolonged treatment with olaparib was particularly unlikely, meaning that a maximum treatment duration of three years may be particularly conservative for patients with pMMR EC.

B.3.15.4 Conclusions

There is a critical unmet need for novel and effective therapies to be made available for patients with newly diagnosed advanced or recurrent EC. These patients experience a significant burden on their HRQoL and face an extremely bleak prognosis, with a median OS of approximately two years for current SoC, as reported in the DUO-E trial.

For patients with dMMR, modelling estimates suggest that SoC + D could result in an increase of 7.65 LYG and 5.37 QALYs gained, respectively, thereby addressing the current unmet medical and patient need for novel and effective treatment options which result in deep and durable responses, improvements in patient HRQoL and prolonged survival. The introduction of SoC + D would also expand the range of available options for this patient population and potentially provide a more hopeful outlook for patients diagnosed with newly diagnosed advanced or recurrent EC that is dMMR.

For the more difficult-to-treat population of patients with pMMR EC, modelling estimates suggest that the introduction of SoC + D + O could result in an increase of 0.89 LYG and 0.67 QALYs, respectively. For a patient population who cannot currently access any innovative treatment options in the first-line setting, the introduction of SoC + D + O would represent a step-change in current UK clinical practice, providing patients with more time with their loved ones at the end of their lives.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for untreated advanced or recurrent endometrial cancer

[ID6317]

Summary of Information for Patients (SIP)

October 2024

File name	Version	Contains confidential information	Date
DUO-E in EC [ID6317]_SIP_2ndOctober24 [NoCON]	FINAL	No	2nd October 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

There are two different medicines that are relevant to this submission. The generic name and the brand name for each of these medicines is listed below:

1. **Generic name**: **Durvalumab**
   Brand name: Imfinzi®
2. **Generic name**: **Olaparib**
   Brand name: Lynparza®

This submission covers two different treatment regimens, which include one or both of these medicines.

In both regimens, **olaparib** and/or **durvalumab** are combined with carboplatin + paclitaxel. Carboplatin + paclitaxel is the current **standard of care** (**SoC**) for **newly diagnosed advanced** or **recurrent** endometrial cancer (see **Section 2c** for more information). Carboplatin + paclitaxel is sometimes called 'platinum-based chemotherapy'. The two regimens covered in this submission are:

1. **Durvalumab** in combination with carboplatin + paclitaxel, followed by **maintenance durvalumab** – this is referred to as SoC + D
2. **Durvalumab** in combination with carboplatin + paclitaxel, followed by maintenance **durvalumab** with **olaparib** – this is referred to as SoC + D + O

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (Section 4b). Cross-references to other sections or documents are highlighted in orange.

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

SoC + D and SoC + D + O will be used for adult patients that are diagnosed with:

- newly diagnosed advanced endometrial cancer or,
- recurrent endometrial cancer.

However, SoC + D and SoC + D + O will be used for different groups of patients with newly diagnosed advanced or recurrent endometrial cancer:

- SoC + D will be used for patients with **deficient mismatch repair (dMMR)** endometrial cancer
- SoC + D + O will be used for patients with **proficient mismatch repair (pMMR)** endometrial cancer

Further information on pMMR and dMMR is provided in Section 2a.

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.

Durvalumab

The **Medicines and Healthcare products Regulatory Agency** (**MRHA**) is reviewing whether durvalumab should be approved and granted **marketing authorisation** as a treatment for primary advanced or recurrent endometrial cancer. The marketing authorisation for durvalumab is therefore pending. More information on this can be found in Document B in Section B.1.2.

Olaparib

The Medicines and Healthcare products Regulatory Agency (MRHA) is reviewing whether olaparib should be approved and granted marketing authorisation as a treatment for primary advanced or recurrent endometrial cancer. The marketing authorisation for olaparib is therefore pending. More information on this can be found in Document B in Section B.1.2.

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:

No relevant disclosures.

SECTION 2: Current landscape

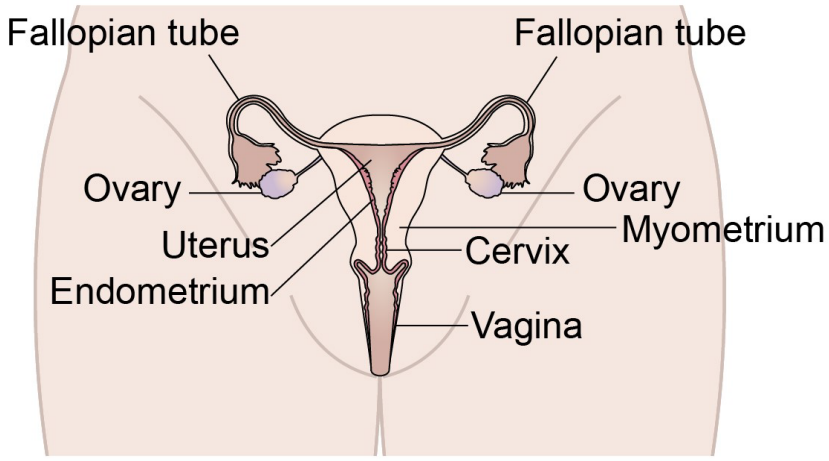
2a) The condition – clinical presentation and impact

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.

What is endometrial cancer?

Endometrial cancer is cancer that occurs in the lining of the womb (**uterus**), known as the **endometrium** (see **Figure 1**).[1] Endometrial cancer is the most common type of womb cancer. It is also the fourth most common cancer among women in the United Kingdom (UK), with around 9,700 diagnoses each year.[2]

Figure 1. Location of the endometrium in the body



What is newly diagnosed advanced endometrial cancer?

Newly diagnosed advanced endometrial cancer describes cancer that has never been treated, and that has spread beyond the uterus to other parts of the body.

Advanced endometrial cancer is more difficult to treat than endometrial cancer that is diagnosed at an earlier **stage** (Section 2b).[3] Advanced cancer is therefore associated with a worse **prognosis** than **early-stage** cancer.[4,5]

What is recurrent endometrial cancer?

Recurrent endometrial cancer describes cancer that has returned after the patient has experienced a period where the cancer could no longer be detected after their initial treatment (known as **remission**).[6,7]

Similar to advanced disease, recurrent endometrial cancer is difficult to treat. Patients diagnosed with recurrent endometrial cancer therefore also face a worse prognosis than those diagnosed with cancer at an early stage.[4]

What is mismatch repair?

Mismatch repair is a system in cells that corrects any mistakes that happen when the genetic code (**DNA**) is copied. The copying of DNA is a natural process that occurs so that the body's cells have the genetic information that they need to function.

When the mismatch repair system is functioning properly, it known as proficient mismatch repair (pMMR). When the mismatch repair system is faulty, it is known as deficient mismatch repair (dMMR).[8]

The status of a patient's mismatch repair system can be determined by laboratory testing. This is done by taking samples of the cancer (known as a **biopsy**) and running tests in a laboratory.[9]

Around 20–30% of patients diagnosed with EC have dMMR, whilst 70%–80% have pMMR endometrial cancer.

Why is mismatch repair status important?

Determining a patient's MMR status is important because it can help doctors plan treatment or predict how well the cancer will respond to treatment.[10-13] For this submission, MMR status is particularly important as it determines which regimen a patient receives (SoC + D or SoC + D + O). This is because a patient's MMR status determines which regimen would work best to treat their endometrial cancer (see Section 3b for more information).

Mismatch repair (MMR) vs. microsatellite instability (MSI)

Microsatellites are short, repetitive sections of DNA that are present in all cells. MMR status is closely related to **microsatellite instability**. This is because when the MMR system is not working properly (dMMR), errors in microsatellites are not corrected. This is known as microsatellite instability. Patients with dMMR endometrial cancer usually show high levels of MSI, called **MSI-High**.

On the other hand, if the MMR system is working (pMMR), errors in microsatellites are corrected. Tumours with pMMR tumours therefore show low or no MSI. This is called **MSI-Low** or **microsatellite stable** (**MSS**).

This submission focusses on MMR status rather than MSI status. This is because MMR status is more commonly tested for in the UK.[14] In addition, the main clinical evidence for

this submission is based on MMR status. Finally, the expected marketing authorisations for olaparib and durvalumab are dependent on MMR status rather than MSI (Section 1c).

What causes endometrial cancer?

There are various causes of endometrial cancer. One of the most common causes of endometrial cancer is a high level of the hormone oestrogen. A high level of oestrogen can occur in patients who:

- Have a high body mass index (BMI)
- Take certain types of hormone replacement therapy
- Have never given birth
- Have **polycystic ovary syndrome** (**PCOS**)
- Went through the **menopause** after age 55

The risk of developing endometrial cancer can also be increased due to factors such as diabetes, a family history of bowel, ovarian, or womb cancer, medicines such as tamoxifen, and receiving radiotherapy on the pelvis.[15] Endometrial cancer can also develop due to Lynch syndrome, as mentioned above.

Women that have gone through menopause are also more likely to develop endometrial cancer. Endometrial cancer therefore typically occurs in women that are in their 60s.[15]

How many people have endometrial cancer?

In the UK, endometrial cancer is the fourth most common cancer. It is also the most common gynaecological cancer. Each year, there are around 9,700 new cases of endometrial cancer diagnosed in the UK.[2]

Out of all the women diagnosed with endometrial cancer each year, around 1 in 4 women are diagnosed with advanced or recurrent disease. Out of these women with advanced or recurrent disease, approximately 1 in 5 women will be diagnosed with dMMR endometrial cancer. The remaining proportion will be diagnosed with pMMR endometrial cancer.

What are the signs and symptoms of advanced or recurrent endometrial cancer?

The most common symptoms of endometrial cancer are:[16-18]

- vaginal bleeding that is unusually heavy during a period, or occurring in between periods
- vaginal discharge that varies in colour from pink and watery, to dark and foul smelling.
- vaginal bleeding after menopause

Other symptoms include pain in the lower back or pelvic region, blood in the urine, unintentional weight loss, or a lump or growth in the lower belly. Sometimes, patients

report bloating, feeling full soon after beginning eating, changes in toilet habits, and pain during sex.[17,18]

What is the impact of advanced or recurrent endometrial cancer?

Life expectancy

Patients with newly diagnosed advanced or recurrent endometrial cancer face a very poor prognosis and short life expectancy. Only around 15% of people diagnosed with the most advanced endometrial cancer (stage 4) will survive for more than 5 years after their diagnosis.[4,5] For patients with recurrent endometrial cancer, only around 20% of patients will survive for more than 5 years after their diagnosis.[4]

Impact on quality of life

Endometrial cancer impacts the lives of patients in many ways. Because of this, people with advanced or recurrent endometrial cancer usually have a lower **quality of life** than the general population.[19] Studies show that patients diagnosed with advanced or recurrent endometrial cancer have a poorer quality of life than people diagnosed with early-stage endometrial cancer.

One of the main causes of decreased quality of life in patients with endometrial cancer are the symptoms of the disease. In particular, the symptoms can impact a patients' ability to function as normal and carry out day-to day activities. Symptoms usually get worse as the disease progresses, and their negative impact on patient wellbeing increases.[16-18]

Side effects of treatment can also impact patient quality of life.[20,21] Side effects of treatment can be debilitating for patients, and can include tiredness, vomiting, and hair loss, which can all impact a patients' day-to-day functioning. For patients with advanced or recurrent endometrial cancer, these side effects may therefore outweigh the limited benefits of current treatment options. Even after a patient finishes treatment, the negative physical impact can continue to interfere with their ability to lead a normal life. Patients who have completed treatment report lasting effects, such as sexual dysfunction,[23] and an ongoing lack of stamina and strength.[24]

Mental impact

There is a significant mental and emotional impact associated with a diagnosis of advanced or recurrent endometrial cancer. Patients report increased anxiety and depression as a result of living with this life-altering disease.[25]

As many women living with advanced or recurrent endometrial cancer are in their 60s, they may worry about their inability to work and support their families. Patients who have finished treatment also report long-lasting negative mental and emotional effects, such as fear and worry around their cancer returning.[24]

Impact on families and carers of people with endometrial cancer

Advanced or recurrent endometrial cancer can have negative effects on families and caregivers of people with the disease. There is a physical and mental burden associated

with caring for a patient. Additionally, having a loved one face a difficult diagnosis and challenging treatment regimen can result in a negative impact on quality of life.[26]

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?

How is endometrial cancer diagnosed?

Endometrial cancer is diagnosed based on an examination by a doctor to assess the tumour size, location, and whether it has spread to anywhere else in the body.[27,28] For advanced or recurrent endometrial cancer, doctors also take a biopsy to classify the cancer through testing in the laboratory.

How is endometrial cancer classified?

Once a patient is diagnosed with endometrial cancer, there are various different ways that it can be classified. Classifying the endometrial cancer helps doctors to determine the best treatment options and the prognosis of the disease.[29]

Staging

Disease staging is used to describe how advanced a patient's endometrial cancer is.[28,30] Staging is based on how much a tumour has spread from its original location to other tissues or organs in the body. There are 4 stages of endometrial cancer, as described in **Table 1**.

Around 80% of patients diagnosed with endometrial cancer have early-stage disease. A smaller proportion of patients (around 1 in 5) are diagnosed with advanced disease.[31]

Table 1. Staging in endometrial cancer

Stage		Description
1	'Early-stage'	Cancer cells are found only in the uterus.
2		The cancer has spread to the cervix (opening of the uterus).
3	'Advanced'	The cancer has spread outside the uterus to the nearby lymph nodes, ovaries, fallopian tubes or vagina. It has not spread to the bladder, rectum or outside the pelvis.

4		The cancer has spread to the bladder, rectum, or outside the pelvis, such as the lungs or stomach.

Tumour histology

Histology is the study of tissues and cells under a microscope. Histological testing is another way that endometrial cancer can be classified. There are four main subtypes. The most common is known as 'endometrioid adenocarcinoma'. The other subtypes are rarer, and are considered more **aggressive cancers**.[32]

Tumour grade

Grading is a way of dividing cancer cells into groups depending on how much the cells look like normal cells. This helps to determine how quickly or slowly the cancer might grow and whether it is likely to spread. There are three grades in endometrial cancer. The lower the grade, the more normal the cells look. Lower grade cancers grow and spread more slowly. On the other hand, higher grade cancers grow and spread more quickly.[33]

Recurrent endometrial cancer

As described in Section 2a, recurrent endometrial cancer is when the cancer returns after a period of remission. Disease recurrence can happen at any disease stage.[6] In the majority of cases, recurrent cancer occurs within three years after treatment. It is estimated that up to one third of patients diagnosed with endometrial cancer could experience disease recurrence in their lifetime.[34]

Molecular classification

Molecular classification is used to check for certain genes, proteins, or other molecules in cancer cells. There are four molecular subgroups in endometrial cancer. One of the key steps for molecular subgrouping is testing for MMR status.

Various methods can be used for molecular classification, but the most common of these is known as **immunohistochemistry**. In the UK, immunohistochemistry is used to determine MMR status in all patients diagnosed with endometrial cancer.[9]

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.

How is endometrial cancer treated in the UK?

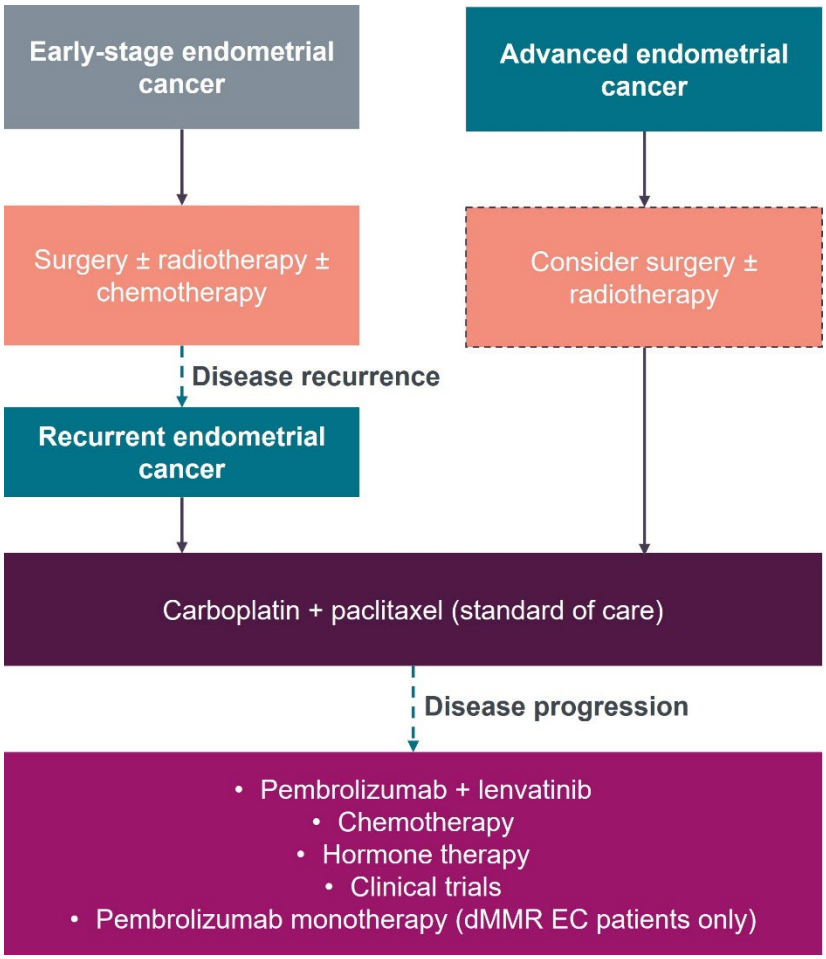
The treatment pathway for endometrial cancer is complex. Treatment for endometrial cancer is based on a range of factors including: cancer stage, cancer grade, molecular classification and patient choice.[29,35,36] The treatment pathway for endometrial cancer in the UK is informed by various guidelines, including the:

- British Gynaecological Cancer Society (BGCS)[36]
- European Society of Medical Oncology (ESMO)[29]
- European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Pathology (ESP).[35]

An overview of the treatment pathway is presented in **Figure 2**. Newly diagnosed advanced or recurrent endometrial cancer are usually treated the same, as they tend to be more difficult to treat than early-stage cancer.

Patients with dMMR and pMMR endometrial cancer are also treated via a similar treatment pathway, but there are a number of different treatments available, as detailed below.

Figure 2. Treatment pathway for endometrial cancer



Footnotes: Please refer to the glossary (Section 4b) for definition of **hormone therapy**.

Initial management of endometrial cancer

Initial management for early-stage disease usually involves surgery, which is given with the intention of curing the cancer. For advanced disease, surgery is less common as it tends to be less successful. However, surgery may sometimes be considered for patients with advanced cancer before or after chemotherapy if the cancer is operable.[29,36]

First-line treatment for advanced or recurrent endometrial cancer

The standard of care **first-line** treatment for advanced or recurrent endometrial cancer is carboplatin + paclitaxel. This treatment became the standard of care based on a 2020 study.[37] However, this study also showed that the combination of carboplatin + paclitaxel was much less effective when only looking at patients with measurable advanced or recurrent endometrial cancer compared with the overall study population.[37]

In some cases, carboplatin + paclitaxel may not be a suitable option as a patient may not be able to cope with this treatment. These patients may instead be offered carboplatin on its own, or hormone therapy, as these treatments usually have fewer side effects. Patients who are unable to tolerate carboplatin + paclitaxel would not be suitable candidates for SoC + D or SoC + D + O in clinical practice, and were also not included in the main clinical trial supporting the use of these regimens in endometrial cancer (DUO-E - Section 3d).

Hormonal therapy is therefore not considered relevant to compare with the treatments presented in this submission.

Second-line treatment for advanced or recurrent endometrial cancer

In the **second-line**, once a patient has progressed after first-line treatment, there is no standard of care treatment. Patients with advanced or recurrent endometrial cancer may therefore receive various different options, including:

- another course of chemotherapy,
- **immunotherapy** with **pembrolizumab** + **lenvatinib** or pembrolizumab alone,
- hormonal therapy, or
- enrolment in a **clinical trial**.

However, many patients are unable to tolerate second-line treatment. Innovative first-line treatments are therefore needed in order to allow as many patients as possible to benefit from improved outcomes.[38]

Treatment options for patients with dMMR newly diagnosed advanced or recurrent endometrial cancer

Patients with advanced or recurrent endometrial cancer that is dMMR have recently become eligible for other innovative therapies. However, many of these treatments are only available through the **Cancer Drugs Fund** (**CDF**). This means that these treatments do not represent standard clinical practice, and are only available on a temporary basis. Given this, they are not considered relevant to compare with the treatments presented in this submission.

The treatments that are recommended for patients with dMMR or MSI-High advanced or recurrent endometrial cancer are:

First-line

- **Dostarlimab** with carboplatin + paclitaxel (via the CDF)

Second-line

- Dostarlimab alone (via the CDF)
- Pembrolizumab alone

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.

Endometrial cancer from the patient perspective

Endometrial cancer can impact many areas of a patient's life and can be difficult for patients to cope with. In particular, the symptoms of the disease and side effects of treatment can make it hard to carry out day-to-day activities, socialise, and perform at work. Based on patient stories, there were some key topics that patients mentioned were particularly challenging. These include:

Coping with treatment

Many patients report that treatment for endometrial cancer is difficult to cope with due to side effects. One patient even described their treatment as "brutal" and "gruelling".[39] Ahead of starting treatment, patients speak about feeling emotionally unprepared for the **aggressive** treatment they are about to start. After treatment, patients report that they feel as though their "life isn't [their] own".[39]

Long-term health impact

Even after treatment finishes, patients who achieve remission report long-term physical and mental effects that include an ongoing lack of stamina and strength. They may also feel afraid about their cancer returning.[24] Patients also report long-term effects, including exhaustion.[40] Many patients report decreased ability, or even inability, to have or enjoy sex after surviving endometrial cancer.[23] These physical and mental effects can stop patients from enjoying their lives, even after they have survived endometrial cancer.

Living a limited life

As mentioned in Section 2a, endometrial cancer has a major impact on patient quality of life. Patients diagnosed with endometrial cancer describe how the "cancer destroys you. It ruins your confidence, your self-esteem and makes you feel like less of a person, less of a woman".[40]

Patients receiving treatment may also have to arrange their lives around hospital appointments. The side effects that can result from this treatment, as described in Section 2a, can further limit a patient's ability to lead a normal life. The mental and emotional burden of living with endometrial cancer takes a severe toll on patients. This can be seen even in cases where treatment has finished and they have survived the disease.

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.

About durvalumab and how it works

Durvalumab is an immunotherapy that is known as a **checkpoint inhibitor**. This means that durvalumab works by helping the body's **immune system** to attack and destroy cancer cells. It does this by blocking the system that helps cancer cells disguise themselves and hide from the immune system. [42]

More information on durvalumab is provided in the Summary of Project Characteristics (SmPC): IMFINZI (Durvalumab) SmPC

About olaparib and how it works

Olaparib is a targeted treatment that is known as a poly (ADP-ribose) polymerase (**PARP) inhibitor**. This means that olaparib works by blocking the system that cancer cells rely on to survive and grow. By doing this, olaparib causes cancer cells to become too damaged to survive.[43]

More information on olaparib is provided in the Summary of Project Characteristics (SmPC): LYNPARZA (Olaparib) SmPC

In SoC + D, durvalumab is combined with carboplatin + paclitaxel. In SoC + D + O, both durvalumab and olaparib are combined with carboplatin + paclitaxel. **Section 3b** explains why the combination of SoC + D is used for dMMR endometrial cancer, whilst SoC + D + O is used for pMMR endometrial cancer.

3b) Combinations with other medicines

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

- Yes / No

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

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

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

As mentioned in **Section 1a**, this submission focusses on two different combination regimens. In the SoC + D and SoC + D + O regimens, durvalumab with or without olaparib are used in combination with carboplatin + paclitaxel. Carboplatin + paclitaxel is the

current standard of care for newly diagnosed advanced or recurrent endometrial cancer (Section 2c).

About carboplatin + paclitaxel and how it works

Carboplatin is a chemotherapy drug. It works by entering cancer cells and damaging their DNA. This damage stops them from growing and dividing, which can slow down or stop the growth of the cancer.[44]

Paclitaxel is another type of chemotherapy drug. It works by attaching to structures inside the cancer cells which are essential for cell division. By attaching to these structures, paclitaxel stops cancer cell division, causing them to die.[45]

When carboplatin + paclitaxel are used together, they are more powerful against cancer cells compared to when they are used alone. This is because they affect different aspects of cancer cell division and growth.

SoC + D for dMMR endometrial cancer

There have been a number of studies which have shown that dMMR endometrial cancer responds well to checkpoint inhibitors. For instance, studies have showed that patients with dMMR endometrial cancer respond well to **dostarlimab**, which is another checkpoint inhibitor.

In SoC + D, carboplatin + paclitaxel affect aspects of cancer cell division and growth, whilst durvalumab works to boost the body's own immune response against cancer cells. The DUO-E study showed that use of SoC + D is highly effective in dMMR endometrial cancer (see Section 3e).

SoC + D + O for pMMR endometrial cancer

Studies have shown that pMMR endometrial cancers are more difficult to treat with immunotherapies when compared with dMMR endometrial cancers.[46] Because of this, combining an immunotherapy with other targeted treatments may be particularly beneficial to these patients.

In SoC + D + O, the addition of olaparib to carboplatin + paclitaxel and durvalumab further suppresses cancer cells, as olaparib targets an additional aspect of cancer cell survival (Section 3a). Importantly, the DUO-E study showed that patients with pMMR endometrial cancer benefitted from of the addition of olaparib in the SoC + D + O regimen (see Section 3e).[47]

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?

How is durvalumab taken for dMMR endometrial cancer?

For patient with dMMR endometrial cancer, treatment with SoC + D is given in the following steps:

- Durvalumab is given via a drip into a vein (**intravenous infusion**) at a dose of 1,120 milligrams (mg) every three weeks.[48]
- At the same time, patients are given carboplatin + paclitaxel every three weeks, also via intravenous infusion. Carboplatin + paclitaxel is given for a minimum of 4 and a maximum of 6 **cycles**.[48]
- Patients stop receiving carboplatin + paclitaxel after 4–6 cycles and are then given durvalumab as a maintenance therapy. During maintenance, durvalumab is given via intravenous infusion at a dose of 1,500 mg every four weeks.[48]

What is a cycle?

Many cancer treatments are given in cycles. Each cycle is usually split into a period where patients receive a treatment, followed by a period where the treatment is stopped to allow their body to recover. The length of each cycle and the split between treatment and rest periods can depend on the type of treatment and on the patient.

How are durvalumab and olaparib taken for pMMR endometrial cancer?

For patients with pMMR endometrial cancer, treatment is given in the same way as for those with dMMR cancer, with the addition of olaparib.

- Durvalumab is given via a drip into a vein (intravenous infusion) at a dose of 1,120 milligrams (mg) every three weeks.[48]
- At the same time, patients are given carboplatin + paclitaxel every three weeks, also via intravenous infusion. Carboplatin + paclitaxel is given for a minimum of 4 and a maximum of 6 cycles.[48]
- Patients stop receiving carboplatin + paclitaxel after 4–6 cycles and are then given durvalumab and olaparib as a maintenance therapy.
- Maintenance durvalumab is given via intravenous infusion at a dose of 1,500 mg every four weeks.[48] Maintenance olaparib is given as a hard capsule by mouth (orally), twice per day. The recommended dose of olaparib is 600 mg per day.[49]

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.

Studies of SoC + D and SoC + D + O in newly diagnosed advanced or recurrent endometrial cancer

The main clinical evidence that is available for SoC + D and SoC + D + O for the treatment of patients with newly diagnosed advanced or recurrent endometrial cancer is from the **DUO-E trial**.[47]

The DUO-E trial was a **Phase 3** clinical trial. It looked at how well SoC + D and SoC + D + O worked to treat endometrial cancer (its **efficacy**) compared to carboplatin + paclitaxel alone (SoC). The DUO-E study also assessed the safety and tolerability of SoC + D and SoC + D + O compared to SoC, and the impact of each regimen on quality of life.[48]

Who was included in the DUO-E trial?

Overall population

DUO-E was a global study carried out across 22 countries. It was carried out in patients with newly diagnosed advanced or recurrent endometrial cancer. The overall study population included 718 patients. These patients received one of three treatment options, as described below.

Subgroup analysis

The DUO-E study also looked at the impact of each treatment regimen based on patient MMR status.[47] The results from the dMMR and pMMR populations supported the marketing authorisation for durvalumab and olaparib in endometrial cancer. They are also the main source of evidence for this submission.

How was the DUO-E trial carried out?

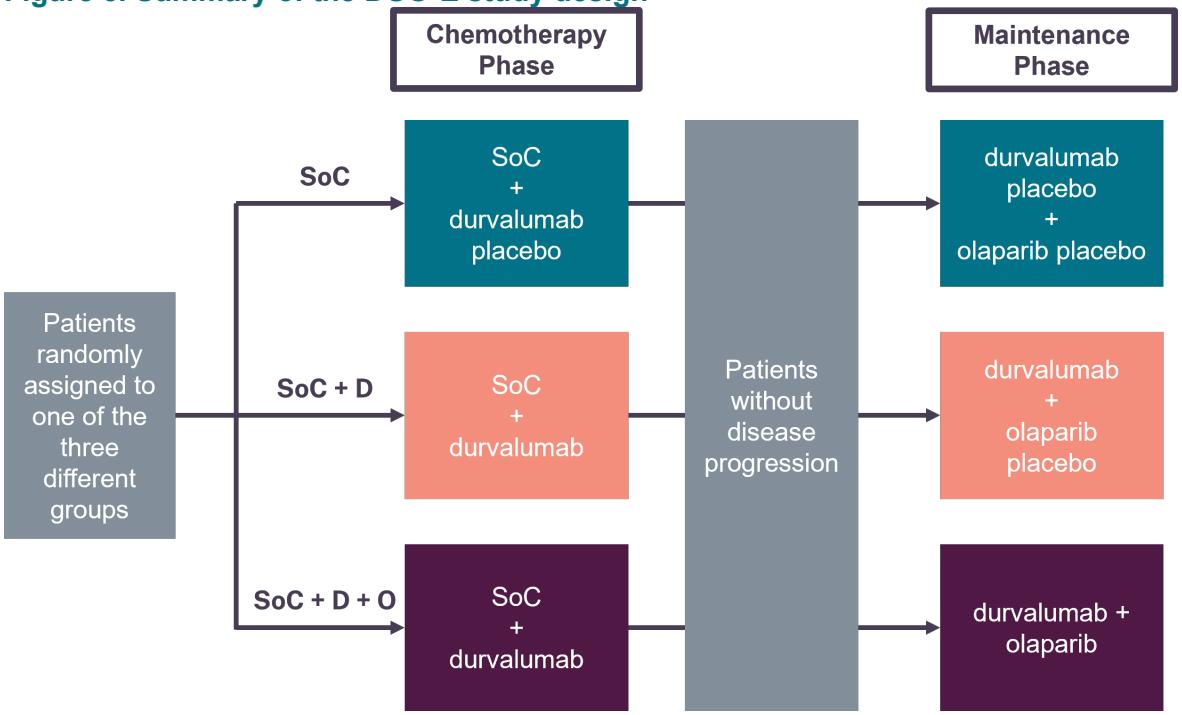
As DUO-E compared three different regimens, patients were given one of the following treatments:

1. SoC (carboplatin + paclitaxel)
2. SoC + D
3. SoC + D + O

DUO-E was a **double-blind study**, which means that neither the patient nor the doctor knew which treatment regimen that each patient was receiving. This helped to reduce **bias** in the study. To keep the patient and doctors blinded, patients were given **placebo** durvalumab if they were in the SoC group. Patients were given placebo olaparib if they were in the SoC + D and SoC group.[47]

A summary of the study design of the DUO-E study is shown in **Figure 3**.

Figure 3. Summary of the DUO-E study design



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.

How was the efficacy of SoC + D and SoC + D + O measured?

In the DUO-E trial, the main measure that was used to measure the efficacy of the treatment regimens was **progression-free survival** (**PFS**). PFS is the time between the start of the trial and signs that the cancer has started to grow again (i.e. the length of time before the disease starts to progress), or death due to any cause.

The other efficacy measures in the DUO-E trial included:

- **Overall survival (OS):** the time between the start of the trial and death due to any cause
- **Objective response rate (ORR):** the percentage of patients whose cancer shrinks (by at least 30%) or disappears completely after treatment
- **Duration of response (DoR):** the length of time that the tumour responds to treatment for without the cancer growing or spreading

The section below presents efficacy results for the overall study population. Efficacy results are then presented for the dMMR population, followed by the pMMR population.

Results from the overall study population

Progression-free survival

In the overall study population, the **median** PFS was:

- 9.6 months in the SoC group
- 10.2 months in the SoC + D group
- 15.1 months in the SoC + D + O group

This shows that both SoC + D and SoC + D + O significantly extended the time that a patient does not experience their cancer getting worse over patients that receive SoC.[47,48]

Overall survival

In the overall study population, an improvement was seen in OS for both the SoC + D and the SoC + D + O arm compared to the SoC arm. This means that both treatment regimens extended the overall length of time that patients survived compared with SoC.

Other measures of efficacy

Other measures of efficacy showed a similar benefit of SoC + D and SoC + D + O in patients with advanced or recurrent endometrial cancer compared with SoC.[47,48]

Subgroup analysis

In subgroup analysis by MMR status, both SoC + D and SoC + D + O increased PFS in patients with dMMR and pMMR endometrial cancer compared with SoC. However, SoC + D + O did not significantly increase PFS over SoC when compared with the improvement seen for SoC + D versus SoC in the dMMR population. This suggests that the addition of olaparib provides limited additional benefit for patients with dMMR endometrial cancer compared to SoC + D.

On the other hand, SoC + D + O improved PFS compared with SoC more than the improvement observed for SoC + D versus SoC in patients with pMMR endometrial cancer. This suggests that the addition of olaparib to durvalumab results in a particular benefit for the pMMR population.

These findings supported the marketing authorisations for SoC + D in patients with dMMR endometrial cancer and SoC + D + O in pMMR endometrial cancer. They also informed the focus of this submission.

Further results for SoC + D in the dMMR population and SoC + D + O in the pMMR population are provided below.

Results for SoC + D in patients with dMMR endometrial cancer

Progression-free survival

An improvement in PFS was seen in the patients with dMMR endometrial cancer that received SoC + D. Of these patients, around 68% experienced no cancer growth at 18 months, compared with around one-third of the patients that received SoC only.

Overall survival

OS was also improved by SoC + D compared with SoC alone in the dMMR population. At 12 months, OS was over 90% in dMMR patients receiving SoC + D compared with around 75% of patients in the SoC arm. At 18 months, OS was seen in around 86% of patients in the dMMR arm compared with around 65% in the SoC arm. This shows a clear benefit in OS for SoC + D compared with SoC in the dMMR population.[47,48]

Other measures of efficacy

- **ORR:** SoC + D resulted in a greater number of patients responding to treatment than SoC in the dMMR population. Over 70% of patients experienced a response in the SoC + D arm compared with around 40% of patients who were given SoC.
- **DoR:** SoC + D improved the length of time that patients responded to treatment compared with SoC. Of patients in the SoC + D arm, around three quarters maintained a response to treatment at 18 months, compared with around half of patients who received SoC alone.
- **Other measures:** SoC + D showed an improvement across all measures of efficacy when compared with SoC alone.

Results for SoC + D + O in patients with pMMR endometrial cancer

Progression-free survival

The use of SoC + D + O showed an improvement in PFS in the pMMR population, with an increase of 5.3 months over patients that received SoC. The PFS rate in the SoC + D + O group was around 42% at 18 months compared with 20% of patients in the SoC group.[47,48]

Overall survival

SoC + D + O showed a meaningful improvement in OS in the pMMR population. Overall, patients who received SoC + D + O had longer OS when compared with patients who received SoC.[47,48]

Other measures of efficacy

- **ORR:** SoC + D + O resulted in a similar number of patients responding to treatment than SoC in the pMMR population. There were over 60% of patients with a response in the SoC + D + O group compared with 59.0% of patients in the SoC group.
- **DoR:** SoC + D + O improved the length of time that patients responded to treatment compared with SoC. Of patients in the SoC + D + O arm, around 50%

maintained a response to treatment at 18 months, compared with just over 10% of patients who received SoC.

- **Other measures:** SoC + D + O showed an improvement across all measures of efficacy when compared to SoC.

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.

How was quality of life measured?

The DUO-E trial measured patient quality of life using various different questionnaires:

- **EORTC-QLQ-C30**: The EORTC-QLQ-C30 is a specific measure for quality of life in people living with cancer, and was used in the DUO-E trial to assess patient health status.
- **EORTC-QLQ-EN24** The EORTC-QLQ-EN24 questionnaire is specific to endometrial cancer. This assessed patient health by asking questions relating to sexual activity. It also included specific questions relating to endometrial cancer symptoms.
- **EQ-5D-5L:** This looked at the effect of endometrial cancer on overall quality of life. This questionnaire assessed topics such as mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.[48]

Quality of life impact of SoC + D and SoC + D + O

The results from the three questionnaires showed the following:

- **EORTC-QLQ-C30:** There were no meaningful differences in patient health status in any of the treatment arms in the DUO-E trial.
- **EORTC-QLQ-EN24:** There were no meaningful differences between the treatment arms for endometrial cancer-specific symptoms, or sexual interest and activity.
- **EQ-5D-5L:** There were also no meaningful differences in the results of this questionnaire in the DUO-E trial.[48]

The similar quality-of-life scores between treatment arms show that adding durvalumab with or without olaparib does not negatively impact patients' quality of life. This shows that the treatment benefits of SoC + D and SoC + D + O (**Section 3e**) do not come at the expense of patient quality of life.

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.

Every medicine has the potential to result in side effects, and the same medicine can produce different effects in different people. Overall, the medicines used in the treatment regimens presented in this submission showed a manageable **safety profile** that was in line with what is already known about each of the individual medicines.[47,48]

In the DUO-E study, the number of patients who experienced side effects was similar across the three treatment groups. All side effects that occurred in patients receiving SoC + D and SoC + D + O were consistent with what is already known about durvalumab and olaparib, except for **arthralgia** (joint pain).[48]

The rate of patients stopping the study treatments due to side effects was slightly higher for those that received durvalumab and/or olaparib when compared to those in the SoC group. However, it is expected that for many patients these side effects will be justified by the added benefits provided by these regimens.[48]

The side effects experienced by the full study population, the dMMR subpopulation, and the pMMR subpopulation were similar in terms of effect and rate they occurred.[48]

A summary of the most common side effects in the DUO-E trial is provided in **Table 2**. Further information on other potential side effects for olaparib is available in the Patient Information Leaflet. Further information on other potential side effects for durvalumab is available in the Patient Information Leaflet.

Table 2.Summary of the most common side effects experienced by patients during the DUO-E trial

Side effect	Percentage of patients with side effect		
	SoC (N=236)	SoC + D (N=235)	SoC + D + O (N=238)
Low red blood cell count	54.2	47.7	61.8
Hair loss	50.0	50.2	50.8
Tiredness and weakness	44.5	43.0	54.2
Nausea	44.5	40.9	54.6
Low white blood cell count	41.5	35.7	41.6
Constipation	34.3	27.2	32.8

Diarrhoea	28.0	31.5	28.2
Low platelet count	22.0	28.1	29.8
Joint pain	24.6	30.2	24.4
Nerve damage	28.0	26.0	25.2
Tingling due to nerve damage	28.0	25.5	25.2
Vomiting	18.2	20.9	25.6
Decreased appetite	19.5	17.9	23.1
Low white blood cell count	19.1	17.0	20.2
Urinary tract infection	21.2	14.0	20.2

Footnotes: These side effects are the most common side effects experienced by patients in the overall duration of the DUO-E study (chemotherapy + maintenance phase; **Section 3d**).

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

Overall benefit of SoC + D and SoC + D + O in patients with advanced or recurrent endometrial cancer

At present, treatment options for people with advanced or recurrent endometrial cancer are limited. In addition, there are currently no standard of care treatments for patients with newly diagnosed advanced or recurrent endometrial cancer in the second-line setting, meaning that the introduction of more effective first-line treatment options is very important for patients.

SoC + D and SoC + D + O have been shown to improve patient outcomes by:

- Increasing the time a patient does not experience worsening of their disease.
- Increasing overall survival of patients.
- Increasing the number of patients who respond to treatment for endometrial cancer.
- Increasing the amount of time that patients are responding to treatment.[47,48]

Adding durvalumab and/or olaparib to SoC also did not reduce patient quality of life.. There was also a low incidence of unexpected side effects experienced by patients as a result of combining these treatments. Overall, this provides evidence for the benefit of these treatments for patients with advanced or recurrent endometrial cancer.

Patients with dMMR advanced or recurrent endometrial cancer will benefit from a new treatment option

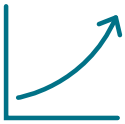
Some patients with dMMR endometrial cancer may receive dostarlimab with carboplatin + paclitaxel as first-line treatment through the CDF. However, this treatment does not represent the current standard of care, and is only available on a temporary basis pending re-appraisal. Patients with newly diagnosed advanced or recurrent endometrial cancer that is dMMR would therefore benefit from a new and effective treatment that could expand the range of treatment options.

Patients diagnosed with pMMR advanced or recurrent endometrial cancer will benefit from the treatment option of SoC + D + O

There are a larger number of patients diagnosed with pMMR endometrial cancer compared to dMMR endometrial cancer. However, patients with pMMR advanced or recurrent endometrial cancer have even fewer treatment options than those with dMMR cancers as there are no options in the CDF for this population. This is partly due to the fact that pMMR cancers are harder to treat with existing innovative therapies, such as dostarlimab. Patients with newly diagnosed advanced or recurrent endometrial cancer that is dMMR would therefore benefit from an innovative therapy.

The key benefits of SoC + D and SoC + D + O for patients with dMMR or pMMR advanced or recurrent endometrial cancer, respectively, are presented below.

Overall benefits of SoC + D and SoC + D for dMMR and pMMR endometrial cancer, respectively:



Improved efficacy compared to SoC

- SoC + D and SoC + D + O help people with experience longer PFS based on subgroup analysis in the DUO-E trial.
- SoC + D and SoC + D + O improve the length of time that a patient survives compared with SoC.
- SoC + D and SoC + D + O also improved all other measures of efficacy in the DUO-E trial compared with SoC, including ORR and DoR.

Manageable safety profile

- The addition of D and O to SoC only slightly increases the side effects compared with SoC alone.
- The side effects of SoC + D and SoC + D + O are known side effects of each medicine that makes up this regimen.

No negative impact on quality of life

- The benefits of SoC + D and SoC + D + O were not achieved at the cost of quality of life in the DUO-E trial.
- There was no meaningful difference in quality of life between SoC + D and SoC + D + O versus SoC groups in the DUO-E trial.

Other benefits of SoC + D for patients with dMMR endometrial cancer

Expanding the range of innovative options

- People with newly diagnosed advanced or recurrent endometrial cancer have limited treatment options.
- Dostarlimab has recently been recommended in the first-line, but only in the CDF.
- The introduction of SoC + D would therefore expand the available options for these patients.

Other benefits of SoC + D + O for patients with pMMR endometrial cancer

Providing the first targeted therapy regimen in the first-line setting

- People with newly diagnosed advanced or recurrent endometrial cancer that is pMMR have very limited treatment options and are harder to treat with immunotherapy alone.
- There are no first-line treatments available for patients with pMMR advanced or recurrent endometrial cancer other than SoC.
- The introduction of SoC + D + O would therefore provide a much-needed option for these patients.

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

Limited treatment response for some patients

The treatment regimens presented within this submission have been proven to be generally well-tolerated and effective. However, as with all treatments, there is a possibility that these treatment regimens will not work for everyone, and there is a chance that some patients may experience limited disease improvement.

Side effects

As with most cancer treatments, patients may experience side effects while receiving treatment. However, the side effects of SoC + D and SoC + D + O are generally manageable based on the DUO-E trial. A similar number of patients stopped treatment as a result of experiencing side effects across all treatment arms.[48] As mentioned in Section 3h, the increase in side effects as a result of adding D and/or O to SoC is only slight

compared with SoC alone. Therefore, the improved efficacy benefits of SoC + D, and SoC + D + O, are likely to outweigh any negative impact of side effects.

Treatment administration

While durvalumab is given to patients the same way as SoC, durvalumab will need to be given as a maintenance therapy after SoC has stopped. Having to receive treatment for a longer duration of time may result in an additional burden to patients. However, the benefits of maintenance treatment for treating endometrial cancer are likely to outweigh this.

Olaparib is given orally and can be taken at home, which some patients may find more convenient. However, some patients may prefer taking all their treatments in hospital.

3i) 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.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the **health economic model** to perform an analysis, which compares the costs and benefits of the new treatment (SoC + D and SoC + D + O) with the standard of care (carboplatin + paclitaxel) in the relevant patient population(s) (dMMR and pMMR newly diagnosed advanced or recurrent endometrial cancer).

How the model reflects endometrial cancer

The economic model was designed to reflect the key features of endometrial cancer and clinical practice in the UK. To do this, a model structure called a **partition survival model** was chosen, as this tool is commonly used to model cancer treatments. The model was used to predict future survival outcomes of patients with endometrial cancer. The model focusses on two comparisons:

- SoC + D versus SoC in patients with dMMR endometrial cancer, and
- SoC + D + O versus SoC in patients with pMMR endometrial cancer

The economic model includes three health states, with "progression free" being the 'best' health state:

- Progression free: the patient's disease is responding to the treatment and not actively progressing to more advanced stages
- Progressed: the patient's cancer has worsened
- Death

Modelling how much SoC + D and SoC + D + O improves clinical outcomes

The results of the DUO-E trial were used to inform the economic model. The main results from the trials that were used in the model were PFS and OS. These were the main results used in the model because they was considered relevant to what would be considered successful outcomes when treating endometrial cancer in clinical practice. Additional outcomes such as response and duration of response were not explicitly included in the model.

The results from the most recent data cut-off of the DUO-E trial were used to inform the model. However, the economic model simulates patients for the rest of their lifetime, a much longer period of time than the length of the trial. Therefore, the model uses extrapolations of the DUO-E trial data to predict long-term outcomes for patients, including OS, PFS and treatment discontinuation.

Modelling how much SoC + D and SoC + D + O improves quality of life

Quality of life data in the model was based on EQ-5D-5L data observed in the DUO-E trial within the overall study population (**Section 3f**). The DUO-E trial data from the overall population represented the best quality of life evidence to inform the model given it was collected in a larger population of patients than the dMMR and pMMR subgroups. Importantly, clinicians indicated that they would not expect quality of life data to differ according to MMR status. These data are also most likely to reflect the quality of life impact of these treatments in clinical practice, given they were specifically collected from patients receiving treatment with SoC + D and SoC + D + O.

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model to account for the differences between the costs of the different treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment
- The cost of subsequent treatment(s), including end-of-life treatments

Uncertainty

Although the most recent data from the DUO-E trial was used in the model, there is uncertainty in how long people would remain alive for each treatment. This is because data are only available for a certain duration of follow-up and therefore predictions need to be used to inform decision-making.

Variations in long-term assumptions in the model were tested and the results of these tests are explained in **Document B, Section B.3.11.**

Benefits of not captured in the economic analysis

Treatment with SoC + D and SoC + D + O may have many different positive impacts for people with dMMR and pMMR endometrial cancer, respectively. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example:

- By delaying or prevention disease progression, SoC + D and SoC + D + O may allow patients to continue with their daily activities for longer and maintain their daily routine.
- SoC + D and SoC + D + O would address an important unmet need for innovative and tolerable therapies that delay disease progression in the first-line setting when patients are able to tolerate these treatments.

Conclusions

This section provides an overview of the modelling performed by the Company. However, the Company's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions that are different from the assumptions that the company used in their model. In addition, some comparator treatments may have confidential discounts that the Company do not have access to.

Given this, the Company have not presented any specific cost-effectiveness results in this summary, but it should be noted that the final cost-effectiveness results for this submission will be discussed in the Committee meeting and will be available on the NICE website once a final decision is made.

3j) 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)

SoC + D is an innovative treatment for patients with dMMR advanced or recurrent endometrial cancer

Durvalumab is an innovative treatment that acts by targeting a key element in the development and growth of dMMR tumours. If SoC + D was recommended, it would expand the range of treatment options that are currently available for these patients. Overall, this would be expected to allow more patients to benefit from effective first-line treatment, resulting in better prognoses for these patients at diagnosis.

SoC + D + O would represent an important advancement in the treatment of pMMR advanced or recurrent endometrial cancer

The majority of patients diagnosed with newly diagnosed advanced or recurrent endometrial cancer have pMMR cancer. However, there have been no advances in the first-line treatment of pMMR advanced or recurrent endometrial cancer since 2020.[37]

SoC + D + O is the first regimen to combine multiple targeted therapies in the first-line setting. Olaparib and durvalumab are two innovative therapies that target different aspects of cancer cell survival, leading to greater destruction of cancer cells. SoC + D + O is particularly beneficial for patients with endometrial cancer that is pMMR, as these patients are harder to treat.

If recommended, SoC + D + O would be the first regimen recommended by NICE that combines a PARP inhibitor and immunotherapy for this patient population in the first-line setting. This would represent a significant treatment advancement, potentially providing these patients with a more hopeful outlook.

3k) 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

Based on recent UK data, there are differences in the number of people diagnosed with womb cancer in different ethnic groups. Compared to the White ethnic group, there are higher rates of womb cancer in the Black ethnic group, lower in people of mixed or multiple ethnicities, and similar in the Asian ethnic group. People belonging to the Black ethnic group also face higher death rates than in other ethnic groups.[50]

Making innovative therapies available for advanced disease may help address these inequalities in survival outcomes across different ethnicities.

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.

Further information on endometrial cancer:

- A UK based charity dedicated to providing healthcare, information, and financial support to those affected by cancer. MacMillan Cancer Support.
- A UK based charity organisation dedicated to endometrial cancer research and awareness. The Eve Appeal – Womb Cancer.
- A UK based charity organisation dedicated to endometrial cancer research and awareness. Peaches Womb Cancer Trust.
- Cancer Research UK's information and guidance relating to endometrial cancer. Cancer Research UK – Womb Cancer.
- NHS information and guidance relating to endometrial cancer. Womb Cancer.
- A clinical knowledge summary provided by NICE. NICE CKS -Gynaecological cancers – recognition and referral.

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Aggressive (cancer)	Describes a cancer or disease that forms, grows, or spreads quickly.
Aggressive (treatment)	An aggressive treatment is one that is more severe or intense than usual.
Arthralgia	Pain or stiffness in the joints, such as knees, elbows, or fingers.
Bias	In a scientific research study or clinical trial, a flaw in the study design or the method of collecting or interpreting information. Biases can lead to incorrect conclusions about what the study or clinical trial showed.
Biopsy	A small sample of tissue taken from the body and examined under a microscope to check whether disease is present.
Cancer Drugs Fund (CDF)	A program that funds cancer medicines in England. When a treatment is recommended for use in the CDF, this means that the medicine shows promising results in trials. But there isn't enough evidence to recommend it at the moment. There is then more time to collect evidence about how well it works. After a period of up to 2 years in the CDF, the medicine is reconsidered and a final decision is made whether to recommend it or not. The aim of the CDF is to give doctors quicker access to new treatments for their patients.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening,

	prevention, diagnosis or treatment of a disease. Also called a clinical study.
Cycles	Many cancer treatments are given in cycles. Each cycle is often divided into a period where a patient receives a treatment, followed by a period of rest from treatment to allow their body to recover from any side effects. The length of each cycle and the split between treatment and rest periods depend on the type of cancer a patient has, where it is in the body, if it has spread and where to.
Deficient mismatch repair (dMMR)	Describes cells that have mutations (changes) in certain genes that are involved in correcting mistakes made when DNA is copied in a cell. Mismatch repair (MMR) deficient cells usually have many DNA mutations, which may lead to cancer. Knowing if a tumour is MMR deficient may help plan treatment or predict how well the tumour will respond to treatment. Also called deficient DNA mismatch repair, dMMR, mismatch repair deficiency, and MMR deficiency..
Deoxyribonucleic Acid (DNA)	Genetic material in cells that provide instructions for making proteins.
Dostarlimab	A drug used alone or with other drugs to treat certain adults with endometrial cancer or other solid tumours that have come back or are advanced and have certain mutations (changes) in genes involved in DNA repair. It is also being studied in the treatment of other types of cancer. Dostarlimab binds to a protein called PD-1, which is found on T cells. Dostarlimab may block PD-1 and help the immune system kill cancer cells. It is a type of monoclonal antibody and a type of immune checkpoint inhibitor. Also called Jemperli®.
Double-blind study	A type of clinical trial where neither the patient nor the doctor knows who is getting the real

	treatment and who is getting a placebo, to reduce bias.
Duration of response (DoR)	The length of time a treatment continues to work and control the disease.
Early-stage	A term used to describe cancer that is early in its growth, and may not have spread to other parts of the body. In endometrial cancer, early-stage cancer refers to cancer that has not spread beyond the uterus.
Efficacy	The ability of a medicine to produce a desired positive effect on a disease or illness in a clinical trial.
Endometrium	The lining inside the uterus that thickens during the menstrual cycle and sheds if there is no pregnancy.
EORTC-QLQ-EN24	A questionnaire used to assess the quality of life specifically in cancer patients with endometrial cancer. This questionnaire asked patients questions pertaining to sexual activity, pain in the lower back or pelvis, urological symptoms, and gastrointestinal symptoms.
EORTC-QLQ-C30	A general questionnaire used to measure quality of life in cancer patients, used in the DUO-E trial to measure patient health status.
EQ-5D-5L	A standard questionnaire that measures patient overall health and quality of life.
First-line	The initial or primary treatment given for a disease.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial

Histology	The study of tissues under the microscope to look for disease.
Hormone therapy	Treatment that adds, blocks, or removes hormones to slow or stop the growth of certain cancers.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immunohistochemistry	A laboratory test that uses antibodies to check for specific proteins in a tissue sample.
Immunotherapy	A treatment that help the immune system fight diseases like cancer.
Intravenous infusion	Medicine or fluids given directly into a patient's vein through a needle or tube.
Lenvatinib	A drug used alone or with other drugs to treat certain types of endometrial cancer, as well as other cancers. Lenvatinib blocks certain proteins, which may help keep cancer cells from growing and may kill them. It may also prevent the growth of new blood vessels that tumours need to grow. Lenvatinib also called Lenvatinib mesylate or Lenvima®.
Lynch Syndrome	An inherited disorder that increases the risk of developing endometrial cancer and many other types of cancer, often before age 50. Lynch syndrome is caused by mutations (changes) in genes that affect mismatch repair. These genes are MLH1, MSH2, MSH6, PMS2, and EPCAM. Also called hereditary nonpolyposis colorectal cancer and HNPCC.
Maintenance (treatment)	Maintenance treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may

	include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Median	A statistics term. The middle value in a set of measurements.
Medicines and Healthcare products Regulatory Agency	The regulatory body that evaluates, approves and supervises medicines throughout the UK.
Menopause	The time of life when a woman's ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50. A woman is said to be in menopause when she hasn't had a period for 12 months in a row. Symptoms of menopause include hot flashes, mood swings, night sweats, vaginal dryness, trouble concentrating, and infertility.
Microsatellites	Short, repeated sequences of DNA that can be prone to mutations.
Microsatellite instability	A change that occurs in certain cells (such as cancer cells) where there are changes in microsatellites. Microsatellite instability may be caused by mistakes that don't get corrected when DNA is copied in a cell. It is found most often in colorectal cancer, gastric cancer, and endometrial cancer, but it may also be found in many other types of cancer. Knowing whether a cancer has microsatellite instability may help plan the best treatment. Also called MSI.
Microsatellite instability high (MSI-H)	Describes cancer cells that have a high number of mutations (changes) within microsatellites. Microsatellite instability-high cancer cells often have dMMR. Microsatellite instability is found most often in colorectal cancer, gastric cancer, and endometrial cancer, but it may also be

	found in many other types of cancer. Knowing whether cancer is microsatellite instability-high may help plan the best treatment. Also called MSI-H cancer.
Microsatellite stability (MSS/MSI-low [L])	Stable or minimal changes in DNA, often meaning lower risk or presence of cancer.
Mismatch repair	A system in cells that corrects any mistakes that happen when the genetic code (DNA) is copied. The copying of DNA is a natural process that occurs so that the body's cells have the genetic information that they need to function.
Objective Response Rate (ORR)	The percentage of patients whose cancer shrinks or disappears after treatment.
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works.
PARP inhibitor	A substance that blocks an enzyme in cells called PARP. PARP helps repair DNA when it becomes damaged. In cancer treatment, blocking PARP may help keep cancer cells from repairing their damaged DNA, causing them to die. PARP inhibitors are a type of targeted therapy. Also called poly (ADP-ribose) polymerase inhibitor.
Partitioned survival model	A type of economic model commonly used to map the life of cancer patients. The model predicts the probability of patients staying in pre-specified states of health over a specific time period
Pembrolizumab	A drug that binds to the protein PD-1 to help immune cells kill cancer cells better and is used to treat many different types of cancer. These include cancers that express the protein PD-L1,

	that have certain mutations (changes) in genes involved in DNA repair, or that have a high number of tumour mutations. Pembrolizumab is used alone or with other drugs to treat certain types of cancer. It is a type of monoclonal antibody and a type of immune checkpoint inhibitor. Also called Keytruda®.
Placebo	A treatment that appears real, but that does not treat the disease. It is used in clinical trials to compare treatments to.
Phase 3 (clinical trial)	A study that tests the safety and how well a new treatment works compared with a standard treatment. In most cases, treatments move into phase 3 clinical trials only after they meet the goals of phase 1 and phase 2 clinical trials. Phase 3 clinical trials may include hundreds of people. Also called phase III clinical trial.
Polycystic ovary syndrome (PCOS)	A condition that may cause infertility, enlarged ovaries, menstrual problems, high levels of male hormones, excess hair on the face and body, acne, and obesity. Women with polycystic ovary syndrome have an increased risk of diabetes, high blood pressure, heart disease, and endometrial cancer.
Prognosis	The likely outcome or course of a disease; the chance of recovery or recurrence.
Newly diagnosed advanced	‘Advanced’ is used to describe cancer that is unlikely to be cured or controlled with treatment. In the case of endometrial cancer, the cancer may have spread beyond the uterus to other parts of the body. Newly diagnosed advanced refers to cancer that has not previously been treated.
Proficient mismatch repair (pMMR)	Describes cells that do not have mutations (changes) in certain genes that are involved in correcting mistakes made when DNA is copied in a cell. Mismatch repair (MMR) proficient cells

	usually have few DNA mutations. Knowing if a tumour is MMR proficient may help plan treatment or predict how well the tumour will respond to treatment. Also called proficient DNA mismatch repair, pMMR, mismatch repair proficiency, and MMR proficiency.
Progression-free survival (PFS)	The length of time during and after the treatment that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Recurrent	Cancer or disease that has returned after a period of remission.
Remission	A period during which the signs and symptoms of cancer are reduced or have disappeared.
Safety profile	Information about the side effects and risks associated with a treatment.
Second-line	The next treatment given when the initial treatment doesn't work or stops working.
Side effects	Unwanted effects of a drug or treatment.
Stage	The extent of a cancer in the body. Staging is usually based on the size of the tumour, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body.

Standard of care (SoC)	The usual and accepted treatment for a particular disease. In this submission, standard of care refers to carboplatin + paclitaxel.
Targeted treatment/therapy	A therapy that targets specific genes, proteins, or the tissue environment that contributes to cancer growth and survival.
Uterus	The hollow, pear-shaped organ in a woman's pelvis. The uterus is where a baby develops and grows. Also called womb.

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for newly diagnosed advanced or recurrent endometrial cancer [ID6317]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
DUO-E in EC [ID6317]_CQ Responses_7November24 [REDACTED]	**FINAL**	**Yes**	**Submitted 7th October 2024 (confidentiality marking updated 21/02/2025)**

Section A: Clarification on effectiveness data

DUO-E population

A1. Priority question. Please provide participant flow diagrams for DUO-E (similar to the one provided for the intention-to-treat [ITT] population in the company submission [CS] appendix D2 figure 3) for the:

a) **mismatch repair deficient (dMMR) subgroup;**
b) **mismatch repair proficient (pMMR) subgroup.**

Participant flow diagrams for each MMR subgroup are not available, but the relevant information has instead been provided in tabular format (see Table 1 below). The patient disposition for each MMR subgroup was generally consistent with the ITT population.

It should be noted that similar to the ITT population, the proportion of patients who initiated olaparib/placebo varied according to treatment arm (with the lowest proportion of SoC patients receiving olaparib/placebo, and the highest proportion of SoC + D + O patients receiving olaparib/placebo). However, this effect was particularly pronounced in the dMMR subgroup, where only [redacted] of SoC patients received olaparib/placebo. The effect is likely to be explained by the fact that patients in the SoC arm, as well as those with dMMR disease status, are the most likely group to experience rapid disease progression before the end of the chemotherapy phase (and hence become ineligible for the maintenance phase, when olaparib/placebo would have been initiated).

However, it is worth noting that in the economic model, the proportion of patients who ultimately initiate olaparib in the maintenance phase is only relevant to the pMMR subgroup. As such, only patients in the pMMR population go on to accrue the acquisition costs for olaparib (whereas patients with dMMR EC only receive SoC + D, so the acquisition cost of olaparib is not applied). In the economic model, the company used a value of [redacted] to model the proportion of patients who go on to receive olaparib in the maintenance phase in the pMMR population, which is sourced from Table 1 below (see value for the pMMR population in the SoC + D + O arm, highlighted yellow). The company provides further rationale underpinning the use of this value in the economic model as part of our response to Question B10.

Table 1. Patient disposition by MMR status

	Number (%) of patients							
	dMMR subgroup				pMMR subgroup			
	SoC	SoC + D	SoC +D + O	Total	SoC	SoC + D	SoC + D + O	Total
Patients randomised	[redacted]							
Full analysis set	[redacted]							
Patients who received any treatment[a]	[redacted]							
Patients who received SoC	[redacted]							
Patients who received durvalumab/placebo	[redacted]							
Patients who received olaparib/placebo	[redacted]						[redacted]	
Patients who did not receive any treatment[a]	[redacted]						[redacted]	
Patients ongoing carboplatin or substitute at data cut-off[b]	[redacted]						[redacted]	
Patients who discontinued treatment of carboplatin or substitute[b]	[redacted]							
Patients ongoing paclitaxel or substitute at data cut-off[b]	[redacted]						[redacted]	
Patients who discontinued treatment of paclitaxel or substitute[b]	[redacted]							
Patients ongoing durvalumab/placebo at data cut-off[b]	[redacted]							
Patients who discontinued treatment of durvalumab/placebo[b]	[redacted]							
Patients ongoing olaparib/placebo at data cut-off[b]	[redacted]							
Patients who discontinued treatment of olaparib/placebo[b,c]	[redacted]							

Patients ongoing any treatment at data cut-off[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinued all initiated treatments (carboplatin, paclitaxel, durvalumab/placebo and olaparib/placebo)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients ongoing study at data cut-off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who terminated study[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Any of the following treatments: durvalumab/placebo, olaparib/placebo, carboplatin or substitute, or paclitaxel or substitute. [b] Percentages are calculated from number of patients who received the treatment. [c] Note: Olaparib is to be administered in the maintenance phase only (per the CSP). [d] Represents patients disposition status at time of discontinuation from study. Some patients subsequently had vital status information collected from publicly available resources (where it is possible to do so under applicable local laws) for the purpose of the overall survival analysis, as detailed in the CSP.

A2. Priority question. Please provide a breakdown of the International Federation of Gynecology and Obstetrics (FIGO) stage at baseline for the newly diagnosed patients in each arm of DUO-E for the:

a) **ITT population;**
b) **dMMR subgroup; and**
c) **pMMR subgroup.**

The FIGO stage at baseline for the requested trial arms and populations within the proportion of patients with newly diagnosed disease is outlined in Table 2.

Within the group of patients with newly diagnosed disease, the proportion with FIGO stage III and IV disease is broadly consistent between the MMR subgroups and the ITT population, with the majority of such patients diagnosed with FIGO stage IV disease. In UK clinical practice, a greater proportion of patients are diagnosed with FIGO stage III disease versus FIGO stage IV disease;[1, 2] however, this difference is explained by the inclusion criteria for the DUO-E trial, which specifies that those patients being enrolled with FIGO stage III disease must have "measurable disease per RECIST 1.1 following surgery or diagnostic biopsy" (whereas FIGO stage IV patients were enrolled with or without disease following surgery or biopsy). This eligibility criteria selected for a particularly high-risk group of patients with FIGO stage III EC.

The company suggests that analyses which sub-divide the MMR subgroups according to FIGO stage at baseline are unlikely to aid decision making or reduce uncertainty in this appraisal, and should not become a core focus, particularly in the economic evaluation. This is because:

- The DUO-E trial demonstrated statistically significant and clinically meaningful benefit in the ITT population. Analyses of subgroups-within-subgroups (such as analyses of FIGO stage at baseline within MMR subgroups) are limited by very small sample sizes, as shown in Table 2, and should therefore be interpreted with caution.
- The types of patients enrolled in the DUO-E trial (FIGO stage III with measurable disease, FIGO stage IV, and recurrent disease with poor potential for cure by surgery alone or in combination) are all treated via the same treatment pathway in the UK, as outlined in Section B1.3.4 of the CS. This has been validated with UK clinicians.[3] Furthermore, it is anticipated that such patients would have a similar baseline prognosis, particularly given that the additional eligibility criteria described above were intended to select for a particularly high-risk cohort of advanced EC patients.
- There has been no indication that FIGO stage of disease at diagnosis is a treatment effect modifier in newly diagnosed patients. Within the company submission, forest plots were presented for the ITT for both the SoC + D vs. SoC and the SoC + D + O vs. SoC comparisons (Figures 8 and 9 in the company submission, respectively), and forest plots specifically within the dMMR and pMMR subgroups have also been published at SGO (see Figure 1 below).[4] Although some analyses (particularly within the dMMR group and the FIGO stage III group) have not been possible due to limited sample sizes, none of the presented analyses indicate any meaningful impact of FIGO stage at baseline on treatment effect.
- In TA963, the topic of efficacy in FIGO stage III patients was raised at the committee meeting, as the EAG queried an apparent lack of efficacy for such patients in the RUBY trial. However, the clinical expert at the meeting stated that this was "unexpected, and that it may be a statistical quirk caused by the low number of people in this subgroup".[5] As such, this was not considered an

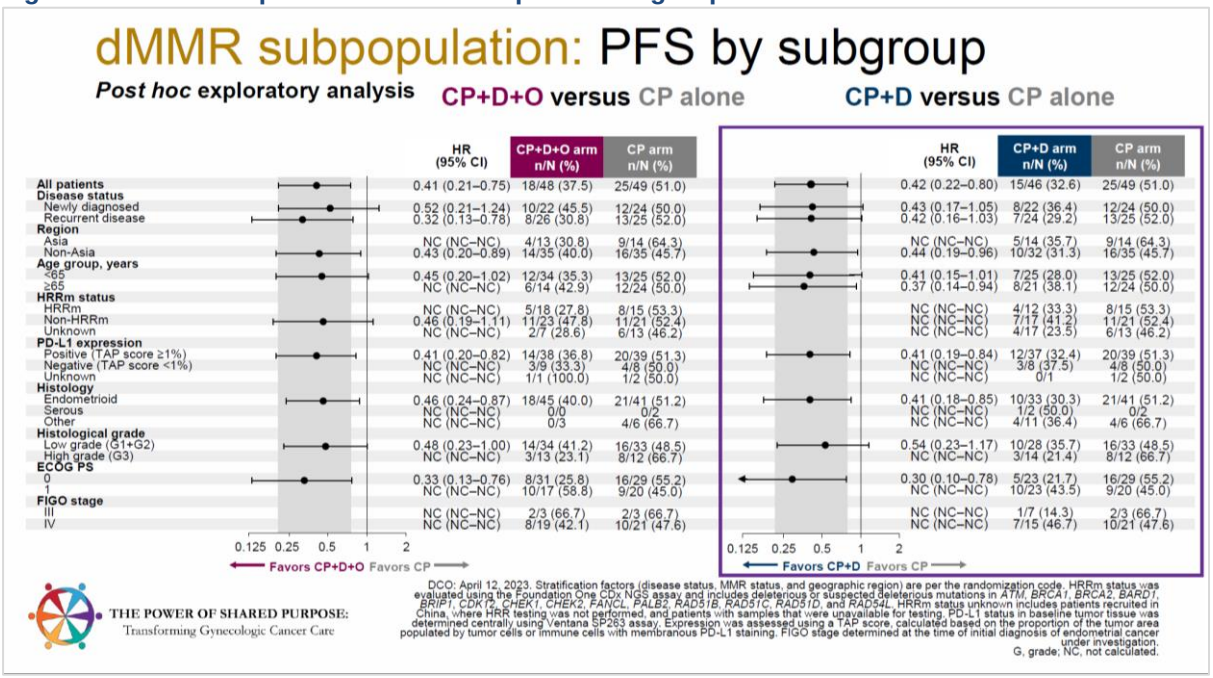
important issue by the committee and was concluded to not need further consideration; the final recommendation covered both FIGO stage III and IV patients. The DUO-E trial faces a similar challenge with low sample sizes in the FIGO stage III group, and any analyses specifically within this group would likely be subject to significant statistical uncertainty.

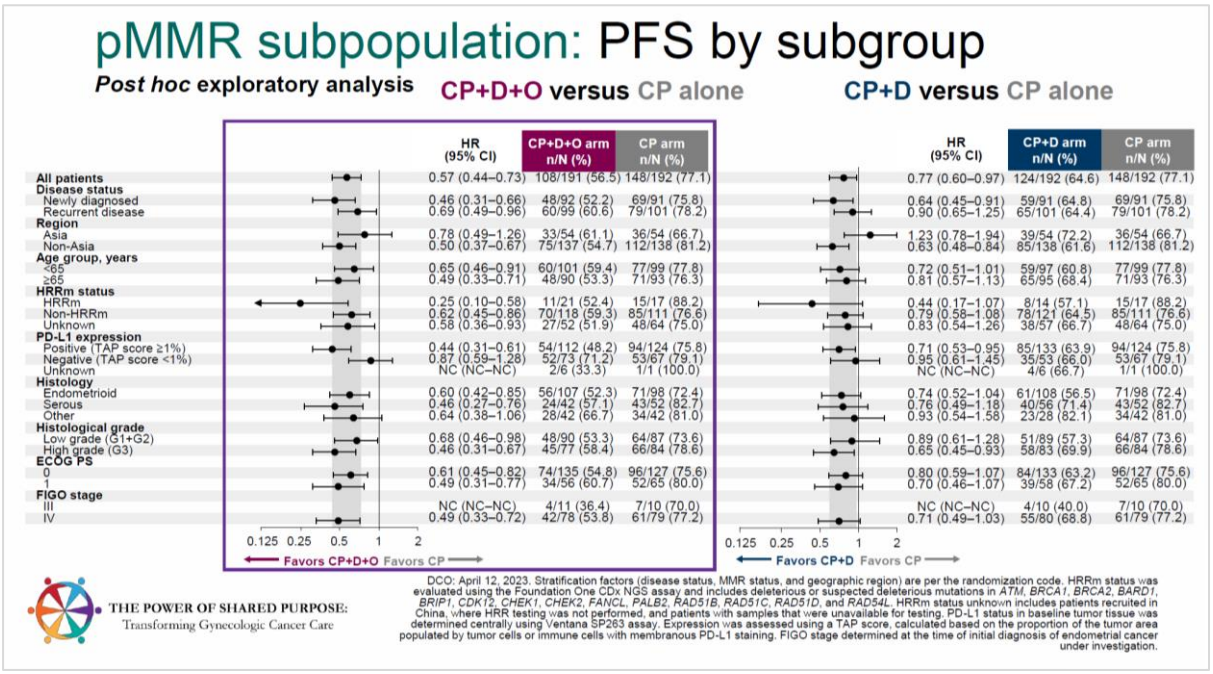
Table 2: FIGO stage at primary diagnosis for newly diagnosed patients (Full analysis set)

	Number (%) of newly diagnosed patients											
	ITT population				dMMR subgroup				pMMR subgroup			
	SoC (N=241)	SoC + D (N=238)	SoC + D + O (N=239)	Total (N=718)	SoC (N=49)	SoC + D (N=46)	SoC + D + O (N=48)	Total (N=143)	SoC (N=192)	SoC + D (N=192)	SoC + D + O (N=191)	Total (N=575)
Newly diagnosed – FIGO stage III	12 (5.0)	17 (7.1)	12 (5.0)	41 (5.7)	3 (6.1)	6 (13.0)	2 (4.2)	11 (7.7)	9 (4.7)	11 (5.7)	10 (5.2)	30 (5.2)
Newly diagnosed – FIGO stage IV	101 (41.9)	96 (40.3)	99 (41.4)	296 (41.2)	21 (42.9)	14 (30.4)	19 (39.6)	54 (37.8)	80 (41.7)	82 (42.7)	80 (41.9)	242 (42.1)
Recurrent	127 (52.7)	125 (52.5)	127 (53.1)	379 (52.8)	25 (51.0)	26 (56.5)	26 (54.2)	77 (53.8)	102 (53.1)	99 (51.6)	101 (52.9)	302 (52.5)

Source: EMA. CHMP assessment report. June 2024.[6]
Footnotes: Percentages are calculated from number of patients who are newly diagnosed.

Figure 1. PFS forest plots for dMMR and pMMR subgroups





A3. Please provide a breakdown of the Eastern Cooperative Oncology Group (ECOG) performance status at baseline for the newly diagnosed and recurrent subgroups in each arm of the ITT population from DUO-E.

The breakdown of ECOG performance status in the newly diagnosed and recurrent subgroups has been provided below in Table 3, and the equivalent data for the ITT population was already provided in Table 7 in the CS. The proportion of patients in each ECOG status group is highly consistent between the newly diagnosed/recurrent subgroups and the ITT population and is also consistent across each arm of the trial.

There was one patient observed in newly diagnosed subgroup in the SoC + D arm who was enrolled with an ECOG status of 2 (which is outside the DUO-E inclusion criteria which specified that patients must have an ECOG status of 0 or 1). This is a known protocol deviation and is captured within the CSR Table 15. Overall, the number of protocol deviations were balanced across treatment arms and were not considered to raise concerns about the conduct of the study, nor relevant for decision making.

The proportions seen in the DUO-E trial also align closely with those seen in other key trials in the first-line advanced and recurrent EC setting (e.g., in the ITT population of RUBY Part 1, 65% of patients were ECOG status 0, while 35% were ECOG status 1). The ECOG status of patients was not considered a key issue for discussion in the TA963 appraisal committee meeting, and therefore would not be expected to represent a significant uncertainty in this appraisal either.[5]

Table 3: ECOG status at baseline in the newly diagnosed and recurrent subgroups (FAS)

	Number (%) of patients							
	Newly diagnosed				Recurrent			
	SoC (N=114)	SoC + D (N=113)	SoC +D + O (N=112)	Total (N=339)	SoC (N=127)	SoC + D (N=125)	SoC + D + O (N=127)	Total (N=379)
(0) Normal activity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(1) Restricted activity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(2) In bed less than or equal to 50% of the time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(3) In bed more than 50% of the time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(4) 100% bedridden	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(5) Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Percentages are calculated from number of patients who are newly diagnosed or recurrent for the summaries for newly diagnosed patients or recurrent patients, respectively.

Outcomes

A4. Priority question. It is noted that the data for overall survival (OS) from DUO-E in the CS are from the first interim analysis using the 12 April 2023 data-cut off. Please clarify when the next OS analysis is expected to be available, and if already available, please provide the results for OS and PFS for the ITT population, pMMR subgroup and dMMR subgroup using the latest data-cut off and update the economic model.

The OS analyses in DUO-E are event-driven; there is therefore uncertainty regarding the date that these will become available. The second interim analysis of OS is expected to be performed when approximately [redacted] OS events ([redacted] of the target number of OS events) have occurred for the comparison of the SoC + D arm versus the SoC arm, as well as the SoC + D + O arm versus SoC. It is currently estimated that this could occur around Q4 2025. As outlined in the company submission, the final OS results would then be anticipated to become available in 2026.

Although the Company believes that the Committee could make a recommendation for routine commissioning from the evidence base provided in the company submission, it is acknowledged that NICE may wish to consider this indication for the Cancer Drugs Fund (CDF), to address any perceived uncertainty in the economic modelling underpinning this appraisal. The company considers that the timing of either the interim or final OS analysis outlined above could facilitate a period of managed access, if deemed appropriate by NICE.

A5. Priority question. Please provide the blinded independent central review (BICR)-assessed progression-free survival (PFS) Kaplan–Meier (KM) plots (including the number of patients at risk, similar to CS document B Figure 4) for each trial arm from DUO-E for the:

a) **dMMR subgroup; and**
b) **pMMR subgroup.**

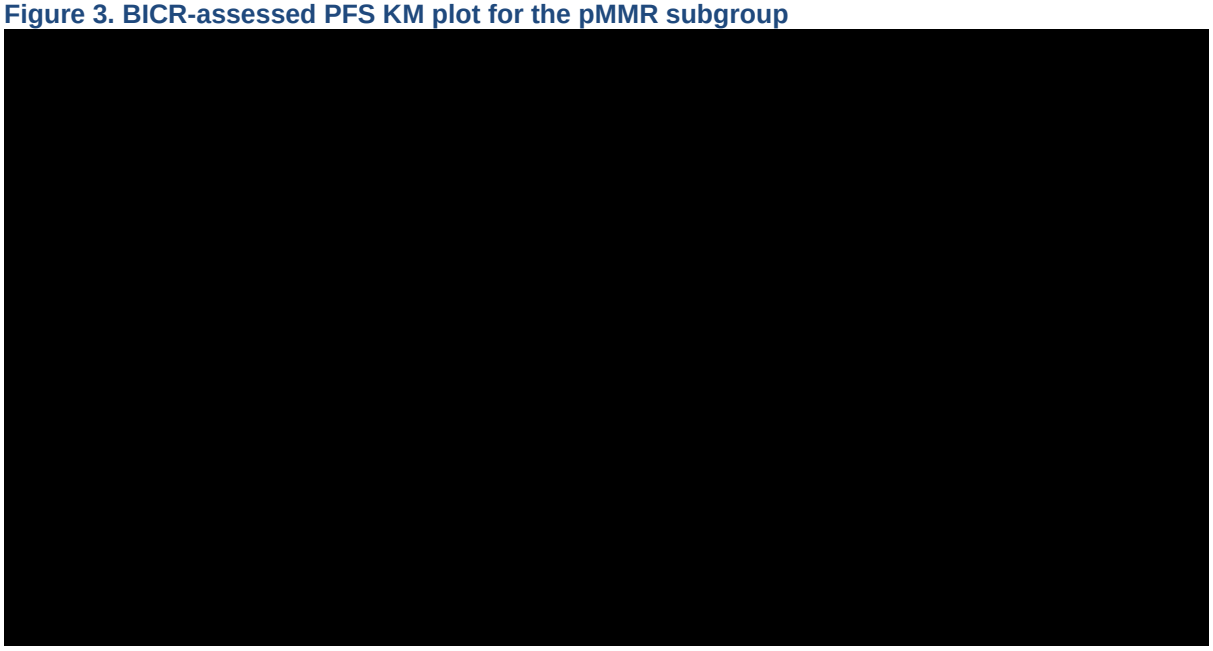
The BICR-assessed PFS KM plots have been provided below in Figure 2 and

Figure 3. As outlined in the company submission, a sensitivity analysis demonstrated that PFS results were consistent based on blinded independent central review (BICR) and Investigator assessment for both comparisons (SoC + D vs. SoC: HR [redacted]; 95% CI [redacted]; SoC + D + O vs. SoC: HR [redacted]; 95% CI [redacted]).

The economic model underpinning this submission uses Investigator-assessed PFS rather than BICR-assessed PFS as Investigator-assessed better represents how progression would be assessed in clinical practice (i.e., by the treating physician), and is aligned to the primary endpoint in the DUO-E trial. Furthermore, given the double-blinded nature of the DUO-E study, the company considers that investigator-assessed PFS should be considered an appropriate endpoint. Given the sensitivity analysis outlined above this would be expected to have a negligible impact on the economic analyses.

Figure 2. BICR-assessed PFS KM plot for the dMMR subgroup

Figure 3. BICR-assessed PFS KM plot for the pMMR subgroup



A6. Please provide the following results from DUO-E for the dMMR and pMMR subgroups:

a) EQ-5D-5L VAS Score at baseline and change from baseline at 90 weeks (similar to the ITT results provided in CS document B table 12);
b) EQ-5D-5L health state index at baseline and change from baseline at 90 weeks (similar to the ITT results provided in CS document B table 12).

The requested EQ-5D-5L data has been provided below in Table 4, alongside the ITT data for comparison (which was already provided in the company submission Table 12). However, it should be noted that this analysis is highly uncertain given the limited sample sizes for each subgroup, and particularly for the dMMR population. Furthermore, UK clinical experts consulted by the company all agreed that MMR status would not be expected to be an independent factor influencing patients' HRQoL.[3] For this reason, the company submission and economic model focussed on HRQoL data and utilities based on the ITT population, as these provide the most robust and reliable estimate of HRQoL in this treatment setting.

Table 4: EQ-5D-5L at DCO1

	ITT			dMMR			pMMR		
	SoC	SoC + D	SoC + D + O	SoC	SoC + D	SoC + D + O	SoC	SoC + D	SoC + D + O
EQ-5D-5L VAS score									
n (Baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (90 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 90 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L health state index									
n (Baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (90 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at 90 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatments

A7. Priority question. Please provide a breakdown of the subsequent treatments received by patients in each arm of DUO-E including the proportion of patients receiving each treatment for the:

a) **ITT population;**
b) **dMMR subgroup; and**
c) **pMMR subgroup.**

The breakdown of subsequent treatments from the DUO-E trial was not provided in the original company submission as they were not considered by UK clinical experts consulted by the company to be at all reflective of UK clinical practice. For this reason, the original company submission focussed on an adapted table of subsequent treatments which was informed by a combination of the DUO-E data as well as clinical expert opinion. This adapted table is what informed the economic model as this was considered more relevant to UK clinical practice.

Nevertheless, for completeness, the subsequent treatments observed in the DUO-E trial itself have now been provided below in Table 5. Given the heterogeneous mix of therapies that were used post-discontinuation, and to facilitate ease of interpretation, Table 5 focusses on overarching treatment classes, and within each class has outlined only those individual therapies which were received by at least 1% of the total (N=718) patients enrolled in the DUO-E trial. The company is happy to provide full tables upon request. It is important to note that, when interpreting Table 5, all percentages are presented as a proportion of the total number of patients in each treatment arm (as opposed to as a proportion of all patients who received a post-discontinuation anti-cancer therapy).

Given that the DUO-E trial was an international trial, the company consulted with five clinical experts who are experienced in treating EC patients in England. The full reports of these interviews was provided in the reference pack of the company submission. The clinicians highlighted a number of key points, including:

- That IO re-challenge is not reimbursed in the UK, and therefore does not constitute current clinical practice (this is also reflected in the Blueteq criteria for the relevant 2L+ therapies which explicitly stipulate that IO rechallenge is not permitted).
- That the total use of IO therapies in the 2L+ setting for patients who had received chemotherapy alone in the 1L setting would be expected to be significantly higher than that seen in the DUO-E trial (~[redacted]% in dMMR patients, and ~[redacted]% in pMMR patients, as a proportion of all patients who received a post-discontinuation anti-cancer therapy).
- That 2L+ carboplatin use would be expected to be higher in the UK compared to what was observed in the DUO-E trial (estimates ~[redacted] of all patients who received a post-discontinuation anti-cancer therapy), while doxorubicin would be lower.
- For some treatments (e.g. radiotherapy) clinicians state that there is little rationale for the use to differ across treatment arms or by MMR status, and that the variation seen in the DUO-E data is likely due to limited sample sizes.

These insights were used to inform the subsequent treatments used in the economic model. The company re-iterates that a robust and methodical approach was used to validate subsequent

treatments with five UK clinical experts, and that it is not appropriate to use the values directly from the DUO-E trial within the economic model, as they do not reflect the realities of UK clinical practice.

Table 5. Post-discontinuation disease-related anticancer therapy (FAS)

	Number (%) of patients receiving post-discontinuation disease-related anticancer therapy											
	ITT population				dMMR subgroup				pMMR subgroup			
	SoC (N=241)	SoC + D (N=238)	SoC + D + O (N=239)	Total (N=718)	SoC (N=49)	SoC + D (N=46)	SoC + D + O (N=48)	Total (N=143)	SoC (N=192)	SoC + D (N=192)	SoC + D + O (N=191)	Total (N=575)
Total number of patients with post-discontinuation anti-cancer therapy	[redacted]											
Immunotherapy												
Pembrolizumab												
Hormonal therapy												
Letrozole												
Megestrol												
Cytotoxic chemotherapy												
Carboplatin												
Cisplatin												
Docetaxel												
Doxorubicin												
Doxorubicin Hydrochloride												
Gemcitabine												
Liposomal Doxorubicin												
Paclitaxel												
Targeted therapy												
Bevacizumab												
Everolimus												

Lenvatinib	[redacted]											
Lenvatinib Mesilate	[redacted]											
Radiotherapy	[redacted]											
Other	[redacted]											

Footnotes: All percentages are presented as a proportion of the total number of patients in each treatment arm (as opposed to as a proportion of all patients who received a post-discontinuation anti-cancer therapy)

Subgroups

A8. Priority question. Please provide forest plots with accompanying hazard ratios and 95% confidence intervals for PFS for the FIGO stage III and FIGO stage IV subgroups of newly diagnosed patients for the ITT population of DUO-E.

The requested forest plots were already provided within the original company submission (see B.2.7.1, Figures 8 and 9). It is acknowledged that the original versions of these figures in the company submission did not explicitly outline the hazard ratios and 95% confidence intervals. Therefore, updated versions of these figures have also been provided below (see Figure 4 and Figure 5).

As reported within these figures, it is already specified that the FIGO stage forest plots are *within* the newly diagnosed subgroup. The efficacy in the FIGO stage IV patients is consistent with the full trial population (for both the comparison of SoC + D vs. SoC as well as the comparison of SoC + D + O vs. SoC). The analyses for the FIGO stage III patients were not feasible to present due to the limited sample size in this subgroup. However, UK clinical experts consulted by the company did not cite any concerns relating to the efficacy in this group, and stated that they would still consider treating such patients with the DUO-E regimen despite the low number of patients enrolled.[3] Furthermore, the global interaction test did not indicate a quantitative interaction according to FIGO stage. Similarly, the global interaction test did not identify any quantitative interaction test relating to newly diagnosed vs. recurrent disease status, and clinical experts consulted by the company did not cite any concerns relating to the efficacy in this group.

As outlined in the response to question A2, the company suggests that analyses which sub-divide the MMR subgroups according to FIGO stage at baseline, or according to newly diagnosed vs. recurrent disease do not aid decision-making or reduce uncertainty in this appraisal. Therefore, they should not become a core focus, particularly in the economic evaluation.

Figure 4. PFS forest plot by subgroup (SoC + D vs. SoC)

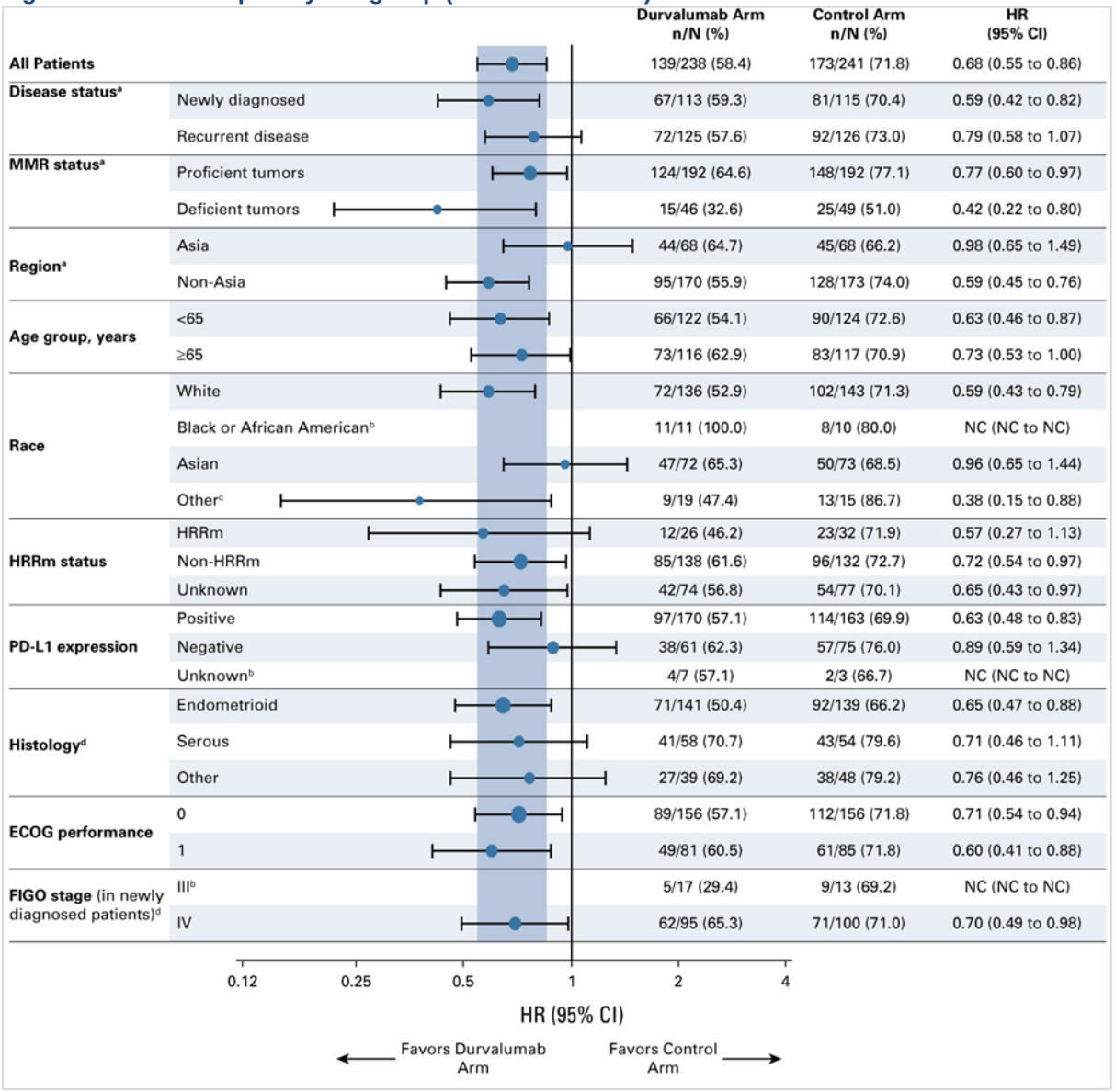
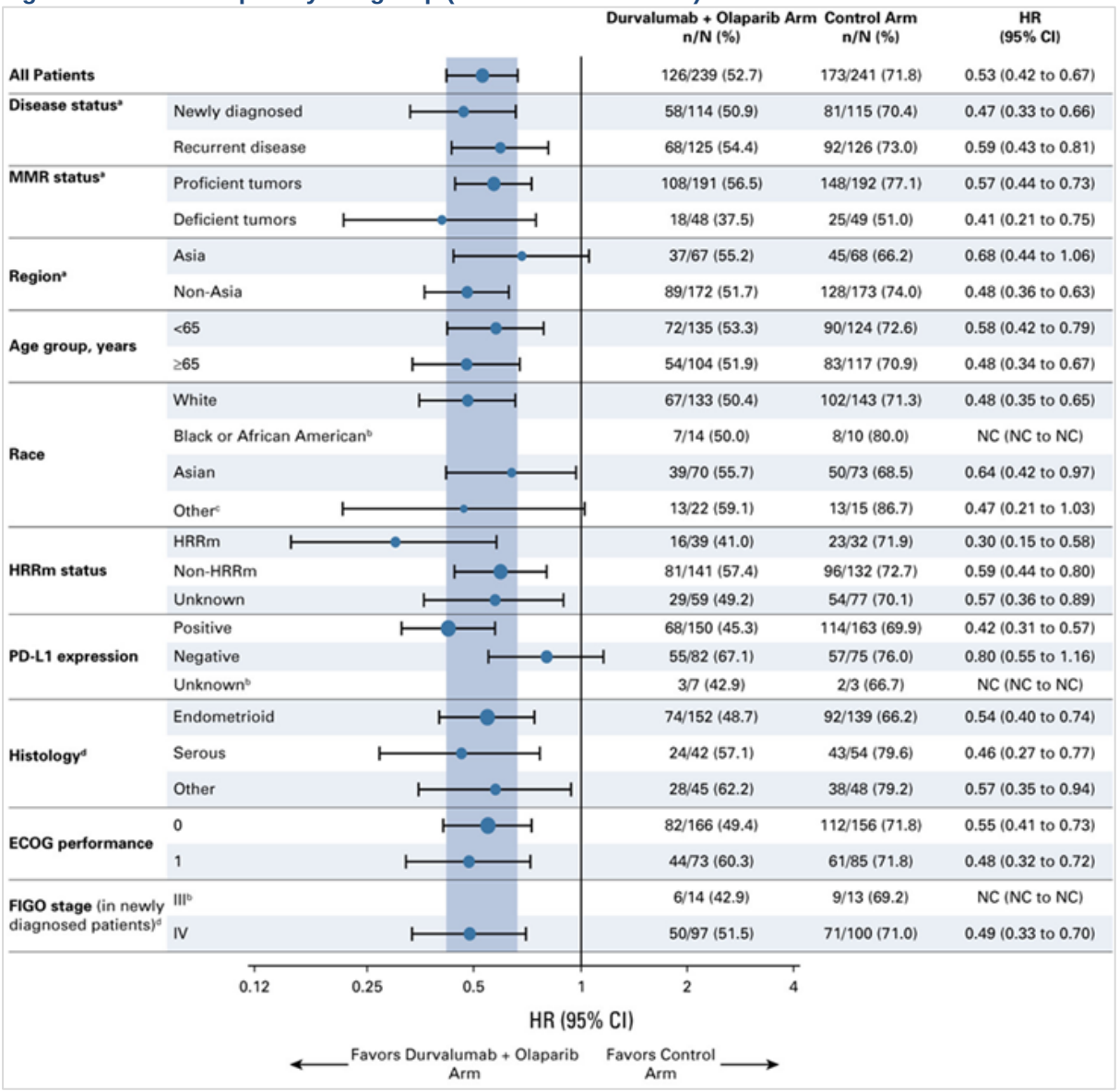


Figure 5. PFS forest plot by subgroup (SoC + D + O vs. SoC)



A9. Please provide forest plots with accompanying hazard ratios and 95% confidence intervals for PFS for each arm of DUO-E for the PD-L1 subgroups in the:

a) dMMR; and
b) pMMR subgroups.

The requested forest plots have been provided above in Figure 4 and Figure 5 as part of our response to question A2, and the equivalent forest plots within the ITT population were already provided as part of the company submission.

It should be highlighted that the analyses within the MMR subgroups are consistent with the trends seen in the ITT population, whereby the PD-L1 positive has a slightly more favourable hazard ratio, as well as narrower confidence intervals when compared to the PD-L1 negative group. The broader confidence intervals are likely to be a result of the smaller sample sizes in the PD-L1 negative group. However, there remains uncertainty about the extent to which the difference in hazard ratios according to PD-L1 status reflect a meaningful biological impact on treatment effect.

As outlined in the company submission, PD-L1 status has not yet been demonstrated to be a strong driver or predictor of response to currently available treatments in EC. Results from different studies investigating immunotherapies in the first-line advanced or recurrent EC (including NRG-GY018, RUBY II, and DUO-E) demonstrate conflicting results by PD-L1 status and used different methods to capture PD-L1 expression. For example, data from the NRG-GY018 study which was presented at SGO 2024 showed an improved hazard ratio in the PD-L1 negative/pMMR group (HR 0.59, 95% CI 0.43–0.80) in patients with pMMR combined positive score (CPS) ≥1 vs. HR 0.44, 95% CI 0.26–0.75 in those with pMMR CPS <1, and consistent hazard ratios for the dMMR patients irrespective of PD-L1 status (HR 0.27, 95% CI 0.16–0.47 in patients with dMMR CPS ≥1 vs. HR 0.30, 95% CI 0.11–0.83 in those with dMMR CPS<1).[7] On the other hand, data from the RUBY part II trial (which was also presented at SGO 2024) demonstrated an impact of PD-L1 status that was more similar to the trends observed in the DUO-E trial (HR in the ITT population for PD-L1 negative patients was 0.67, 95% CI 0.40–1.12 vs. 0.56, 95% CI 0.37–0.83 in the PD-L1 positive population).[8]

Given the inconsistency in these results, the biological mechanisms behind them require further exploration before they are used to inform clinical practice. Multiple hypotheses need to be evaluated, including whether other biomarkers that co-exist with PD-L1 may be confounding the observed results in each trial. Furthermore, the impact of different PD-L1 scoring systems and thresholds must be established given the variability in approaches used across recent trials in EC.

Until a robust clinical understanding is established regarding the role of PD-L1 status in EC and its impact on response to immunotherapies, the company suggest that analyses which sub-divide the MMR subgroups according to PD-L1 status are unlikely to aid decision-making or reduce uncertainty in this appraisal. Such analyses would also be subject to significant uncertainty due to the very small sample sizes associated with such subgroups-within-subgroups.

Furthermore, it is worth re-iterating that the DUO-E trial demonstrated statistically significant benefits in the ITT population, and clinically meaningful benefits in both MMR subgroups. There is no reason that the prevalence of PD-L1 status seen in the DUO-E trial would differ to that seen in UK clinical practice, and therefore the impact of PD-L1 status on efficacy would already be implicit in the cost-effectiveness analyses presented for each MMR subgroup.

Adverse events

A10. Priority question. Please clarify if the adverse events from the full analysis set (FAS) or the safety analysis set (SAS) have been used in the economic model (company submission, Table 60), and if the FAS has been used please justify this decision.

The company have reviewed Table 60 of the company submission and can confirm that it is mis-labelled. The data from this table (which was also used in the economic model) was sourced from the safety analysis set (SAS) rather than the full analysis set (FAS). However, given that the FAS included 718 patients and the SAS included 709 patients, it is not anticipated that the choice of analysis set to inform the adverse events would have any meaningful impact on the cost effectiveness analyses.

A11. Priority question. Please clarify why the percentages of adverse events for hypertension and pulmonary embolism in the SoC + D and SoC + D + O arms of company submission Table 60 differ from the percentages reported in Table 48 of the clinical study report for DUO-E and provide a table with the number of patients with each adverse event (n, N).

The company have reviewed Table 60 of the company submission and have identified that the rows for hypertension and pulmonary embolism contain typos in the percentages of adverse events. A corrected version has been provided below in Table 6 (with updated values highlighted in yellow), and the economic model has been updated accordingly. The impact on the cost-effectiveness estimates is negligible.

Table 6: Percentage of patients experiencing grade ≥3 AE by treatment arm (sourced from the SAS set of DUO-E)

AE	SoC + D (N = 235)	SoC + D + O (N = 238)	SoC (N = 236)
Anaemia	15.7%	23.50%	14.4%
Neutropenia	8.5%	11.3%	5.9%
Neutrophil Count Decreased	11.5%	13.4%	15.3%
Lymphocyte Count Decreased	2.1%	1.3%	2.1%
White Cell Count Decreased	3.8%	4.2%	4.7%
Hypertension	2.1%	2.5%	3.0%
Pulmonary Embolism	1.7%	2.1%	1.3%
Hypokalaemia	2.6%	2.9%	0.8%

Biomarkers

A12. The EAG is aware that NICE has approved olaparib for the maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA962) and after 2 or more courses of platinum-based chemotherapy (TA908). Please can the company provide a clinical rationale for why BRCA mutation status is not a consideration for the maintenance treatment with durvalumab and olaparib in the current submission for newly diagnosed advanced or recurrent endometrial cancer?

Although olaparib has been approved in BRCA mutation positive indications in some ovarian cancer indications (TA962 based on data from the SOLO-1 trial, and TA908 based on the SOLO-2 trial), it should be noted that it has also been approved in other indications outside of patients with BRCA mutations, such as:

- TA946 (based on data from the PAOLA-1 trial): high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose cancer is homologous recombination deficiency (HRD) positive (a broader biomarker group which includes BRCA mutations as well as other causes of genomic instability)
- TA951 (based on data from the PROpel trial): untreated hormone-relapsed metastatic prostate cancer in adults who cannot have or do not want chemotherapy (no biomarker restriction)

Kim DS *et al.* (2021) provide an overview of how the understanding of the mechanism of action of PARP inhibitors has evolved over time, and why there is growing acceptance of the therapeutic value of such treatments in broader patient populations beyond BRCA-mutated (BRCAm) cancers.[9] It is highlighted that although early research and development efforts for PARPi focussed on the genetic concept of synthetic lethality (which was particularly tested in tumours with HRD deficiency and/or BRCA mutations), there is now a growing understanding that PARPi may have much broader roles including the regulation of chromatin structure, gene expression, RNA processing, ribosome biogenesis, and translation in cancer (supported by several pre-clinical and clinical studies).

In the DUO-E regimen, as outlined in the company submission, the effect of olaparib is related to immune priming. Through inhibition of PARP, olaparib induces DNA damage, which can result in tumour cell death and enhanced immune priming via activation of proinflammatory signalling. This can promote a more robust anti-tumour response than durvalumab alone, particularly in pMMR tumours which are heterogenous with scarce immune cell infiltration.

As well as considering the evolving understanding of the mechanism of action of PARP inhibitors, it is also worth reflecting on the fact that ovarian and ECs are distinct tumour types, with different risk factors and drivers of disease. Although the role of BRCAm has long been established in ovarian cancer, this is not the case for EC; a recent systematic review and meta-analysis by Zakerinasab F *et al.* discusses the contradictory results of multiple studies in patient with EC, and the uncertainty as to the extent to which BRCAm impacts an individual's risk of developing the disease.[10] BRCAm has also not been established as a prognostic biomarker in this setting. As a result, patients were randomised in DUO-E based on MMR status but irrespective of BRCAm status.

Within the DUO-E trial specifically, it should be re-iterated that a statistically significant and clinically meaningful PFS benefit was observed in the ITT population. However, an exploratory post hoc analysis was conducted to explore the PFS by BRCAm status; this analysis was presented at ASCO

2024.[11] The results of this analysis are presented below in Figure 6. This descriptive analysis should be interpreted with caution given the limited sample sizes.

The analysis shows that within the DUO-E trial there was a low prevalence of BRCAm overall (dMMR: 12.6% BRCAm, 61.5% non-BRCAm, 25.9% unknown; pMMR: 4.0% BRCAm, 65.9% non-BRCAm, 30.1% unknown). The slightly higher proportions of BRCAm patients in the dMMR subgroup compared to the pMMR subgroup is expected based on published literature linking MMR deficiency and hypermutation.[12] The focus of the EAG question is presumably on the pMMR subgroup, where we anticipate marketing approval for the SoC + D + O regimen. Importantly, the PFS results for the SoC + D + O vs. SoC in pMMR non-BRCAm patients (HR 0.57, 95% CI 0.42–0.78) were consistent with the overall pMMR subgroup (HR 0.57, 95% CI 0.44–0.73).

Given this clinical rationale, and the results of the post hoc analysis presented at ASCO, it is not anticipated that BRCAm status would inform treatment decisions for the use of the SoC + D + O regimen; as such, the company suggest that this should not be a focus of this appraisal.

Figure 6: Post-hoc analysis of PFS in the DUO-E trial according to BRCAm status

		ITT			BRCAm			Non-BRCAm			Unknown		
PFS		CP	CP+D	CP+D+O	CP	CP+D	CP+D+O	CP	CP+D	CP+D+O	CP	CP+D	CP+D+O
ITT	Events, n/N (%)	173/241 (72)	139/238 (58)	126/239 (53)	12/15 (80)	5/11 (45)	6/15 (40)	107/149 (72)	92/153 (60)	91/165 (55)	54/77 (70)	42/74 (57)	29/59 (49)
	Median, months	9.6	10.2	15.1	9.8	9.7	NR	9.7	11.3	15.1	9.5	9.9	12.4
	HR (95% CI) vs CP*		0.71 (0.57–0.89)	0.55 (0.43–0.69)		NC	NC		0.72 (0.54–0.95)	0.56 (0.42–0.74)		0.65 (0.43–0.97)	0.57 (0.36–0.89)
	P value		*P*=0.003	*P*<0.0001									
pMMR	Events, n/N (%)	148/192 (77)	124/192 (65)	108/191 (57)	8/10 (80)	2/6 (33)	4/7 (57)	92/118 (78)	84/129 (65)	77/132 (58)	48/64 (75)	38/57 (67)	27/52 (52)
	Median, months	9.7	9.9	15.0	9.9	NR	15.2	9.7	9.9	15.0	9.5	9.7	12.3
	HR (95% CI) vs CP*		0.77 (0.60–0.97)	0.57 (0.44–0.73)		NC	NC		0.77 (0.57–1.04)	0.57 (0.42–0.78)		0.83 (0.54–1.26)	0.58 (0.36–0.93)

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("Settings" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Progression-free survival

B1. Please explain why spline odds models were not explored for the mismatch repair deficient (dMMR) progression-free survival (PFS) extrapolation? If they were explored and not reported in the company submission (CS), please provide those details.

The 'normal' spline models were selected for the extrapolation of PFS in the dMMR population because, beyond the final knot, this model follows a log-normal distribution. This was considered an advantage as the log-normal curve was considered the better fitting parametric model compared to the log-logistic distribution (which the 'odds' spline models uses beyond the last knot) based on AIC and long-term clinical plausibility. Moreover, using the normal spline model for PFS (which follows a log-normal extrapolation beyond the final knot) aligns with log-normal OS extrapolations chosen in the model.

Importantly, landmark survival for 'normal' spline models align more closely to estimates from five UK clinicians consulted as part of this appraisal compared with 'odds' spline models. Specifically, most clinicians agreed that the 'normal' spline models presented (one-knot and two-knot) were the most representative models. The 'normal' spline models also align more closely than the 'odds' spline models with the landmark survival estimates presented by the clinical expert consulted as part of TA963. In light of this, and the aforementioned considerations for the extrapolations beyond the final knot, the 'odds' spline model was considered inappropriate for decision-making and not considered further.

B2. Priority question: In Section B.3.3.3.2 (page 109 of the CS), it states that spline models were explored for PFS for the mismatch repair proficient (pMMR) subgroup but details of this are not provided. In Figure 24, there appears to be a change in the hazard for standard of care (SoC) at around month 6, which spline models may be better able to capture and extrapolate

more appropriately than standard parametric models (all models explored appear to underpredict the observed PFS data from months 6 to 8).

a) **As such, please provide details of the spline models explored.**
b) **Please include the spline models in the economic model and provide scenario analyses for the best-fitting curve.**

To respond to this question, the company will first explore the clinical rationale for the change in hazards at 6 months, and will then move on to explore the broader rationale for preferring standard parametric models over spline models in the pMMR subgroup. Despite a preference for standard parametric models, the company will then present a scenario analysis using spline models for the pMMR subgroup PFS extrapolations.

Clinical rationale for the observed change in hazards at 6 months

The change in the hazard from 6–8 months, as identified by the EAG, is expected to be due to the frequency of tumour imaging (scans), used to identify disease progression. As per the DUO-E protocol, scans occur at 9-week (±1 week) intervals until 18 weeks, and then at 12-week intervals (±1 week) thereafter. Therefore, scans would be expected at approximately 2.1 months, 4.1 months and 6.9 months, and then approximately every 3 months thereafter.

The KM curves for PFS on the pMMR subgroup (provided in Figure 14 of the original company submission) show that recorded progression events are 'clustered' around these approximate times, especially at each 3 month interval following approximately 7 months, giving a 'step-like' visual in the KM curve. The company therefore do not agree that the progression events recorded from 6–8 months in the control arm represents a rapid change in the true underlying hazard of progression.

This interpretation is supported by the empirical hazard functions for PFS in the pMMR population, presented in Figure 7 below. Whilst the hazards for the SoC arm increase after approximately 6 months, the smoothed hazard functions do not suggest a consistent change in the hazards between 6 and 8 months for the SoC arm. Moreover, the raw hazards functions (piecewise exponential) show that, from 6 months onwards, the hazards show a consistent trend of having one high and one low interval, with each interval being approximately 1.5 months. This aligns with the KM curves and scan frequencies described above, and suggests that most patients will receive a scan at ~6.9 months (with progression events recorded in that interval), and patients would then not receive their next scan for approximately 3 months thereafter, resulting in the next 1.5-month interval having few progression events. This further supports the use of the smoothed hazards to estimate the long-term trend in the hazard.

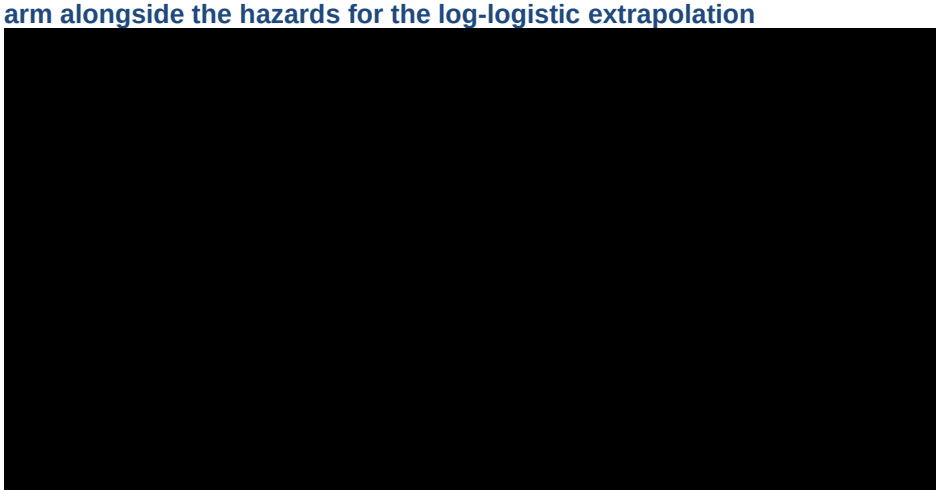
Figure 7. Overlaid raw and smoothed hazards – pMMR PFS

Broader rationale for preferring standard parametric models over spline models in the pMMR subgroup

The survival analysis used to inform survival extrapolation in the original company base case closely followed NICE guidelines TSD14 and included the fitting of a series of standard parametric models to the patient level data. The choice of survival model for the base case was based on goodness-of-fit to trial data and the clinical plausibility of model extrapolations and landmark survival estimates. The best fitting standard models (log-logistic) were judged to provide a reasonable fit to the trial data and to yield plausible long-term extrapolations.

Flexible survival models, including cubic spline models, were explored as part of model development, recognising that they can provide an improved fit to complex hazard shapes when compared with standard models. In both arms of DUO-E, the shape of the empirical smoothed hazard for PFS had followed a relatively simple pattern (as observed in Figure 8). As noted in TSD21, standard models such as log-logistic, log-normal and generalised gamma can represent hazards that “initially increase and then decrease (i.e. with one turning point)”. To avoid overfitting to the trial data, standard models were therefore preferred to cubic splines in the base case. This choice is further supported by the fact that the selected parametric extrapolation for the SoC curve closely aligns to the empirical smoothed hazard function observed in the trial, as demonstrated in the Figure 8 below.

Figure 8. Overlayed empirical smoothed hazard function observed in the DUO-E pMMR SoC arm alongside the hazards for the log-logistic extrapolation



Given the clinical rationale for the change in hazards from 6 months, as well as the broader considerations outlined above, the company reiterate that spline models in the pMMR population are not justified for the PFS endpoint.

Scenario analysis exploring the use of pMMR spline models for PFS

Despite the above rationale outlining the company rationale for preferring the use of standard parametric models in this subgroup, the company have provided the best fitting spline model for PFS in the pMMR population for transparency. Since the base case extrapolation follows the log-logistic extrapolation, spline odds were considered. As per the smoothed hazard plots below (see Figure 9), there was clear overfitting in both arms for 4 and 5 knot splines. These were also the worst fitting according to AIC (see Table 7 below) and were therefore not considered further.

Figure 9. Predicted hazards of presented spline models for PFS in the pMMR subgroup

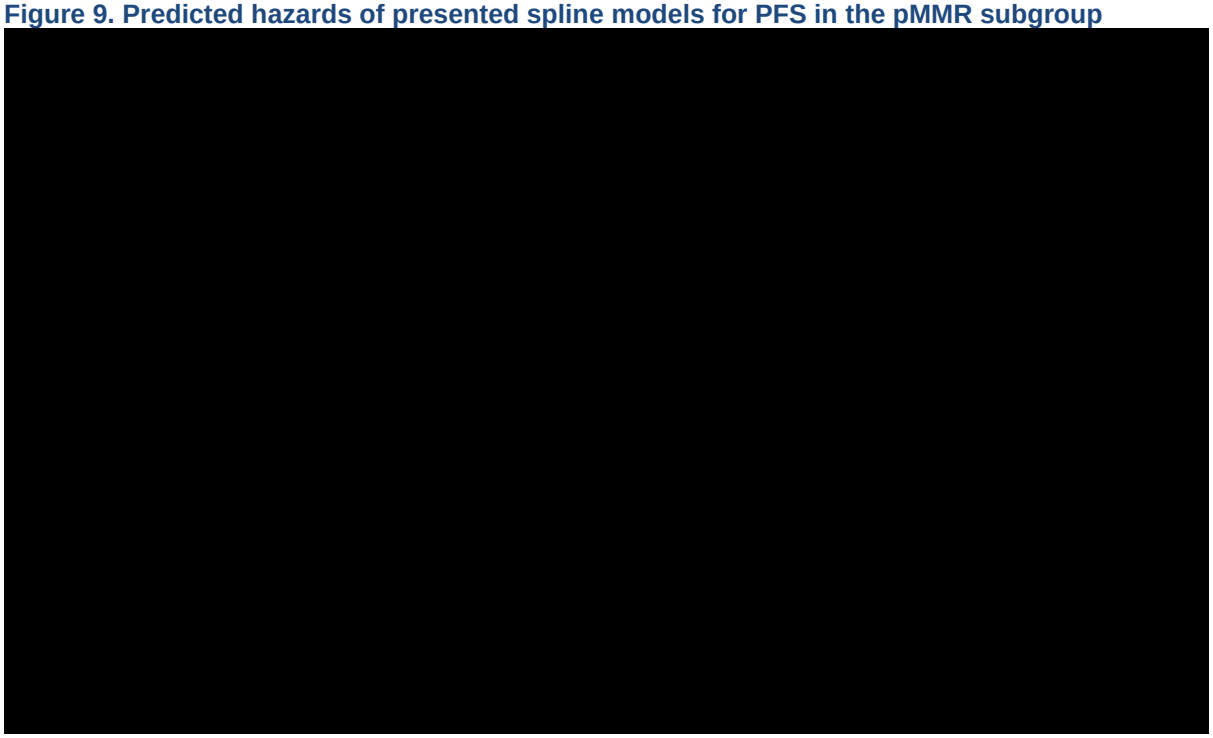


Table 7. AIC and BIC of presented spline models for PFS in the pMMR subgroup

Model	AIC (rank)		BIC (rank)	
	SoC	SoC + Durvalumab + Olaparib	SoC	SoC + Durvalumab + Olaparib
Scale=odds (1 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (3 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (4 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (5 knots)	[redacted]	[redacted]	[redacted]	[redacted]

Of the spline models with 1–3 knots, the 2-knot and 3-knot models for SoC provide the best fit to the smoothed hazard function. For SoC + D + O, the 2-knot and 3-knot models provide the best fit to the smoothed hazard towards the tail; however, the 3-knot model may be overfitting. Overall, the 2-knot spline odds model was considered to provide the best fit to the data for both SoC and SoC + D + O.

The 2-knot models were overlaid with the KM curves observed in the DUO-E trial, as well as the standard log-logistic parametric model used in the original company base case (see Figure 10 below). The model fits and extrapolations for the 2-knot spline are similar to those estimated by the log-logistic PFS extrapolation used in the original company base case analysis. This further supports that the spline models provide limited additional benefit above the standard parametric model extrapolations.

Figure 10. Overlay of 2-knot spline, standard parametric models, and DUO-E KM data for the pMMR subgroup PFS data

A scenario was applied in the model using the 2-knot spline odds model PFS survival extrapolations for the SoC and SoC + D + O arms in the pMMR subgroup. As shown in Table 8, this had a negligible impact on the ICERs (the updated base case ICER in the pMMR population is [redacted]/QALY, so the use of splines results in [redacted] ICER impact).

Table 8. Cost-effectiveness results for pMMR population for scenario applying 2-knot spline odds model to PFS extrapolations for SoC and SoC + D + O

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,941.19	4.57	3.27	[redacted]	0.89	0.67	[redacted]

B3. Priority question: In tab "Survival calculations", cells J21 and O21, PFS exceeds overall survival (OS), but the limit in the model is that OS cannot be less than PFS. As such, the PFS proportion for the model cycle is used (PFS is the upper limit). Typically in partitioned survival model (PSM) models, the cap used is that PFS cannot exceed OS, thus in this situation, PFS would be equal to OS (OS is the upper limit).

a) Please justify the approach used in the model?

b) Please provide a scenario where PFS is capped to OS.

A limit was built into the model to ensure that OS curves do not fall below the PFS curve. This was performed to avoid a scenario in which a negative proportion would occupy the progressed disease health state. The model assumes that, if the OS curve is estimated to fall below the PFS curve, the OS curve follows the trajectory of the PFS curve (i.e. OS curve is equal to PFS). This assumption was made due to the possibility for patients to experience a long-term PFS response, which aligns to clinical expectations in this indication; during the clinical validation conducted by the company, it was noted that endometrial cancer related events were rarely seen after 10 years if still 'progression free'.[3]

The company highlight that there is no default structural approach to this assumption (i.e., it is not necessarily typical to use either PFS or OS as the upper limit; rather, the chosen approach should reflect the survival data and the disease prognosis). In this case, it was considered preferable to use PFS as the upper limit (rather than OS as the upper limit), given that the additional maturity of the PFS curve provides more events to accurately estimate the change in the hazard of progression over time and, in particular, captures the plateau in the hazard of progression expected. This approach (OS following the trajectory of PFS) has been accepted in previous NICE appraisals where the risk of progression shows decreasing hazards over time (e.g. cure models), such as TA962.[13]

It should also be noted that, in the model, long-term extrapolations of PFS exceed OS only in the dMMR extrapolations in the SoC + D arm at month 354 (year 29.5) which indicates that capping PFS to OS will have minimal impact on the results in the model.

Despite the above rationale supporting the approach taken in the original company submission, scenario analyses have been presented for the dMMR and pMMR populations in Table 9 and Table 10, respectively, where PFS is capped to OS in the model. These results demonstrate that the approach suggested by the EAG has a minimal impact on the cost-effectiveness results in both subgroups. Both approaches (capping OS to PFS, or capping PFS to OS) allow for the potential of a long-term PFS response. However, as mentioned above, the approach taken in the original company submission is considered more robust, as long-term survival is based on the more mature PFS data (vs. less mature OS data).

Table 9. Cost-effectiveness results for dMMR population for scenario with PFS capped to OS

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.11				
SoC	60,482.43	3.70	2.73	[redacted]	7.64	5.38	[redacted]

Table 10. Cost-effectiveness results for pMMR population for scenario with PFS capped to OS

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,788.03	4.57	3.28	[redacted]	0.89	0.66	[redacted]

Progression events

B4. Priority question: The proportion of newly progressed patients per model cycle in the model is a key driver of costs as a one-off cost of subsequent treatments is applied to those patients. The Evidence Assessment Group (EAG) considers that the company's estimation of newly progressed disease patients, using a constant proportion of 92.2% (non-fatal progression events from DUO-E) does not accurately calculate the proportion of newly progressed patients per cycle.

Additionally, the company's assumption means that in every model cycle there will be newly progressed patients, but in reality, there may be periods of time when the only PFS events are death, especially for patients in long-term remission. As such, costs of subsequent treatments are likely to be overestimated in the model.

a) **For the dMMR subgroup, please explain why, in tab "Trace SoC" cell N17, the proportion of newly progressed is equal to the proportion of**

newly dead patients (0.004) when in cell K17, the proportion occupying the progressed disease (PD) health state is zero?

b) For the pMMR subgroup, please explain why, in tab "Trace SoC" cell N17, the proportion of newly progressed is 0.005 when in cell K17, the proportion occupying the PD health state is zero?

c) Please provide the DUO-E time-to-event data for PFS with disease progression as the only event of interest for SoC and SoC and durvalumab with or without olaparib (SoC + D [+/-O]) for the dMMR and pMMR subgroups separately. Please implement this in the model to estimate newly progressed patients per cycle.

d) If the scenario requested in B4c is not feasible, please explore in a scenario the following calculation in the model to estimate newly progressed patients for all arms of the model.

$$PD_{new} = (OS_t - PFS_{t)}) - (OS_{t-1} - PFS_{t-1}) * (\frac{OS_t}{OS_{t-1}})$$

Across the DUO-E trial, [redacted] of PFS events are recorded at disease progression, whilst the remaining [redacted] were deaths in the absence of progression. Table 11 shows the percentage of PFS events that are non-fatal, at 6-month intervals. Overall, the proportion is high throughout, with a marginally lower proportion of non-fatal progression events ([redacted] in the first 6 months. There is therefore no evidence from the DUO-E trial follow-up to date that supports the EAG hypothesis that the proportion of non-fatal progression events may reduce over time. However, the company acknowledge that there remains uncertainty about how these trends will develop with longer follow up.

Table 11. Proportion of non-fatal PFS events observed over time in the DUO-E study

Time from randomisation (months)	Percentage of PFS events that are non-fatal	Non-fatal progression events/All progression events (cumulative)
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
>18 (total duration of DUO-E follow-up)	[redacted]	[redacted]

Part A and B: The PSM structure does not track individuals in the PD health state, and health state occupancy is simply the difference between the PFS and OS curves. For any given model cycle, it is not possible to identify the proportion of progression events which are (non-fatal) disease progression vs. those which are death events. Attempting to estimate the proportion of progression events that are non-fatal from changes in the PFS and OS curves, as suggested in part D of this question, is not a reliable or accurate method to estimate this (the company address this directly below). Instead, the base case model uses a simple proportion of patients assumed to have a non-fatal progression event and makes a simplifying assumption that this is constant over time.

dMMR: Due to the shape of the parametric survival curves, the first model cycle for dMMR population estimates a PFS higher than OS ([redacted]). As such, OS is set equal to PFS, which results in zero PD health occupancy. Costs are therefore applied based on the simple assumption that a proportion of progression events are non-fatal. We would like to note that (for dMMR population) this is the only cycle in the model (aside from at month 354 for the dMMR extrapolations in the SoC + D arm which has been discussed in the response to question B3) where PFS exceeds OS, and this is for the SoC arm only.

pMMR: The same situation occurs in the pMMR population, as described above in the dMMR population. Again, PFS does not exceed OS in any cycle other than month 1 in the SoC arm.

Overall – across both dMMR and pMMR populations, the issue identified by the EAG is simply a nuance of the first cycle estimated by the parametric survival extrapolations.

Part C: since a low proportion of the progression events in DUO-E were fatal, the time to progression (TTP) curves are likely to closely mirror the PFS curves used in the model. Since a higher proportion of death events occur early in trial period (rather than the opposite trend hypothesised by the EAG), using this approach may lead to TTP extrapolations crossing the PFS curve due to the shape of the extrapolations of the trial data. Whilst structural limits can be placed in the model to avoid this, it would still assume TTP is equal to PFS, in which instance 100% of progression events would be non-fatal.

Since the DUO-E trial provides no evidence to date (given current duration of follow-up) that the proportion of PFS events that are fatal increases over time, the company suggest that any scenario analyses which explore a hypothesised future change in the proportion of fatal/non-fatal progression events (e.g. when patients experience long-term remission) should be interpreted with caution, given that these would be entirely arbitrary (rather than evidence-based).

Despite the lack of data from the DUO-E trial to inform such a scenario analysis, the company have explored the impact of a lower proportion of non-fatal progression events being applied in the model (75% assumed at 60 months, although it is acknowledged that this is not based on specific data from the DUO-E trial). The results for this scenario are presented in Table 12 and Table 13 for the dMMR and pMMR subgroups, respectively.

Table 12. Cost-effectiveness results for the dMMR population for scenario with reduced proportion of non-fatal progression events

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,003.34	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 13. Cost-effectiveness results for the pMMR population for scenario with reduced proportion of non-fatal progression events

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,800.72	4.57	3.27	[redacted]	0.89	0.67	[redacted]

As stated in the response to part A and B, the approach taken in the original submission is reflective of the DUO-E trial and is considered to be an appropriate, evidence-based methodology. However, the scenario conducted above indicates that applying a lower proportion (75% versus 92.2%) of non-fatal progression events at 60 months has a minimal impact on the model results for both populations.

Part D: the equation to calculate the number of non-fatal progression events at each cycle that is suggested by the EAG estimates a negative number of progression events between months 55 and 294 in the base case analysis (dMMR, SoC trace), demonstrating that this is not an appropriate calculation to use.

Moreover, when using this calculation is used for the dMMR population, the model estimates that, across both treatment arms, 36–44% of progression events are deaths at 30 months (similar to the DUO-E trial period follow-up). This is far higher than observed trial data ([redacted] of progression events are deaths). For these reasons, we do not believe it is reasonable to implement the calculation suggested.

Overall survival

B5. Priority question: In TA963, the company's estimate of incremental quality adjusted life years (QALYs) associated with dostarlimab for the dMMR/ high microsatellite instability (MSI-H) population was 4.26 QALYs, although the committee recognised this estimate was uncertain because data from RUBY-1 are immature (36 months follow-up, 56% PFS maturity and 26% OS maturity at the time of the dostarlimab appraisal). Data for the dMMR subgroup from DUO-E are similarly immature with 32 months follow-up at the April 2023 data cut-off, 41% PFS maturity and 22% OS maturity. The company base case estimate of incremental QALYs for durvalumab in the dMMR subgroup is 5.37 QALYs.

While the EAG appreciates that dostarlimab is not a direct comparator in this appraisal, the EAG considers it to be a useful benchmark for committee decision-making due to the same critical issue of immature PFS and OS. Hazard ratios (HRs) from RUBY-1 and DUO-E are presented in the table below. Please provide a clinical justification for why durvalumab is estimated to result in 5.37 incremental QALYs vs 4.26 incremental QALYs associated with dostarlimab.

Comparison	PFS HR (95% CI)	OS HR (95% CI)
Dostarlimab + carboplatin/paclitaxel vs carboplatin/paclitaxel	0.28 (0.16 to 0.50)	0.30 (0.13 to 0.70)
Durvalumab + carboplatin/paclitaxel vs carboplatin/paclitaxel	0.42 (0.22 to 0.80)	0.34 (0.13 to 0.79)

Despite OS often being a key driver of incremental QALY gain in partitioned survival models, and the fact that hazard ratios for OS presented above appear, at first glance, to be similar between the DUO-

E and RUBY part 1 regimens, the company would like to highlight that such a side-by-side comparison is overly simplistic, and is inappropriate for decision-making for several reasons:

- There are several differences in the trial populations for DUO-E and RUBY part 1 which could meaningfully impact the efficacy results observed in each trial. For example, the DUO-E trial included a much larger proportion of Asian patients, and a lower number of primary stage III patients compared to RUBY part 1. Additionally, the inclusion criteria for the DUO-E and RUBY part 1 studies differed with respect to the required treatment-free interval since completion of adjuvant systemic therapy for patients with recurrent disease (12 months in DUO-E versus 6 months in RUBY part 1).[8, 14] In the absence of a matched adjusted indirect treatment comparison, it is therefore overly simplistic to assume that these regimens must produce equal QALY gains.
- Furthermore, OS is only one factor which influences the incremental QALY gains in a PSM. Given that the company does not have access to the economic model used in the TA963 appraisal, nor the underpinning confidential (redacted) data, it is not possible to identify which other inputs and assumptions drive the difference in incremental QALY gains. However, it could be speculated that there may be differences in many factors, including adverse event disutilities and health state utility values.

In conclusion, the company strongly object to such an overly simplistic side-by-side comparison being used to inform decision-making in this appraisal, particularly given that dostarlimab is not a comparator in this appraisal as it is recommended within the CDF. As the EAG themselves have highlighted in question B18, medicines in the CDF should not be considered standard of care or used as comparators (formally or informally) according to established NICE methods.[15]

Adverse events

B6. Priority question: In TA963, the committee preferred a broader range of adverse events (AEs) to be included in the model (those affecting at least 2% of people). As such, please provide a scenario in the model where costs and disutility of AEs are based on grade ≥3 AEs occurring in ≥2% of patients in at least one of the treatment arms from the safety population (SAS) in DUO-E (Table 48 of the clinical study report [CSR]).

It is not considered standard practice across NICE TAs to include a full set of adverse events occurring in ≥2% of patients in at least one of the treatment arms. It should be noted that, in TA963, the reason that such a scenario was requested by the EAG was because the "limited follow-up and small sample size may result in the true impact of AEs being under-reported, and their impact underestimated".[5] However, the same rationale does not necessarily apply to the DUO-E data, which had a larger sample size. ITT data was used to inform the company submission for TA963 (placebo arm, N=249; intervention arm, N=245, resulting in a total sample size of N=494);[5] ITT data was also used to inform the company base case for the current appraisal, but the three-arm nature of the study design in DUO-E increases the total sample size (SoC, N=236; SoC + D, N=235; SoC + D + O, N=238, resulting in a total sample size of N=709).

Furthermore, dostarlimab is not a comparator in this appraisal, and assumptions that applied in that appraisal should not necessarily be used to inform the current appraisal unless the same underlying rationale is deemed to apply to the evidence base provided.

However, for transparency, the company have explored the impact of a broader range of AEs as a scenario analysis, as requested by the EAG (presented below). To conduct this analysis, a further 13 individual AEs were added into the model. Each of these AEs require an incidence proportion, cost per event, duration of event, and disutility. Due to the limited time available it was not possible to systematically source these data inputs across each additional AE (aside from the incidence proportions which were sourced directly from the DUO-E trial). Instead, a simple methodology was employed to match the cost per event, duration of event, and disutility to the respective inputs already used in the original model for existing AEs based on the following algorithm:

1. Costs for additional AEs requested by the EAG were identified from the NHS national schedule of reference costs (2022/23). If available, they were compared and matched to the cost of the most comparable cost for existing AEs in the model.
    a. For example, the cost of syncope ranges between £593 (score 0–1) and £2,804 (score 13+) which was deemed to match most closely to the cost of hypertension used in the model (£720.94), Therefore, it was assumed that cost per event, event duration, and disutility for syncope was equal to hypertension.
2. Where costs for AEs were unavailable in the NHS schedule of reference costs (2022/23), AEs were matched based on closest similarity to the condition, as determined by the company.

Table 14 below presents the final list of AEs with associated incidence proportions included in the modelled scenario analysis.

Table 14. List of original and additional adverse events included in the scenario analysis

Adverse events	"Original" AE to which cost and disutility have been matched	SoC + D	SoC + D + O	SoC
Original AEs in the company model				
Source	***N/A***	***DUO-E***	***DUO-E***	***DUO-E***
N	N/A	235.00	238.00	236.00
Anaemia	N/A	15.7%	23.5%	14.4%
Neutropenia	N/A	8.5%	11.3%	5.9%
Neutrophil count decreased	N/A	11.5%	13.4%	15.3%
Lymphocyte count decreased	N/A	2.1%	1.3%	2.1%
White cell count decreased	N/A	3.8%	4.2%	4.7%
Hypertension	N/A	2.1%	2.5%	3.0%
Pulmonary embolism	N/A	1.7%	2.1%	1.3%
Hypokalemia	N/A	2.6%	2.9%	0.8%
Additional AEs requested by the EAG				
Febrile neutropenia	Neutropenia	2.6%	3.4%	3.8%
Leukopenia	White cell count decrease	0.9%	2.1%	0.8%
Platelet count decreased	Anaemia	3.8%	2.5%	3.8%

Gamma-glutamyltransferase increased	Hypokalaemia	2.1%	0.8%	0.8%
Urinary tract infection	Hypertension	0.9%	2.9%	3.4%
Syncope	Hypertension	0.9%	2.9%	0.4%
Peripheral sensory neuropathy	Hypertension	0.0%	0.8%	2.5%
Nausea	Hypertension	0.4%	2.9%	1.3%
Diarrhoea	Hypertension	1.7%	1.3%	2.5%
Constipation	Hypertension	0.9%	0.0%	2.1%
Hyponatremia	Hypokalaemia	2.1%	1.3%	1.7%
Asthenia	Hypertension	1.3%	2.9%	1.7%
Fatigue	Hypertension	2.1%	2.1%	1.7%

When applying the additional AEs requested by the EAG as a scenario, the results demonstrate minimal impact on the ICER (Table 15 and Table 16), demonstrating that the analysis in the original company submission is robust, and should be considered sufficient to inform decision-making.

Table 15. Cost-effectiveness results in the dMMR subgroup for scenario applying additional AEs to SoC and SoC + D

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.09				
SoC	60,862.24	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 16. Cost-effectiveness results in the pMMR subgroup for scenario applying additional AEs to SoC and SoC + D + O

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	55,155.75	4.57	3.27	[redacted]	0.89	0.67	[redacted]

B7. The EAG's clinical experts considered the duration of pulmonary embolism should be 3 months instead of 1 months (as assumed in the company base case) to adequately capture costs and disutility. Therefore, please conduct a scenario analysis where the duration of pulmonary embolism is 3 months.

There is precedent in prior NICE appraisals to use a 1-month duration for pulmonary embolism (e.g., TA963 used values derived from the prior TA411 appraisal, in which the company applied a 30.4-day duration to PE). This precedent informed the original company base case in the current appraisal.

However, the company acknowledge that there may be variability and uncertainty around the average duration over which a PE meaningfully impacts costs and HRQoL. Therefore, in line with the EAG's suggestion, a scenario analysis has been conducted to explore the impact of increasing the duration of pulmonary embolism from 1 month to 3 months; this is presented below in Table 17 and Table 18 for the dMMR and pMMR populations, respectively. Overall, the results demonstrate a very marginal impact on the ICER for both populations.

Table 17. Cost-effectiveness results in the dMMR subgroup for scenario applying increased duration of PE for SoC and SoC + D

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.09				
SoC	60,570.19	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 18. Cost-effectiveness results in the pMMR subgroup for scenario applying increased duration of PE for SoC and SoC + D + O

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.93				
SoC	54,863.71	4.57	3.27	[redacted]	0.89	0.66	[redacted]

Health-related quality of life

B8. Please clarify how many patient responses inform the progression-free (PF) and PD utility estimates.

The PF utility estimate is informed by [redacted] observations, while the PD utility estimate is informed by [redacted] observations. The number of observations collected in the DUO-E trial is in line with expectation for a study of this size and in this therapy area, considering that in oncology trials for advanced or recurrent disease, response rates can be limited by the fact that patients may either be in a poor health state or lost to follow-up post-progression. The company considers that the utility estimates provided in the company submission are the most reliable estimate available, and demonstrate the efficacy and tolerability of the SoC + D and SoC + D + O regimens.

B9. Please provide the results of model 2 for the dMMR and pMMR subgroups.

Results of model 2 for the dMMR and pMMR subgroups were not provided in the original submission as there is no evidence to suggest that utility would differ based on the MMR biomarker status. This assumption was also validated with five UK clinical experts who agreed that there would be no clinical or biological reason to assume that HRQoL may differ based on MMR biomarker status.[3] Nonetheless, the utility values requested by the EAG have been provided in Table 19 below.

Table 19. Utility values in the dMMR, pMMR and ITT

	dMMR	pMMR	ITT
Progression	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

As expected, and in line with expert clinical opinion, there are negligible differences in utility between the MMR subgroups and the ITT. Whilst the utility values (particularly for progressed disease) for the pMMR subgroup are marginally lower compared to the dMMR subgroup, this is likely driven by the comparatively low observation numbers for this subgroup rather than any true differences, given that there is no clinical rationale for a difference in utility based on MMR status. For these reasons, the company maintain that use of the ITT utility values is more appropriate for decision-making, as per the original company base case.

Treatment acquisition costs

B10. Priority question: In the model, tab "TDT computation", cell F9, it is assumed that [redacted] of pMMR durvalumab patients will initiate olaparib, but there is limited discussion of this assumption in the CS.

a) **In DUO-E, please explain why not all patients who completed the chemotherapy phase with durvalumab and were still progression-free did not receive olaparib as part of their maintenance treatment.**

b) **Please provide a scenario where 100% of pMMR patients receive olaparib at the start of the maintenance phase of treatment.**

As outlined in response to question A1, the company used a value of [redacted] to model the proportion of patients who go on to receive olaparib in the maintenance phase. For the avoidance of doubt, the value of [redacted] represents [redacted] of a total of all [redacted] patients randomised in the pMMR population cohort on SoC + D + O arm that had initiated treatment with olaparib. This value is sourced directly from the DUO-E trial (see Table 1 value for the pMMR subgroup in the SoC + D + O arm, highlighted yellow).

In the DUO-E trial, not all patients went on to receive olaparib in the maintenance phase. This occurred for two reasons:

1. Some patients experienced disease progression whilst in the chemotherapy phase, and hence did not become eligible to enter the maintenance phase at all.
2. Some patients who remained progression-free at the end of the chemotherapy phase did not meet the eligibility criteria for the maintenance phase. These eligibility criteria are fully detailed in Section 9.3 of the CSR, but a summarised version is also provided in Figure 11 below.

In the CEM, [redacted] was applied to the TDT extrapolation models at week 18 in the model. This aligns with the earliest opportunity for maintenance in the DUO-E trial design, for patients completing six cycles of chemotherapy. This assumes that the chemotherapy phase of treatment involves six 3-week cycles, therefore 18 weeks in total. It is at that point from which it is assumed that the maintenance phase begins. This is a conservative approach, as the median time from randomisation to the initiation of olaparib in the DUO-E trial was 137 days (19.6 weeks) in the pMMR population (in the SoC + D + O arm). Furthermore, the proportion of patients on durvalumab at week 18–19 in the model in the pMMR subgroup is [redacted] based on the parametric survival curve selected. This demonstrates that, for SoC + D + O, the durvalumab and olaparib components are closely aligned.

Given that the patients enrolled in DUO-E have advanced EC, and therefore must receive a gruelling regimen of platinum-based chemotherapy before becoming eligible for the maintenance phase, it is unsurprising that not all patients remain fit enough to actually receive olaparib in the maintenance phase. This will be particularly true in real-world clinical practice, as it is widely acknowledged that patients in clinical trials tend to be fitter than those in wider clinical practice. The company therefore considers it highly inappropriate and unrealistic to consider a scenario whereby 100% of the patients go on to receive olaparib in the maintenance setting. As such, this scenario requested by the EAG has not been presented.

Figure 11. Summarised version of eligibility criteria for the maintenance phase from the DUO-E CSR

- Patients were to receive a maximum of 6 cycles of chemotherapy and were to have had a minimum of 4 cycles of platinum-based chemotherapy to continue onto maintenance treatment.
- Following completion of chemotherapy, durvalumab/placebo dosing schedule was to then change to 1,500 mg Q4W. Patients were to also receive olaparib/placebo treatment following completion of chemotherapy (treatment was to commence a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion).
- The patient MUST have met the following requirements within 3 days prior to dosing in order to receive olaparib/placebo:
    - Adequate organ and bone marrow function, defined according to specific thresholds for haemoglobin, neutrophil count, platelet count, bilirubin, aspartate aminotransferase/ALT
    - Creatinine clearance of ≥ 51 mL/minute, estimated using either the Cockcroft-Gault equation, a 24-hour urine test or another validated test as per local practice
    - It must have been confirmed that patients were not receiving any prohibited concomitant medications in order to receive treatment with olaparib/placebo.
- If a patient could not start olaparib/placebo maintenance within 9 weeks from the last day of chemotherapy infusion, the patient should have continued durvalumab/placebo at 1,500 mg Q4W (durvalumab/placebo should also have continued during the 3-to-9-week window after the last day of chemotherapy infusion, if the olaparib/placebo start criteria had not yet been met).

B11. Please explain the inclusion of the proportion of patients on chemotherapy and costs for the SoC + D treatment arm for the pMMR subgroup in Tables 67 and 68 of the CS? The EAG understands that only the SoC + D + O treatment arm is relevant for the pMMR subgroup.

The SoC + D arm was only provided for completeness in Tables 67 and 68 of the company submission, and the EAG is correct that only the SoC + D + O arm is relevant for the pMMR subgroup. The company suggests that the EAG should disregard the SoC + D arm in these tables.

Time on treatment

B12. Priority question: The draft summary of product characteristics (SmPCs) for durvalumab and olaparib states that treatment should be given until progression or unacceptable toxicity, and this was also included in the trial protocol for DUO-E. The company states that treatment-stopping rules exist for pembrolizumab (2 years) and dostarlimab (3 years) for treating endometrial cancer (EC), but does not acknowledge that treatment-stopping rules are included in the SmPCs for these medicines as well as being part of the design of the key trials used for marketing authorisation. The company's approach estimates that mean time on durvalumab treatment is [redacted] years for the dMMR

subgroup. For the pMMR subgroup, mean time on treatment for durvalumab is estimated to be [redacted] years and [redacted] years for olaparib.

a) **Please justify the base case estimates of mean time to treatment discontinuation (TTD) for durvalumab and olaparib. The company's clinical experts suggested that patients would discontinue treatment within 5 years and long-term remission is expected after 5 years progression-free. Also, please explain how the treatment-stopping rules for pembrolizumab and dostarlimab support the company's treatment-stopping assumption for durvalumab, given the design of DUO-E did not include a stopping rule and this is not included in the draft SmPC.**

b) **Please provide the below scenarios and subsequent mean TTD estimates for both the dMMR and pMMR subgroups, where the treatment-stopping rule of 3 years is removed to reflect the recommended treatment regimens in DUO-E and the draft SmPCs for durvalumab and olaparib. Also, please exclude the exponential drop off setting in cell E90 in the "Settings" tab.**

- **For the dMMR subgroup, the exponential, generalised gamma and gamma (company base case) distributions for the durvalumab TTD extrapolation have a natural decline down to zero with a good visual fit to the observed data. As such, please explore these distributions in scenario analysis and also present the mean TTD estimate for each distribution.**

- **For the pMMR subgroup, the exponential, Weibull, log-logistic (company base case) and gamma distributions for both the durvalumab and olaparib TTD extrapolations have a natural decline to zero with a good visual fit to the observed data. Please note that the exponential curves for durvalumab and olaparib converge around 36 months, which may be appropriate depending on the response to B14. As such, please explore these distributions in scenario analysis and also present the mean TTD estimate for each distribution.**

To provide a point of clarification and to avoid any misinterpretation, time on treatment should be calculated from the 'Adjusted' TDT data table in the 'TDT Computation' tab, and not from the raw parametric curves. This is for two reasons:

1. Calculating from the raw parametric curves does not take into consideration the fitted exponential function applied between years 3 and 5 (if applicable).
2. It does not take into consideration that patients in the pMMR subgroup initiate treatment at week 18 (i.e., not from randomisation). The proportion of patients initiating olaparib after week 18 is [redacted]%.

Also, the maximum time on treatment set in the base case (36 months) should be considered when calculating the time on treatment in the base case. For transparency, the suggested formulae to calculate the time on treatments (in weeks) in the base case have been provided below:

1. Durvalumab in SoC + D: [redacted]
2. Durvalumab in SoC + D + O: = [redacted]
3. Olaparib in SoC + D + O: [redacted]

Based on the approach outlined above, the mean time on treatment for each respective component should equate to:

1. Durvalumab in SoC + D: [redacted]
2. Durvalumab in SoC + D + O: [redacted]
3. Olaparib in SoC + D + O: [redacted]

Part A: the company wishes to be clear that a stopping rule is not being proposed. The fixed treatment durations in the RUBY-I trial and NRG-GY018 were not referenced in the company submission to support the approach taken in the base case in the model, but rather to draw parallels with how other IO therapies may be used in the first-line setting in UK clinical practice.

The approach taken, as outlined in the original submission, is to align with feedback from UK clinical experts and the reality of how patients are managed in practice. UK clinicians estimated that most patients would discontinue olaparib after two to three years, and all patients would discontinue treatment by five years. This is the primary motivation for this approach. In the company submission, a conservative approach was taken where any patients remaining on treatment with durvalumab and olaparib after three years are assumed to discontinue treatment. Therefore, the EAG's suggestion to use the full parametric extrapolations for durvalumab and olaparib would contradict clinical opinion, and as such, are not considered by the company to be relevant for decision-making.

The company also notes that an alternative scenario was presented in the company submission where treatment duration is set to 5 years, with TDT modelled using parametric curves for the first three years, and an exponential function used to calculate the drop-off of patients on treatment between years three and five. It is the company's view that that this is the second most appropriate approach to modelling TDT in this appraisal and not the approach suggested by the EAG.

Part B.i: in line with the EAG request, scenarios have been conducted where the full TDT parametric extrapolation for durvalumab in SoC + D have been performed using the exponential (Table 20), generalised gamma (Table 21) and gamma (Table 22; company base case) distributions.

Table 20. Cost-effectiveness results for the dMMR population for scenario exploring the exponential distribution for durvalumab TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,570.19	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Mean ToT: [redacted]

Table 21. Cost-effectiveness results for the dMMR population for scenario exploring the Generalised gamma distribution for durvalumab TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,570.19	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Mean ToT: [redacted]

Table 22. Cost-effectiveness results for the dMMR population for scenario exploring the gamma distribution for durvalumab TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,570.19	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Mean ToT: [redacted]

Given the mean time on treatment estimates above, the exponential distribution is the most appropriate distribution based on clinical opinion previously described and the DUO-E trial data.

Part B.ii: in line with the EAG request, scenarios have been conducted where the full TDT parametric extrapolation for durvalumab and olaparib in SoC + D + O have been performed using the exponential (Table 23), Weibull (Table 24), log-logistic (Table 25; company base case), and gamma distributions (Table 26). The Gamma distribution has been added as it is the most reflective distribution of clinical opinion and results from the DUO-E trial.

Table 23. Cost-effectiveness results for the pMMR population for scenario exploring the exponential distribution for durvalumab and olaparib TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,863.71	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Mean ToT (D): [redacted], mean ToT (O): [redacted], proportion on treatment at 5 years:

Table 24. Cost-effectiveness results for the pMMR population for scenario exploring the Weibull distribution for durvalumab and olaparib TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,863.71	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Mean ToT (D): [redacted], mean ToT (O): [redacted]

Table 25. Cost-effectiveness results for the pMMR population for scenario exploring the log-logistic distribution for durvalumab and olaparib TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	£54,863.71	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Mean ToT (D): [redacted], mean ToT (O): [redacted]

Table 26. Cost-effectiveness results for the pMMR population for scenario exploring the gamma distribution for durvalumab and olaparib TDT

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	£54,863.71	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Mean ToT (D): [redacted], mean ToT (O[redacted]

In conclusion, the company does not consider any of the scenarios requested by the EAG to be reflective of UK clinical practice, as the use of the full parametric models overestimate proportion of patients on treatment by extending the time on treatment in the model. The company stresses that the original base case assumptions are the most appropriate for decision-making.

B13. Priority question: In the final guidance for TA963, the Cancer Drugs Fund (CDF) lead noted that treatment effect waning is typically applied after treatment has stopped. As such, please justify why in the company's base case, a treatment-stopping rule of three years has been applied without applying a treatment effect waning assumption. Please explain in your justification, how the DUO-E treatment protocols, the benefit observed based on these protocols in DUO-E, and the draft SmPC guidance of treat until progression align with the company's proposed stopping-rule.

In this question, the company will address why no waning assumption has been applied in the economic model. The second part of the EAG question, relating to the TTD assumptions applied in the model, has already been addressed in response to question B12.

The company would like to highlight that the statement from the CDF lead during TA963 has been quoted out of context in this question. The actual statement from the CDF lead was that "the treatment effect waning is typically applied after treatment has stopped, not while treatment is ongoing", and was made specifically in response to an EAG scenario in this appraisal where they proposed a waning assumption beginning at 80 weeks (i.e., while patients would still be on treatment).[5] Therefore, the company's interpretation of this statement from the CDF lead was not intended to specify that a waning assumption must be applied in this setting as soon as treatment is stopped, but was rather intended to prevent an overly pessimistic waning assumption from being applied.

It is also worth noting that there was much debate in TA963 as to the appropriateness of applying a waning assumption at all, as well as the most suitable methodology. Notably, clinical experts highlighted a durable treatment effect in people with dMMR/MSI-H EC, as well as in other related cancer types. The committee also noted that there was not a clear waning effect seen in the RUBY-1

data, and concluded that there was insufficient evidence to know "if, and when, the dostarlimab treatment effect wanes". Rather than landing on a specific preferred waning assumption, they instead reiterated that they did not prefer the EAG methodology and requested that a range of scenarios should be presented during the CDF exit appraisal for dostarlimab in this setting.

For this reason, the company did not consider that there was necessarily a clinical rationale to apply a waning effect, nor a strong precedent from prior appraisals to do so. Furthermore, the company highlights an analysis presented at ISPOR 2023 which explored the predictive accuracy of treatment waning methods when applied to an IO therapy across 6 different NICE oncology appraisals.[16] This analysis concluded that "when extrapolations were selected based on clinical plausibility, all waning methods tended to underestimate LYs compared to realised LYs; the predicted LYs aligned most closely with realised LY estimates when no waning was applied (mean absolute difference: 4.6%)".[16] Given that all extrapolations applied in the DUO-E cost-effectiveness model were robustly validated with UK clinical experts, this supports our approach of not applying a waning effect.

B14. In Figure 37 of the CS, at around 36 months, the TTD curves for durvalumab and olaparib cross, such that some patients discontinue olaparib before durvalumab. As this treatment regimen is a combination, please explain if in UK clinical practice pMMR patients will be permitted to remain on either olaparib or durvalumab if they have discontinued the other treatment (thus treated as monotherapy)?

In section 7.1 of the DUO-E study protocol, it specifically states that "any patient receiving treatment with investigational products (durvalumab/placebo or olaparib/placebo) who has an AE that contraindicates further dosing and is considered to be attributable to one of the study treatments but not the others, may continue on study and continue to receive the therapies that have not been considered to be the cause of the AE (a discontinuation of one drug should not affect the dosing schedule of the other drugs)".[17] This explains why the duration of exposure for the durvalumab/placebo and olaparib/placebo treatments differed slightly within the maintenance phase for each arm of the study (as outlined in Table 23 of the company submission).

It is anticipated that this flexibility would also be permitted in UK clinical practice (pending confirmation in the final marketing authorisation and Blueteq criteria for this indication). Furthermore, UK clinical experts consulted by the company also highlighted that they would consider the discontinuation of each drug independently, noting that there would be a particular reluctance to use the olaparib component of the DUO-E regimen long-term due to the mechanism of action and concerns about acute myeloid leukaemia associated with prolonged PARPi exposure.[18]

The TTD curves used in the economic model therefore reflect both the study design as well as the expected real-world usage of the DUO-E regimen according to UK clinicians, and should therefore be considered the most appropriate methodology by which to model TTD.

B15. In tab "TDT computation", cells BL19:BL2634, the data are described as PFS adjusted for long-term responders but this is not described in the CS nor does it appear to be adjusted to include a long-term response assumption? Please explain if the label in the model is correct?

The label in the model is incorrect and should be 'Adjusting for all-cause mortality'. This has now been renamed in the updated version of the model.

B16. Priority question: The EAG notes that because TTD is calculated using weekly cycles and is capped to PFS, that a PFS curve based on weekly cycles has been estimated (tab "TDT", cells BE25:BI2634). However, there are differences between the PFS curves based on monthly and weekly cycles.

a) **Please provide a graph that visually compares the PFS curve estimated based on weekly model cycles with the PFS curve estimated using monthly model cycles and if differences are observed, please discuss how this could impact the cost-effectiveness results.**

b) **Please explain why using weekly cycles would affect the computational efficiency of the model, given that in Table 29 of the CS, 3 out of the 5 published models used weekly cycles, and all models used one cycle length for consistency.**

c) **For simplicity, the EAG considers that the model cycle length should be one week. Please estimate PFS and OS in the model for all treatment arms using weekly cycles. If this is not possible, please demonstrate/justify that using different cycle lengths isn't an issue in the current model**

Part A: The monthly model cycle was expected to adequately capture the natural history of the disease and the change in progression-free survival as, in the DUO-E trial, patients received tumour imaging every 9 weeks (±1 week) for 18 weeks, and then every 12 weeks (±1 week) thereafter. For TDT, the company incorporated a weekly model cycle to accurately capture the treatment costs, since chemotherapy and IO treatments could be administered every 3 or 4 weeks depending on the phase of treatment.

For the dMMR population, a plot comparing the PFS curves estimated without adjustment for background mortality over the duration of the model time horizon has been provided. These curves were derived from the following cells outlined in Table 27 in the dMMR population.

Table 27. Cell references for the dMMR population for PFS curve derivation

Treatment arm	PFS curve type	PFS Curve Cell References	
		Monthly	Weekly
SoC + D	Unadjusted	PFS AA61:AA661	TDT_Computation BF61:BF661
	Population mortality adjusted	PFS AG61:AG661	TDT_Computation BL61:BL661
SoC	Population mortality adjusted	PFS P61:P661	TDT_Computation BN61:BN661

A comparison of the weekly and monthly PFS estimations for SoC + D are provided below, with and without population mortality adjustment. As expected, the plots are overlayed, such that it is not possible to distinguish between the two curves when comparing monthly and weekly cycles;

Figure 12. All plots are therefore shown separately in

Figure 13 below, for transparency.

Figure 12. Monthly PFS estimations for SoC + D with and without population adjustment

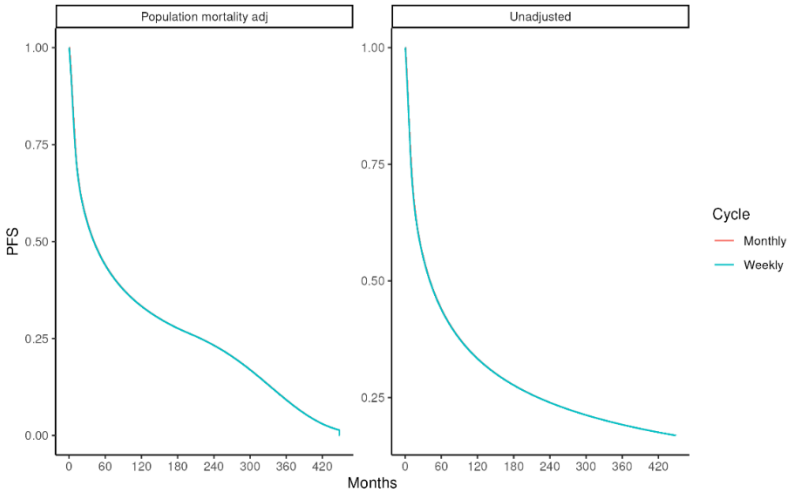
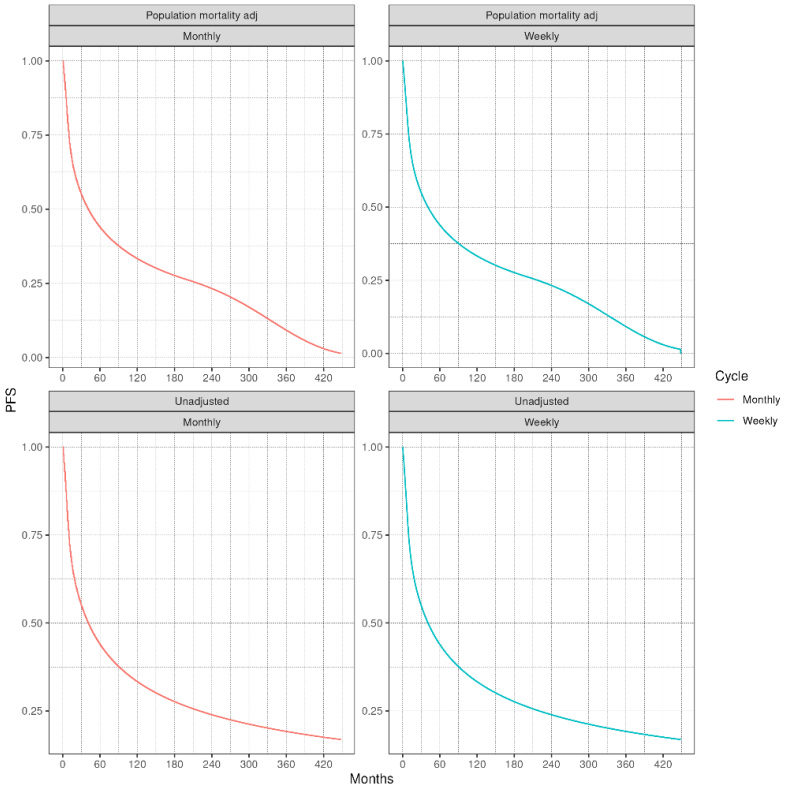


Figure 13. Weekly and monthly PFS estimations for SoC + D with and without population adjustment



Part B and C: An analysis of RMST was performed to evaluate the difference in the estimated RMST when using a monthly and weekly approach for the dMMR population. Over the model time horizon,

the difference in RMST was 0.25% (without population mortality adjustment) and 0.32% (with population mortality adjustment) for SoC + D.

A comparison of the incremental differences (SoC + D vs. SoC) in RMST in the dMMR population PFS curves (adjusted for background mortality), showed a 0.016% difference in incremental RMST (85.65 months vs. 85.66 months), when comparing the weekly and monthly estimates of PFS. For this reason, the company has not re-programmed the economic model to use daily cycle lengths (as requested in question part C).

Overall, as demonstrated, the company does not propose that implementing a weekly cycle would have a significant impact on the estimated outcomes in the model. In addition, the company approach represents a reasonable trade-off between model simplicity and transparency versus model granularity, noting that the monthly cycles do reduce the overall size of the economic model (and thereby the speed of PSA simulations).

It should also be noted that the outcomes of the model (as estimated from monthly cycle lengths) are half-cycle corrected in the base case analysis. These results are not presented in response to this question from the EAG. The estimation of PFS in weekly cycles for TDT calculations are not half-cycle corrected.

Subsequent treatments

B17. Priority question: In the submission, it is assumed that [redacted] of patients will go on to have a subsequent treatment, based on observed data from DUO-E.

a) **Please provide the percentage of patients by MMR subgroup and treatment arm from DUO-E that went on to receive a subsequent treatment (fill out table below).**

	dMMR		pMMR	
	SoC	SoC + D	SoC	SoC + D + O
Number of patients with a non-fatal progression event				
% (n) receiving at least one subsequent treatment				

b) **Please run a scenario analysis for the dMMR and pMMR subgroups using the data requested in part a).**

Part A: in the economic model, the [redacted] figure which was used to inform the proportion of patients receiving a subsequent therapy was based on the observed data from the DUO-E trial in the ITT

population, summed across all treatment arms (i.e., a total of 404 patients experienced a non-fatal progression event, of which 314 [redacted] received at least one subsequent therapy). Using the ITT data was considered the most reliable approach as it maximises the sample size of the underpinning DUO-E data. This approach was also validated by UK clinicians, who agreed that a proportion of 70–80% would be reflective of expected UK clinical practice; the clinicians did not cite any expected variation in this percentage according to MMR status.[18]

The observed data from the DUO-E trial for the MMR subgroups is provided in Table 28 below. However, it should be noted that within the subgroups (particularly for dMMR) the sample size of patients who have experienced a non-fatal progression event is small. Considering this, as well as the aforementioned clinical validation, the company maintain that using the ITT data is the most robust approach to model subsequent treatments.

Table 28. Patients receiving at least one subsequent treatment in the DUO-E trial according to MMR status

	dMMR		pMMR	
	SoC	SoC + D	SoC	SoC + D + O
Number of patients with a non-fatal progression event	[redacted]	[redacted]	[redacted]	[redacted]
N (%) receiving at least one subsequent treatment*	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: * Percentage expressed as a proportion of all patients who experienced a non-fatal progression event

Part B: in line with the EAG's request, a scenario has been provided in Table 29 and Table 30 for the dMMR and pMMR population, respectively, where the proportion of patients receiving at least one subsequent treatment is informed by the MMR subgroup-specific data from the DUO-E trial.

Table 29. Cost-effectiveness results in the dMMR subgroup for scenario where the proportion of patients receiving at least one subsequent treatment is informed by the dMMR-specific data from the DUO-E trial

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	63,098.91	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 30. Cost-effectiveness results in the pMMR subgroup for scenario where the proportion of patients receiving at least one subsequent treatment is informed by the pMMR-specific data from the DUO-E trial

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	55,199.93	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Whilst these results show a minimal decrease of the ICER results in the model, the company maintains that the value used in the base case submission should be used for decision-making.

B18. Priority question: The EAG's clinical experts outlined that dMMR SoC patients would not be treated with pembrolizumab monotherapy in UK clinical practice. Additionally, dostarlimab is only approved for use in the CDF at

second-line and therefore NICE has advised that this cannot be considered as a subsequent treatment for this appraisal. Please conduct a scenario increasing the proportion of dMMR patients assumed to receive subsequent treatment with pembrolizumab and lenvatinib (assumed to represent combination treatment) to 70%.

a) **Please run a second scenario for both the dMMR and pMMR subgroups, where subsequent treatment proportions sum to 100%. Please ensure to exclude dostarlimab and assumptions around pembrolizumab monotherapy usage for the dMMR subgroup.**

The company considers that there are three distinct considerations within this question, and will address each of these in turn:

1. The EAG suggestion to exclude dostarlimab as a 2L+ treatment in the dMMR SoC arm.
2. The EAG suggestion to increase the proportion of patients receiving pembrolizumab + Lenvatinib (rather than pembrolizumab monotherapy).
3. The EAG request for subsequent treatments to sum to 100%.

Exclusion of dostarlimab as a 2L+ treatment in the dMMR SoC arm

With respect to the use of dostarlimab in the second-line setting in patients with dMMR EC, the company acknowledge that this is approved within the CDF, and have therefore removed it from the base case economic analysis. However, it is important to note that UK clinical experts consulted by the company have highlighted that, in a hypothetical world in which dostarlimab was not reimbursed in this setting, they would instead treat such patients with an alternative available IO therapy, such as pembrolizumab. Therefore, in the revised base case analysis (see Appendix A) the company have maintained the proposed total use of IO in this setting, and have simply redistributed those patients who were modelled to receive dostarlimab to receive pembrolizumab instead. This approach is most reflective of UK clinical practice in the eventuality that dostarlimab did not enter baseline commissioning at the end of the managed access period.

Proportion of patients receiving pembrolizumab + lenvatinib

With respect to the use of pembrolizumab in the second-line setting, the company would like to highlight that according to the recommendation in TA914, dMMR SoC patients would be eligible to receive pembrolizumab monotherapy in this setting.[19] Furthermore, the approach taken in the original company base case was extensively validated with five UK clinical experts, who highlighted that for dMMR SoC patients (where there is a choice between the use of pembrolizumab monotherapy or combination therapy) many clinicians would actually prefer to offer IO monotherapy, given that that the pembrolizumab + lenvatinib combination regimen has a much more significant toxicity profile.[3]

Given the redistribution of patients receiving 2L+ dostarlimab to receive 2L+ pembrolizumab instead (as outlined above), the revised company base case now has an increased proportion of pembrolizumab usage (increased from [redacted] in the original company base case to [redacted] in the revised company base case). In addition, the company has provided a scenario analysis in Table 31 which reflects the EAG request to a) reduce the total IO use to 70%, and b) to assume that pembrolizumab

is always given in combination with lenvatinib. This has been done by setting the use of pembrolizumab and lenvatinib to 70% each (with 0% dostarlimab, as outlined above).

Table 31. Cost-effectiveness results for dMMR subgroup for scenario where IO use is reduced and pembrolizumab is always given in combination with lenvatinib

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	65,080.15	3.69	2.72	[redacted]	7.65	5.37	[redacted]

The results of this scenario analysis demonstrates a minimal decrease in the ICER. Despite this, the company reiterates that the approach used in the original company base case is the most clinically plausible distribution.

Subsequent treatment proportions summing to 100%

There is clear clinical rationale as to why the subsequent treatment proportions used in the economic model sum to greater than 100%. This reflects two factors:

- The subsequent treatments in the model are for second-line and beyond; therefore, some patients would be expected to receive multiple lines of subsequent therapy.
- Some of the subsequent therapies are given in combination (for example pembrolizumab + lenvatinib, as well as some combination chemotherapy regimens).

Furthermore, it is worth considering that not all patients who experience disease progression would actually remain fit enough to receive a subsequent therapy.

It is therefore not appropriate or clinically plausible to artificially set the total use of subsequent therapies equal to 100% as this would not reflect any of the clinical realities highlighted above and would unnecessarily underestimate the total use of subsequent treatments for second-line and beyond in UK clinical practice. As such, the company have not included this element of the EAG request in the scenario analyses presented.

B19. Priority question: The EAG notes that the one-off subsequent treatment costs reported in the company submission (Tables 77 and 78) report costs inconsistent with those calculated in the model. Please confirm the one-off subsequent treatment costs calculated in the model are the company's preferred base case assumptions?

a) Please describe the assumptions that were implemented for the costs reported in Tables 77 and 78 of the company submission.

Treatment arm	Submission one-off subsequent treatment acquisition costs	Model one-off subsequent treatment acquisition costs
SoC + D	£48,926	£256
SoC + D + O	£37,630	£255
SoC (dMMR subgroup)	£42,934	£65,699

SoC (pMMR subgroup)	£47,280	£59,008

The company can confirm that the one-off subsequent treatment costs reported in the submission (Tables 77 and 78) are incorrect. The costs calculated in the model are correct and should be considered for decision-making. Due to changes resulting in the revised company base case (outlined in Appendix A) based on feedback from the EAG, revised tables for one-off subsequent treatment costs are presented below in Table 32 and Table 33 for the dMMR and pMMR populations, respectively. These differ from the table provided by the EAG above and have been provided for transparency.

Table 32. Corrected subsequent treatment costs for the dMMR population

Treatment arm	Drug acquisition cost (one-off)	Drug administration cost (one-off)	Total cost (one-off)
SoC + D	£256	£2,464	£2,720
SoC	£46,184	£5,555	£51,740

Table 33. Corrected subsequent treatment costs for the pMMR population

Treatment arm	Drug acquisition cost (one-off)	Drug administration cost (one-off)	Total cost (one-off)
SoC + D + O	£255	£2,495	£2,750
SoC	£34,306	£3,905	£38,212

B20. Priority question: Please provide the source of the subsequent treatment administration cost (£399.92) assumed in the model.

The source for the subsequent treatment administration cost (£399.92) assumed in the model is NHS reference costs 2021/22: "SB15Z deliver subsequent elements of a chemotherapy cycle".[20]

Whilst not requested by the EAG, a scenario analysis was conducted where the subsequent treatment administration cost was set to cell E42 in the 'Cost Inputs' tab. This cell contains the cost for the 2022/23 for delivery of a subsequent element of a chemotherapy cycle (£393.16) which is more up to date. The results of this analysis are presented below in Table 34 and Table 35 for the dMMR and pMMR populations, respectively.

Table 34. Cost-effectiveness results for dMMR population for scenario with updated subsequent treatment administration costs

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,517.39	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 35. Cost-effectiveness results for pMMR population for scenario with updated subsequent treatment administration costs

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94	-	-	-	-
SoC	54,828.37	4.57	3.27	[redacted]	0.89	0.67	[redacted]

As demonstrated in Table 34 and Table 35, this update has a negligible impact on the ICER results in the model in both populations.

Health care resource use

B21. Priority question: The EAG's clinical experts provided alternative estimates of healthcare resource use (HCRU), outlined in the table below. The EAG's clinical experts considered that:

- **Patients on immunotherapy treatments will receive cortisol, kidney and liver function tests while on treatment.**
- **Patients on immunotherapy will continue to receive outpatient visits every month while still on treatment.**
- **SoC Patients will not receive thyroid tests.**
- **The HCRU frequency for PD durvalumab patients (with or without olaparib) is more likely to be that which has been assumed for SoC patients during maintenance.**
- **The HCRU frequency for SoC PD patients is more likely to be that which has been assumed for durvalumab patients during maintenance as these patients will now be receiving immunotherapies.**

Please conduct a scenario analysis based on the EAG's experts views on HCRU as presented in the table below.

Treatment arm	Health state	Resource use per monthly cycle									
		Outpatient visit	CT scan	Complete blood count	Specialist nurse visit	GP visit	Cancer antigen (CA)-125*	Thyroid function tests (TSH, T3 and T4)	Liver function tests	Kidney function tests	Cortisol level tests
SoC + D	PF: Chemotherapy phase	1.30	0.57	1.43	0.48	0.00	1.43	1.43	1.43	1.43	1.43
	PF: Maintenance phase	1	0.26	0.96	0.30	0.04	0.96	0.96	0.96	0.96	0.96
	PD	0.35	0.22	0.26	0.43	0.04	0.39	0	0	0	0
SoC + D + O	PF: Chemotherapy phase	1.30	0.57	1.43	0.48	0.00	1.43	1.43	1.43	1.43	1.43
	PF: Maintenance phase	1	0.26	0.96	0.30	0.04	0.96	0.96	0.96	0.96	0.96
	PD	0.35	0.22	0.26	0.43	0.04	0.39	0	0	0	0

SoC	**PF: Chemotherapy phase**	**1.30**	**0.57**	**1.43**	**0.48**	**0.00**	**1.43**	**0**	**0**	**0**	**0**
	PF: Maintenance phase	**0.35**	**0.22**	**0.26**	**0.43**	**0.04**	**0.39**	**0**	**0**	**0**	**0**
	PD	**1**	**0.26**	**0.96**	**0.30**	**0.04**	**0.96**	**0.96**	**0.96**	**0.96**	**0.96**

The HCRU estimates used in the original company submission were validated by five UK clinical experts. The clinical experts agreed that all key costs had been captured and that the frequencies were broadly reflective of UK practice.[18] Importantly, with respect to the frequency of some HCRU items (e.g., outpatient visits), clinical experts specifically stated that there would be variation across centres. Therefore, the frequencies used in the original company submission were intended to reflect a plausible average across the UK.

However, the company acknowledges that the EAG has also consulted a clinical expert who has proposed additional HCRU items and alternative frequencies. As such, the company have also provided a scenario analysis which reflects the EAG preferred alterations to HCRU estimates (Table 36 and Table 37 for dMMR and pMMR populations, respectively); this scenario has minimal impact on the ICER.

Table 36. Cost-effectiveness results for dMMR population for scenario with EAG-preferred alterations to HCRU estimates

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	62,182.50	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 37. Cost-effectiveness results for dMMR population for scenario with EAG-preferred alterations to HCRU estimates

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	58,485.24	4.57	3.27	[redacted]	0.89	0.67	[redacted]

Underlying hazard plots

B22. Priority question: Please provide the underlying hazard plots for PFS and OS for the dMMR and pMMR subgroups.

a) If long-term remission for patients is anticipated after 5 years progression-free, the EAG considers that the underlying hazard of progression for SoC and SoC + D(+/-O) would be similar. The difference between the two treatment arms would be that the occupancy in the progression-free health state is likely to be less for SoC. As such, if the underlying hazard plots for PFS demonstrate that after 5 years, the hazard of progression per cycle is not similar between the SoC and SoC + D(+/-O), please provide a scenario where the hazard of progression per cycle is the same for each treatment arm after 5 years for the dMMR and pMMR subgroups, separately.

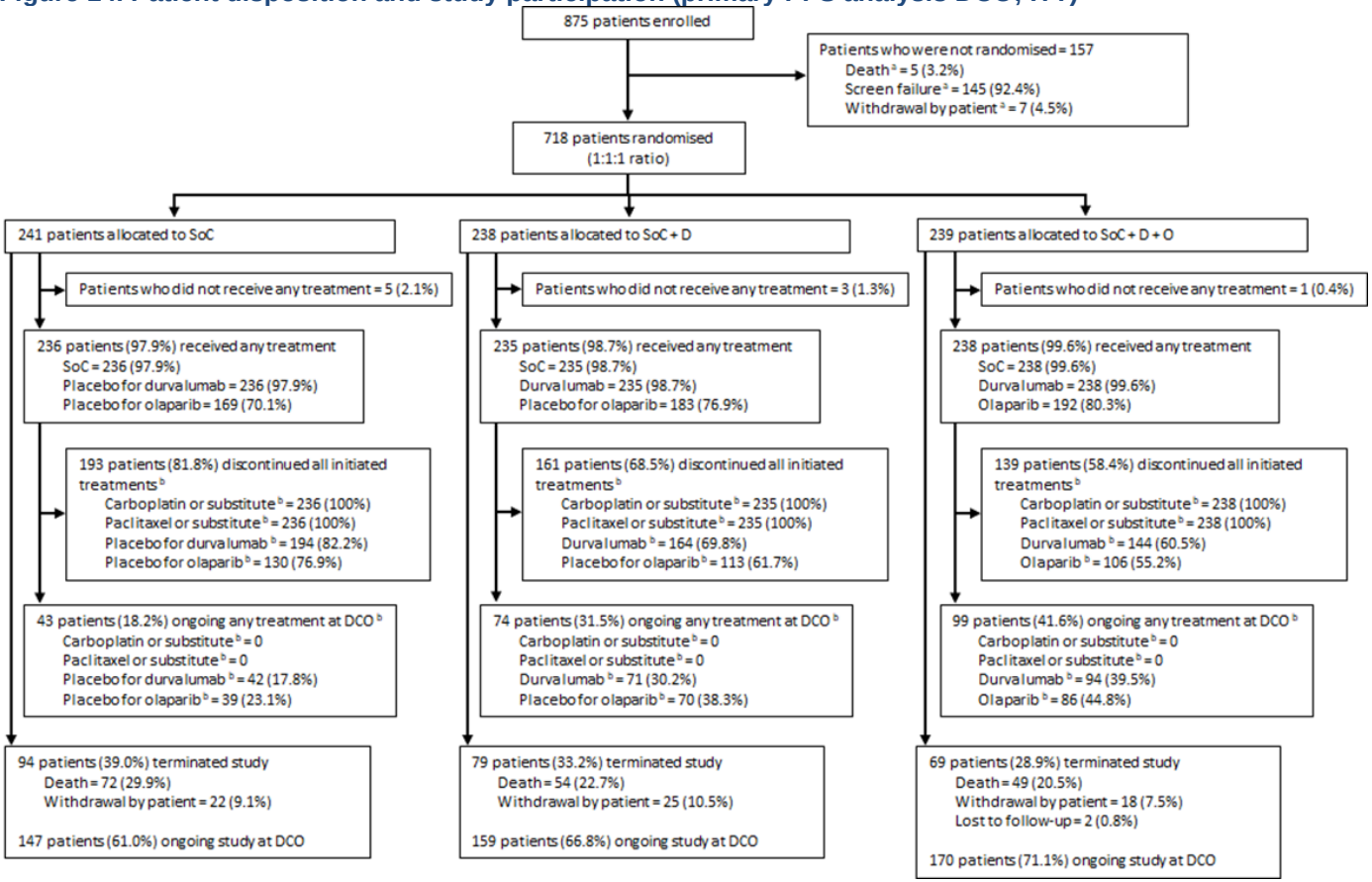
The response to B22 will be provided at a later date, as outlined in the company email to NICE

Section C: Textual clarification and additional points

C1. Please clarify if the text and numbers in Appendix D2 figure 3 reported as “Placebo for durvalumab = 164 (69.8%)” relate to the number of patients discontinuing treatment with durvalumab from the SoC + D study arm in the ITT population and if not, please provide an updated figure to show participant flow in each trial arm of the ITT population of DUO-E.

The company has reviewed Appendix D2 Figure 3, and identified a typographical error in this image. The correct version can be found in the CSR (Figure 3), and has also now been provided below in Figure 14. Based on the correct image, the company confirms that the “Placebo for durvalumab = 164 (69.8%)” should actually read “Durvalumab = 164 (69.8%)”, and that this figure does relate to the number of patients discontinuing treatment with durvalumab from the SoC + D study arm in the ITT.

Figure 14. Patient disposition and study participation (primary PFS analysis DCO; ITT)

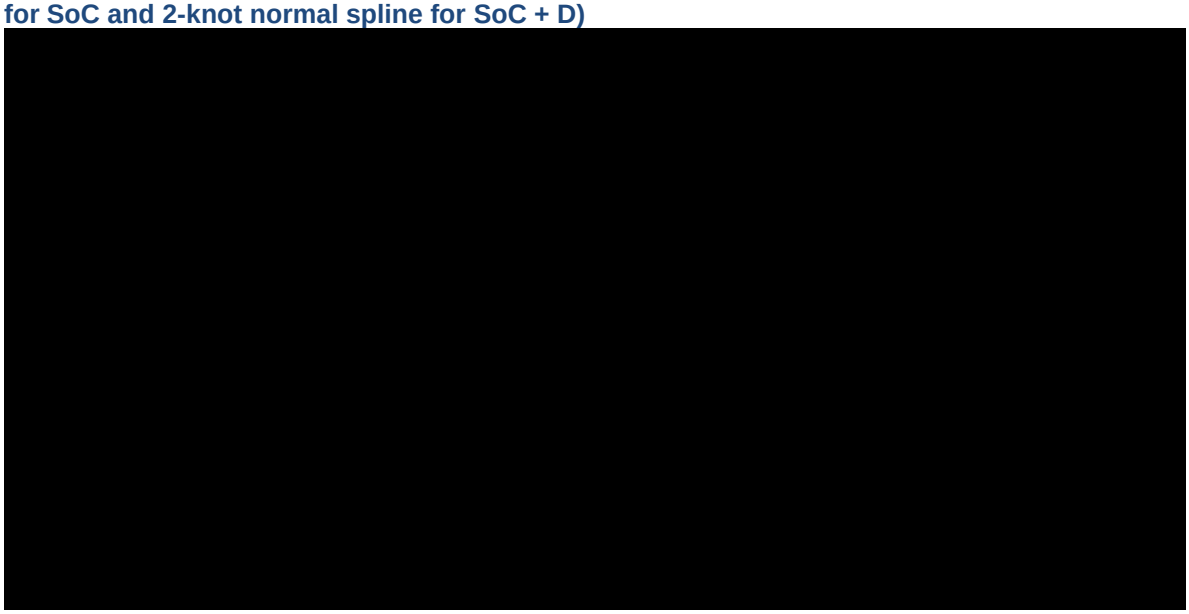


Footnotes: [a]Percentages were calculated from number of patients who were not randomised. [b]Percentages were calculated from number of patients who received the treatment.

C2. Figure 23 in the CS does not reflect the PFS survival plot in the model (presented below). Please clarify if the submission or the model is correct. If it is the submission, please clarify the settings in the model to reproduce the graph.

The company confirms that the graph in the submission is incorrect. Please consider the graph in the model and presented below in Figure 15 as correct.

Figure 15: dMMR PFS base case fitted curves from the economic model (1-knot normal spline for SoC and 2-knot normal spline for SoC + D)



C3. Figure 29 in the CS does not reflect the OS survival plot in the model (presented below). Please clarify if the submission or the model is correct. If it is the submission, please clarify the settings in the model to reproduce the graph.

The company confirms that the graph in the submission is incorrect. Please consider the graph in the model and presented below in Figure 16 as correct.

Figure 16: dMMR OS base case fitted curves from the economic model (lognormal)

C4. In the model, tab “PFS” cells N59 and AE59, should the column labels be “Prob of progression or death” instead of “Prob of death”? If so, please correct for clarity.

The company confirms that this has been corrected in the updated version of the model shared with the EAG. For the avoidance of doubt on how the calculations are labelled in the “PFS” tab, cells N59, AE59, and AV59 have been relabelled to “Prob of PFS event”. Cells O59, AF59, and AW59 have been relabelled to “Prob of PFS event (adjusted)”.

Appendix A – updated company base case

Based on feedback and inaccuracies highlighted by the EAG, the company has updated the following inputs in the base of the economic model submitted to NICE. These updates are as follows:

1. Updating the percentage of patients experiencing hypertension and pulmonary embolism in the SoC + D and SoC + D + O arms in the economic model to match the values reported in the CS and CSR.
2. Updating the dosage of subsequent pembrolizumab use in the economic model from 400mg to 200mg to reflect the 3-week dosing regimen for pembrolizumab.
3. Setting the utilisation of dostarlimab as a subsequent treatment for dMMR patients in the SoC arm to [redacted] as this therapy is funded through the CDF.
    a. To correctly capture clinician estimates on the total IO usage in 2L or beyond, the utilization of pembrolizumab use as a subsequent treatment for dMMR patients in the SoC arm was set to [redacted].

The updated company base case incorporating these changes is presented in Table 38Table 24 and Table 39, respectively.

Table 38. Updated company base case for pMMR population

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.10				
SoC	60,570.19	3.69	2.72	[redacted]	7.65	5.37	[redacted]

Table 39. Updated company base case for pMMR population

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.46	3.94				
SoC	54,863.71	4.57	3.27	[redacted]	0.89	0.67	[redacted]

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Additional clarification question received via a separate later request from the EAG

B22. Priority question: Please provide the underlying hazard plots for PFS and OS for the dMMR and pMMR subgroups.

b) If long-term remission for patients is anticipated after 5 years progression-free, the EAG considers that the underlying hazard of progression for SoC and SoC+D(+/-O) would be similar. The difference between the two treatment arms would be that the occupancy in the progression-free health state is likely to be less for SoC. As such, if the underlying hazard plots for PFS demonstrate that after 5 years, the hazard of progression per cycle is not similar between the SoC and SoC+D(+/-O), please provide a scenario where the hazard of progression per cycle is the same for each treatment arm after 5 years for the dMMR and pMMR subgroups, separately.

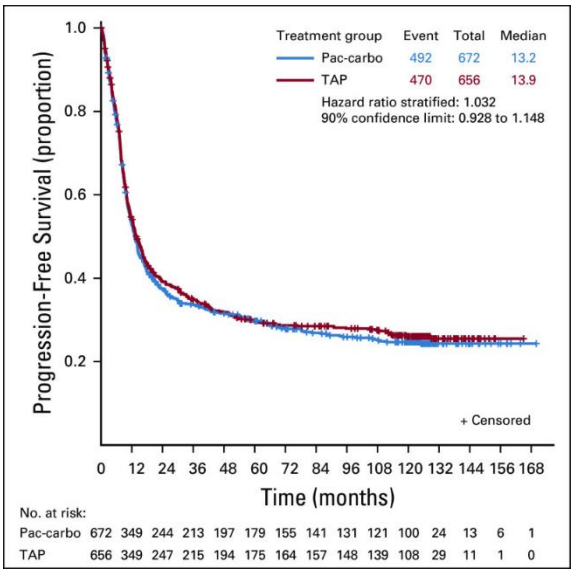
The company response to this question will first explore the current clinical understanding of the concept of long-term remission in EC, before moving on to explore how this relates to the DUO-E data and the way in which this was modelled in the original company submission. Finally a series of new scenario analyses are presented exploring the impact of different assumptions relating to long-term remission.

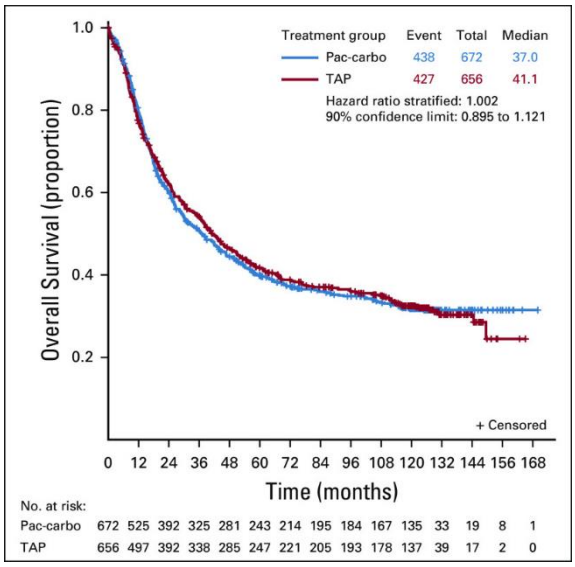
Current clinical understanding of long-term remission in EC:

There are several studies which support the fact that a proportion of EC patients may be able to achieve long-term remission even without receiving an IO therapy in the first line setting. For example, the GOG-0209 study was a noninferiority study comparing the paclitaxel-doxorubicin-cisplatin (TAP) regimen versus carboplatin plus paclitaxel in advanced or recurrent EC patients. Long-term follow-up from this study clearly demonstrates a plateau in both PFS and OS (as outlined in

Figure ***17*** below), with the PFS plateau occurring from around 3 years[(1)].

Figure 17: KM data from the GOG-0209 study for both PFS and OS





However, what remains uncertain is how patient and tumour characteristics impact the feasibility of achieving long-term remission, the time-point at which long-term remission may be considered, and the interplay between these factors. UK clinical experts consulted by the company highlight that they expect a proportion of patients to achieve long-term remission post-treatment. They specifically highlighted that many tumour characteristics would impact the curative potential of an individual patient (including stage, presence and site(s) or recurrence, degree of response, and MMR status)[(2)]. This is informed by multiple studies exploring the impact of such factors. The GOG-0209 study found that the plateau in OS was higher for patients with no measurable disease (compared to those with measurable disease), indicating that this may impact potential for long-term remission. Sorbe B et al reported plateaus in PFS for both primary advanced EC as well as recurrent EC, but notably the plateau for primary advanced EC occurred at an earlier timepoint (at around 2 years versus 3 years for recurrent patients) and for a greater proportion of patients[(3)]. Finally an analysis of Flatiron data between 2013 and 2022 explored the impact of MMR status, and demonstrated plateaus in survival probability for both pMMR and dMMR; however this analysis was notably limited by the small number of patients with known MMR status (the vast majority of the dataset had MMR unknown status, which is unsurprising given that this has only become an important classifier of EC in recent years)[(4)].

This uncertainty around which patients would achieve long-term remission, and when they might do so is apparent in the feedback from UK clinical experts relating to expected treatment duration for EC patients receiving the DUO-E regimen. Clinicians stated that they would consider individual patient factors to inform if/when to discontinue treatment; they envisage beginning conversations about treatment discontinuation between years 1 and 3 of treatment, but would expect the vast majority of

patient to be off-treatment within 5 years[5]. This wide range in time-points reflects the perceived complexity in predicting if and when a patient is in long-term remission.

DUO-E – underlying hazards and approach to long-term remission in the original company submission:

As detailed in the CS, the DUO-E trial data used for this appraisal is based on DCO1 (12 April 2023) with the available follow up durations detailed below in Table 40:

Table 40. DCO1 follow up (months)

Treatment arm	Duration of follow up (months) – median (range)
SoC (dMMR)	10.2 (0.0, 26.4)
SoC + D (dMMR)	15.5 (0.0, 29.1)
SoC (pMMR)	12.8 (0.0, 31.6)
SoC + D + O (pMMR)	15.2 (0.0, 31.7)

Therefore, the company is unable to assess and provide the 5 year hazard plots for PFS as the maximum trial follow up duration does not exceed 31 months in any of the subgroups or corresponding treatment arms. However, the company is able to provide the hazard plots in line with the maximum trial follow up periods detailed in Figure 18 and Figure 19. These are presented below:

Figure 18: Overlaid raw and smoothed hazards – pMMR PFS

Figure 19: Overlaid raw and smoothed hazards – dMMR PFS

Based on the hazard plots provided, the original CS did not explicitly model long-term remission as it was not considered appropriate for the following reasons:

1. When assessing the shape of the smoothed hazard for PFS in both MMR subgroups, there are noticeable differences in the observed hazards between the two treatment arms, indicating that hazard of progression between arms are not equal and do not clearly demonstrate a plateauing of the observed hazard in the trail.

2. Due to the limited trial follow up, it is un-clear from the smoothed hazard plots, or the Kaplan-Meir curves presented in the CS, that there is no reason to believe that a 'cure point' had been reached i.e., a hazard ration of <1 up to a cure point and hazard ratio =1 beyond that point. Instead, it was considered more appropriate to only consider standard parametric models in the pMMR subgroup and spline models in the dMMR subgroup for the full time horizon in the model (which has been extensively described in the CS and responses to questions B1 and B2 in this document).

The company also considered the uncertainty in the clinical literature (as described above) regarding which patients have the greatest probability of achieving long-term remission, and the timepoint at which this may occur.

Supplementary scenario analyses exploring long-term remission in DUO-E patients:

Despite the uncertainty in the clinical literature and the underlying hazard plots from DUO-E, the company considers the EAG's request to further explore the impact of long-term remission in DUO-E patients to be reasonable, and as such has conducted two additional scenario analyses which explicitly programme an assumption of long-term remission into the model. The approach taken was to implement a simple cure assumption where the standard and flexible parametric distributions are used in the model until a cure timepoint (i.e., 'boundary knot') is reached. Once this timepoint is reached, background general population mortality rates are then directly utilised in the model for both treatment arms. Thereby, setting the same hazard of progression per cycle for each treatment arm.

The scenarios conducted assume a cure timepoint of 5 years (as suggested by the EAG) and 3 years (this is the company preferred scenario as it aligns with UK clinical expert opinion that patients would begin to discontinue treatment between years 1 and 3, and because it better aligns with clinical literature such as the GOG-0209 study). The results are presented below.

Cure point at 5 years

Results in the dMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.15	-	-	-	-
SoC	60,004.34	4.17	3.07	[redacted]	7.17	5.08	[redacted]

Results in the pMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	5.46	3.98	-	-	-	-
SoC	54,637.02	4.57	3.28	[redacted]	0.89	0.70	[redacted]

Cure point at 3 years

Results in the dMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.34	8.19	-	-	-	-
SoC	59,710.94	4.88	3.58	[redacted]	6.46	4.62	[redacted]

Results in the pMMR subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	6.01	4.39	-	-	-	-
SoC	53,993.96	4.57	3.30	[redacted]	1.44	1.09	[redacted]

In conclusion, the company considers the original modelling approach presenting in the CS to be the most robust. Though, if long-term remission was to be explicitly modelled, the company preference would be to assume this occurs from 3 years onwards in line with the assumption in the CS that patients would discontinue treatment if progression free by 3 years and that most progression free events would occur before 5 years.

References

1. Miller DS et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). J Clin Oncol. 2020 Nov 20;38(33):3841-3850.
2. AstraZeneca. Durvalumab with or without olaparib in advanced or recurrent endometrial cancer - clinical interviews May 2024, 2024.
3. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer. 2008 Jul-Aug;18(4):803-8.
4. Chase DM, Kobayashi M, Gomez P, et al. 1424 Treatment patterns and outcomes by mismatch repair/microsatellite instability (MMR/MSI) status among patients with primary advanced or recurrent endometrial cancer (pA/rEC) in the United States. Journal for ImmunoTherapy of Cancer 2023;11
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for newly diagnosed advanced or recurrent endometrial cancer [ID6317]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
DUO-E in EC [ID6317]_Additional requests after CQs_15November24 [REDACTED]	FINAL	Yes	15th November 2024

EAG request: For the updated base case, please can the company supply the PSA, OWSA or updated results for the scenarios they ran for the original submission?

B.3.11 updates after change to the company base case.

dMMR probabilistic results

In the probabilistic base-case analysis for the dMMR population, SoC + D was associated with [redacted] incremental costs and 4.92 incremental QALYs compared to SoC alone, which corresponds to an ICER of [redacted] per QALY gained (Table 92).

The ICEP, CEAC and CEAF for the dMMR population are presented in Figure 38 to Figure 40, respectively. 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, SoC + D has a [redacted] chance of being cost-effective and at a WTP threshold of £20,000 per QALY, SoC + D has a [redacted] chance of being cost-effective.

Table 1. PSA base-case results – dMMR

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D	[redacted]	11.21	8.01	-	-	-	-
SoC	61,026.71	4.21	3.09	[redacted]	6.99	4.92	[redacted]

Figure 1. Incremental cost-effectiveness plane (ICEP) – dMMR

Figure 2. Cost-effectiveness acceptability curve (CEAC) – dMMR

Figure 3. Cost-effectiveness acceptability frontier (CEAF) – dMMR

pMMR probabilistic results

In the probabilistic base-case analysis for the pMMR population, SoC + D + O was associated with [redacted] incremental costs and 0.69 incremental QALYs compared to SoC alone, corresponding to an ICER of [redacted] per QALY gained (Table 93).

The ICEP, CEAC and CEAF for the pMMR population are presented in Figure 41 to Figure 43, respectively. 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, SoC + D + O has a [redacted] chance of being cost-effective and at a WTP threshold of £20,000 per QALY, SoC + D + O has a [redacted] chance of being cost-effective.

Table 2. PSA base-case results – pMMR

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
SoC + D + O	[redacted]	5.50	3.97	-	-	-	-
SoC	55,185.60	4.59	3.28	[redacted]	0.92	0.69	[redacted]

Figure 4. Incremental cost-effectiveness plane (ICEP) – pMMR

Figure 5. Cost-effectiveness acceptability curve (CEAC) – pMMR

Figure 6. Cost-effectiveness acceptability frontier (CEAF) – pMMR

Deterministic sensitivity analysis

dMMR OWSA results

Figure 7. OWSA tornado diagram – dMMR

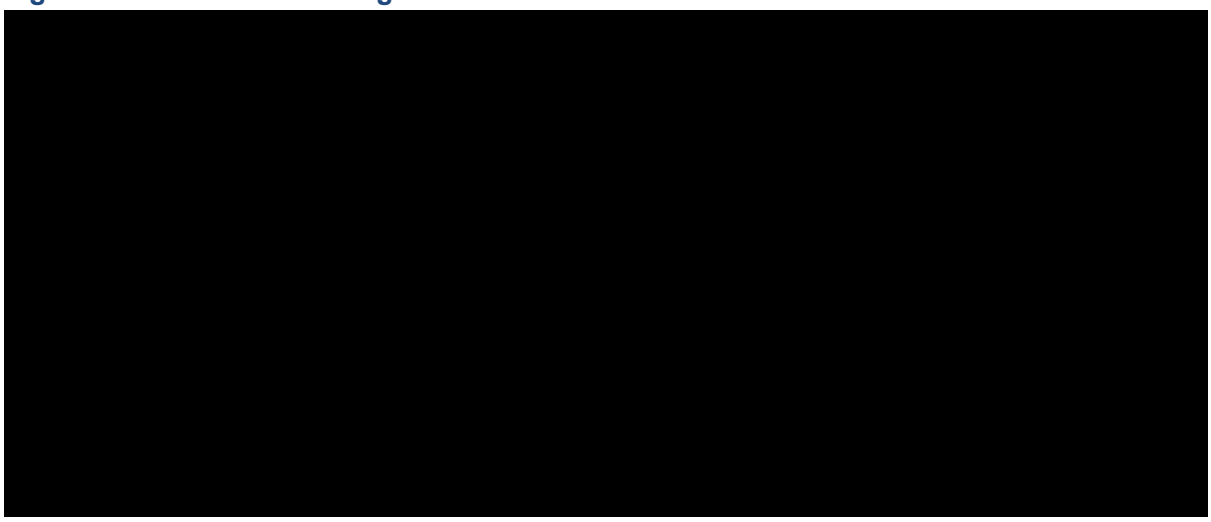


Table 3. Tabulated OWSA results – dMMR

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Drug administration cost : IV subsequent attendance	[redacted]	[redacted]	[redacted]
Pembrolizumab proportion as a subsequent therapy in : SoC	[redacted]	[redacted]	[redacted]
Outpatient Visit unit cost	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month : PD Health State : SoC + Durvalumab	[redacted]	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy in each cycle : SoC	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit unit cost	[redacted]	[redacted]	[redacted]
Total cost of EOL care	[redacted]	[redacted]	[redacted]
CT scan unit cost	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit resource units per month : PD Health State : SoC + Durvalumab	[redacted]	[redacted]	[redacted]
Proportion of non-fatal PFS events per monthly cycle	[redacted]	[redacted]	[redacted]

pMMR OWSA results

Figure 8. OWSA tornado diagram – pMMR

Table 4. Tabulated OWSA results – pMMR

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Pembrolizumab proportion as a subsequent therapy in : SoC	[redacted]	[redacted]	[redacted]
Drug administration cost : IV subsequent attendance	[redacted]	[redacted]	[redacted]
Utility for PF state	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month : PD Health State : SoC	[redacted]	[redacted]	[redacted]
Proportion of progressed patients receiving subsequent therapy in each cycle : SoC	[redacted]	[redacted]	[redacted]
Lenvatinib/Lenvatinib mesilate proportion as a subsequent therapy in : SoC	[redacted]	[redacted]	[redacted]
Outpatient Visit resource units per month : PD Health State : SoC + Durvalumab + Olaparib	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit resource units per month : PD Health State : SoC	[redacted]	[redacted]	[redacted]
Specialist Nurse Visit resource units per month : PD Health State : SoC + Durvalumab + Olaparib	[redacted]	[redacted]	[redacted]
CT scan resource units per month : PD Health State : SoC	[redacted]	[redacted]	[redacted]

dMMR scenario analyses results

Table 5. Results for scenario analyses explored in the cost-effectiveness analysis – dMMR

No.	Category	Base-case value	Scenario value	Inc. costs	Inc. QALYs	ICER (£/QALY)
Base case	-	--	-	[redacted]	5.37	[redacted]
1	Time horizon	Lifetime	25 years	[redacted]	4.96	[redacted]
2	Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	[redacted]	6.86	[redacted]
3	PFS: SoC + D and SoC	SoC + D: Spline, k = 2 SoC: Spline, k = 1	Spline, k = 1	[redacted]	5.28	[redacted]
4			Spline, k = 2	[redacted]	5.14	[redacted]
5	OS: SoC + D and SoC	Log-normal	Gamma	[redacted]	4.12	[redacted]
6			Log-logistic	[redacted]	4.60	[redacted]
7	TDT (applies to all treatments)	Treatment duration 3 years, **parametric curve** approach for 1-3 years. Drop to zero at year 3.	Treatment duration **2 years**, **parametric curve** approach for 1–2 years. Drop to zero at year 2.	[redacted]	5.37	[redacted]
8			Treatment duration **5 years**, **parametric curve** approach for 1–3 years, **exponential** drop-off 3–5 years	[redacted]	5.37	[redacted]
9			Treatment duration 3 years, **Weibull distribution** for 1–3 years	[redacted]	5.37	[redacted]
10	Half cycle correction	Included	Excluded	[redacted]	5.36	[redacted]
11	Source for age-adjusting utilities	Alava *et al.* (2022)	Ara and Brazier (2010)	[redacted]	5.42	[redacted]
12	Wastage	Excluded	Included	[redacted]	5.37	[redacted]
13	Source for health state utility values (HSUV)	DUO-E ITT	NICE TA914[32]	[redacted]	4.93	[redacted]
14	AE disutilities	Included	Excluded	[redacted]	5.38	[redacted]
15	Baseline age	62.6	67.1 (TA963)[30]	[redacted]	4.89	[redacted]
16			[redacted]	[redacted]	5.39	[redacted]

17	End-of-life care cost	Included	Excluded	[redacted]	5.37	[redacted]
18	Life tables	2017-19	2020–22	[redacted]	5.35	[redacted]
19	Radiotherapy unit cost	£3,672.00	£763.00	[redacted]	5.37	[redacted]
20	Carboplatin AUC units	100% AUC 6 units	100% AUC 5 units	[redacted]	5.37	[redacted]

pMMR scenario analyses results

Table 6. Results for scenario analyses explored in the cost-effectiveness analysis – pMMR

No.	Category	Base-case value	Scenario value	Inc. costs	Inc. QALYs	ICER (£/QALY)
Base case	-	-	-	[redacted]	0.67	[redacted]
1	Time horizon	Lifetime	25 years	[redacted]	0.65	[redacted]
2	Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	[redacted]	0.78	[redacted]
3	PFS: SoC + D + O and SoC	Log-logistic	Log-normal	[redacted]	0.67	[redacted]
4	OS: SoC + D + O and SoC	Log-logistic	Log-normal	[redacted]	0.96	[redacted]
5			Gamma	[redacted]	0.69	[redacted]
6	TDT (applies to all treatments)	Treatment duration 3 years, **parametric curve** approach for 1-3 years. Drop to zero at year 3.	Treatment duration **2 years**, **parametric curve** approach for 1–2 years. Drop to zero at year 2.	[redacted]	0.67	[redacted]
7			Treatment duration **5 years**, **parametric curve** approach for 1–3 years, **exponential** drop-off 3–5 years	[redacted]	0.67	[redacted]
8			Treatment duration 3 years, **Exponential distribution** for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
9			Treatment duration 3 years, **Gompertz distribution** for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
10	Half cycle correction	Included	Excluded	[redacted]	0.67	[redacted]
11	Source for age-adjusting utilities	Alava *et al.* (2022)	Ara and Brazier (2010)	[redacted]	0.67	[redacted]
12	Wastage	Excluded	Included	[redacted]	0.67	[redacted]

13	Source for HSUV	DUO-E ITT	NICE TA914[121]	[redacted]	0.62	[redacted]
14	AE disutilities	Included	Excluded	[redacted]	0.68	[redacted]
15	Baseline age	62.6	67.1 (TA963)[30]	[redacted]	0.65	[redacted]
			[redacted]	[redacted]	0.67	[redacted]
17	End-of-life care cost	Included	Excluded	[redacted]	0.67	[redacted]
19	Life tables	2017-19	2020–22	[redacted]	0.67	[redacted]
20	Radiotherapy unit cost	3672	763	[redacted]	0.67	[redacted]
21	Carboplatin AUC units	100% AUC 6 units	100% AUC 5 units	[redacted]	0.67	[redacted]

EAG request: additional clarification question - follow-up question to B10

B23. The company has explained that [redacted]% of SoC+D+O patients in the pMMR subgroup did not initiate olaparib maintenance treatment because of disease progression or not meeting the eligibility criteria. The intervention under consideration for decision problem for the pMMR subgroup is induction durvalumab with platinum-based chemotherapy followed by maintenance durvalumab with olaparib. As such, the EAG is concerned that a proportion of patients who were not eligible to initiate olaparib were therefore on durvalumab monotherapy, which is a different treatment regimen to the one under consideration and which will be used in clinical practice for the pMMR subgroup. Additionally, maintenance durvalumab monotherapy may be associated with different outcomes to maintenance durvalumab with olaparib.

a) **Please provide the following:**

   i) **The breakdown of patients in the SoC+D+O treatment arm in the pMMR subgroup who did not initiate maintenance treatment with olaparib because of:**

      1) **Disease progression.**

      2) **Not meeting eligibility criteria for the maintenance (but are progression-free)**

   ii) **The number of SoC+D+O patients that received maintenance durvalumab monotherapy (i.e. were never initiated on olaparib maintenance).**

b) **Please provide an explanation of why pMMR patients in the SoC+D+O arm were allowed to continue on durvalumab if they could not have olaparib, which is part of the combination for the treatment arm?**

c) **Please clarify the following:**

i) **If the company are seeking a recommendation in the pMMR subgroup for both durvalumab with olaparib (in patients that can receive olaparib) AND durvalumab monotherapy (in patients that cannot received olaparib).**

ii) **If, in UK clinical practice, clinicians would be permitted to keep patients on maintenance durvalumab if they are ineligible for olaparib (i.e. is this in the draft SmPCs for both treatments in this indication?)**

Part A:

As outlined in table 1 below, a total of [redacted] patients in the SoC+D+O arm of the DUO-E trial did not receive any maintenance treatment at all (either olaparib or durvalumab), either due to the fact that they had already experienced disease progression ([redacted]), or because they were ineligible for other reasons (e.g., not meeting maintenance eligibility criteria, discontinuation due to adverse events, patient choice etc, [redacted]). Of the patients who did go on to receive some form of treatment in the maintenance setting ([redacted]) the vast majority of went on to receive SoC+D+O ([redacted]), while only a very small minority received durvalumab as monotherapy ([redacted]). Therefore, the total number of patients who did not receive olaparib in the maintenance setting for reasons other than disease progression is [redacted].

Table 1: Disposition of patients in the pMMR subgroup within the SoC+D+O arm

		Patients (n)	% of all randomised patients
Total patients randomised		[redacted]	[redacted]
Patients who received any treatment		[redacted]	[redacted]
Received durvalumab with or without olaparib as maintenance	Patients who started the maintenance phase and received at least one dose of olaparib/placebo	[redacted]	[redacted]
	Patients started durvalumab/placebo at maintenance dose but did not receive at least one dose of olaparib/placebo	[redacted]	[redacted]

Did not receive any maintenance treatment	Patients who did not become eligible for the maintenance phase (either olaparib or durvalumab) due to disease progression	[redacted]	[redacted]
	Patients did not initiate the maintenance phase (either olaparib or durvalumab) for other reasons (e.g., not meeting eligibility criteria, study discontinuation due to adverse events or patient choice, etc)	[redacted]	[redacted]

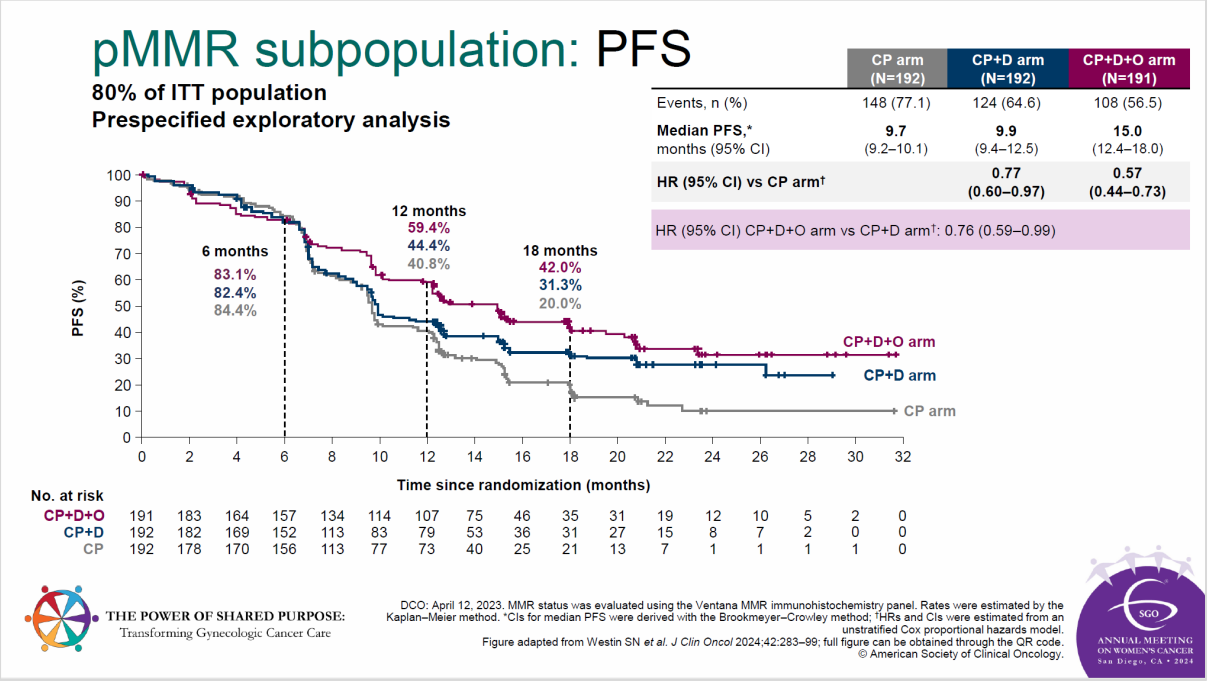
Part B:

Although olaparib and durvalumab were used as a combination in the SoC+D+O arm, it is important to recall that these are distinct treatments, with their own specific set of contraindications and toxicity considerations. As such, there will inevitably be patients in clinical practice for whom their treating clinician considers it appropriate to offer one of these drugs but not the other, given individual patient factors and comorbidities. Furthermore, patient fitness is inherently variable over a patient's individual treatment journey.

In a situation where a patient is specifically not considered suitable for treatment with olaparib in the maintenance phase of the DUO-E regimen, with a set of specific eligibility criteria defined in the study protocol, the alternative options are either to allow them to continue durvalumab alone, or to discontinue all treatment (i.e., they receive only routine surveillance in the maintenance setting). In the DUO-E trial, although the best efficacy for pMMR patients was observed with the combination of SoC+D+O, the efficacy of the SoC+D regimen was still superior to SoC alone (see figure 1 below). There is therefore clinical rationale to allow some patients who cannot initiate olaparib maintenance to receive SoC+D maintenance instead. Also, it must be highlighted that this occurred in a minority of patients in the DUO-E trial ([redacted] as outlined in table 1) and would be expected to occur in a similarly small minority of patients in real-world practice.

Furthermore, it is important to reiterate that the DUO-E trial efficacy analysis was conducted on an intention-to-treat basis. Therefore, the KM curves and hazard ratios outlined below in figure 1 (and which are used to inform the economic analyses) already account for the fact that a proportion of patients who were originally intended to receive the SoC+D+O regimen do not remain eligible for it following the induction phase. Hence the economic case presented by the company already takes into consideration the complexities of real-world clinical practice in this regard.

Figure 1: DUO-E observed PFS in the pMMR subpopulation



Part C:

The company anticipates that use in clinical practice for pMMR patients will be on an intention-to-treat basis which mirrors how it was used in the DUO-E trial itself.

[redacted]

The company is seeking a NICE recommendation which is aligned to the anticipated marketing authorisation, and which enables a degree of flexibility for the small minority of patients who become ineligible for olaparib after receiving the chemotherapy phase of their treatment plan (expected to be [redacted] of patients based on the DUO-E trial, as outlined in table 1). If such flexibility is not permitted within the NICE recommendation for the DUO-E pMMR subgroup, it risks creating inequity of access whereby such patients who commence the DUO-E regimen are ultimately not able to receive any maintenance treatment, whereas those patients who commence future chemotherapy+IO regimens that do not include a PARPi (e.g. the future chemotherapy+pembrolizumab regimen based on the NRG-GY018 trial) would not face this risk.

In conclusion the company would like to highlight that for the pMMR subgroup they are simply seeking a NICE recommendation which aligns with the DUO-E study design [redacted], and which permits a degree of pragmatism for the small minority of patients who become ineligible for olaparib after completing the chemotherapy treatment phase. This has already been accounted for in the presented efficacy results as well as the economic analyses presented by the company, given the intention-to-treat analysis used in the DUO-E trial. For this reason, the company do not regard this to be a source of significant uncertainty within this appraisal.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

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	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Peaches Womb Cancer Trust is a charitable organisation with the mission to improve the lives of those affected by womb cancer by funding vital womb cancer research, increasing public awareness and providing support during and after diagnosis and treatment. The charity is funded through fundraising and donations. Peaches Womb Cancer Trust also hosts 'Peaches Patient Voices', a patient and public involvement group for people affected by womb cancer. We work with, and advocate for, people affected by womb cancer – diagnosed at all stages – and their loved ones.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Nones

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Peaches Womb Cancer Trust has contributed the views, insights, and expertise of our Peaches Patient Voices network, and used our evidence to highlight the difficult situation many patients face when diagnosed with newly diagnosed advanced or recurrent endometrial cancer. As an organisation, we have presented our evidence on the impact of advanced and recurrent endometrial cancer, and available treatments, on our Patient Voices community. Peaches Womb Cancer Trust has valued the opportunity to use evidence obtained from members of Peaches Patient Voices to demonstrate the both the potential positive outcomes, and possible negative impacts, of the proposed technology for many people facing newly diagnosed advanced or recurrent endometrial cancer. The following submission includes evidence obtained from extensive patient engagement, including: • focus groups and questionnaires that informed our previous submissions (ID3811 and ID3968) and involved women with lived experience of advanced or recurrent endometrial cancer • these focus groups included women with stage 3 and 4 endometrial cancer and, in the focus group that informed ID3968, two carers of women with stage 4 endometrial cancer who had undergone primary treatment with surgery and/or chemotherapy and radiotherapy. • previously used statement of a patient expert with lived experience of being on a PD-1 inhibitor immunotherapy (Hannah) – along with updated statement from the same patient to reflect her experiences following finishing immunotherapy, in line with the 2 year stopping rule.

	Note that some quotes or experiences may reflect a PD-1 inhibitor immunotherapy that is not the same as the one in the technology under appraisal here. The rationale for including these is that side effects are likely to be similar.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of advanced endometrial cancer has a significant impact on every aspect of women's lives. Many found their physical symptoms debilitating. At the time of diagnosis, these included vaginal bleeding, pain and discomfort, watery vaginal discharge, urinary urgency/ incontinence, reduced appetite, nausea, fatigue, and abdominal swelling. These symptoms impacted their quality of life, due to the practical implications of bleeding and urge incontinence, and some women found it challenging to leave the house to socialise and work. Many women experienced diagnosis-induced feelings of terror and fear at having to face one's own mortality, and many of those diagnosed with stage 3 cancer felt in 'limbo' following treatment due to the uncertainty of recurrence. Some felt unable to cope with small things following treatment, affecting their previously positive outlook and crying more easily. Many felt like a different person following their diagnosis and treatment, in part due to feeling physically different, but mostly due to the psychological impact. Many felt that their relationships with family and friends altered following their diagnosis, and that people treated them differently. There was also ongoing worry and anxiety about how their diagnosis would impact family members and children, and how they would cope. One woman described how her teenage son's anxiety had become significantly worse following her diagnosis resulting in him needing additional mental health support. Other patients reported: *"I panicked about dying. Nobody definitively told me I wouldn't. I cried about not seeing my children get married; maybe never holding my grandchildren."* *"I worry about dying if the treatment stops working. We try to make the most of my good days, but always worry what is round the corner, will I see my youngest grandchild start school? How far ahead can we make plans? Can I think about skiing next year, or will I be dead by Christmas?"* *"I am constantly anxious and hypervigilant for any signs of recurrence. I have symptoms that could be recurrence and have my 3-monthly check up in 2 weeks. So, even though I finished treatment [last year], cancer is still part of my daily life."*

	"Current treatments do not negate the possibility of recurrence, so the fear of recurrence is real and present. I have asked, but no one will make assurances or predictions for me. They generalise and make hopeful comments, whilst acknowledging they have no crystal ball. They know, and I know, that everyone did their best for me, but that sometimes the best still fails." Women with stage 4 cancer are likely to report debilitating symptoms caused by the cancer. One of the women with stage 4 disease had ascites (fluid build-up in the abdomen) at the time of diagnosis. This caused significant pain and a reduction in her mobility, as well as impacting her ability to perform activities of daily living, leaving her increasingly reliant on friends and family for help. The ascites required recurrent drains resulting in frequent trips to the hospital with associated costs and impact on quality of life. As her cancer progressed, she also required bilateral nephrostomies due to ureteric obstruction, which impacted her physically, reducing her mobility. Another woman had ongoing bowel problems, including pain and constipation at the time of diagnosis due to a recurrence resulting in a tumour in her upper rectum. People caring for those with advanced or recurrent endometrial cancer face significant challenges. Many described the emotional challenges of being a carer, the constant feeling of helplessness, and the psychological impact on them. Caring for someone at home who is end of life causes significant challenges, both physically and psychologically. Many will require care around the clock, resulting in carers having to take time off work, impacting financially, but also resulting in fatigue, burnout, guilt, frustration and grief. *"The carer takes over the huge burden of looking after the patient, the family, continuing work and providing emotional as well as physical support to the patient. They might be taking the patient to the hospital appointments, encounter long waiting times, arrange for GP appointments, etc. All these commitments for a carer are on top of all the other family commitments the carer has to take on."* *"[It's] terrible to watch your loved one failing and relying on you for support. My health and wellbeing [were] impacted trying to be strong and keep things together. The emotional support of*

	loved ones is seriously lacking as they have to be strong, but it is deeply emotional and resulted in me suffering from panic attacks and prescribed antidepressants." *"You feel guilt that you cannot fix it or do it for them."* One carer described the pain of anticipatory grief of caring for someone who is at the end of their life: *"You are constantly wondering when they will stop replying to your messages, or when the ticks on WhatsApp will stop turning blue."* Following the death of someone from advanced or recurrent endometrial cancer, there is a long-term impact of grief, including uncertainty about how you acted; whether you could have done more; whether you could have spent more time with them; or whether you should have done something differently.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**1. Women were dissatisfied and frustrated by current treatments for advanced and recurrent endometrial cancer, which include surgery, chemotherapy and radiotherapy.** Women found chemotherapy challenging due to a multitude of short- and long-term side effects, which have affected their quality of life. Short term effects included fatigue, nausea and vomiting, mouth pain, hair loss, change in bladder and bowel habit and neutropenia. Many had to take additional medication to reduce side effects, but they also experienced other side effects from these medications. Several women mentioned the effect of chemotherapy on the immune system and felt it left them vulnerable. This significantly impacted their quality of life, with many unable to work face to face, requiring time off, or unable to go out and spend time with family and friends. Some were also unable to undertake activities such as swimming due to the risk of infection. *"I worry about the side effects of treatment, ending up in hospital […] with a fever."* **2. Many patients reported long term, often debilitating side effects from treatment that prevent them from living a fulfilling life.** Long term side effects of current treatments for newly diagnosed advanced or recurrent endometrial cancer included pain, bowel and bladder issues, lymphoedema and fatigue, which have left women anxious. For some, it has affected their confidence going out to social events/ gatherings due to tiredness, access to the toilet and fear of 'accidents' such as urinary leakage. For others, limited mobility and pain means they are unable to leave the house. This also takes a significant toll on their mental health. Chemotherapy-induced peripheral neuropathy can cause pain in hands and feet. One patient reported: *"I still have neuropathy in my feet, sharp enough to make me yelp in surprise sometimes, painful enough to be annoying, but not life changing."* *"I experienced fatigue like never before. At times I would be doing ok and then it would feel as if something had been 'switched off' – no run down, gradual descent, just instantaneous."*

	3. Many patients have been left unable to work, due to after-effects of treatment, or have to work less than full time, affecting them financially. This leads to additional concerns and anxiety around how they might afford the cost of living. Even if they have felt well enough to go back to work, women report anxiety around controlling their treatment-related symptoms at work and access to a private toilet. Patients reported: *"I was left virtually incontinent of both bladder and bowel […] and although I have had physio for this, there has not been a huge amount of improvement. It is affecting my ability to return to a job I love."* *"I couldn't work for about 18 months so I ran out of sick pay, and I'm currently on a phased return to work, so reduced pay as I can only manage about 18 hours a week at the moment."* *"It has had a huge impact on my work, family and social life. I have lost a lot of confidence due to the effects I still struggle with and rarely go out on an evening. At the weekend I can't manage to do something sociable during the day and then go out on an evening too".* *"I had to stop work for 11 months because of my treatment. I was told unequivocally by my oncologist at the start that I wouldn't be returning to [work] that year. At the time, this seemed incredible to me, but the roller-coaster of all the treatment cycles (fatigue/ nausea/ low neutrophil counts/ frequent hospital visits which were a two hour round trip) meant that it would have been impossible for me to continue going to work."* **4. Womb cancer treatment has a substantial financial impact on patients.** Patients reported significant financial impact both through the time it takes to receive treatment and the long-term side effects. This included: • cost of travel to treatment and parking at the hospital • long term sick leave with implications to pay • cost of living at home (e.g. heating)

- cost of complementary therapies to support wellbeing or manage side effects

5. Some women are unable to live fully independently due to physical symptoms and limited mobility

Due to the impacts of treatment, some women have had to access help from family members for a number of activities of daily living, including; cooking, cleaning, help with bathing and medications. This leaves them feeling frustrated and a burden on family members. As a carer, this impacts financially due to time off work, psychologically due to constant worry and anxiety about your loved one and less time for yourself, and physically due to the additional activities on top of your own day to day living.

> *"I don't have the energy to do normal daily tasks which means that […] my husband took on more work/chores, my 76-year-old mother had to come over to do washing for me."*

One of the carers we spoke to cared for her friend who sadly passed away from endometrial cancer in her mid to late thirties. She told us of the additional challenges of undergoing treatment when one is pre-menopausal with no children. Her friend struggled with menopausal symptoms following surgical treatment, including hot flushes, fatigue and difficulty sleeping. The psychological impact of treatment for endometrial cancer on fertility is huge, and delays in diagnosis leading to advanced stage disease may mean that fertility options are not available, leaving women angry, frustrated and distressed.

6. Treatments including hysterectomy and radiotherapy also significantly impacted on sexual intimacy These impacts are due to multiple factors, including vaginal discomfort, bleeding and the vulnerability and trauma that comes with repeated intimate examinations.

> *"It was very traumatised by the diagnosis process regarding intimate examinations, which included painful examinations in an emergency situation and other multiple different examinations. This meant brachytherapy was particularly difficult for me, and my oncologist kindly performed the procedures, rather than the nursing team, because I trusted her. This has also greatly impacted my sexual function – both due to the trauma of invasive and difficult*

	examinations and the long-term side effects of a shortened vagina from surgery, stenosis (narrowing) caused by radiotherapy, and menopause."

8. Is there an unmet need for patients with this condition?	**Urgent need for earlier access to innovative first-line treatments for women with advanced or recurrent endometrial cancer** There is a significant unmet need for patients with all molecular subtypes of newly diagnosed advanced or recurrent endometrial cancer to gain earlier (first-line) access to effective and innovative treatment options. Currently, there are limited effective treatments available for these patients, with the standard of care being "bog standard" chemotherapy, which has limited effectiveness and causes significant side effects. Receiving effective and innovative treatments earlier in the treatment pathway would reduce the overall treatment burden and offer people with newly diagnosed advanced or recurrent endometrial cancer hope for living with no, or well-managed disease, for longer. Patients have clearly articulated the need for earlier access to innovative and effective treatment options. Access to immunotherapy is currently delayed until the second-line setting, with options such as pembrolizumab combined with lenvatinib, or pembrolizumab monotherapy for those with dMMR endometrial cancer. Although some patients can access dostarlimab in the first-line setting, this is limited to certain individuals with dMMR (high microsatellite instability) endometrial cancer through the Cancer Drugs Fund. Accessing treatment this way, or through special license, can lead to delays in obtaining necessary care. One patient, speaking about her deceased mother, said: *"[My mother's] cancer was aggressive and oestrogen sensitive. There is a lot of paperwork and red tape to get funding; patients and their families don't have time to wait for approvals. It needs to be available and ready."* The unmet need for innovative and effective treatment is even greater for those with pMMR endometrial cancer, who currently have no access to first-line immunotherapy, which has been shown to be less effective than in people with dMMR endometrial cancer. This underscores the urgent need for an effective and innovative treatment for those with pMMR endometrial cancer. **Unmet need for patients with stage 3 endometrial cancer**

	For patients with newly diagnosed stage 3 disease, the current pathway requires them to wait for a recurrence before they can access immunotherapy. Living with the knowledge of a relatively high risk of recurrence - and the possibility of facing aggressive treatment, with the cancer potentially becoming incurable - creates ongoing fear and uncertainty about the future. The unmet need in this situation is for a treatment that prevents recurrence or progression to incurable stage 4 cancer. Such a treatment would offer hope for living free of cancer for longer, or even a potential cure. Women we spoke to who had experienced stage 3 endometrial cancer commented: *"The current approach is geared towards expecting a recurrence and then adding a more effective second-line treatment. It is paramount to offer endometrial cancer patients a first-line treatment that will further reduce the chance of the cancer recurring."* *"I have […] twice been subject to clinical investigation for suspected recurrent disease. Being aware that survival rates for advanced disease are considered poor and knowing that my only treatment option offered by the NHS would be 'bog standard chemotherapy' as first line filled me with dread and fear."* **Unmet need for patients with stage 4 or recurrent endometrial cancer** For patients with stage 4 or recurrent disease, standard of care means that they must endure chemotherapy first, despite receiving this devastating diagnosis, before being able to access immunotherapy as a second-line treatment. By this time, their cancer may have progressed, and/or their health may have worsened, leading to further devastating impacts on their well-being and reducing their ability to tolerate subsequent treatments. Access to earlier, more effective treatment would provide better symptom control, extend the time before cancer progresses, and improve the possibility of a more meaningful and longer life. **Unmet need for equal access to effective treatments for women with advanced or recurrent endometrial cancer**

	Many women expressed frustration, disappointment, anger, and feelings of abandonment due to the limited effective first-line treatment options for advanced endometrial cancer. They felt left behind or not prioritised for effective treatment options, believing that women affected by endometrial cancer had fewer effective treatment options compared to other cancers. Several patients referred to the availability of multiple lines of treatment for breast cancer and expressed a desire for access to similar multiple lines of treatment for womb cancer. One patient expressed that: *"The UK has some of the poorest cancer survival rates compared to Europe. However, where improvements in cancer survival rates are seen, it is in those cancers where a combined treatment approach is clinically available on the NHS, involving traditional chemotherapy plus newer targeted treatments. In many cancers, these are available in both first-line and second-line treatments. All patients, regardless of their cancer type, should have equal access to the potential survival benefits that these newer cancer treatments may offer."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The main advantages of the technology that patients identified are: 1. **Access to effective first-line treatment for people with stage 3 cancer** Patients with stage 3 endometrial cancer would benefit from a first-line treatment that may reduce the chance of recurrence. *"[I want] the cancer to be gone and the risk of recurrence to be hugely, (ideally completely), eliminated."* 2. **Benefits for people with stage 4 disease and recurrence** For patients with stage 4 endometrial cancer or those experiencing recurrence, the technology offers several key advantages: • **Extended progression-free survival:** Patients can achieve longer periods without cancer progression. • **Improved overall quality of life:** Allowing more time with family and friends, and fostering hope of living a meaningful life. *"I want a treatment that will stop the spread, reduce the size of, or get rid of the cancer. Preferably the latter. I want my life prolonged, the worry to stop, and to get back to normal."* • **Bridging to future treatments:** Staying well for longer improves the likelihood of accessing further innovative treatments in the future. 3. **Impact on treatment pathway and independence** Gaining access to more effective treatments earlier in the treatment pathway could lead to: • **Better symptom control:** Fewer debilitating symptoms in the long term.

- **Longer remission or stable disease:** Patients desire treatments that keep them in remission or maintain stable disease for extended periods, which allows them to retain independence longer and live life as fully as possible.

5. **Potential to avoid additional surgeries**
   Earlier access to effective treatments may prevent the need for further surgeries to manage tumour growth after initial treatment. For instance, recurrence following stage 3 or progression of stage 4 cancer often necessitates additional surgical interventions. For example, in the case of Hannah (whose story is shared below), a recurrence in her rectum required a Hartmann's procedure to create a colostomy. Earlier intervention with immunotherapy and ongoing maintenance treatment might have prevented this additional surgery.

6. **Hope through immunotherapy**
   Access to immunotherapies offers hope for patients facing an advanced endometrial cancer diagnosis. One patient with stage 4 disease expressed the impact of being granted access to PD-1 inhibitor immunotherapy (not durvalumab):

   "HOPE… Optimism for a future. A treatment without the brutal side effects, a treatment that doesn't take over your life. A treatment that enables you to travel and plan for a future, giving me a belief that I might see my granddaughter start school. [...] Hope is the most important, an option when other doors are closing."

Patient story:

	Hannah* was diagnosed with stage 4, grade 3 endometrial cancer in November 2019, age 30, and underwent hysterectomy, platinum-based chemotherapy, radiotherapy and brachytherapy. Hannah has dMMR subtype, having being diagnosed with Lynch Syndrome. She relapsed 6 months after finishing treatment for her primary cancer – with tumours in her bowel, scar tissue and one near her liver. After undergoing surgery which removed 3 of 4 tumours, she started a PD-1 inhibitor immunotherapy (not durvalumab) as a monotherapy which shrunk the final tumour so that there is nothing visible on her scans. She has now finished treatment and has been in remission for over a year. Hannah has also been able to live a "healthier and more fulfilling life" despite an incurable cancer diagnosis and has been 'living well with cancer' for over 3 years both on and off immunotherapy. Although there have been a couple of setbacks (mainly underactive thyroid due to the treatment) and fatigue, the benefits much outweigh these – and are much easier to manage than those she experienced on chemotherapy. Hannah reported: *"I have found the treatment to be much kinder and more manageable than any others that I have had and I have experienced fewer side effects. With [immunotherapy], I feel much more relaxed and able to live a normal life and am able to go to the office, meet friends, occasionally go out dancing and attend social and family events. I am grateful every day that I am able to live my life fully and without many of the side effects of previous treatments. Sometimes, I even forget that I have stage 4 cancer!"* Hannah has since finished treatment and has been off treatment for over a year with no evidence of disease on scans. During this time, she has been able to have an active social and work life, travel to Greece and Costa Rica and attend festivals. *Pseudonym used

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As we have been unable to identify anyone who has, undergone treatment with the technology, we have based the below on similar immunotherapies (i.e., PD-1 inhibitor immunotherapies). Key disadvantages of the technology that patients identified include: **1. Fatigue** Some patients receiving either chemotherapy combined with an immunotherapy or immunotherapy as a monotherapy report fatigue. One patient with recurrent endometrial cancer describes how she has experienced worse fatigue than when her primary tumour was treated *"I have one complete day when I can do nothing, I get exhausted walking up stairs."* Patient on an immunotherapy with chemotherapy) One patient, who received an immunotherapy as a monotherapy, reported: *"Whilst I was on treatment, I was able to life a nearly normal life, although I needed to rest more and avoid overdoing it. However, [the immunotherapy] had a cumulative impact on my energy levels and I have been living with fatigue for the past couple of years even after treatment. I have some periods of more intense fatigue where I struggle to do as much. However, without [the immunotherapy], I would not be alive so it's worth it."* **2. Impact on biochemical markers** Immunotherapies may have additional impact on biochemical markers. *"I'm taking magnesium supplements for low levels which hasn't happened before, and I know my haemoglobin levels are low."* (Patient on an immunotherapy with chemotherapy) "*I have had some challenges with very low ferritin levels following immunotherapy. Although I am not sure if they are linked, I had to get an iron infusion to top them up and stop feeling so tired."* (Patient on an immunotherapy as a monotherapy)

	3. Immune-related adverse impacts One patient reported that they were diagnosed with an underactive thyroid caused by immunotherapy. Initially this led to feelings of profound fatigue. Following levothyroxine treatment, the patient does not have any ongoing side effects although treatment is lifelong. *"Due to the initial impact on my thyroid, I became incredibly fatigued (the worst of the entire treatment) and struggled to even get off the sofa and do basic things like cook or shower. It took a little while for my thyroid to completely stop functioning and I couldn't have treatment until then. This meant I had to live with debilitating fatigue for 4-6 weeks until I could start the treatment. It took another month or two to feel the benefit of the levothyroxine. This was one of the most difficult times on treatment."*

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People with mismatch repair deficient (dMMR) tumours are likely to respond better to immunotherapy compared to those with mismatch repair proficient (pMMR) tumors. The pMMR group consists of three molecular subtypes of endometrial cancer: POLE, NSMP, and p53abn. It is possible that individuals with these different subtypes may experience varying levels of benefit from immunotherapy.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None identified

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	1. There is a significant unmet need for earlier access to effective, innovative treatments for all molecular subtypes of newly diagnosed advanced or recurrent endometrial cancer, with an especially urgent need for patients with pMMR endometrial cancer. 2. People with stage 3 disease need treatments that prevent or delay recurrence, stop progression to incurable stage 4 cancer, and help reduce fear of their cancer returning. 3. People with stage 4 or recurrent disease want immediate access to effective treatments to prevent their condition from worsening and enable them to live a meaningful life for longer. 4. People with newly diagnosed advanced or recurrent endometrial cancer feel frustrated and abandoned due to the lack of effective first-line treatments, especially when compared to other cancers with multiple available lines of treatment.

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating <<this condition>> and current treatment options

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

1. Your name	Gemma EMINOWICZ
2. Name of organisation	University College London Hospital
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with newly diagnosed advanced or recurrent endometrial cancer? ☐ A specialist in the clinical evidence base for newly diagnosed advanced or recurrent endometrial cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for newly diagnosed advanced or recurrent endometrial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Main aim of treatment is to improve quality of life and control disease (ie tumour shrinkage with subsequent delay in progression of disease, thereby reducing disease burden and symptoms extending survival) Historically these patients are not cured. However, with the use of targeted treatments for isolated recurrence and oligometastatic disease as well as the introduction of immunotherapy in MMR deficient (MMRd) cases there are a proportion of these patients who may be more likely to be 'cured'.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Clinically meaningful improvement in quality of life ie improvement in functional status meaning patients can do what they want to do. Length of extension of survival depends upon the duration of treatment and toxicity burden
10. In your view, is there an unmet need for patients and healthcare professionals in newly diagnosed advanced or recurrent endometrial cancer?	Yes, these patients often have extensive symptoms and, depending upon their disease pattern, may be a significant burden on healthcare resources eg with bowel obstruction, fluid accumulation (pleural or ascitic). With the current access to dostarlimab for MMRd, I see that there is more of an unmet need now in the MMR proficient (MMRp) population which is a much more heterogenous group of patients and includes the very poor prognosis p53abnormal group.
11. How is newly diagnosed 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 across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Overall the pathway of care is well defined within my practice (which is within England) but across the country I am aware that the pathway of care is not always well defined. In general guidance such as the ESMO/ESP/ESTRO guidance are followed but these are not very specific and other guidelines such as BGCS uterine cancer guidelines have not been updated particularly recently. If patients have disease that is amenable to surgical resection without any anticipated residual they may be operated on. This, however, is not consistent practice across the country and depends upon surgical expertise and experience. This surgery would then be followed by chemotherapy and possibly radiotherapy if disease was pelvic confined and/or nodal confined. If patients have single site of disease they may undergo surgery, radiotherapy or other focal therapy to try to remove or ablate the disease.

	The TCGA molecular classification should impact the treatment offered. However, even the testing for MMR, p53 and POLE which are all essential to be able to molecularly classify a patient is not consistently carried out across the country. P53abnormal disease is generally treated with chemotherapy (6 cycles of carboplatin and paclitaxel) and possibly radiotherapy depending upon disease pattern. NB This cohort has the poorest prognosis MMRd disease is usually treated now with carboplatin paclitaxel and dostarlimab immunotherapy (aka RUBY trial- CDF) Hormone positive low grade disease (NSMP) may be managed with systemic hormonal therapy if the symptom burden is not significant. All other disease, ie multisite inoperable disease which is MMRp/NSMP, is generally treated with palliative chemotherapy – carboplatin and paclitaxel up to 6 cycles and perhaps radiotherapy depending upon disease pattern. This, however, is a very heterogenous group and response can be variable. Second line therapy may depend upon how long an interval it has been since the first line treatment as in a scenario of long interval (several years) then rechallenge with the same chemotherapy may be appropriate. Otherwise, second line therapy is Pembrolizumab and Lenvatinib up to 2 years if MMRp or single agent immunotherapy if MMRd and not already received immunotherapy. Third line therapy is generally trials (including ADCs) or weekly paclitaxel chemotherapy. If there was access to chemotherapy plus durvalumab and maintenance durvalumab and olaparib for all patients irrespective of molecular classification then the pathway may change to carboplatin paclitaxel durvalumab and olaparib for all patients first line and weekly taxol or trials second line.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	In the MMRd cohort there is already access to carboplatin paclitaxel and dostarlimab (RUBY regimen) in this setting. This treatment combination with durvalumab in my view does not have any clear advantages in regard to efficacy

• 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)	or safety and the duration of treatment is until progression compared to 3 years of RUBY regimen. The addition of the Olaparib does not benefit this MMRd population. In the MMRp population this would be new to the first line setting and would reduce the use of pembrolizumab and Lenvatinib in the second line setting. This treatment would only be delivered in specialist cancer centres. In general, as immunotherapy is used second line and for many other tumour sites there should be no additional training or equipment etc. However, this would increase the burden on the chemotherapy treatment suites due to the longer duration of treatment first line. The introduction of PARP inhibitors would also be unfamiliar for clinical oncologists in general but gynae oncology teams are experienced in treating with these and therefore it should be easy to implement. One could argue that the burden on chemotherapy treatment suites will be similar to the current second line therapy but there may be a higher proportion of patients who receive this as they may not be fit enough when they need second line therapy
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In my view there is no efficacy advantage with this combination over the RUBY regimen in the MMRd population. I therefore do not expect any clinically meaningful benefits compared to the standard of care and I certainly would not expect MMRd patients to receive PARPinhibitors. NEED TO ADD DUO E DATA HERE . Regarding the MMRp population, the published data Durvalumab and Olaparib in combination with chemotherapy in the first line setting (DUO-E) shows median progression free survival was improved by 5.5 months (HR 0.55 ie 45% reduction in risk of progression or death). The OS data is immature but has an equally compelling HR of 0.59 which indicated 41% reduction in risk of death with the addition of this combination therapy. I have not seen published quality of life/ patient reported outcome data. During treatment there will probably be very similar quality of life to standard of care.

	During the 5.5 months where the patients would have progressed and have not we could assume there may be some improvement in quality of life due to the lack of progressive disease but if this is picked up early and treated this may not be a very significant difference. Of note, Pembrolizumab and Lenvatinib in the second line setting provides a progression free survival advantage of approximately 3 months in these patients with overall survival advantage of 5 months (KEYNOTE 775, Makker et al NEJM 2022). We do have long enough duration of follow up yet to fully appreciate what the overall survival advantage is using immunotherapy upfront compared to second line. With the introduction of immunotherapy in the first line setting second line treatment options will be more limited and a significant proportion of patients may not be fit enough for trials.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In exploratory analyses it appears that the p53 abnormal patients are most likely to gain largest benefit from the combination of immunotherapy and PARPinhibitors (HR 0.47) and this also fits with the biology of how PARPinhibiotors work and therefore I believe this is the cohort that should be treated with this combination.
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)	It is more burdensome to add immunotherapy first line to chemotherapy due to longer duration of treatment and need to monitor hormone bloods tests and increased burden on clinic appointments as well as chemotherapy suite. However, most clinicians should be getting experience with immunotherapy and should now be familiar with managing the toxicities etc and have referral pathways etc in place. This specific combination also included maintenance PARPinhibitors and this would be new for clinical oncologists in general but departments will have established PARPinhibitor pathways due to ovarian cancer and even nurse led pathways etc so again should not be difficult to implement.

	Monitoring treatment response every 9-12 weeks with cross sectional imaging (usually CT CAP) would be standard if on maintenance therapy and this is probably not being currently done when only on surveillance. Some centres only monitor patients off treatment clinically and others may scan every 6-12 months but there is no set standard.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Toxicity and progression will be the reasons to stop therapy. Regular cross sectional imaging every 9-12 weeks will be done which is probably additional to current standard of care.
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, I think QALY will capture everything
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?	This treatment is a step change in endometrial cancer treatment and immunotherapy alone is revolutionary in the MMRd setting. However, in view of the heterogeneity of the MMRp population I am unsure if all patients will gain substantial benefit and it may be we need to be more selective in the population that this is delivered to. In my view this combination maintenance approach is most beneficial for p53abnormal cohort which also has the poorest prognosis therefore addresses the largest unmet need in this setting.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is a significant risk of toxicity with this treatment but it does appear to all be manageable and as centres/clinicians are becoming more confident with management of immunotherapy toxicity this is not impacting quality of life for patients detrimentally. Regarding PARP inhibitors in general oncology teams are

	used to managing the relevant toxicities and thereby minimising impact of quality of life.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes the clinical trials do reflect current UK practice.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	I am not aware of any RWE of the combination of IO and PARPi in this setting.
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	In general the trials do not include as many ethnic minority patients as we see in clinical practice – this may mean that certain groups are underrepresented but also that in real world practice more aggressive histologys will be seen (black often have higher aggressive histology and more likely to have p53abnormal disease). There is also some data suggesting differential responses to immunotherapy in certain populations such as Asian but difficult to interpret impact of this on the data.

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:

Locally advanced and recurrent endometrial cancer is a very heterogenous group of patients
The aim of treatment is generally to improve quality of life and survival where possible, but the introduction of immunotherapy for MMRd disease is potentially improving long term survival to the point of potential cure in a significant proportion of patients
The use of durvalumab and Olaparib improves progression free survival and appears to improve overall survival although published overall survival data is immature.
Exploratory analyses suggest that the combination of durvalumab and Olaparib is most beneficial in p53abnormal cohort which is the cohort with the poorest prognosis
Implementation of immunotherapy with/without PARPinhibitor within the NHS should be feasible in view of the expanding use of immunotherapy already within endometrial cancer treatment pathways and the experience of using PARPinhibitors for ovarian cancer.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

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 newly diagnosed advanced or recurrent endometrial cancernewly diagnosed advanced or recurrent 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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

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.

Patient expert statement

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with newly diagnosed advanced or recurrent endometrial cancer

Table 1 About you, newly diagnosed advanced or recurrent endometrial cancer, current treatments and equality

1. Your name	Helen White
2. Are you (please tick all that apply)	☐ A patient with newly diagnosed advanced or recurrent endometrial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with newly diagnosed advanced or recurrent endometrial cancer? ☒ A patient organisation employee or volunteer? ☒ Other (please specify): An individual with previous experience of early 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

Patient expert statement

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

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 newly diagnosed advanced or recurrent endometrial cancer? **If you are a carer (for someone with newly diagnosed advanced or recurrent endometrial cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for newly diagnosed advanced or recurrent endometrial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for newly diagnosed 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 durvalumab with platinum-based chemotherapy, then with or without	

olaparib, 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 durvalumab with platinum-based chemotherapy, then with or without olaparib, 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 durvalumab with platinum-based chemotherapy, then with or without olaparib, over current treatments on the NHS please describe these. For example, are there any risks with durvalumab with platinum-based chemotherapy, then with or without olaparib? 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 durvalumab with platinum-based chemotherapy, then with or without olaparib, 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 newly diagnosed advanced or recurrent endometrial cancer and durvalumab with platinum-based chemotherapy, then with or without olaparib? 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?	

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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.

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Patient expert statement

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with newly diagnosed advanced or recurrent endometrial cancer

Table 1 About you, newly diagnosed advanced or recurrent endometrial cancer, current treatments and equality

1. Your name	Grace Teeling
2. Are you (please tick all that apply)	☒ A patient with newly diagnosed advanced or recurrent endometrial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with newly diagnosed advanced or recurrent 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 – *NB attended previous teleconference for another TA recently* ☐ I have not completed part 2 of the statement
6. What is your experience of living with newly diagnosed advanced or recurrent endometrial cancer? **If you are a carer (for someone with newly diagnosed advanced or recurrent endometrial cancer) please share your experience of caring for them**	I was originally diagnosed with at least stage 3c (likely stage 4) endometrial cancer in December 2019 – for which I received a hysterectomy, 4 rounds of chemotherapy (paclitaxel and carboplatin), 25 rounds of radiotherapy and 3 rounds of brachytherapy. My cancer returned in May 2021 (only 8 months after finishing treatment). Scans showed tumours in my bowel and locally in my pelvis and I was given surgery (Hartmann's procedure and tumour resection) which removed all visible tumours. After a baseline scan, there was another small tumour identified near to my liver. Following 2 years of successful treatment with an immunotherapy (pembrolizumab) monotherapy, I have been in remission and off any treatment. I now have check-up appointments every 3 months and monitoring scans every 9-12 months.
7a. What do you think of the current treatments and care available for newly diagnosed advanced or recurrent endometrial cancer on the NHS?	**7a.** The lack of options for advanced, metastatic or recurrent endometrial cancer are very limited. If I did not have access to pembrolizumab, at the point at which I was diagnosed with recurrence (May 2021), there were very few options available for me as I had not responded well to chemotherapy. What is very scary is that, at

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	the age of 32, I may have been having very difficult conversations with my oncologist. I have been through 4 rounds of paclitaxel/carboplatin, 25 radiotherapy and 3 brachytherapy when I was first diagnosed. I found chemotherapy quite difficult physically and mentally. Physically, I struggled with debilitating fatigue – and also had a minor allergic reaction which meant my medical team decided to double my steroids for the days after chemotherapy. I have outlined further side effects under question 8. I consider myself very lucky to have received immunotherapy when I did. However, if I had had access to more effective treatment earlier in my cancer journey, it may have prevented a recurrence in the first place. My diagnosis was likely stage 4 and there may have been a missed opportunity for more effective treatment because they weren't available. I also needed to have Hartmann's procedure and now have a colostomy which is likely to be permanent. If I had had earlier treatment, it may have prevented the need for further surgery to prevent bowel obstruction. **7b.** Most of my friends and acquaintances in the 'cancer world' (I am involved in several support groups) see chemotherapy as 'belts and braces' – something to just get through and accept that your quality of life won't be great for a while. When facing an incurable diagnosis, chemotherapy alone feels like a poor option to many of us. I don't know anyone else on immunotherapy, but I do feel like I was able to live life and thrive on it in a way I wouldn't be able to, based on my experience of chemotherapy. I also have friends who are missing out on immunotherapy, and rely on chemotherapy, and their outlook on life is not as positive. One of my friends stopped responding to my messages a couple of years ago – I am too scared to find

	out whether or not she made it. By contrast, I am now in remission and moving on with my life.
8. If there are disadvantages for patients of current NHS treatments for newly diagnosed advanced or recurrent endometrial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	**Short-term effects resulting in relapse and surgery** Despite receiving the current standard of care at my initial diagnosis (surgery, chemo, radiotherapy and brachytherapy), I relapsed within 6-9 months with tumours in my bowel. This meant I needed to have further major surgery (Hartmann's procedure) and now have a colostomy. Earlier access to more innovative treatment may have prevented the need for later life-changing surgery. **Impact on quality of life** For me, the most challenging side effect of chemotherapy was (at least) 4-7 days of debilitating fatigue every 3-week cycle. I found it very challenging to do simple tasks such as showering and dressing. Even lying on the bed or sitting on the sofa felt exhausting. With steroids, I also couldn't sleep, and I felt as though I was in a state of suspended animation in which time passed very slowly. This was very physically and psychologically difficult as a side effect. I still get flashbacks two years later, despite psychological support. I have had to put significant time (years) and money into counselling to deal with the impacts of treatment. I also needed to take two different anti-emetics to manage nausea – though these did prevent most of the nausea. I did have a reduced appetite for the first few days each cycle. I also had quite bad diarrhoea around 4-5 days after each cycle. I also struggled with intense hot flushes for the first few days after treatment as well as myoclonic jerks which made it difficult to sleep (though this could've been due to anxiety around my immune system).

	Mental impact Psychologically, I also really struggled with anxiety related to my white blood cells dipping in the middle of each cycle. This was to the extent that I had panic attacks and some days I felt too scared to go to sleep in case I had an infection which might lead to neutropenic sepsis. Prior to COVID-19, I was also advised to avoid crowds at certain periods which meant missing important activities for my wellbeing, such as choir or having an active social life. I was also unable to work due to fatigue and brain fog; unable to be as active as I would like due to fatigue; and I had to change plans and limit my social life to avoid infection in the middle of each cycle (even for the first two cycles prior to COVID-19 pandemic). **Long-term impacts** By the end of all of my initial treatment, I felt as though I had to climb a mountain to recover – and it took a year to even feel remotely back to my normal self. (By which time I had relapsed) And I feel lucky to have escaped without long-term side effects such as pelvic radiation disease or peripheral neuropathy. It has had long term impact on sexual function due to surgery and radiotherapy damage.
9a. If there are advantages of durvalumab with platinum-based chemotherapy, then with or without olaparib, 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?	**9a.** I did not have the durvalumab but a different immunotherapy (pembrolizumab) which I received as a monotherapy. I have had also received platinum-based chemotherapy as an earlier treatment for my first diagnosis. 1. **Living well for longer**

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does durvalumab with platinum-based chemotherapy, then with or without olaparib, 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**	The biggest advantage is the impact on survival compared with current treatments. This is particularly when used in the first-line setting as I did not receive immunotherapy until relapse (and needed to go through an approvals process). Effective and innovative treatment options such as durvalumab (with/without Olaparib) offer hope to patients of longer and more meaningful lives. I do not feel that there would have been many options available to me had immunotherapy not been available. The conversations with my doctors would have been very different – likely palliative – had my recurrence happened before it was available. I did not respond well to chemotherapy resulting in a relapse shortly after finishing treatment. From conversations with my oncologist, it seems as though there would be few available options which is not a conversation that I wanted to have at 32. By contrast, I recently had a big birthday party with my friends to celebrate being '35 and still alive'. **2. Possible prevention of life-altering surgery** Because I didn't receive immunotherapy until I relapsed, I then needed to undergo a surgical procedure (Hartmann's) which has resulted in a colostomy. Earlier access to an effective and innovative treatment option may have prevented recurrence in my bowel (or at all) and prevented the need for further major and life-changing surgery. If I had received more effective treatment (such as durvalumab) after initial diagnosis with endometrial cancer, it may have prevented later treatment and psychological distress from a relapse and additional surgery.

	3. Quality of life As I didn't receive durvalumab, I cannot comment specifically on the technology. However, I did receive another immunotherapy which I felt really improved my quality of life: to the extent that I feel that I was able to thrive whilst on active treatment. I found the treatment to be much kinder and more manageable than any others that I have had, (chemotherapy, radiotherapy and brachytherapy), and I experienced far fewer side effects. It has also meant there is currently no evidence of cancer on my most recent CT scan. Following treatment, I have been in remission for 18 months – this means not spending time in hospital and being able to instead get on with my life! I am honestly grateful every day that I am able to live my life fully and without many of the side effects of previous treatments. Whilst I was on treatment with the immunotherapy, I was able to be active (taking part in outdoor swimming, climbing, paddleboarding, cycling, hill walking and daily dog walking), continue to work and actively develop a career which I thought was over and live a fulfilling and happy life. **4. A second chance at life** I feel that I have been offered a second chance at life. I moved back to Bristol from Scotland 18 months ago and have been living a very full life with my family and friends. I have made my 5-year-old nephew's birthday party which I never thought I would make! Access to novel treatments at earlier stages are crucial to offering this second chance to patients. In the time since beginning treatment, I have had two promotions (including one while on active treatment). I have travelled to Prague, Greece, Costa Rica and I recently returned to New Zealand and Australia for a month. I met my Australian best friend's 3-year old daughter who I never thought I would get to meet. I have

	also recently started training to be a yoga teacher so I can offer yoga retreats for people living with advanced cancer. **9b.** My priority for my life, as someone living with stage 4 cancer, is to live a full life, where I don't constantly feel like a cancer patient, and I am able to thrive for as long as possible. In my case, being in remission feels like a miracle. The biggest advantage of access to durvalumab is that it offers patients time to live and thrive for longer. **9c.** My experience of the immunotherapy that I did receive was that it was much kinder and more tolerable than any previous treatments (chemotherapy, radiotherapy and brachytherapy) with fewer side effects and less of an impact on my quality of life. Although there is still chemotherapy as an option in this situation, access to further treatment options offers hope for the future which helps to deal with the side effects and get through the short-term challenges.
10. If there are disadvantages of durvalumab with platinum-based chemotherapy, then with or without olaparib, over current treatments on the NHS please describe these. For example, are there any risks with durvalumab with platinum-based chemotherapy, then with or without olaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Although I have outlined disadvantages here, they were much more tolerable than chemotherapy: 1. **Fatigue:** I have needed to more actively manage tiredness and fatigue to make sure that I don't overdo it – this usually means arranging rest days and not taking on too many things at once (which is often easier said than done). I still have fatigue which has, at times, been difficult to manage, even after treatment. This has slowly and steadily improved over the past year or so. I am managing much better now than on treatment and immediately after.

	2. **Thyroid issues:** I did have issues with an underactive thyroid as a result of treatment that led to more extreme tiredness. Combined with a viral infection that caused some lung inflammation (consistent with symptoms of pleurisy), it meant I needed a month off work, but once the levothyroxine started to work, I felt I had got back to my baseline level of wellbeing. I have also learned how to manage my tiredness (and prevent other side effects) on the whole – through a combination of rest, stress management, nutrition and exercise. All of these have improved my experience of having treatment and meant that I am able to maximise my energy levels and support my immune system to tolerate the treatment by keeping healthy and active. I would also like to highlight that there is a significant difference between my experience of fatigue on chemotherapy and tiredness/fatigue on immunotherapy which may not be easily captured, without the qualitative input of patient experts. My experience of fatigue during chemotherapy was that it was debilitating for at least the first week. Towards the end of my initial treatment (chemotherapy, radiotherapy and brachytherapy), I was also completely exhausted all the time. By contrast, I did get more tired on immunotherapy and had times of debilitating fatigue – but it was something I was often able to manage to enable me to live my life to the full – to work, socialise, volunteer and exercise.
11. Are there any groups of patients who might benefit more from durvalumab with platinum-based chemotherapy, then with or without olaparib, or any who may benefit less? If so, please describe them and explain why	I cannot comment on this point comprehensively. As someone with Lynch Syndrome, I am aware that I was lucky enough to be eligible to receive an immunotherapy-based treatment. Those with pMMR tumours still face having to wait for progression to receive treatment and face fewer treatment options. This is scary and they may be less able to tolerate the treatment after going through the

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	first line. A friend of mine recently lost their Mum who was unable to tolerate second-line combination therapy. As a younger person with endometrial cancer, I am also aware that many premenopausal women get diagnosed at more advanced stages because of doctors failing to identify the possibility of cancer. I saw at least three gynaecologists – all of whom missed my advanced cancer diagnosis, despite having most of the common symptoms and being very unwell with pain and PV bleeding. I feel I was let down by the healthcare system in failing to diagnose my cancer early enough that I was likely to have a 'treatment to cure'. Instead I am living with recurrent cancer which is life-limiting at the age of 35. I feel that access to immunotherapy is one of the best possible treatments to extend my life for as long as possible, despite late diagnosis. I would also like to highlight that immunotherapy has been truly life changing for me and my quality of life and life expectancy has been transformed as a result. The reason that I wanted to take part in this NICE appraisal is because I feel that people with advanced endometrial cancer deserve access to treatment options that enable them to live longer and fuller lives and even thrive with a cancer diagnosis. I would like to see this option offered to as many people as possible.
12. Are there any potential equality issues that should be taken into account when considering newly diagnosed advanced or recurrent endometrial cancer and durvalumab with platinum-based chemotherapy, then with or without olaparib? Please explain if you think any groups of people with this condition are particularly disadvantage	

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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:

- Access to an immunotherapy has been life changing for me in terms of quality of life and impact on my survival. Despite living with recurrent, advanced endometrial cancer, I am currently in remission. My most recent scan in February was clear even though I have also been off treatment for 18 months.
- If I had earlier access to a novel and more effective treatment, it may have prevented an additional surgery which has resulted in a colostomy which is likely to be permanent.
- My experience of current treatments has been that they have a significant impact on quality of life and are a ‘belts and braces’ treatment which are physically and psychologically difficult to manage. They also offer limited hope for the future.
- Access to more effective and innovative treatment has given me hope and offers the potential to provide hope to so many patients in terms of their ability to live longer and fuller lives and even thrive with a cancer diagnosis. This can feel like the difference between ‘living with’ cancer (as a more chronic condition) and ‘dying from’ cancer.
- People with advanced, recurrent or metastatic endometrial cancer diagnosis deserve to ‘live well with cancer’ rather than be faced with a lack of options which make us feel abandoned and hopeless. In my experience, immunotherapy is a much kinder treatment, with fewer debilitating side effects, which has enabled me to thrive and live my life fully.

Thank you for your time.

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STA Report

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 169598.

Title:	Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London, Clare Dadswell, Clinical Evidence Manager, BMJ-TAG, London Tracey Jhita, Health Economist Manager, BMJ-TAG, London Archie Walters, Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Clare Dadswell	Critical appraisal of the company's submission; and critical appraisal of the clinical evidence.
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
AUC	Area under the curve
BGCS	British Gynaecological Cancer Society
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BMI	Body mass index
BNF	British National Formulary
BRCA1	Breast cancer susceptibility 1
CA	Cancer antigen
CAA	Commercial access agreement
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPH	Cox proportional hazards
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company Submission
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DCO	Data cut-off
DCO1	Primary data cut-off
dMMR	Mismatch repair deficient
DoR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
EC	Endometrial cancer
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items
EORTC QLQ-EN24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Endometrial Cancer Module

EQ-5D	European Quality of Life scale-5-Dimensions
EQ-5D-3L	European Quality of Life scale-5-Dimensions-3-Levels
EQ-5D-5L	European Quality of Life scale-5-Dimensions-5-Levels
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full analysis set
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GFR	Glomerular filtration rate
GP	General practitioner
HER2	Receptor tyrosine-protein kinase erbB-2
HR	Hazard ratio
HRQoL	Health-related quality of life
HRRm	Homologous recombination repair mutation
HSE	Health Survey of England
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IQR	Interquartile range
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
LYG	Life years gained
MHRA	Medicines and Healthcare Products Regulatory Agency
MMR	Mismatch repair
MMRM	Mixed model for repeated measures
MSI	Microsatellite instability
MSI-H	High microsatellite instability
MSS	Microsatellite stable
NHSCII	NHS Cost Inflation Indices
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PARP	Poly ADP ribose polymerase
PAS	Patient Access Scheme

PD	Progressed disease
PDL1	Programmed cell death ligand 1
PF	Progression-free disease
PFS	Progression-free survival
PH	Proportional hazards
pMMR	Mismatch repair proficient
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QQ	Quantile-quantile
RCT	Randomised controlled trial
RDI	Relative dose intensity
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SoC+D	Standard of care in combination with durvalumab
SoC+D+O	Standard of care in combination with durvalumab and olaparib
SoC+D(+/-O)	Standard of care in combination with durvalumab (with or without olaparib)
TA	Technology appraisal
TTD	Time to treatment discontinuation
TSD	Technical Support Document
TSH	Thyroid-stimulating hormone
TTE	Time-to-event
TTP	Time-to-progression
UK	United Kingdom
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
US	United States
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Commercial access agreement (CAA) discounts are available for durvalumab and olaparib of [redacted]% and [redacted]%, respectively. The CAA discounts for durvalumab and olaparib were used in the economic model and all results are reported in this document include these discounts. The EAG highlights that the company provided an addendum with updated base case results to reflect an update in the CAA that occurred after the factual accuracy check.

A confidential PAS discount is available for the subsequent treatments, lenvatinib and pembrolizumab. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of durvalumab with platinum-chemotherapy, then with or without olaparib for the treatment of newly diagnosed advanced or recurrent endometrial cancer (EC).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Immaturity of data from DUO-E	4.2.3
2	Potential bias in clinical outcomes from DUO-E	2.3.2 and 3.2
3	Cap on treatment duration included in the company's model	4.2.4
4	Proportion initiating olaparib maintenance treatment in the pMMR subgroup	4.2.6.2
5	Estimation of newly progressed patients per model cycle	4.2.6.6

Abbreviations: EAG, External Assessment Group

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Alternative assumptions for long-term progression-free survival (PFS) and overall survival (OS) for patients with mismatch repair deficient (dMMR) EC.
- How long patients will remain on treatment with durvalumab and olaparib in the long-term.
- How many patients with mismatch repair proficient (pMMR) EC who have not experienced their disease getting worse will start on maintenance treatment with olaparib in addition to durvalumab.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing survival.

Overall, the technology is modelled to affect costs by:

- Its higher unit price than current treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- How long-term survival for dMMR patients is estimated.
- Patients remain on treatment with durvalumab and olaparib until their disease gets worse or they can no longer tolerate treatment.
- How many patients with mismatch repair proficient (pMMR) EC who have not experienced their disease getting worse will start on maintenance treatment with olaparib in addition to durvalumab.

1.3 The clinical and cost effectiveness evidence: summary of the EAG's key issues

Table 2. Issue 1: Immaturity of data from DUO-E

Report section	4.2.3
Description of issue and why the EAG has identified it as important	In the CS, the company indicates that data from DUO-E are immature. At the primary data cut off (April 2023), overall maturity of PFS and OS outcomes in the dMMR subgroup was 40.6% and 21.7%, respectively. For the pMMR subgroup, PFS data were relatively more mature at 66.1% but

	OS was immature at 29.2%. Notably, outcome data are more immature for the SoC+D arm of the dMMR subgroup and SoC+D+O arm of the pMMR subgroup of DUO-E. The EAG considers that OS is extremely immature and, that as a result of this, the long-term extrapolations for each treatment arm and each subgroup are subject to a substantial amount of uncertainty. The EAG also notes that the company has relied on the committee discussion for dostarlimab (TA963) as part of long-term survival validation in the economic model, but the EAG considers this is potentially problematic when comparing the incremental QALY gain of each technology over SoC.
What alternative approach has the EAG suggested?	The EAG explored alternatives to the company's survival extrapolations for dMMR, as these were subject to the most uncertainty. However, the EAG acknowledges that its preferred approach is similarly uncertain. Nonetheless, for the extrapolation of PFS for the SoC+D arm of the model for the dMMR subgroup, the EAG preferred the use of the 1-knot spline as it had a better statistical fit and considered that the extrapolation better captured the tail of the KM curve. For OS, the EAG preferred the use of log-logistic extrapolation as it produced estimates of OS for SoC+D that are closer to the clinical expert estimates provided in TA963. Results for the SoC arm using a log-logistic extrapolation are similar to the company base case extrapolation using the lognormal distribution. The EAG also conducted exploratory indirect comparisons of SoC+D versus dostarlimab for OS and PFS in the dMMR population. The EAG acknowledges that dostarlimab is not considered to be a relevant comparator for this appraisal as it is currently only available via the CDF and that dostarlimab use is restricted to adults with high microsatellite instability (MSI-H) or dMMR who are candidates for systemic therapy. The EAG presents these results to give context to the assumptions the company has made based on TA963 and also to aid committee in consistency of decision-making. In summary, the hazard ratios for both PFS and OS from the indirect treatment comparisons favour treatment with dostarlimab, albeit the 95% confidence intervals cross 1. However, the EAG considers the results should be interpreted with caution due to the differences in baseline characteristics (including potential difference in MSI-H) and subgroup nature of the data used in the analyses. The company reported that their exploratory internal analysis indicated that adjusting for patient baseline characteristics would have a significant impact on the results of any such ITC and would not support the EAG's conclusions. However, the company did not provide its analyses for assessment by the EAG and so the EAG cannot comment on the robustness of the analyses or the company's interpretation of the results. In addition, the EAG considers that any such analyses conducted by the company are likely to have broken randomisation.
What is the expected effect on the cost-effectiveness estimates?	Only a limited range of scenarios are possible based on the immaturity of the trial data. As such, until more mature data are available their impact on the ICER remains unknown. Nonetheless, below the EAG presents the results of the scenarios it conducted (described above). For the PFS scenario, the company base case post FAC ICER increased from [redacted] to [redacted].

	For the OS scenario, the company base case post FAC ICER increased from [redacted] to [redacted]. The combined impact of both of the scenarios increased the company base case post FAC ICER increased from [redacted] to [redacted].
What additional evidence or analyses might help to this key issue?	The EAG considers that the uncertainty around the long-term clinical outcomes assumed in the model can only be overcome by additional data collection in DUO-E. The company has indicated that the final OS analysis from DUO-E is expected in [redacted]. In order to mitigate the fundamental uncertainties in the analysis, the committee may want to consider applying a lower ICER threshold for decision making.

Abbreviations: CS, company submission; dMMR, mismatch repair deficient; EAG, External Assessment Group; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 3. Issue 2: Potential bias in clinical outcomes from DUO-E

Report section	2.3.2 and 3.2
Description of issue and why the EAG has identified it as important	The EAG is concerned that there is potential bias in some of the clinical outcomes from DUO-E as a result of the subsequent treatments not aligning with UK clinical practice. In particular, the EAG is concerned about the use of subsequent [redacted] not reflecting UK clinical practice. For example, [redacted] but in DUO-E [redacted]% of SoC+D patients in the dMMR subgroup and [redacted]% of SoC+D+O patients in the [redacted]. In addition, [redacted], was considered by the EAG's and company's clinical experts to be [redacted] than expected. The EAG is therefore concerned that [redacted].
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The clinical efficacy of SoC+D and SoC+D+O may be [redacted] in the economic model and as such the ICER is potentially [redacted]. However, the magnitude of change in the ICER is uncertain.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 4. Issue 3: Cap on treatment duration included in the company's model

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company has assumed that the maximum treatment duration for durvalumab and olaparib is three years. In DUO-E for treatment with durvalumab and olaparib was until disease progression or unacceptable toxicity, and this is the recommendation in the draft SmPC.
What alternative approach has the EAG suggested?	Based solely on the treatment regimens in DUO-E and the draft SmPC guidance for durvalumab and olaparib of treat until progression or unacceptable toxicity, the EAG considers that the cap on treatment duration should be removed and extrapolations with a natural decline to zero are preferred. For the dMMR subgroup, the EAG preferred the use of the gamma distribution to extrapolate TTD and for the pMMR subgroup, the exponential distribution for TTD was preferred.
What is the expected effect on the cost-effectiveness estimates?	For the dMMR subgroup, the company base case post FAC ICER increased from [redacted] to [redacted]. For the pMMR subgroup, the company base case post FAC ICER increased from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	More mature TTD data from DUO-E will resolve any uncertainties in the extrapolation of TTD.

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; SmPC, summary of product characteristics; TTD, time-to-treatment discontinuation.

Table 5. Issue 4: Proportion initiating olaparib maintenance treatment in the pMMR subgroup

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The proportion of patients initiating olaparib in the model is based on data from DUO-E, where [redacted]% of patients randomised to SoC+D+O in the pMMR population initiated treatment with olaparib in the maintenance phase of treatment. Reasons why patients did not initiate treatment with olaparib included disease progression and ineligibility for treatment, such as not meeting maintenance eligibility criteria, discontinuation due to adverse events, patient choice etc. The company also explained that a small proportion of pMMR patients in the SoC+D+O arm of DUO-E received durvalumab as monotherapy during the maintenance phase of the trial ([redacted] of all randomised patients) The draft SmPC for durvalumab and olaparib for the pMMR population recommends durvalumab in combination with olaparib after a minimum of 4 and up to 6 cycles of treatment durvalumab monotherapy in combination with carboplatin and paclitaxel. The company does not expect to receive a marketing authorisation for the SoC+D regimen for pMMR patients. However, the company does not expect there to be any wording within the SmPC that excludes the use of durvalumab monotherapy in the maintenance setting for patients who were initially intended to receive the SoC+D+O regimen at the point of treatment initiation, but who subsequently become ineligible to receive olaparib in the maintenance phase of treatment.

	The company is seeking a NICE recommendation for the pMMR population that is aligned to the marketing authorisation (SoC+D+O), but with flexibility in the recommendation for patients to continue durvalumab monotherapy in the maintenance phase if they are unable to initiate olaparib.
What alternative approach has the EAG suggested?	The EAG considers that the company's base case assumption of the proportion of patients initiating olaparib is an underestimate as olaparib treatment acquisition costs are only applied to patients in the model who are alive and progression-free after week 18 and so including patients who have already had disease progression in the calculation is not appropriate. Instead, the EAG considers that it is more appropriate to estimate a proportion based on the number of patients who received olaparib out of the total number of patients who received some form of active maintenance therapy (durvalumab monotherapy or durvalumab with olaparib), which is [redacted]%. With regards to the NICE recommendation the company is seeking for the pMMR subgroup, the EAG is concerned that the company's base case does not necessarily wholly align with the anticipated marketing authorisation. As such, the EAG has performed a scenario where 100% of progression-free patients in the SoC+D+O arm of the model receive olaparib.
What is the expected effect on the cost-effectiveness estimates?	For the scenario which assumes [redacted]% of pMMR patients initiate olaparib, the company's base case post FAC ICER increased from [redacted] to [redacted]. For the scenario which assumes 100% of pMMR patients initiate olaparib, the company's base case post FAC ICER increased from [redacted] to [redacted]. The EAG notes that this scenario is subject to uncertainty as the model includes survival data from DUO-E that does includes a proportion of SoC+D+O patients who did not receive olaparib in the maintenance phase of treatment and so potentially may be underestimating treatment effectiveness in [redacted]% of patients.
What additional evidence or analyses might help to resolve this key issue?	The wording of the final SmPC and marketing authorisation for durvalumab and olaparib should inform committee and any potential NICE recommendation. Nonetheless, the EAG's two scenarios provide the impact on the ICER if greater usage of olaparib is assumed.

Abbreviations: EAG, External Assessment Group; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; SmPC, summary of product characteristics; SoC+D+O, standard of care with durvalumab and olaparib.

Table 6. Issue 5: Estimation of newly progressed patients per model cycle

Report section	4.2.6.6
Description of issue and why the EAG has identified it as important	The company's estimation of newly progressed disease patients in the model (for which the one-off costs of subsequent treatments is applied), is based on a constant proportion of [redacted]% of patients experiencing a non-fatal progression event, based on data from DUO-E. The use of a constant proportion potentially overestimates the proportion of newly progressed patients per cycle because in every model cycle there will be newly progressed patients, but in reality, there may be periods of time when the only PFS events are death, especially for patients in long-term remission.

What alternative approach has the EAG suggested?	The EAG considers that the number of newly progressed patients per cycle can be calculated directly from the partitioned survival model. To estimate newly progressed patients per cycle using the model survival extrapolations the EAG considers the following formula might be more appropriate: $$PD_{new} = (OS_t - PFS_{t)}) - (OS_{t-1} - PFS_{t-1}) * (\frac{OS_t}{OS_{t-1}})$$ The EAG acknowledges that its calculation has limitations, in that the OS adjustment includes both patients dying from the PF and PD health state, but it is equivalent to the company's assumption that a fixed proportion of deaths will be from the PF health state. As such, both approaches rely on an implicit assumption around deaths from the PF health state, but the EAG's approach is a useful alternative scenario to explore as it allows changes over time.
What is the expected effect on the cost-effectiveness estimates?	For the dMMR subgroup, the company base case post FAC ICER increased from [redacted] to [redacted]. For the pMMR subgroup, the company base case post FAC ICER increased from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	More mature time-to-progression data from DUO-E will help to understand the long-term trends of non-fatal progression events. Given that the EAG's calculation has limitations and data from DUO-E (although immature) suggests that the majority of progression events are non-fatal, based on approximately 30 months of follow-up, the EAG has not implemented its calculation in its base case, but considers the scenario provides committee with the impact of an alternative assumption.

Abbreviations: EAG, External Assessment Group; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival.

1.4 Summary of EAG's preferred assumptions and resulting ICER

Table 7 and Table 8 present the EAG's preferred assumptions as well as the EAG deterministic and probabilistic base case ICERs for the dMMR and pMMR subgroups.

Table 7. EAG preferred assumptions and deterministic base case ICER – dMMR subgroup

Scenario	Cumulative incremental costs	Cumulative incremental QALYs	ICER (change from company base case
Company base case	[redacted]	**5.37**	[redacted]
EAG scenario 1 - 1-knot spline to extrapolate PFS for SoC+D	[redacted]	5.29	[redacted]
Log-logistic distribution to extrapolate OS	[redacted]	4.51	[redacted]
Removal of the treatment duration cap and use of the gamma distribution to extrapolate TTD for durvalumab	[redacted]	4.51	[redacted]
Inclusion of drug wastage	[redacted]	4.51	[redacted]

Most recent SB15Z cost from NHS reference costs for subsequent treatments administration cost	[redacted]	4.51	[redacted]
EAG's preferred deterministic base case - combination of all scenarios	[redacted]	**4.51**	[redacted]
EAG's preferred probabilistic base case - combination of all scenarios	[redacted]	**3.93**	[redacted]

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab; TTD, time-to-treatment discontinuation.

Table 8. EAG preferred assumptions and deterministic base case ICER – pMMR subgroup

Scenario	Cumulative incremental costs	Cumulative incremental QALYs	ICER (change from company base case
Company base case	[redacted]	**0.67**	[redacted]
Removal of the treatment duration cap and use of the exponential distribution to extrapolate TTD for durvalumab and olaparib	[redacted]	0.67	[redacted]
EAG scenario 2 - proportion of patients initiating olaparib assumed to be [redacted]% (pMMR subgroup only)	[redacted]	0.67	[redacted]
Inclusion of drug wastage	[redacted]	0.67	[redacted]
Most recent SB15Z cost from NHS reference costs for subsequent treatments administration cost	[redacted]	0.67	[redacted]
EAG's preferred deterministic base case - combination of all scenarios	[redacted]	**0.67**	[redacted]
EAG's preferred probabilistic base case - combination of all scenarios	[redacted]	**0.66**	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab; TTD, time-to-treatment discontinuation.

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2 and 6.3.1.

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of durvalumab (Imfinzi®, AstraZeneca) with platinum-based chemotherapy (hereafter referred to as standard of care [SoC]), then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer (EC). The company reported that there is anticipated to be two separate durvalumab treatment regimens, with each regimen having a different target patient population:

- Durvalumab in combination with platinum-based chemotherapy (carboplatin + paclitaxel), followed by maintenance durvalumab (SoC+D) for patients with newly diagnosed advanced or recurrent EC that is mismatch repair (MMR) deficient (dMMR); and
- Durvalumab in combination with platinum-based chemotherapy (carboplatin + paclitaxel), followed by maintenance durvalumab with olaparib (SoC+D+O) for patients with newly diagnosed advanced or recurrent EC that is MMR proficient (pMMR).

It is noted that the target populations are subgroups of the population of people with newly diagnosed advanced or recurrent EC that was specified in the National Institute for Health and Care Excellence (NICE) final scope[1], but they align with the anticipated marketing authorisations for durvalumab and olaparib in the EC indication (expected December 2024):[2, 3]

- Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:
    - Durvalumab as monotherapy in EC that is dMMR;
    - Durvalumab in combination with olaparib in EC that is pMMR.
- Olaparib in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

In addition, the EAG considers it important to highlight that advanced EC is defined as International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV disease in this appraisal.

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of EC including:

- disease classification, progression, recurrence and staging (Section B.1.3.1);
- molecular classification including MMR status, microsatellite stability and PD-L1 status in EC (Section B.1.3.1.5 and B.1.3.1.6);
- epidemiology (B.1.3.2); and
- burden of disease for advanced or recurrent EC (B.1.3.4).

EC originates in the lining of the womb (uterus), known as the endometrium[4] and the focus of this submission is patients with advanced or recurrent EC. EC is classified as advanced (FIGO Stage III or Stage IV) once the cancer has spread beyond the uterus, and the definition of disease recurrence is disease which cannot be detected after primary treatment, but then returns at a later point in time.[4-6]

EC can be classified according to the presence and absence of specific molecular features on biopsy, such as MMR status. The EAG's clinical experts agreed with the company that MMR status is one of the routine tests currently available for patients with advanced and recurrent EC in UK clinical practice.

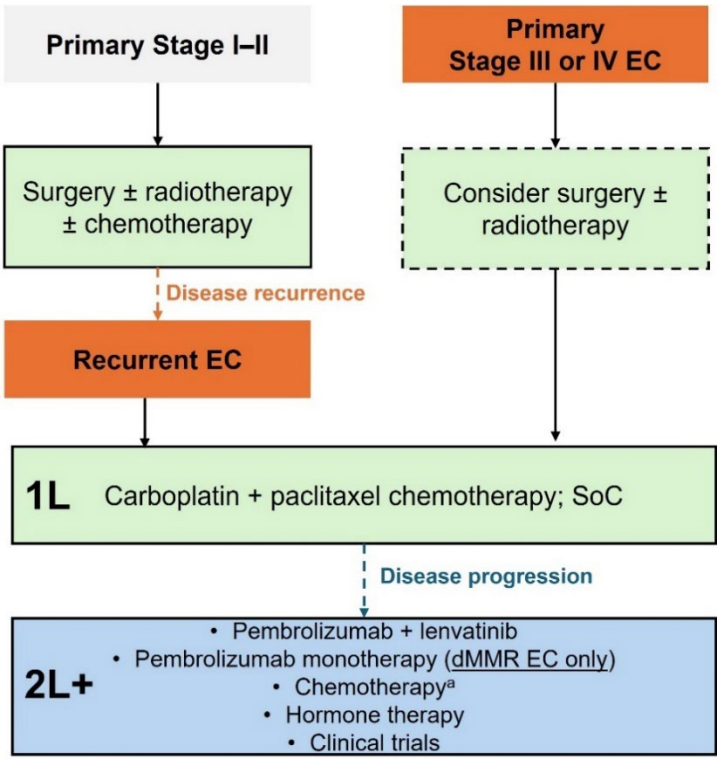
In EC, tumours can be classified as either MMR deficient (dMMR) or MMR proficient (pMMR) depending on the functionality of the MMR system and approximately 20-30% of EC is dMMR.[7, 8] In dMMR EC, errors during DNA replication are not properly corrected, whereas in pMMR EC, DNA repair mechanisms remain intact and so mutations are corrected.[9] EC that is dMMR has a high tumour mutational burden (TMB) and is highly immunogenic and more susceptible to treatment with immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 therapies compared to pMMR tumours which typically have low TMB.[10]

2.2.1 Current treatment pathway and positioning of new treatment(s)

The EAG notes that there is no standard UK-specific clinical guidance for the treatment of advanced or recurrent EC, although there is guidance from the British Gynaecological Cancer Society (BGCS) for uterine cancer[11] and NICE guidance for some specific interventions e.g. pembrolizumab with lenvatinib.[12] Figure 1 presents the company's overview of the current treatment pathway for EC in UK clinical practice, which the EAG's clinical experts are broadly in agreement with, although some

experts reported that they would expect most Stage III patients in clinical practice to receive surgery plus radiotherapy plus chemotherapy. The EAG notes that newly diagnosed advanced or recurrent EC (that is unlikely to be cured by surgery alone) are usually treated via the same treatment pathway in the UK, but there are some differences in the availability of treatments for pMMR and dMMR advanced or recurrent EC that are discussed further below.

Figure 1. Company's treatment pathway for EC in UK clinical practice (Reproduced from CS document B, Figure 1)



Footnotes: Options recommended via the CDF are not presented as these do not represent part of established clinical practice as per the NICE processes and methods.[13] In the first-line setting, these options include dostarlimab with platinum-based chemotherapy for patients with advanced or recurrent EC that is MSI-H or dMMR [TA963]. In the 2L setting, these options include dostarlimab monotherapy [TA779] for previously treated EC that is dMMR or MSI-H or dMMR.

[a]As per BGCS guidelines, further platinum-based is generally only considered for patients who relapse more than 6 months after receiving carboplatin + paclitaxel.

Source: Morrison, *et al.* (2022);[11] Oaknin, *et al.* (2022);[14] NICE (2024).[15]

Abbreviations: dMMR, mismatch repair deficient; EC, endometrial cancer; SoC, standard of care.

2.2.1.1 First-line treatment and first-line maintenance therapies for advanced or recurrent EC

The EAG notes that the company is positioning SoC+D as a first-line treatment for patients with advanced or recurrent dMMR EC and SoC+D+O as a first-line treatment for patients with advanced or recurrent pMMR EC.

Current clinical guidelines recommend the use of platinum-based chemotherapy (carboplatin + paclitaxel) as the first-line treatment for patients with recurrent or advanced EC.[11, 14] In addition, it is noted that the British Gynaecological Cancer Society (BGCS) uterine cancer guidelines recommend hormone therapy as an alternative first choice for patients where chemotherapy may not be well-tolerated (such as those who are older with multiple comorbidities), those in the palliative setting or patients with low grade, hormone-receptor positive tumours.[11] However, the company reported that patients who would be offered hormonal therapy were excluded from the DUO-E trial (the primary trial informing the clinical evidence in the CS), and would not be considered suitable candidates for SoC+D or SoC+D+O in clinical practice.[16] The EAG's clinical experts also considered this to be reasonable and that the omission of hormonal therapy as a comparator in the company submission and economic analysis to be reasonable.

The EAG notes that dostarlimab with platinum-based chemotherapy (carboplatin + paclitaxel) has been recommended by NICE for use as a first-line treatment in patients with dMMR (or MSI-H) advanced or recurrent EC [TA963]. The EAG's clinical experts reported that dostarlimab with platinum-based chemotherapy (carboplatin + paclitaxel) is now generally considered standard first-line treatment for dMMR advanced or recurrent EC patients in UK clinical practice. However, it is only available through the CDF and therefore is not deemed to be a relevant comparator for this appraisal based on the NICE process.[13, 17]

2.2.1.2 Second-line treatment for advanced or recurrent EC

There is currently no standard second-line treatment for EC and treatments partly depend on MMR status and prior therapy.[14, 18] Pembrolizumab monotherapy is recommended by NICE in the second-line setting for adult patients with dMMR or MSI-H advanced or recurrent EC that has progressed during or after a platinum-based therapy, who cannot have curative surgery or radiotherapy (TA914)[19] and pembrolizumab in combination with lenvatinib is recommended as a treatment for advanced or recurrent EC in adults whose cancer has progressed on or after platinum-based chemotherapy and who cannot have curative surgery or radiotherapy regardless of MMR status (TA904).[12] Dostarlimab monotherapy is also recommended by NICE for previously treated advanced or recurrent endometrial cancer with high MSI or dMMR (TA779), but similar to in the first-line setting, dostarlimab is only available via the CDF.[20]

The EAG notes that immunotherapy re-challenge is not reimbursed in UK clinical practice and the company reported that pembrolizumab was unlikely to be an eligible second-line treatment

following primary treatment with a durvalumab-based regimen. Subsequent treatments following SoC+D or SoC+D+O are discussed further in Sections 2.3, 3.2 and 4.2.6.5.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE, together with the rationale for any deviation from it, in Section B.1.1 of the CS. This is summarised in Table 9 below and more detailed comments from the EAG are provided in the subsections that follow. Overall, the EAG considers the decision problem addressed, and the evidence used to address it, to be in line with the NICE final scope or any deviations to be reasonable given the rationale provided.

Table 9. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with newly diagnosed advanced or recurrent EC	People with newly diagnosed advanced or recurrent EC that is dMMR	People with newly diagnosed advanced or recurrent EC that is pMMR	Aligned with the expected marketing authorisations for durvalumab and olaparib in the EC indication and the expected use of SoC+D and SoC+D+O in United Kingdom (UK) clinical practice.[21] The EAG notes that the proportion of newly diagnosed advanced EC patients with FIGO Stage III disease at diagnosis who were enrolled in the DUO-E trial was low compared to the proportion of patients with Stage IV disease (See Section 2.3.1 for further details).
Intervention	Durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with or without olaparib.	Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab (SoC+D)	Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC+D+O)	Aligned with the expected marketing authorisations for durvalumab and olaparib in the EC indication. Further details are provided in CS Sections B.1.3.6 to B.1.3.7 and Section 2.3.2 below.
Comparator(s)	Following treatment options, followed by routine surveillance: • Platinum-based chemotherapy (such as paclitaxel, carboplatin, cisplatin, doxorubicin and cyclophosphamide)	Platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance (standard of care [SoC]) for both dMMR and pMMR populations.	The final NICE scope proposes that hormone therapy is a relevant comparator for patients newly diagnosed with advanced or recurrent EC that is pMMR or dMMR. The Company do not consider that this is a relevant	The EAG's clinical experts agree with the company that the primary comparator of relevance is platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and note this was a comparator in the NICE final scope and the DUO-E trial. However, the

	• Hormone therapy (such as medroxyprogesterone acetate and megestrol)		comparator for the following key reasons: **Hormone therapy in the first-line setting is only considered in a small minority of EC cases**. As stated in section 9.2 of the British Gynaecological Cancer Society (BGCS) guidelines, hormone therapy is only recommended as an alternative option in the palliative setting and is mainly suitable for patients with low-grade, hormone-sensitive tumours, and for patients where chemotherapy may not be well-tolerated (such as those who are older with multiple comorbidities). Furthermore, these recommendations are supported by Grade C evidence, and it is explicitly stated that there is, "no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival (OS)". **Patients who would receive hormone therapy would not be suitable for SoC+D or SoC+D+O**. Given that hormonal therapy is only usually considered for the minority of	EAG notes that both the company and the EAG clinical experts do not consider the subsequent treatments used in DUO-E to align with UK clinical practice. Of particular note, in clinical practice, [redacted]. The EAG's clinical experts also agree with the company that hormone therapy is used in only a small proportion of patients and these patients generally would not be considered suitable for chemotherapy. Based on clinical expert opinion, the EAG considers the company omission of hormone therapy on the basis it is deemed not a relevant comparator to be reasonable. See Section 2.3.3 for further detail.

			patients who are not suitable for chemotherapy, SoC+D and SoC+D+O (which both include chemotherapy) would not be considered an appropriate option for these patients. This is reflected in the DUO-E trial (which represents the primary evidence base for SoC+D and SoC+D+O), which specifically enrolled patients who exhibited a good performance status. **There is no precedent for the consideration of hormone therapy as a relevant comparator in the setting proposed in this submission**. In the recent NICE appraisal of dostarlimab with platinum-based chemotherapy [TA963] in the first-line setting for advanced or recurrent EC that is dMMR, hormone therapy was not listed as a comparator in the final scope. Hormonal therefore should therefore not be considered a comparator in this appraisal within the same setting. In summary, the only appropriate comparator for this appraisal (for both the dMMR and pMMR populations) is	

			platinum-based chemotherapy followed by routine surveillance, which is currently recommended as the first-line SoC in this setting.[11]	
Outcomes	• Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	As per the NICE final scope	N/A	All outcomes specified in the NICE final scope were captured in the DUO-E trial and reported in the CS. The EAG notes that the data on HRQoL and AEs that were used in the model are based on the ITT population rather than the relevant dMMR or pMMR subgroup. However, based on expert opinion the EAG does not consider this to be unreasonable. The EAG is concerned about the reliability of the OS data from DUO-E due to its immaturity, and notes that the data used in the CS are from an interim analysis with a further analysis anticipated in Q4 2025 and the final analysis predicted to be in 2026. See Section 2.3.4 for further details
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	The cost-effectiveness of the treatments is expressed in terms of incremental cost per quality-adjusted life year. The cost-effectiveness model uses a partitioned survival analysis approach, whereby extrapolated OS, PFS and TTD	Where commercially confidential discounts apply to subsequent treatments, list prices are assumed.	The economic analysis adheres to the reference case and reflects the final scope.

	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	outcomes are used to estimate the distribution of patients across health states over time. Model health states are progression-free, progressed disease and death, with the progression-free health state subdivided into on and off treatment. A lifetime time horizon is considered. Costs are considered from an NHS and Personal Social Services perspective. Generic prices are applied to treatments available in generic form. List prices are applied for subsequent treatments with a confidential commercial discount.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Molecular subgroups, such as mismatch repair (MMR) status • Level of PD-L1 expression • Local vs metastatic recurrence • People who have had primary debulking surgery vs	• Mismatch repair (MMR) status (MMR-deficient or MMR-proficient). Within the intention-to-treat (ITT) population, a range of other prespecified subgroups are presented, including analyses by PD-L1 status.	As detailed above, the focus of this submission will be subgroups by MMR status (pMMR and dMMR), to align with the expected full marketing authorisations for olaparib and durvalumab in the EC indication and the expected use of SoC+D and SoC+D+O in clinical practice. The company have also presented a range of pre-specified subgroup analyses	The EAG notes that the focus of the CS is on the pMMR and dMMR subgroups with relevant data from DUO-E reported for these subgroups. In addition, it is noted that PFS subgroup data by PD-L1 status at baseline were also provided for the ITT population in the CS, and PFS results for the dMMR and pMMR subgroups were provided in the company's response to clarification questions. The EAG is concerned that

	those who have had not had surgery		within the ITT, to demonstrate the consistent effect of SoC+D and SoC+D+O irrespective of key demographic and disease-related baseline characteristics. However, the Company do not consider that additional economic analyses which sub-divide the MMR subgroups would aid decision making or reduce uncertainty within this appraisal. This is because the DUO-E trial was not powered to perform these types of analyses, and such 'subgroups-within-subgroups' would have very limited sample sizes. Therefore, the results of such analyses would not be sufficiently robust to inform decision-making. Additionally, these analyses were not stratified, and so would be subject to potential imbalances in baseline characteristics which risks confounding the results. Finally, some of the suggested analyses in the final scope lack appropriate clinical/biological evidence to warrant their implementation. **PD-L1**	the dMMR and pMMR populations comprise subgroups and recommends further subgroup analyses within these populations using the DUO-E data are interpreted with caution. See Appendix 8.3 for further details. The EAG notes that subgroup data for local vs metastatic recurrence and primary debulking surgery vs no surgery were not reported in the CS for the reasons outlined by the company. The EAG notes that they were not pre-planned subgroups in DUO-E and the EAG's clinical experts did not consider these subgroups likely to be of particular clinical importance.

			As part of these pre-specified subgroup analyses in the ITT, the Company will present subgroups according to PD-L1 status (as per the NICE final scope). However, these analyses should not be a core focus of the appraisal for several reasons. Firstly, PD-L1 status was not a stratification factor in the DUO-E trial, and PFS analyses by PD-L1 status were only exploratory (i.e., the DUO-E trial was not powered for this analysis). Secondly, as discussed further in Section B.1.3.2.6, the clinical significance of PD-L1 expression in EC is currently unclear. Specifically, evidence surrounding PD-L1 status as a prognostic marker for survival is inconclusive. There is also inconsistent evidence regarding whether PD-L1 expression is a driver or predictor of response to currently available treatments in EC.[22, 23] It is possible that any observed impact of PD-L1 status could in fact simply represent a high correlation with other biomarkers. The Company therefore consider that MMR	

			status should be the primary focus of the appraisal, given that the implications of MMR status are well-established, and given that this biomarker is already routinely measured and used to inform clinical practice in the UK for EC patients. Other subgroups listed in the final scope are not presented in the Company Submission due to the following limitations which affect the feasibility and reliability of such analyses for decision making: **Local vs metastatic recurrence:** The DUO-E trial enrolled patients with newly diagnosed EC as well as those with recurrent disease (this classification was a stratification factor). Within the newly diagnosed cohort, the Company presents a subgroup analysis according to International Federation of Gynecology and Obstetrics (FIGO) stage, (which provides details on the extent of local or distant metastatic spread of the tumour). However, within the subgroup of patients with recurrent disease, there	

			was no further subgroup analysis conducted to further segment such patients into local or distant sites of recurrence. Eligibility criteria for the DUO-E trial specified that patients with recurrent disease must have a poor potential for cure by surgery alone or in combination. For this reason, such patients were already pre-selected to have a similar baseline prognosis, and further subgroup analyses according to specific site(s) of recurrence will not be informative. **With or without primary debulking:** Across the three treatments arms in the DUO-E trial, only a small proportion (13.4% to 16.2%) received no prior surgery. The reliability of such a subgroup analysis would therefore be limited by small sample sizes. Furthermore, the decision to offer primary debulking surgery is based on multiple clinical tumour characteristics, as well as subjective local and regional clinician preferences. This would confound the results of such an	

			analysis and limit its value for decision-making.	

Abbreviations: AEs, adverse events; CS, company submission; dMMR, mismatch repair deficient; EAG, External Assessment Group; EC, endometrial cancer; FIGO, Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival; PD-L1, Programmed cell death ligand 1; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

2.3.1 Population

The population specified in the NICE final scope was people with newly diagnosed advanced or recurrent EC and, as discussed in Section 2, the population covered in the CS is split into dMMR and pMMR patents to align with the expected marketing authorisations for durvalumab and olaparib in EC. The EAG notes that the DUO-E trial, which provides the primary efficacy and safety data informing the CS, stratified patients based on MMR status (proficient vs deficient) and the data for dMMR and pMMR are thus subgroup data.

The EAG also notes that disease status (newly diagnosed vs recurrent), and geographic region (Asia vs rest of world [RoW]) were additional stratification factors in DUO-E. The EAG's clinical experts considered the proportion of Asian patients in DUO-E is likely to be higher than expected in UK clinical practice and the ITT population of the trial is potentially comprised of a slightly younger and fitter population compared to in clinical practice.

In the company's economic model, baseline characteristics for the dMMR and pMMR subgroups are based on the final analysis set (FAS) of the intention-to-treat (ITT) population of the DUO-E trial (see Section 3.2 for more details of the trial). The company explained that the baseline characteristics for the ITT population were used for the economic model because of the larger sample size. Additionally, the company considered that there were no clinically meaningful differences in baseline characteristics for dMMR and pMMR subgroups (see Appendix 1.1 for further details). However, the company explored using baseline mean age for the dMMR and pMMR subgroups in scenario analyses, presented in Section 5.2.2. Table 10 presents the baseline characteristics included in the economic model.

Table 10. Patient baseline characteristics included in the model – DUO-E trial (reproduced from Table 30 of the CS)

Parameter	Value
Mean age (years)	62.60
Mean weight (kg)	73.80
Mean height (cm)	159.4
Mean body surface area (m2)	1.77
Glomerular Filtration Rate (ml/min)	125.00
Abbreviations: CS, company submission	

The EAG's clinical experts noted that in UK clinical practices, patients with EC at this stage in the treatment pathway tend to be older (late sixties) but noted that in trials, younger patients tend to be recruited. Additionally, in TA963, the committee preferred to use a baseline mean age of 67.1 years to reflect the UK population. However, the EAG notes that clinical outcomes implemented in the model are taken directly from the DUO-E trial, it is preferable that the baseline characteristics are reflective of this data. As such, the EAG considers the company's base case approach is reasonable. Nonetheless, the company did explore the preferred mean baseline age of 67.1 years from TA963 in scenario analysis for the committee to consider and this had minimal impact on the ICERs for the dMMR and pMMR subgroups (see Section 5.2.2). Additionally, for committee consideration, the EAG provides a scenario around its base case exploring a mean age of 67.1 years, presented in Section 5.2.2.

The EAG's clinical experts also noted that the GFR included in the model was high and the EAG notes that only the maximum value from DUO-E was reported in the CS (mean nor range was reported in either the CS or the CSR). In the model, GFR is used to estimate target dose for carboplatin. The EAG explored changes to the GFR in the model and notes that it has minimal impact on the cost-effectiveness of results (including use of extreme values).

DUO-E enrolled patients with newly diagnosed FIGO Stage III and Stage IV disease at baseline although the Stage III subgroup comprised of low patient numbers and was notably smaller than the Stage IV subgroup of the ITT population (5.7% and 41.2%, respectively [company response to clarification questions, Table 2]). In response to clarification question A2, the company reported that a greater proportion of patients are diagnosed with FIGO Stage III disease versus FIGO Stage IV disease in UK clinical practice which the EAG notes is in contrast to the population enrolled in the DUO-E trial.[24, 25] However, the company considered this difference to be explained by the inclusion criteria for the DUO-E trial, which specified that patients with FIGO Stage III disease must have, "measurable disease per RECIST 1.1 following surgery or diagnostic biopsy" (FIGO Stage IV patients were enrolled with or without disease following surgery or biopsy). The company reported that this eligibility criteria resulted in the enrolment of a particularly high-risk group of patients with FIGO Stage III EC in DUO-E.

The company further explained that the patients enrolled in the DUO-E trial (FIGO Stage III with measurable disease, FIGO Stage IV, and recurrent disease with poor potential for cure by surgery alone or in combination) are all treated via the same treatment pathway in the UK, as outlined in

Section B1.3.4 of the CS, and that this was validated by the company's clinical experts.[21] In addition, the company anticipated that these patients would have a similar baseline prognosis and the company highlighted that FIGO Stage is not considered to be a treatment effect modifier in newly diagnosed advanced EC patients.

The EAG notes that a potential lack of efficacy in FIGO Stage III patients was raised at the committee meeting for TA963 and the company reported that a clinical expert at the meeting stated that this was, "unexpected, and that it may be a statistical quirk caused by the low number of people in this subgroup".[15] The committee did not consider it to require further consideration and the final recommendation covered both FIGO Stage III and IV patients. The company stated that the DUO-E trial also has low sample sizes in the FIGO Stage III group, and that any analyses specifically within this group would likely be subject to significant statistical uncertainty. While the EAG considers it unusual that a statistical anomaly would occur in the same subgroup in two different trials, the EAG agrees with the company that in DUO-E specifically, the sample size for FIGO Stage III newly diagnosed EC patients in the dMMR and pMMR subgroups is small (n=10 and n=21, respectively for the trial arms of interest) and also notes that FIGO Stage was not a subgroup specified in the NICE final scope (see Appendix 8.3 for further details on DUO-E subgroup analyses).

In summary, the EAG notes that the dMMR and pMMR populations of interest are subgroups of the DUO-E trial and have been included in the economic model. The EAG considers the population in the NICE final scope to have been addressed appropriately based on the anticipated marketing authorisations for durvalumab and olaparib in EC.

2.3.2 Intervention

The intervention specified in the NICE final scope was durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with or without olaparib. The CS covers these as two separate treatment regimens:

- induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab (SoC+D); and
- induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC+D+O).

Prior to initiation of SoC+D or SoC+D+O, patients must have confirmation of MMR status using a validated test which clinical experts report is part of the routine management of patients with newly

diagnosed advanced or recurrent EC. In DUO-E, to be eligible to continue treatment into the maintenance phase of the trial, patients had to have received between 4 and 6 cycles of chemotherapy, and in order to commence olaparib (or olaparib placebo) they must have had adequate organ and bone marrow function (detailed maintenance phase eligibility criteria are outlined in the CSR).[26]

Durvalumab (Imfinzi®) is an immunotherapy that acts as an anti-programmed cell death ligand 1 (PDL1) monoclonal antibody.[2, 16] The anticipated MHRA marketing authorisation indication of relevance to this appraisal is for the use of durvalumab in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with:

- durvalumab as monotherapy in EC that is dMMR; or
- durvalumab in combination with olaparib in EC that is pMMR.

The anticipated recommended dose of durvalumab is 1,120 mg administered via an intravenous line with platinum-based chemotherapy (carboplatin + paclitaxel) every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles, followed by maintenance with 1,500 mg every 4 weeks as either a monotherapy or in combination with olaparib.

Olaparib (Lynparza®) is a poly (ADP-ribose) polymerase (PARP) inhibitor that works to disrupt the DNA-repair processes, which ultimately destroys tumour cells.[27] The anticipated indication of relevance to this appraisal for olaparib is for its use in combination with durvalumab for the maintenance treatment of adult patients with primary advanced or recurrent EC that is pMMR whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. The expected recommended dose of olaparib is 300 mg (2 x 150 mg tablets) orally administered twice daily (equivalent to a daily dose of 600 mg).

The treatment regimens for durvalumab and olaparib outlined above have been used in the economic model. However, the EAG notes that a small proportion of pMMR patients in the SoC+D+O arm of DUO-E received durvalumab as monotherapy during the maintenance phase of the trial [redacted] of all randomised patients). The reasons for not receiving combination maintenance therapy with olaparib are unclear but the EAG considers that for entry into DUO-E, patients were required to be considered eligible for treatment with olaparib and that the anticipated marketing authorisation for pMMR patients is for only the full combination of SoC+D+O and not SoC+D

monotherapy. However, the EAG also notes from the draft summary of product characteristics that, "treatment withholding or discontinuation may be required based on individual safety and tolerability".

In addition, the EAG notes that the subsequent treatments used in DUO-E are not reflective of UK clinical practice and the company has used expert opinion to help inform the model inputs. However, the EAG is concerned that there is potential bias in the results for OS from DUO-E given the efficacy data does not directly align with the subsequent treatments received in UK clinical practice (**Key issue 2** in Section 1). Of particular note, based on clinical expert opinion, the EAG considers [redacted]

Subsequent treatments in DUO-E are summarised and discussed further in Section 3.2.

In summary, the EAG considers the treatment regimens for durvalumab and olaparib to be reasonable and to align with the anticipated marketing authorisations which are expected from the MHRA in December 2024. In addition, the EAG considers the subsequent treatments used in DUO-E not to be reflective of UK clinical practice and [redacted]

2.3.3 Comparators

The NICE final scope lists platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and hormone therapy followed by routine surveillance as comparators of interest. The EAG's clinical experts agree with the company that the primary comparator of relevance is platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and note this was a comparator in the DUO-E trial. In DUO-E the treatment regimen for platinum-based chemotherapy was carboplatin AUC, 5 or 6 mg/mL/min and paclitaxel 175 mg/m^2

intravenously every three weeks for six cycles and this has been included in the economic model. The EAG's clinical experts reported this is consistent with UK clinical practice.

The EAG's clinical experts agree with the company that hormone therapy is used in only a small proportion of advanced or recurrent EC patients, and the patients likely to receive first-line hormone therapy are unlikely to be suitable for SoC+D or SoC +D + O. The EAG therefore considers the company's decision that hormone therapy is not a relevant comparator to be reasonable (Table 9).

The EAG is concerned that the [redacted]

For the pMMR subgroup, the EAG notes that dostarlimab is not currently approved in the UK but pembrolizumab with lenvatinib would be a treatment option at second-line for SoC patients. The EAG considers it difficult to ascertain how reflective the subsequent treatments received by the pMMR SoC patients in DUO-E are compared with UK clinical practice partly because [redacted]. Subsequent therapies are discussed in more detail in Sections 3.2 and 4.2.6.5.

Finally, the EAG notes that the company has relied on the committee discussion for dostarlimab (TA963) as part of long-term survival validation in the economic model, but the EAG considers this is potentially problematic when comparing the incremental QALY gain of each technology over SoC. The EAG has therefore conducted exploratory indirect comparisons of SoC+D versus dostarlimab for OS and PFS in the dMMR population and these results are provided in Section 3.4. However, as discussed in Section 2.2.1, the EAG notes that dostarlimab is not considered to be a relevant

comparator due to its present availability only via the CDF. The EAG presents these results to give context to the assumptions the company has made based on TA963 and also to aid committee in consistency of decision-making.

In summary, the EAG agrees with the company that the primary comparator of relevance is platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance and notes this was a comparator in the NICE final scope and the DUO-E trial. The EAG also notes that the subsequent therapies received by patients in the SoC arm of DUO-E are not reflective of UK clinical practice, with a key difference reported by clinical experts to be [redacted] (**Key issue 2** in Section 1).

2.3.4 Outcomes

The outcomes specified in the NICE final scope are:

- progression-free survival (PFS);
- overall survival (OS);
- response rate;
- duration of response;
- adverse effects (AEs) of treatment; and
- health-related quality of life (HRQoL).

The EAG notes that data for all of the outcomes specified in the NICE final scope are available for the overall trial population in DUO-E and that only data on PFS, OS, HRQoL and AEs are used in the economic model. The economic model focuses separately on the dMMR and pMMR patient populations. The EAG notes that while subgroup data from these populations for PFS and OS are used in the model, data from the overall trial population are used for HRQoL and AEs (intention-to-treat [ITT] and safety analysis set [SAS] populations, respectively).

Investigator-assessed PFS was the primary efficacy endpoint in DUO-E and is used to inform PFS in the economic model with blinded independent central review (BICR) PFS included in DUO-E as a sensitivity analysis. The EAG considers the use of investigator-assessed PFS in the economic model to be reasonable, as the trial incorporated a double-blind design for treatments. The trial results for BICR PFS were also provided by the company in the CS for the ITT population and the clarification question response provided BICR PFS for the dMMR and pMMR subgroups.

OS data from DUO-E are from the first interim analysis and as such are immature with data maturity in the ITT of 30.7% for the SoC vs SoC+D arms, and 27.9% for the SoC vs SoC+D+O arms.[26] The EAG is therefore concerned about the reliability of the OS data from DUO-E and the resulting extrapolations used in the company's economic model (**Key issue 1** in Section 1). Nevertheless, the EAG notes that there are no further data-cuts available at present and thus considers these OS data to represent the most appropriate data for use in the model until more mature data become available. In response to clarification, the company reported that the second interim analysis of OS is expected to be performed when approximately [redacted] OS events ([redacted] of the target number of OS events) have occurred, and this is currently estimated to be likely to occur Q4 2025. The final OS results are predicted to become available in 2026. Further discussion on the OS results and the modelling of OS are provided in Sections 3.3.1.2, 3.3.2.2, 4.2.3.5 and 4.2.3.9.

HRQoL was captured in DUO-E using EORTC QLQ-C30, EORTC QLQ-EN24 and EQ-5D-5L, with the EQ-5D-5L data mapped to EQ-5D-3L for use in the economic model. In their response to clarification questions, the company provided the EQ-5D-5L results for the dMMR and pMMR subgroups of DUO-E and these are discussed in Section 3.3.4. However, based on clinical expert opinion, the EAG considers the company's use of the ITT overall trial population data in the economic model to be reasonable as HRQoL is not expected to vary for pre-progression or progressed EC patients in relation to MMR status.

Adverse events used in the economic model were any AEs of grade ≥3 occurring in ≥5% of patients in at least one of the comparator treatments of the DUO-E trial with data sourced from the overall SAS population. Similar to HRQoL, the EAG's clinical experts do not consider the occurrence of AEs likely to be related to MMR status and therefore the EAG considers the company's use of the SAS population for AEs in the model to be reasonable. The EAG notes that in the technology appraisal of dostarlimab [TA963], the committee preferred a broader range of adverse events (AEs) to be included in the model (those affecting at least 2% of people). As such, the EAG requested the company provide a scenario in the model where costs and disutility of AEs are based on grade ≥3 AEs occurring in ≥2% of patients in at least one of the treatment arms from the SAS population in DUO-E. This is discussed further in Section 3.3.5.

Additionally, the EAG notes that data from DUO-E on time to study treatment discontinuation or death (TDT, also known as time to treatment discontinuation [TTD]) were also included in the company's economic model.

In summary, the EAG considers data for all relevant outcomes from the NICE final scope are available from DUO-E but the EAG is concerned about the uncertainty of the data for OS due to its immaturity and the difference in subsequent treatments between the trial and UK clinical practice.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR) to identify relevant clinical evidence on the efficacy and safety of SoC+D, and SoC+D+O and their comparators for the treatment of newly diagnosed advanced or recurrent EC. The company's SLR was conducted in September 2023 and updated in May 2024.

In total, the SLR and its update resulted in the identification of 166 studies that met the inclusion criteria and these related to 93 unique studies. The 93 studies comprised 29 randomised controlled trials (RCTs) and 64 non-RCTs. One RCT was identified that directly addressed the comparisons of interest and investigated the safety and efficacy of SoC+D versus SoC, and SoC+D+O versus SoC in newly diagnosed advanced or recurrent EC: the DUO-E trial.[23] This trial was the focus of the CS and is discussed further in the sections that follow. The remaining included studies were not used to inform the efficacy or safety data presented in the CS and therefore are not discussed in this report.

Appendix 8.1 provides a summary and the EAG's critique of the company's SLR. In summary, the EAG considers the methods utilised by the company to be appropriate and that it is unlikely any relevant head-to-head studies have been omitted.

3.2 Critique of trials of the technology of interest: DUO-E

The DUO-E RCT (NCT04269200/GOG-3041/ENGOT-EN10)[23] was the only study identified in the company's SLR and included in the CS to provide evidence on the clinical efficacy and safety of SoC+D, and SoC+D+O for patients with newly diagnosed advanced or recurrent EC that is dMMR or pMMR, in comparison with SoC.

DUO-E is an ongoing Phase III randomised, multicentre, international, double-blind, 3-arm placebo-controlled RCT that enrolled adult female patients with newly diagnosed Stage III or IV EC, or recurrent EC with a low potential for cure by surgery alone or in combination with other EC therapies. DUO-E was conducted at trial sites across 22 countries worldwide although none were in the UK.

The interventions in the 3-treatment arms in DUO-E were as follows:

- Platinum-based chemotherapy (carboplatin: area under the time-concentration curve [AUC], 5 or 6 mg/mL/min; paclitaxel: 175 mg/m^2) in combination with durvalumab placebo intravenously every three weeks for six cycles, followed by maintenance durvalumab placebo intravenously every four weeks plus olaparib placebo tablets twice daily (SoC arm);
- Platinum-based chemotherapy in combination with durvalumab 1,120 mg intravenously every three weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every four weeks plus olaparib placebo tablets twice daily (SoC+D arm); and
- Platinum-based chemotherapy plus durvalumab 1,120 mg intravenously every 3 weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously every 4 weeks plus olaparib 300 mg tablets twice daily (SoC+D+O arm).

The EAG notes that DUO-E did not exclusively randomise dMMR patients to receive SoC+D or pMMR patients to receive SOC+D+O, although randomisation was stratified by MMR status, and dMMR and pMMR were prespecified subgroup analyses for the analysis of investigator-assessed PFS. However, analyses of the dMMR and pMMR subgroups for other outcomes were post hoc. Also, as discussed in Section 2, the MHRA marketing authorisations for durvalumab and olaparib are expected to stipulate that SoC+D is indicated for the dMMR primary advanced or recurrent EC population, while SoC+D+O is indicated for the pMMR primary advanced or recurrent EC population. The EAG therefore notes that the relevant clinical efficacy data for each of the populations of interest is limited to subgroup data from DUO-E, although the HRQoL and AE data used in the economic model are from the ITT population. The EAG's critique of the DUO-E trial is summarised in Table 12 and the focus of the results discussed in this report are on the relevant treatment arms in the patient population subgroups of relevance to this appraisal.

The EAG considers the immaturity of the OS data from DUO-E presented in the CS to be a critical area of concern; it is noted that at the time of writing, data are only available from the first interim analysis. A second interim OS analysis is planned prior to the final OS analysis. The company reported uncertainty around the exact timing of the next DCO due to the event-driven nature of the analyses, but it is estimated that the final OS DCO will be in 2026.

A further area of concern with regards DUO-E is the subsequent treatment usage not reflecting UK clinical practice. [redacted]

[redacted]

Subsequent treatments used in DUO-E are summarised in Table 11 and the subsequent treatments used in the economic model are discussed in Section 4.2.6.5. The EAG considers that [redacted] (**Key issue 2** in Section 1).

Table 11. Post-discontinuation disease-related anticancer therapy (FAS) (adapted from CQ response Table 5)

Subsequent therapy	dMMR subgroup		pMMR subgroup	
	SoC (N=49)	SoC+D (N=46)	SoC (N=192)	SoC+D+O (N=191)
Total number of patients with post-discontinuation anti-cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Hormonal therapy	[redacted]	[redacted]	[redacted]	[redacted]
Cytotoxic chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin or Doxorubicin Hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Targeted therapy	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib Mesilate	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: All percentages are presented as a proportion of the total number of patients in each treatment arm who received a post-discontinuation anti-cancer therapy and were calculated by the EAG

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 12. EAG's summary of the design, conduct and analysis of DUO-E

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation		**Appropriate** Patients were randomised 1:1:1 to each of the three study arms with randomisation stratified by MMR status (proficient vs. deficient), disease status (newly diagnosed vs. recurrent), and geographic region (Asia vs. rest of world [RoW]). A centrally computer-generated random sequence was used to assign patients to treatment groups along with an interactive web response (IWRS); the same block randomisation list was used by all centres.
Concealment of treatment allocation		**Appropriate** Study arm assignment was based on a computer-generated random sequence using an IWRS with sequential randomisation codes within each stratum. The company reported that the IWRS provided the kit identification number to be allocated to the patient at the randomisation visit and subsequent treatment visits.
Eligibility criteria		**Appropriate** The EAG's clinical experts generally considered the DUO-E trial inclusion and exclusion criteria to be reasonable but the EAG notes that the dMMR and pMMR populations of interest for this appraisal are subgroups in the trial.
Blinding		**Appropriate** The study was double-blind and utilised an IWRS to assign treatments with matching placebo durvalumab and/or placebo olaparib given where necessary. The IWRS allocated a kit identification number to each patient at the dispensing visit and provided this number to the investigator(s) or pharmacists.
Baseline characteristics		**No major concerns although it is noted that the ITT population characteristics are used in the economic model rather than the relevant pMMR or dMMR subgroup baseline characteristics. Also, potentially some discrepancies compared to the UK population.** Baseline characteristics were reasonably well balanced between trial arms in the ITT, pMMR and dMMR populations but the EAG notes that the dMMR population of relevance to this appraisal (N=95 [SoC n=49 and SoC+D n=46) is relatively small compared to the pMMR population of relevance (N=383 [SoC n=192 and SoC+D+O n=191]). In addition, the EAG notes that the ITT population baseline characteristics are used in the company base case in the economic model, although scenarios using the relevant subgroup baseline age data were also presented. The EAG considers there to be little difference in mean age between the different populations: 62.6 years for the ITT population, 62.5 years in the dMMR population and 62.4 years in the pMMR population. The EAG's clinical experts considered the proportion of Asian patients in DUO-E likely to be higher than expected in UK clinical practice and

		that the ITT population of the trial potentially comprised of a slightly younger and fitter population compared to UK clinical practice (see Table 67 and Table 68 for the baseline characteristics for the ITT population of DUO-E).
Dropouts	CQ response	[redacted] The EAG notes [redacted] The EAG also notes there was [redacted] The EAG notes that a total of 75.8% of the patients who were randomised in the overall trial ITT population met the criteria to continue to receive treatment into the maintenance phase of the study (i.e. received at least one dose of olaparib or olaparib placebo). By arm, the proportion of patients who entered the maintenance phase in the SoC+D and SoC+D+O arms were similar (76.9% and 80.3%, respectively), while the proportion who entered the maintenance phase in the SoC arm was lower (70.1%). Data on patients entering the maintenance phase for the dMMR and pMMR subgroups were not reported in the CS.
Statistical analysis		
Sample size and power		**Appears appropriate for the ITT population** Recruitment was planned for approximately 699 patients to be randomised (1:1:1) into the study, in order to achieve approximately 299 PFS events (data maturity of 64%) for the comparison of the SoC+D arm vs SoC, and approximately 281 PFS events (data maturity of 60%) for the comparison of the SoC+D+O vs SoC. A total of 718 patients were recruited for the ITT population therefore the ITT was in keeping with the planned sample size. For the primary outcome, assuming a median PFS of 12 months for the SoC arm and an average true PFS HR of 0.70 for SoC+D vs SoC and 0.55 for SoC+D+O vs SoC, there was 80% and >99% power to demonstrate a statistically significant difference for PFS at the overall two-sided significance level of 2.5% for each comparison, respectively. The EAG notes that the sample size and power calculation are for the ITT population in DUO-E and the populations of interest to this appraisal are the pMMR and dMMR subgroups.
Handling of missing data		**Appears reasonable** No methods were used to account for missing data and efficacy analyses were conducted using the ITT population.

Outcome assessment		**Appropriate although the relevant dMMR and pMMR populations are subgroups of DUO-E, data for outcomes other than investigator-assessed PFS from the dMMR and pMMR subgroups were *post hoc*, and the data for OS are immature** The EAG considers the outcomes assessed to be appropriate and to have used appropriate methods/questionnaires. The coprimary endpoints of the DUO-E study were investigator-assessed PFS for both the SoC+D and SoC+D+O arms vs SoC. Secondary endpoints included OS, objective response rate (ORR), and time to study treatment discontinuation or death (TTD). EQ-5D-5L was an exploratory endpoint. Efficacy and safety analyses were performed in accordance with a detailed Statistical Analysis Plan[28] and the analyses presented in the CS are from the primary DCO (12 April 2023). The full analysis set (FAS) or ITT population (n=718) was used for the efficacy and HRQoL analyses, and the safety analysis set (SAS; n=709) was used for adverse events. Data for the final analysis of OS are not yet available and the dMMR and pMMR populations of relevance to this appraisal comprise subgroups of the ITT population. In addition, it is noted that apart from investigator-assessed PFS, the pMMR and dMMR subgroup data are from *post hoc* analyses.

Abbreviations: CS, company submission; DCO, data cut-off; dMMR, mismatch repair deficient; EAG, External Assessment Group; ITT, intention to treat; IWRS, interactive web response; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

3.3 Critique of the clinical effectiveness analysis and interpretation

The EAG presents the results for the key endpoints of relevance to the decision problem included in the economic model, focusing on the SoC+D versus SoC comparison in the dMMR population and the SoC+D+O versus SoC comparison for the pMMR population. In addition, the results for objective response rate are discussed below with the results for duration of response and other secondary endpoints available in the CS. The only results for the overall trial population that are presented in this report are those that are of relevance to the economic model: HRQoL, AEs and TTD.

All of the results presented below are from the first data cutoff for DUO-E (12 April 2023) and these comprise a median follow-up of 12.6 months in the SoC arm and 15.4 months in the SoC+D and SoC+D+O arms.

3.3.1 Clinical effectiveness results: SoC+D in the dMMR population

3.3.1.1 PFS at DCO1 (12 April 2023)

At DCO1, data maturity in the dMMR population was 40.6% and median investigator-assessed PFS was not reached in the SoC+D trial arm. The results of investigator-assessed PFS in the dMMR subgroup demonstrated an improvement in PFS with SoC+D when compared to SoC (HR 0.42; 95% CI: 0.22 to 0.80 [Table 13]). The Kaplan-Meier (KM) plot for investigator-assessed PFS in the dMMR population is presented in Figure 2 and shows that the SoC and SoC+D arms appear to cross before separating at approximately 4 months, with treatment beyond this timepoint favouring SoC+D.

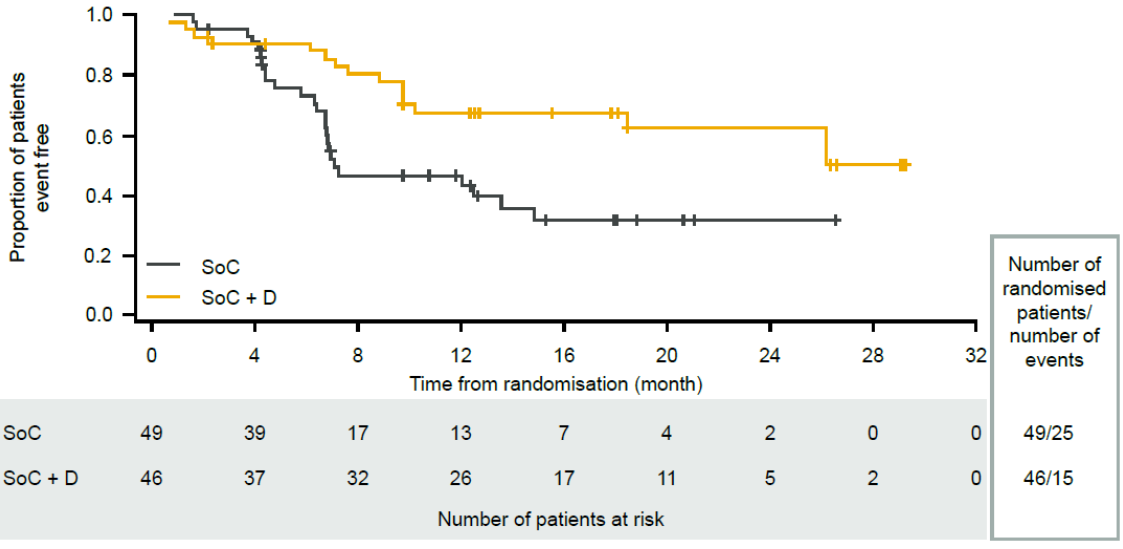
Table 13. Investigator-assessed PFS in the dMMR population at DCO1 (12 April 2023) (reproduced from CS Table 14)

	SoC (N=49)	SoC+D (N=46)
Events, n (%)	25 (51.0)	15 (32.6)
Median, months (95% CI)	7.0 (6.7 to 14.8)	NR (NR to NR)
HR (95% CI) vs SoC	-	0.42 (0.22 to 0.80)
PFS rate at 6 months (95% CI)	73.1 (56.6 to 84.2)	90.6 (76.9 to 96.4)
PFS rate at 12 months (95% CI)	43.3 (27.3 to 58.3)	67.9 (51.1 to 80.0)
PFS rate at 18 months (95% CI)	31.7 (16.7 to 47.9)	67.9 (51.1 to 80.0)

Source: AstraZeneca. Data on File. 2023.[29] Chon et al.[30]

Abbreviations: CI, confidence interval; CS, company submission; DCO1, primary data cut-off; dMMR, mismatch repair deficient; HR, hazard ratio; NR, not reported; PFS, progression-free survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

Figure 2. KM plot for Investigator-assessed PFS in the dMMR population at DCO1 (12 April 2023) (reproduced from CS Figure 10)



Source: AstraZeneca. Data on File. 2023.[29] Chon *et al.*[30]

Abbreviations: CS, company submission, DCO1, primary data cut-off; dMMR, mismatch repair deficient; KM, Kaplan-Meier; PFS, progression-free survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

In response to clarification questions, the company provided the KM plot for BICR-assessed PFS in the dMMR subgroup (Figure 3) which the EAG notes is broadly consistent with the KM plot for investigator-assessed PFS (Figure 2). The HR and 95% confidence interval for the analysis of BICR-PFS in the dMMR subgroup was not reported.

Figure 3. BICR-assessed PFS KM plot for the dMMR subgroup (reproduced from company response to CQ's Figure 2)

Abbreviations: BICR, blinded independent central review; dMMR, mismatch repair deficient; KM, Kaplan-Meier; PFS, progression-free survival; SoC, standard of care; SoC+Durva, standard of care with durvalumab.

3.3.1.2 OS at DCO1 (12 April 2023)

As noted above, the data for OS are extremely immature and are reported from the first interim analysis which has an overall maturity of 21.7% for the dMMR subgroup (**Key issue 1** in Section 1). The HR suggests an improvement in OS with SoC+D arm compared with the SoC arm (HR 0.34; 95% CI: 0.13 to 0.79 [Table 14]). The EAG notes that the KM plot for OS in the dMMR population (Figure 4) demonstrates crossing of the curves until approximately 4 months followed by a separation similar to the KM plots for PFS.

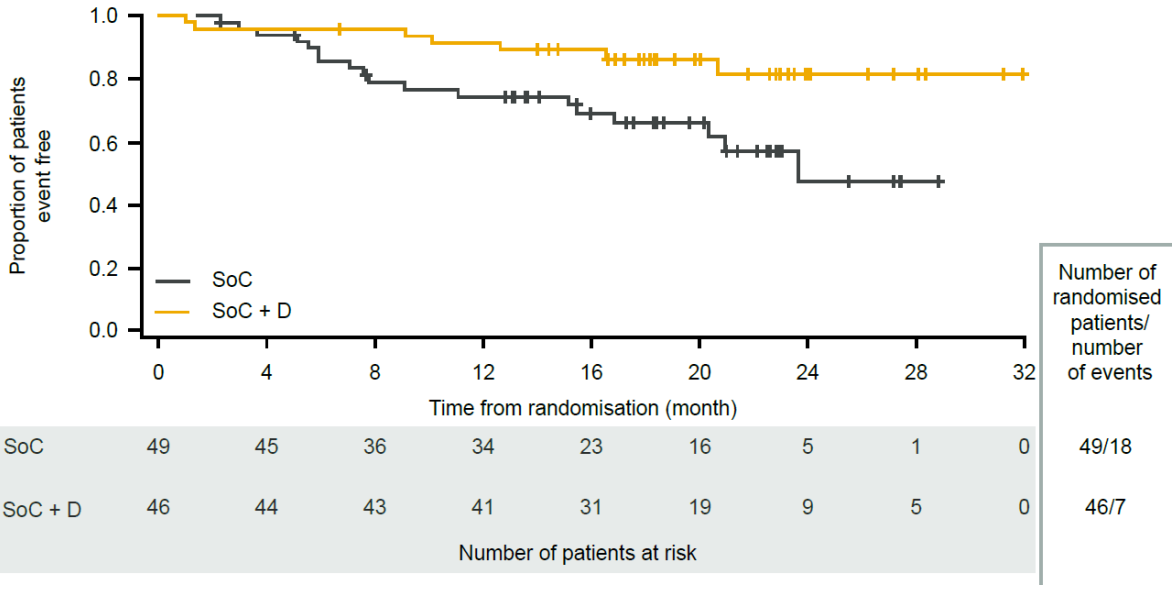
Table 14. OS in dMMR population at DCO1 (12 April 2023) (reproduced from CS Table 15)

	SoC (N=49)	SoC+D (N=46)
Events, n (%)	18 (36.7)	7 (15.2)
Median, months (95% CI)	23.7 (16.9 to NR)	NR (NR to NR)
HR (95% CI) vs SoC	-	0.34 (0.13 to 0.79)
OS rate at 6 months (95% CI)	85.3 (71.5 to 92.7)	95.7 (83.7 to 98.9)
OS rate at 12 months (95% CI)	74.4 (59.4 to 84.6)	91.2 (78.2 to 96.6)
OS rate at 18 months (95% CI)	65.8 (49.4 to 78.0)	86.1 (71.5 to 93.6)

Source: AstraZeneca. Data on File. 2023.[31] Baurain 2024.[32]

Abbreviations: CI, confidence interval; CS, company submission; DCO1, primary data cut-off; dMMR, mismatch repair deficient; HR, hazard ratio; NR, not reported; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

Figure 4. KM plot of OS in the dMMR subpopulation at DCO1 (12 April 2023) (reproduced from CS Figure 11)



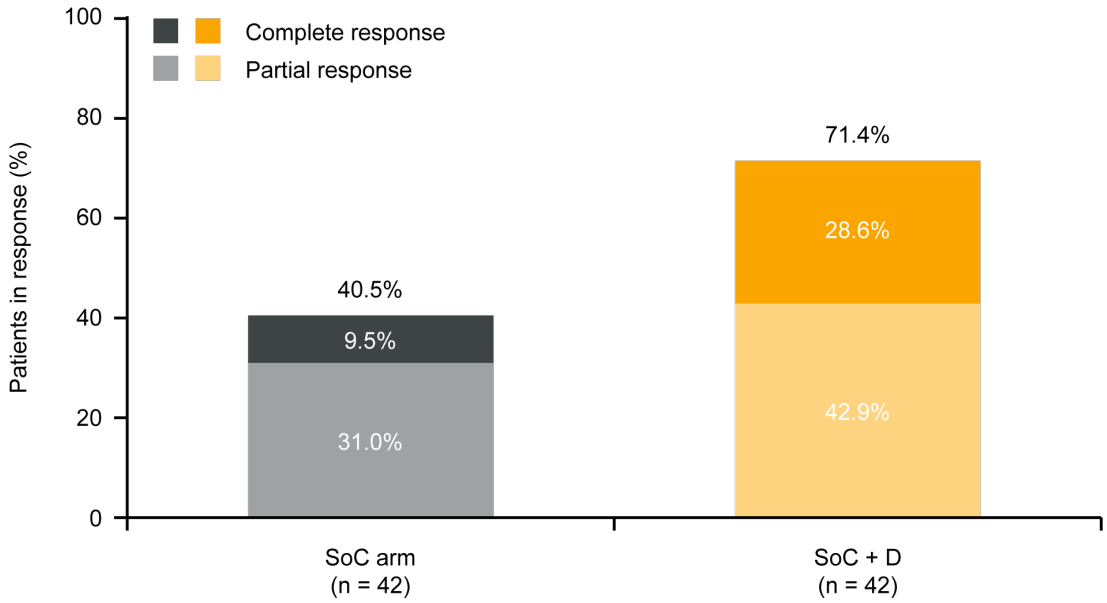
Source: AstraZeneca. Data on File. 2023.[31] Baurain 2024.[32]

Abbreviations: CS, company submission, DCO1, primary data cut-off; dMMR, mismatch repair deficient; KM, Kaplan-Meier; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

3.3.1.3 ORR at DCO1 (12 April 2023)

In the dMMR population, a higher ORR was observed for SoC+D (30 patients [71.4%]) when compared with SoC (17 patients [40.5%]). The resulting odds ratio for SoC+D versus SoC in the dMMR population was 3.68 (95% CI: 1.51 to 9.39) and the proportion of patients experiencing a complete response in the SoC+D arm was markedly higher compared with the SoC arm (28.6% versus 9.5%, respectively [Figure 5]).

Figure 5. ORR in the dMMR population at DCO1 (12 April 2023) (reproduced from CS Figure 12)



Footnotes: n numbers refer to the number of patients with measurable disease at baseline

Source: Chon 2024.[30]

Abbreviations: CS, company submission, DCO1, primary data cut-off; dMMR, mismatch repair deficient; ORR, objective response rate; SoC, standard of care; SoC+D, standard of care with durvalumab.

3.3.2 Clinical effectiveness results: SoC+D+O in the pMMR population

3.3.2.1 PFS at DCO1 (12 April 2023)

In the pMMR population, the overall data maturity for investigator-assessed PFS was 66.1% and SoC+D+O was associated with an improvement in investigator-assessed PFS when compared to SoC (median PFS: 15.0 months vs 9.7 months, respectively; HR 0.57; 95% CI: 0.44 to 0.73 [Table 15]).

The KM plot for investigator-assessed PFS in the pMMR population is presented in Figure 6 and shows crossing of the curves until approximately 7 months from randomisation. Beyond month 7 the curves separate and suggest a benefit in investigator-assessed PFS in favour of SoC+D+O compared with SoC.

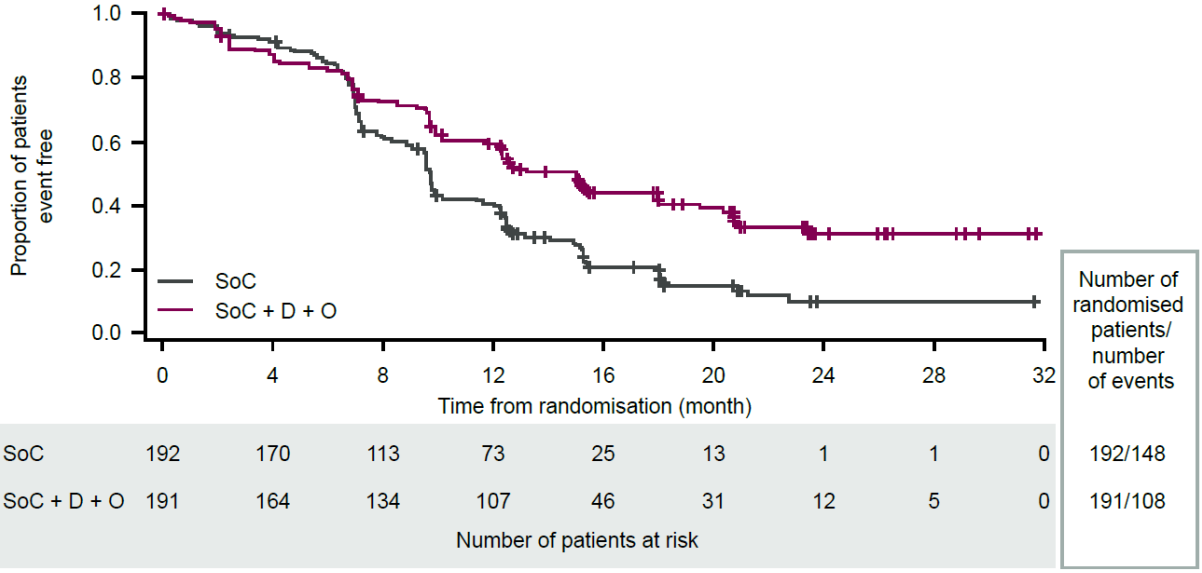
Table 15. Investigator-assessed PFS in the pMMR population at DCO1 (12 April 2023) (reproduced from CS Table 19)

	SoC (N=192)	SoC+D+O (N=191)
Events, n (%)	148 (77.1)	108 (56.5)
Median, months (95% CI)	9.7 (9.2 to 10.1)	15.0 (12.4 to 18.0)
HR (95% CI) vs SoC	-	0.57 (0.44 to 0.73)
PFS rate at 6 months (95% CI)	84.4 (78.4 to 88.9)	83.1 (77.0 to 87.7)
PFS rate at 12 months (95% CI)	40.8 (33.6 to 47.8)	59.4 (52.0 to 66.0)
PFS rate at 18 months (95% CI)	20.0 (14.1 to 26.7)	42.0 (34.1 to 49.6)

Source: AstraZeneca. Data on File. 2023.[31] Chon *et al.*[30]

Abbreviations: CI, confidence interval; CS, company submission; DCO1, primary data cut-off; HR, hazard ratio; NR, not reported; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; S SoC+D+O, standard of care with durvalumab and olaparib.

Figure 6. KM plot for Investigator-assessed PFS in the pMMR population (reproduced from CS Figure 14)



Source: AstraZeneca. Data on File. 2023.[31] Chon, *et al.*[30]

Abbreviations: CS, company submission, KM, Kaplan-Meier; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

In response to clarification questions, the company provided the KM plot for BICR-assessed PFS in the pMMR subgroup (Figure 7), which the EAG notes is broadly consistent with the KM plot for investigator-assessed PFS (Figure 6). The HR and 95% confidence interval for the analysis of BICR-PFS in the pMMR subgroup was not reported.

Figure 7. BICR-assessed PFS KM plot for the pMMR subgroup (reproduced from company response to CQ 's Figure 3)

Abbreviations: BICR, blinded independent central review, CS, company submission, KM, Kaplan-Meier; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+Durva+Olap, standard of care with durvalumab and olaparib.

3.3.2.2 OS at DCO1 (12 April 2023)

As discussed previously, OS data from DCO1 are extremely immature (**Key issue 1** in Section 1); the overall data maturity at DCO1 was 29.2% in the pMMR population. Nevertheless, SoC+D+O u0.47 s; Table 16). The KM plot for OS in the pMMR population is presented in Figure 8 and shows crossing of the curves in the first few months following randomisation before a separation of the SoC+D+O and SoC curves beyond approximately 8 months from randomisation. The separation favours treatment with SoC+D+O and is maintained in favour of the SoC+D+O arm throughout the follow-up period.

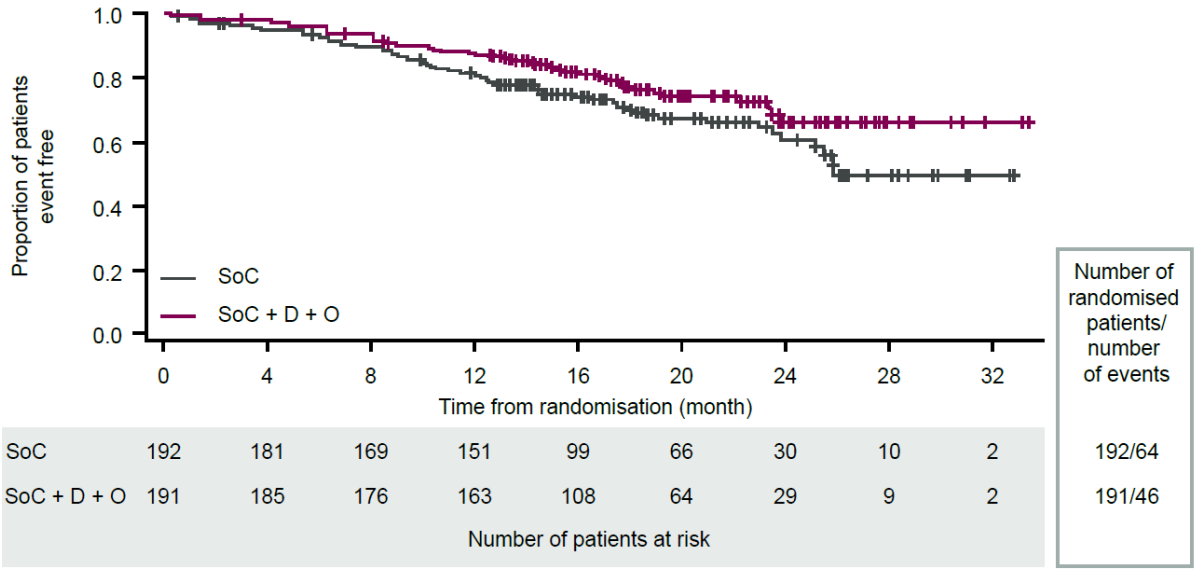
Table 16. OS in pMMR population at DCO1 (12 April 2023) (reproduced from CS Table 20)

	SoC (N=192)	SoC+D+O (N=191)
Events, n (%)	64 (33.3)	46 (24.1)
Median, months (95% CI)	25.9 (25.1 to NR)	NR (NR to NR)
HR (95% CI) vs SoC	-	0.69 (0.47 to 1.00)
OS rate at 6 months (95% CI)	92.7 (87.9 to 95.6)	95.8 (91.8 to 97.9)
OS rate at 12 months (95% CI)	81.0 (74.6 to 85.9)	87.3 (81.7 to 91.3)
OS rate at 18 months (95% CI)	69.9 (62.3 to 76.2)	76.9 (69.5 to 82.7)

Source: AstraZeneca. Data on File. 2023.[31] Baurain 2024.[32]

Abbreviations: CI, confidence interval; CS, company submission; DCO1, primary data cut-off; HR, hazard ratio; NR, not reported; OS, overall survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

Figure 8. KM plot of OS in the pMMR subpopulation at DCO1 (12 April 2023) (reproduced from CS Figure 15)



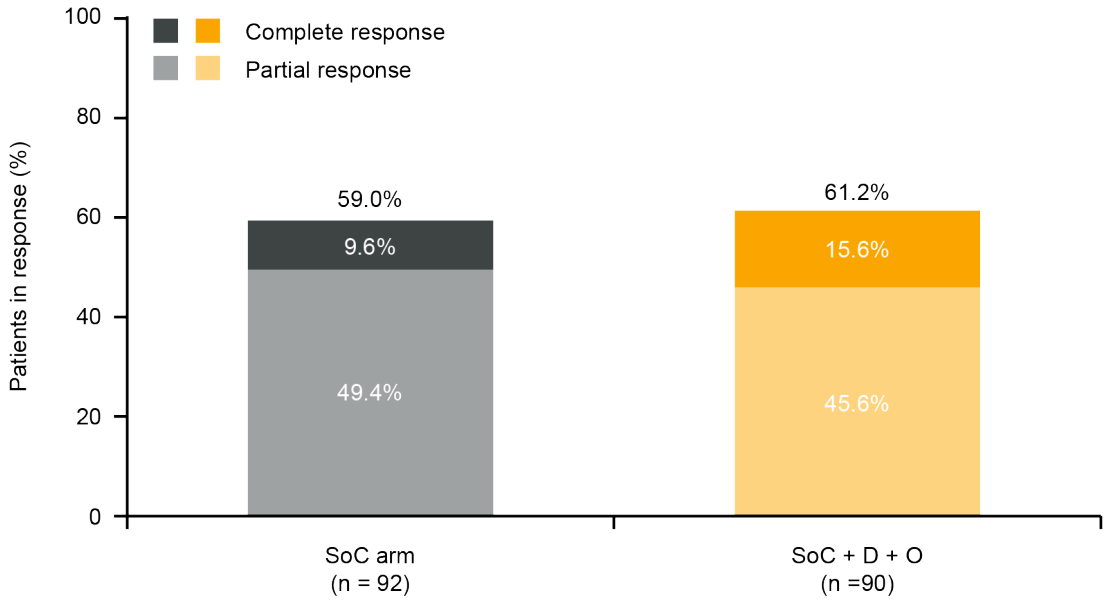
Source: AstraZeneca. Data on File. 2023.[31] Baurain 2024.[32]

Abbreviations: CS, company submission, KM, Kaplan-Meier; OS, overall survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

3.3.2.3 ORR at DCO1 (12 April 2023)

The ORR was similar in the SoC+D+O and SoC arms of the pMMR subgroup (90 patients [61.2%] in the SoC+D+O arm vs 92 patients [59.0%] in the SoC arm) with an OR of 1.10 (95% CI: 0.69 to 1.74 [Figure 9]). However, the proportion of patients that experienced CR was higher in the SoC+D+O arm (15.6%, n=23) compared to the SoC arm (9.6%, n=15).

Figure 9. ORR in the pMMR population at DCO1 (12 April 2023) (reproduced from CS Figure 16)



Footnotes: n numbers refer to the number of patients with measurable disease at baseline

Source: AstraZeneca. Data on File. 2023.[31] Chon, *et al*.[30]

Abbreviations: CS, company submission, DCO1, primary data cut-off; ORR, objective response rate; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

3.3.3 Time to study treatment discontinuation or death (TTD) at DCO1 (12 April 2023)

Results for time to treatment discontinuation (TTD) from the ITT population were used to inform the company base case in the economic model and the subgroup data were used in scenario analyses. The EAG notes that the TTD results for the ITT population were consistent with the findings for the relevant comparisons in the dMMR (SoC+D vs SoC) and pMMR (SoC+D+O vs SoC) subgroups and demonstrated an improvement in TTD with SoC+D compared with SoC and SoC+D+O compared with SoC. Further detail on the TTD results and use in the economic model are discussed in Section 4.2.4.

Table 17. Summary of results for TTD from DUO-E using DCO1 (adapted from CS Tables 11, 17 and 22)

Population	SoC			SoC+D				SoC+D+O			
	Events, (%)	Median, months	12-month rate, %	Events, (%)	Median, months	12-month rate, %	HR vs. SoC (95% CI)	Events, (%)	Median, months	12-month rate, %	HR vs. SoC (95% CI)
ITT	82.2	8.8	NR	68.5	9.9	NR	0.74 (0.60 to 0.91)	58.2	15.1	NR	0.51 (0.41 to 0.63)
dMMR	37 (75.5)	6.7 (5.1 to 7.9)	28.6	22 (47.8)	21.2 (9.3 to NR)	58.2	0.47 (0.27 to 0.79)	NA	NA	NA	NA
pMMR	161 (83.9)	9.3 (8.0 to 9.9)	33.3	NA	NA	NA	NA	117 (61.3)	13.4 (10.6 to 15.6)	55.0	0.54 (0.43 to 0.69)

Abbreviations: CI, confidence interval; CS, company submission; DCO1, primary data cut-off; dMMR, mismatch repair deficient; HR, hazard ratio; NA, not applicable; NR, not reported; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib; TTD, Time to treatment discontinuation.

3.3.4 Health-related quality of life

HRQoL in DUO-E was assessed using the cancer-related tool, EORTC-QLQ-C30, the EC-specific instrument, EORTC-QLQ-EN24, and the EQ-5D-5L questionnaire. The EAG notes that the EQ-5D-5L data from the ITT population of DUO-E were used to inform the economic model and the company's UK clinical experts indicated that HRQoL was not expected to differ for pre-progression or progressed EC patients based on MMR status[21]. The EAG's clinical experts agreed with the company's experts. In the company response to clarification questions, EQ-5D data for the dMMR and pMMR subgroups were provided and these along with the data from the ITT population are discussed below. EORTC-QLQ-C30 and EORTC-QLQ-EN24 data were only available for the overall ITT population and given they do not directly inform the economic model they are not presented below. However, the EAG notes that for the ITT population it was reported that there were no clinically meaningful changes in HRQoL (defined as a mean absolute change of ≥10 points) on the EORTC-QLQ-C30 or the EORTC-QLQ-EN24.

3.3.4.1 EQ-5D-5L at DCO1 (12 April 2023)

The EQ-5D-5L is a generic measure of health status that takes the form of a questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, plus a visual analogue scale (VAS). The company reported that compliance rates for the EQ-D-5L questionnaire for the ITT population were high at baseline and generally similar between arms (80.0% for SoC, 78.7% for SoC+ D, and 84.8% for SoC+D+O), although they decreased over time across all treatment arms. Beyond Week 30, compliance rates for the EQ-5D-5L had started to fall below 60%.[26]

The EAG notes that baseline EQ-5D-5L scores were [redacted] (Table 18). Change from baseline to 90 weeks using DCO1 in the EQ-5D-5L VAS score was [redacted]. However, [redacted] but the EAG also notes that [redacted], and therefore the results should be interpreted with caution.

EQ-5D-5L health state index change from baseline to 90 weeks (DCO1) [redacted] (Table 18).

Table 18. EQ-5D-5L at DCO1 (reproduced from company response to CQ's Table 4)

	ITT			dMMR			pMMR		
	SoC	SoC+D	SoC+D+O	SoC	SoC+D	SoC+D+O	SoC	SoC+D	SoC+D+O
EQ-5D-5L VAS score									
n (Baseline)	[redacted]								
Baseline	[redacted]								
n (90 weeks)	[redacted]								
Change from baseline at 90 weeks	[redacted]								
EQ-5D-5L health state index									
n (Baseline)	[redacted]								
Baseline	[redacted]								
n (90 weeks)	[redacted]								
Change from baseline at 90 weeks	[redacted]								

Abbreviations: CQ's, clarification question's; DCO1, primary data cut-off; dMMR, mismatch repair deficient; EQ-5D-5L, European Quality of Life scale-5-Dimensions-5-Levels; ITT, intention to treat; NA, not applicable; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

3.3.5 Safety

The ITT SAS (safety analysis set) from DCO1 (12 April 2023) was used to provide the AE data from DUO-E in the economic model for SoC, SoC+D and SoC+D+O to maximise the available sample size because it was not expected that AEs for any of the interventions in DUO-E would vary depending on MMR status. The EAG notes that the company also provided safety data for the dMMR and pMMR populations in the CS Appendix F and the findings are broadly consistent with the overall trial AEs. In addition, the EAG's clinical experts agreed that it was reasonable to use the overall trial AEs in the economic model.

The company reported that over half of the patients enrolled in the SoC and SoC+D trial arms of DUO-E reached 9 months of treatment, while in the SoC+D+O arm, over half of the patients reached 13 months of treatment.[2]

Nearly all patients in DUO-E experienced at least one AE and over half of patients experienced a Grade 3 or 4 AE (Table 19). The EAG notes that the proportion of patients experiencing a Grade ≥3 AE was higher in the SoC+D+O arm compared to the SoC+D and SoC arms (67.2% vs 54.9% and 56.4%, respectively). The company reported that the safety profiles across treatment arms were generally consistent with the known profiles of each treatment. The EAG notes that the AEs with a ≥5% higher frequency in the SoC+D+O arm compared with the SoC arm were anaemia (61.8% vs. 54.2% [grouped terms: anaemia and haemoglobin decreased]), nausea (54.6% vs 44.5%), vomiting (25.6% vs 18.2%), neutropenia (41.6% vs 41.5%), COVID-19 (20.2% vs 13.6%), asthenia (19.3% vs 10.2%), back pain (14.7% vs 9.3%), thrombocytopenia (29.8% vs 22.0% [grouped terms: platelet count decreased and thrombocytopenia]), hypothyroidism (13.9% vs 3.4%), and ALT increased (12.6% vs 7.6%). These AEs were all known AEs for SoC+D+O with the exception of arthralgia, COVID-19 and back pain.

AEs occurring with a ≥5% higher frequency in the SoC+D arm compared with the SoC arm in DUO-E were arthralgia (30.2% vs 24.6%), thrombocytopenia (28.1% vs 22.0% [grouped terms: platelet count decreased and thrombocytopenia]), hypothyroidism (15.7% vs 3.4%), ALT increased (12.8% vs 7.6%), and rash (17.4% vs 11.4%). The company reported that these were all known AEs for SoC+D, with the exception of arthralgia.

Table 19. Summary of AEs, overall study duration and maintenance phase (SAS) at DCO1 (12 April 2023) (reproduced from CS Table 24)

AEs,[a] n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	SoC (N=236)	SoC+D (N=235)	SoC+D+O (N=238)	SoC (N=169)	SoC+D (N=183)	SoC+D+O (N=192)
Any AEs	236 (100.0)	232 (98.7)	237 (99.6)	143 (84.6)	158 (86.3)	184 (95.8)
Grade ≥3 AEs	133 (56.4)	129 (54.9)	160 (67.2)	28 (16.6)	30 (16.4)	79 (41.1)
Serious AEs	73 (30.9)	73 (31.1)	85 (35.7)	19 (11.2)	22 (12.0)	42 (21.9)
AEs with outcome of death	8 (3.4)	4 (1.7)	5 (2.1)	2 (1.2)	0	3 (1.6)
AESIs to olaparib	4 (1.7)	5 (2.1)	14 (5.9)	2 (1.2)	4 (2.2)	9 (4.7)

myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New primary malignancies[b]	3 (1.3)	1 (0.4)[e]	2 (0.8)	2 (1.2)	1 (0.5)[e]	1 (0.5)
Pneumonitis[c]	1 (0.4)	4 (1.7)	12 (5.0)	0	3 (1.6)	8 (4.2)
Any immune-mediated AEs[d]	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)
AEs leading to discontinuation of study treatment	44 (18.6)	49 (20.9)	58 (24.4)	7 (4.1)	11 (6.0)	27 (14.1)
AEs leading to discontinuation of carboplatin/paclitaxel	32 (13.6)	31 (13.2)	31 (13.0)	NA	NA	NA
AEs leading to discontinuation of durvalumab/placebo	19 (8.1)	26 (11.1)	22 (9.2)	4 (2.4)	9 (4.9)	16 (8.3)
AEs leading to discontinuation of olaparib/placebo	5 (2.1)	11 (4.7)	21 (8.8)	5 (3.0)	10 (5.5)	21 (10.9)
AEs leading to dose interruption/delay of study treatment[f]	118 (50.0)	128 (54.5)	164 (68.9)	37 (21.9)	52 (28.4)	113 (58.9)
AEs leading to dose reduction of olaparib/placebo	5 (2.1)	14 (6.0)	65 (27.3)	4 (2.4)	13 (7.1)	63 (32.8)

Footnote: [a]The data presented here includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). [b]MDS/AML and new primary malignancies include AEs from first dose of investigational product (durvalumab/olaparib/placebo) until the end of the study (includes cases reported beyond the safety follow-up period); [c]Grouped term: includes pneumonitis, bronchiolitis, and interstitial lung disease; [d]As assessed by the Investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related; [e]Excludes one event of basal cell carcinoma; [f]For durvalumab/placebo, this includes dose interruption during infusion as well as doses that were skipped or delayed.

Source: DUO-E CSR.[26] Westin *et al.* (2023)[23]

Abbreviations: AEs, adverse events; DCO1, primary data cut-off; dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

In the economic model, the company included grade 3 or higher treatment-emergent adverse events (TEAEs) that were reported by at least 5% of patients in the SAS population in any treatment arm of DUO-E, presented in Table 20. The rate and duration of AEs was included in the economic model to estimate a one-off utility decrement and cost applied in the first model cycle for each treatment arm and these are described further in Section 4.2.4 and 4.2.6.9.

During the clarification stage, the EAG requested the company explore a scenario using a lower threshold of at least 2% of patients in the SAS population in any treatment arm of DUO-E experience TEAEs to align with the committee preferences in TA963.[15] The company supplied the requested scenario of the impact of broadening AEs in the economic model (results presented in Section 5.2.2). The company's scenario used data from DUO-E, but because of time limitations, mapped the costs

and disutilities already in the model to the additional AEs included because of the lower threshold for inclusion. The scenario should only be considered illustrative as costs and disutilities were not sourced specifically for each additional AE, even though published data are available. Nonetheless, the EAG considers that the company's scenario demonstrates that broadening the inclusion of AEs in the model has minimal impact on the ICERs.

Table 20. List of original and additional grade ≥3 adverse events included in the scenario analysis (reproduced from company response to CQ's Table 14)

Adverse events	"Original" AE to which cost and disutility have been matched	SoC+D	SoC+D+O	SoC
Original AEs in the company model				
Source	N/A	DUO-E	DUO-E	DUO-E
N	N/A	235	238	236
Anaemia	N/A	15.7%	23.5%	14.4%
Neutropenia	N/A	8.5%	11.3%	5.9%
Neutrophil count decreased	N/A	11.5%	13.4%	15.3%
Lymphocyte count decreased	N/A	2.1%	1.3%	2.1%
White cell count decreased	N/A	3.8%	4.2%	4.7%
Hypertension	N/A	2.1%	2.5%	3.0%
Pulmonary embolism	N/A	1.7%	2.1%	1.3%
Hypokalemia	N/A	2.6%	2.9%	0.8%
Additional AEs requested by the EAG				
Febrile neutropenia	Neutropenia	2.6%	3.4%	3.8%
Leukopenia	White cell count decrease	0.9%	2.1%	0.8%
Platelet count decreased	Anaemia	3.8%	2.5%	3.8%
Gamma-glutamyltransferase increased	Hypokalaemia	2.1%	0.8%	0.8%
Urinary tract infection	Hypertension	0.9%	2.9%	3.4%
Syncope	Hypertension	0.9%	2.9%	0.4%
Peripheral sensory neuropathy	Hypertension	0.0%	0.8%	2.5%
Nausea	Hypertension	0.4%	2.9%	1.3%
Diarrhoea	Hypertension	1.7%	1.3%	2.5%

Constipation	Hypertension	0.9%	0.0%	2.1%
Hyponatremia	Hypokalaemia	2.1%	1.3%	1.7%
Asthenia	Hypertension	1.3%	2.9%	1.7%
Fatigue	Hypertension	2.1%	2.1%	1.7%

Abbreviations: AEs, adverse events; EAG, External Assessment Group; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

3.4 Indirect treatment comparison

As discussed in Section 2.3.3, the EAG notes that the company has relied on the committee discussion for dostarlimab (TA963) as part of long-term survival validation in the economic model but the EAG considers this is potentially problematic when comparing the incremental QALY gain of each technology over SoC. The EAG has therefore conducted exploratory indirect comparisons of SoC+D versus dostarlimab for OS and PFS in the dMMR population and these results are provided below. The EAG notes that dostarlimab is not considered to be a relevant comparator for this appraisal as it is currently only available via the CDF but the EAG presents these results to give context to the assumptions the company has made based on TA963 and also to aid committee in consistency of decision-making.

It should be noted that the EAG has selected the RUBY trial[33] for this indirect treatment comparison as it was the primary trial of dostarlimab informing TA963 and a full SLR was not conducted to identify other potentially relevant studies. RUBY (ClinicalTrials.gov number: NCT03981796)[34] was a Phase 3, global, double-blind, randomised, placebo-controlled trial of dostarlimab (500 mg) plus carboplatin (area under the concentration–time curve, 5 mg per millilitre per minute) and paclitaxel (175 mg per square meter of body-surface area), every 3 weeks (six cycles), followed by dostarlimab (1000 mg) every 6 weeks for up to 3 years. RUBY enrolled patients with primary advanced Stage III or IV or first recurrent endometrial cancer and the primary end points were PFS as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and OS.

A total of 118 (23.9%) patients enrolled in RUBY had mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumours with 53 of these patients in the dostarlimab arm. The EAG notes that treatment in RUBY continued for up to 3 years or until disease progression, treatment discontinuation due to toxic effects, patient withdrawal, investigator decision to withdraw the patient, or death. In contrast, treatment in DUO-E had no maximum duration of treatment.

Limited baseline characteristics were available for RUBY but based on those available the EAG considers them to be broadly comparable to DUO- E with the exception of race. In addition, the EAG notes there may be a difference in MSI-H biomarker status between the studies as all patients in the dMMR subgroup of RUBY were MSI-H but it is unclear what proportion of the dMMR DUO-E patients were MSI-H. The proportion of white patients were lower in DUO-E, the proportion of Asian patients were higher in DUO-E, and the proportion of patients with FIGO Stage IV disease at diagnosis were higher in DUO-E (Table 70), compared to RUBY. The EAG's clinical experts also highlighted that the prior adjuvant therapy inclusion criteria for the RUBY and DUO-E differed, with RUBY allowing patients who had been treated with neoadjuvant or adjuvant systemic therapy and had recurred or progressed at least 6 months after completion of treatment (first recurrence), whereas in DUO- patients were required to have ≥ 12 months since last treatment with adjuvant chemotherapy before disease relapse. The overall impact of these differences between the RUBY and DUO-E trial populations on the results of the indirect comparison is unclear but based on the duration of remaining recurrence-free after prior adjuvant therapy, patients in DUO-E may have had a better prognosis than patients in RUBY.

Both RUBY and DUO-E were placebo-controlled RCTs and therefore the EAG conducted exploratory indirect treatment comparisons (ITCs) using the Bucher method for the outcomes of investigator-assessed PFS and OS. The results of the indirect treatment comparison are summarised in Table 21. The EAG considers the results should be interpreted with caution due to the differences in baseline characteristics and subgroup nature of the data used in the analyses. However, the EAG notes that for both PFS and OS the hazard ratios based on the ITCs favour treatment with dostarlimab albeit the 95% confidence intervals cross 1. The company reported that their exploratory internal analysis indicates that adjusting for patient baseline characteristics would have a significant impact on the results of any such ITC and would not support this conclusion. However, the company did not provide its analyses for assessment by the EAG and so the EAG cannot comment on the robustness of the analyses or the company's interpretation of the results. In addition, the EAG considers that any such analyses conducted by the company are likely to have broken randomisation.

Table 21. Summary of results for indirect comparison of SoC+D versus dostarlimab in dMMR

Outcome	SoC+D versus SoC HR (95% CI)	Dostarlimab versus SoC HR (95% CI)	SoC+D versus dostarlimab HR (95% CI)
PFS	0.42 (0.22 to 0.80)	0.28 (0.16 to 0.50)	1.50 (0.63 to 3.55)*
OS	0.34 (0.13 to 0.79)	0.30 (0.13 to 0.70)	1.13 (0.33 to 3.89)†

* PFS for dostarlimab vs SoC+D = HR 0.67 (95% CI: 0.28 to 1.58)

† OS for dostarlimab vs SoC+D = HR 0.88 (95% CI: 0.26 to 3.03)

Abbreviations: CI, confidence interval; dMMR, mismatch repair deficient; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the decision problem addressed by the company to be appropriate, with any differences relating to the National Institute for Health and Care Excellence (NICE) final scope being in line with the anticipated marketing authorisation for SoC+D and SoC+D+O in this indication or supported by clinical rationale (see Section 2.3). The SLR performed to identify clinical evidence was reasonable and the EAG considers it unlikely that any relevant head-to-head studies of SoC+D vs SoC or SoC+D+O vs SoC have been missed (see Section 3.1).

The EAG considers the DUO-E trial to be at low risk of bias but notes that the key data to inform the relevant populations in the CS are subgroups of DUO-E with many of the outcomes for these subgroups comprising *post hoc* analyses (see Section 3.2 and 3.3). Feedback from the EAG's clinical experts highlighted that the proportion of Asian patients in DUO-E was higher than likely to be seen in the UK population and age potentially lower but otherwise the baseline characteristics of patients were broadly consistent with the UK population (see Section 2.3.1 and Section 3.2) and this was not considered to be an area of major concern.

The exclusion of hormone therapy as a comparator is considered to be reasonable by the EAG, with the EAG's clinical experts agreeing with the company that hormone therapy is used in only a small proportion of advanced or recurrent EC patients, and the patients likely to receive first-line hormone therapy are unlikely to be suitable for SoC+D or SoC+D+O. The EAG therefore considers the company's decision that hormone therapy is not a relevant comparator to be reasonable (see Section 2.3.3).

Data for OS from DUO-E are considered to be extremely immature, (see Section 2.3.4, 3.3.1.2 and 3.3.2.2). While this is an unresolvable issue currently, the EAG highlights this as a key issue of this appraisal given OS is a key outcome in the economic model and the extrapolations for long-term OS are thus highly uncertain (**Key Issue 1,** in Section 1).

A further area of concern with regards DUO-E is the subsequent treatment usage not reflecting UK clinical practice. [redacted]

[redacted]

The EAG considers that [redacted] (**Key issue 2** in Section 1).

Clinical effectiveness results from DUO-E (see Section 3.3) suggest statistically significant benefits of SoC+D compared to SoC in the dMMR subgroup for investigator-assessed PFS, OS and ORR. For SoC+D+O compared to SoC in the pMMR subgroup, a statistically significant benefit was seen for investigator-assessed PFS and the hazard ratio for OS favoured SoC+D+O, although the upper bound of the 95% confidence interval was 1. The results for ORR for SoC+D+O vs SoC in the pMMR population were similar between trial arms with an odds ratio of 1.10 (95% CI: 0.69 to 1.74).

The EAG notes that HRQoL, TTD and AE data from the ITT population were used in the economic model rather than data from the relevant dMMR and pMMR subgroups. In their response to clarification questions, the company provided the EQ-5D-5L results for the dMMR and pMMR subgroups of DUO-E and these were broadly consistent with the results for the ITT population (see Section 3.3.4). However, based on clinical expert opinion, the EAG considers the company's use of the ITT overall trial population data for these outcomes in the economic model to be reasonable as HRQoL for pre-progression or progressed EC patients, TTD and AEs are not expected to vary in relation to MMR status.

In terms of safety, the EAG notes that the proportion of patients experiencing a Grade ≥3 AE was higher in the SoC+D+O arm compared to the SoC+D and SoC arms (67.2% vs 54.9% and 56.4%, respectively). However, the EAG's clinical experts agreed with the company that the AEs were generally in keeping with the known AEs of each of the interventions (see Section 3.3.5). In the economic model, the company included grade 3 or higher treatment-emergent adverse events (TEAEs) that were reported by at least 5% of patients in the SAS population in any treatment arm of DUO-E. In response to a clarification question the company conducted a scenario analysis using a

lower threshold of at least 2% of patients in the SAS population in any treatment arm of DUO-E with a TEAE. This scenario analysis was to align with the committee preferences in TA963 and resulted in the inclusion of additional AE events in the model (see Section 3.3.5).

Finally, the EAG notes that the company has relied on the committee discussion for dostarlimab (TA963) as part of long-term survival validation in the economic model, but the EAG considers this is potentially problematic when comparing the incremental QALY gain of each technology over SoC. The EAG therefore conducted exploratory indirect comparisons of SoC+D versus dostarlimab for OS and PFS in the dMMR population and for both PFS and OS. The resulting hazard ratios favour treatment with dostarlimab, albeit the 95% confidence intervals cross 1, and there are potential imbalances in baseline characteristics between the trials (See Section 3.4). The EAG also notes that the company reported that their exploratory internal analysis indicates that adjusting for such patient baseline characteristics would have a significant impact on the results of any such ITC and would not support this conclusion. However, the company did not provide its analyses for assessment by the EAG and so the EAG cannot comment on the robustness of the analyses or the company's interpretation of the results. In addition, the EAG considers that any such analyses conducted by the company are likely to have broken randomisation.

The EAG acknowledges that dostarlimab is not considered to be a relevant comparator for this appraisal as it is currently only available via the CDF but the EAG presents these results to give context to the assumptions the company has made based on TA963 and also to aid committee in consistency of decision-making.

4 Cost effectiveness

As discussed in Section 2, the target populations and associated interventions that are the focus of the appraisal are as follows:

- Patients with newly diagnosed advanced or recurrent endometrial cancer (EC) that is mismatch repair (MMR) deficient (dMMR). The intervention that these patients receive is standard of care (SoC) with durvalumab monotherapy for the chemotherapy phase of treatment, followed by durvalumab monotherapy for the maintenance phase of treatment (hereafter known as SoC+D).
- Patients with newly diagnosed advanced or recurrent EC that is mismatch repair proficient (pMMR). The intervention that these patients receive is SoC with durvalumab for the chemotherapy phase of treatment, followed by durvalumab and olaparib for the maintenance phase of treatment (hereafter known as SoC+D+O).

The comparator for both populations is SoC, which consists of carboplatin with paclitaxel. The company's position is aligned with expected marketing authorisations for durvalumab and olaparib. The company provided base case results, which were updated post clarification, separately for the dMMR and pMMR subgroups and these are presented in Table 22 and Table 23 below. Results presented in this document are inclusive of commercial access agreement (CAA) discounts for durvalumab ([redacted]) and olaparib ([redacted]). The EAG highlights that the company provided an addendum with updated base case results to reflect an update in the CAA that occurred after the factual accuracy check.

Table 22. Updated (post FAC) company base case results – dMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	60,570	3.69	2.72	-	-	-	-
SoC+D	[redacted]	11.34	8.10	[redacted]	7.65	5.37	[redacted]
Probabilistic results							
SoC	60,963	4.18	3.07	-	-	-	-
SoC+D	[redacted]	11.29	8.06	[redacted]	7.10	5.00	[redacted]

Abbreviations: CAA, commercial access agreement; dMMR, mismatch repair deficient; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

Note: The EAG noted a very minor discrepancy in the estimation of the percentage of durvalumab patients with hypertension and pulmonary embolism in the company's economic model that was provided with the addendum compared

with the clarification response model. The company's clarification response economic model provided a more accurate representation of the AEs and as such, the EAG has used this model to provide updated company base case results inclusive of the updated CAAs for durvalumab and olaparib.

Table 23. Updated (post FAC) company base case results – pMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	54,864	4.57	3.27	-	-	-	-
SoC+D+O	[redacted]	5.46	3.94	[redacted]	0.89	0.67	[redacted]
Probabilistic results							
SoC	55,171	4.59	3.29	-	-	-	-
SoC+D+O	[redacted]	5.49	3.96	[redacted]	0.90	0.67	[redacted]

Abbreviations: FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; LY, life year; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

Note: The EAG noted a very minor discrepancy in the estimation of the percentage of durvalumab patients with hypertension and pulmonary embolism in the company's economic model that was provided with the addendum compared with the clarification response model. The company's clarification response economic model provided a more accurate representation of the AEs and as such, the EAG has used this model to provide updated company base case results inclusive of the updated CAAs for durvalumab and olaparib.

4.1 EAG comment on the company's review of cost effectiveness evidence

The company conducted a systematic literature review (SLR) in December 2023 (with an update in May 2024) to identify published cost-effectiveness, health-related quality of life (HRQoL) and cost and resource use studies relevant to the appraisal.

The company searched an appropriate selection of data sources, including electronic literature databases such as Embase, MEDLINE, MEDLINE In-Process, The University of York Centre for Reviews and Dissemination (CRD), the National Health Service Electronic Evaluations Database (NHS EED), and the International Network of Agencies for Health Technology Assessment (INAHTA) database. Hand-searching was also conducted of conference proceedings, health technology assessment (HTA) bodies and reference lists of included publications.

A summary of the External Assessment Group's (EAG's) critique of the company's methods to identify relevant evidence is presented in Table 24.

Table 24. EAG critique of company SLR methods

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G.1.1	Appendix H.1.1	Appendix I.1.1	**Appropriate**
Inclusion/ exclusion criteria	Appendix G.1.2	Appendix H.1.2	Appendix I.1.2	**Appropriate**
Screening	Appendix G.1.2	Appendix H.1.2	Appendix I.1.2	**Appropriate**
Data extraction	Appendix G.1.2	Appendix H.1.2	Appendix I.1.2	**Appropriate**
Quality assessment of included studies	Appendix G.1.2	Appendix H.1.2	Appendix I.1.2	**Appropriate**

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health-related quality of life; SLR, systematic literature review.

Across the SLRs, 4,274 records were retrieved from electronic databases. Of these, 238, 238 and 239 records reached full-text screening following the removal of duplicates and exclusions at the tile/abstract stage for the economic evaluation, HRQoL and, resource use and cost SLRs, respectively.

From the full-text screening of included studies and supplementary searching of HTA bodies, 29 economic evaluations, 18 HRQoL studies and 14 cost and resource use studies were deemed potentially relevant by the company to the decision problem with a list of these studies provided in Tables 40, 45 and 49 in Appendix G of the company submission (CS).

Of the economic evaluations identified, none provided a previous model for the evaluation of SoC+D or SoC+D+O, thus the company developed a *de novo* survival partitioned model.

Similarly, of the HRQoL studies identified, the company considered that none provided utility values more appropriate or relevant to the decision problem than the utility data captured in the DUO-E trial; the values of which have been applied in the company's base case (see Section 4.2.4).

Finally, resource use and cost inputs in the model were based on NICE TA963[15] (dostarlimab with platinum-based chemotherapy for treating advanced or recurrent EC with high microsatellite instability [MSI-H] or dMMR) which was identified in the SLR. Other studies from the SLR were not considered appropriate as the perspective was either Canadian or USA based, or because more appropriate UK sources, such as UK databases, were available.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 25 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 25. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the reference case.
Perspective on costs	NHS and PSS	Adheres to the reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the reference case.
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Base case QALYs estimated using EQ-5D-5L data from DUO-E, mapped to the EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data obtained directly from patients in DUO-E, mapped to EQ-5D-3L using the Hernadez-Alava mapping algorithm as recommended by NICE.[13, 35]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in DUO-E are generally representative of the UK patient population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Adheres to the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the reference case.

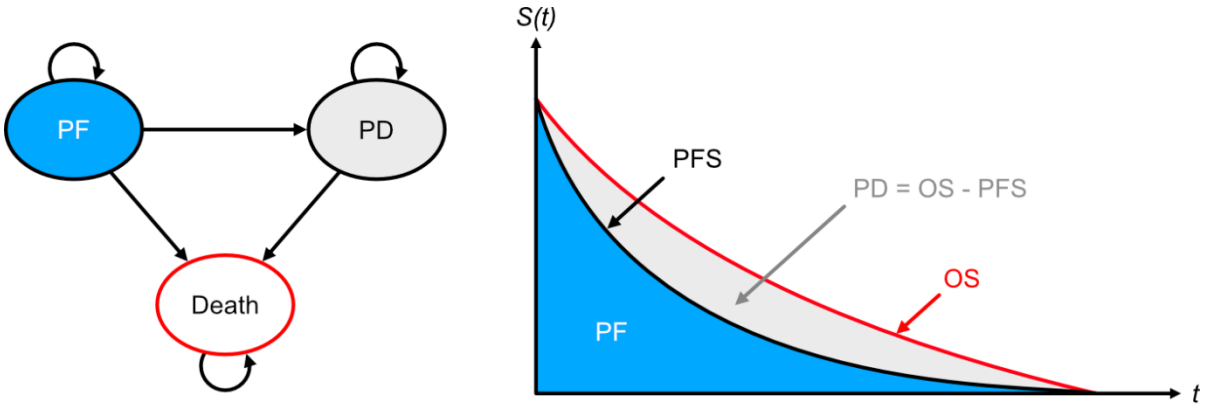
Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 *Modelling approach and model structure*

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of the addition of durvalumab with or without olaparib to platinum-based chemotherapy (carboplatin and paclitaxel, hereafter known as SoC) for the treatment of patients with newly diagnosed advanced or recurrent EC that is dMMR and pMMR. As discussed in Sections 2.3.1 and 2.3.2, dMMR and pMMR subgroups are assessed separately for cost-effectiveness as the maintenance treatment regimens differ for each subgroup: durvalumab is given as a monotherapy for dMMR patients and in combination with olaparib for pMMR patients. A single economic model was developed by the company to assess each subgroup.

The model uses a partitioned survival analysis model (PSM) structure, with three main health states: progression-free, progressed and dead. The progression-free health state is further subdivided into progression-free on treatment and progression-free off treatment, with proportions determined by time to treatment discontinuation (TTD) data. Figure 10 presents the company's PSM structure. The company stated that the chosen model structure is in line with previous health technology appraisal (HTA) EC models (TA963, TA779, TA904 and TA914).[12, 15, 19, 20]

Figure 10. Model structure (reproduced from Figure 18 of the company submission)



Abbreviations: PD, progressed disease; PF, progression-free; PFS, progression-free survival; OS, overall survival; S, survival; t, time.

All patients enter the model in the progression-free health state and are assumed to be on either SoC or SoC with durvalumab (SoC+D) for the first six cycles of the model for both the dMMR and pMMR subgroups. Durvalumab patients who occupy the progression-free health state after the first

six cycles move on to maintenance treatment depending on MMR status: durvalumab monotherapy for the dMMR subgroup or durvalumab with olaparib (SoC+D+O) for the pMMR subgroup. For patients in the progression-free health state on active treatment (durvalumab with or without olaparib), during each model cycle they can be either progression-free and on maintenance treatment or progression-free and off maintenance treatment if they are experiencing unacceptable toxicity or they have had been on maintenance treatment for 3 years (company's assumed cap on maintenance treatment duration).

For all patients regardless of treatment strategy, they can remain in the progression-free health state until disease progression, at which point they transition to the progressed health state or die (transitioning to the dead health state). When patients transition into the progressed health state, they remain in this health state until death.

The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes of progression-free survival (PFS) (used to model the progression-free health state), overall survival (OS) and TTD (used to estimate the proportion of patients who are progression-free and on durvalumab and olaparib maintenance treatment [pMMR subgroup only]). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 4.2.3 and 4.2.4.

A cycle length of one month was implemented in the model for PFS and OS with half-cycle correction applied. For TTD, the company used a one-week cycle length to estimate weekly drug acquisition costs. The model time horizon was set to 38 years. The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[13]

4.2.2.1 EAG critique

The EAG considers the structure of the company's model to be appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models, especially for EC. The one-month cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been

appropriately applied in the model to prevent over or underestimation of costs and quality-adjusted life years (QALYs).

Notably for estimation of TTD, the company used a weekly model cycle to estimate drug acquisition costs for durvalumab and olaparib. In the model, TTD is capped to PFS. As such, for the cap, the company re-estimated PFS using weekly cycles. In essence, in the model, PFS is estimated both monthly and weekly for different purposes. The EAG was concerned by the differing cycle lengths for PFS, especially as it is being used as an upper limit to treatment duration and thus drug acquisition costs. During the clarification stage, the EAG requested, and the company provided, a comparison of weekly versus monthly model cycles for PFS, which showed no significant inconsistencies in the approach. Thus, while the EAG considers that it would have been internally coherent for there to be a weekly cycle length across the entire model, it is reassured that the company's approach is not introducing bias in the model results.

4.2.3 Treatment effectiveness

Clinical data included in the economic model for durvalumab (with or without olaparib) and SoC are based on individual patient-level data from DUO-E (split by MMR subgroup) and include PFS, OS, adverse events (AEs) and TTD outcomes. Please refer to Sections 3.3.5 and 4.2.4 for further details of AEs and TTD included in the model.

In the CS, the company indicates that data from DUO-E are immature. Table 26 outlines the maturity for PFS, TTD and OS for the dMMR and pMMR subgroups at the primary data cut-off (12 April 2023), which informs the economic model. Notably, PFS [redacted] for the SoC+D arm of the dMMR subgroup are quite immature. The EAG considers that OS is extremely immature and, that as a result of this, the long-term extrapolations for each treatment arm and each subgroup are subject to a substantial amount of uncertainty. The EAG has critiqued and considered alternatives to the company's base case approach, but highlights its assumptions, while conservative, also are subject to the same uncertainty as the company's base case.

Consequently, the EAG considers that the uncertainty around the long-term clinical outcomes assumed in the model can only be overcome by additional data collection in DUO-E (**Key Issue 1** in Section 1). The company has indicated that the final OS analysis from DUO-E is expected in 2026. As such, the committee may want to consider accounting for this critical uncertainty by using a lower incremental cost-effectiveness ratio (ICER) threshold for decision-making.

The remainder of this Section covers the company's base case approach to treatment effectiveness included in the model and the EAG's critique.

Table 26. Maturity of outcomes form DUO-E

Outcomes	Maturity (n/N) - dMMR subgroup		Maturity (n/N) - pMMR subgroup	
	SoC	SoC+D	SoC	SoC+D+O
PFS	51.0% (25/49)	32.6% (15/46)	77.1% (148/192)	56.5% (108/191)
OS	36.7% (18/49)	15.2% (7/46)	33.3% (64/192)	24.1% (46/191)
TTD	-	[redacted]	-	[redacted]

Abbreviations: dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib; TTD, time-to-treatment discontinuation.

4.2.3.1 Overview of the company's approach to survival analysis

To extrapolate the DUO-E Kaplan-Meier (KM) data, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[36] The company first tested whether the assumption of proportional hazards (PH) held for PFS and OS outcomes for the dMMR and pMMR subgroups by producing log-cumulative hazard, Schoenfeld residual and quantile-quantile (QQ) plots (Appendix N of the CS).

The company used the results of the PH assessment to decide to either jointly or independently fit survival distributions. Based on the diagnostic plots, the company determined that the PH assumption did not hold for PFS and OS for both the dMMR and pMMR subgroups and independently fit survival distributions for each treatment arm of the model.

Extrapolations of the KM data were then explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log normal, log-logistic, gamma and generalised gamma). If standard parametric models were considered a poor fit to the data, the company explored spline flexible models in accordance with DSU TSD 21.[37] To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the model. A key assumption underlying the clinical plausibility of the extrapolations was long-term remission after five years without disease progression.

Table 27 presents an overview of the company's survival curve selection for each outcome by subgroup and Sections 4.2.3.2 - 4.2.3.8 provides more detail on the company's approach to extrapolating PFS and OS. Please refer to Section 4.2.4 for further details on the TTD extrapolations.

The EAG notes that the company has implemented the following limits in the model to ensure that model outcomes pass clinical and face validity:

- Risk of progression or mortality risk per cycle cannot fall below age-matched general population mortality, based on ONS life tables from 2017-2019.[38] The company explained that older life tables are used in the model because the most recent life tables (2020-2022) are impacted by excess mortality caused by COVID-19 and this is in accordance with the guidance in DSU TSD 23.[39] Nonetheless, a scenario was explored using recent ONS life tables and this had minimal impact on the ICER (see Section 5.2.2 for results).
- OS cannot fall below PFS (i.e. OS is capped to PFS).
- TTD cannot exceed PFS.
- A treatment cap of three years is applied to the TTD curves for durvalumab and olaparib (see Section 4.2.4 for further details).

Table 27. Overview of company's survival curve selection by outcome and subgroup

Outcome	dMMR subgroup		pMMR subgroup	
	SoC	SoC+D	SoC	SoC+D+O
PFS	1-knot spline	2-knot spline	Log-logistic	Log-logistic
OS	Log normal	Log normal	Log-logistic	Log-logistic
TTD	KM data	Gamma	KM data	Log-logistic

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib; TTD, time-to-treatment discontinuation

4.2.3.2 EAG critique

Overall, the EAG considers the company's general approach to extrapolating outcomes for PFS, OS and TTD to be appropriate. The EAG has a minor issue with the use of OS capped to PFS in the model (PFS is the upper limit). The EAG considers that typically, in PSMs, the cap used is that PFS cannot exceed OS (OS is the upper limit). For example, in the model for the dMMR subgroup, SoC OS is less than PFS in model cycle one, but because of the cap, PFS for that cycle is used to estimate OS (OS = PFS). However, the EAG considers that it is more appropriate that PFS should be equal to OS and queried this with the company during the clarification stage.

In their clarification response, the company explained that it was preferable to cap OS to PFS due to the maturity of the PFS data from DUO-E, which they considered provided more events to accurately estimate the change in the hazard of progression over time and has also been accepted in previous technology appraisals which use cure models. However, the EAG notes that in the company's cost-effectiveness analysis, a cure assumption has not been included. Since there remains substantial uncertainty around the estimation of long-term OS in the model due to the immaturity of the data from DUO-E, the EAG considers that the company's rationale to cap OS to PFS based on PFS data maturity is not unreasonable. Nonetheless, the company supplied a scenario capping PFS to OS, which had minimal impact on the ICER.

With regards to modelling of a cure assumption, the company's and the EAG's clinical experts advised that for patients who are progression-free longer than five years, it is likely that they have achieved long-term remission and this was also discussed by committee in TA963.[15] As such, the EAG considered that after five years, the underlying hazards of progression or death would likely be similar between the SoC and SoC+D(+/-O) arms of the model. During the clarification stage, the EAG requested the company to investigate the underlying hazards of PFS and OS for the dMMR and pMMR subgroups. In their response, the company explained that it is clinically plausible that PFS and OS for SoC patients could plateau in the long-term and this supported by data from the GOG-0209 study.[40] However, the company noted that individual tumour characteristics can impact the curative potential for an individual patient and so trends may vary.

Nonetheless, the company explored the observed hazards from DUO-E (response to clarification question B22) but noted that maximum follow-up in any treatment arm or subgroup did not exceed 31 months and so there was not enough evidence to model long-term remission. The EAG agrees that longer follow-up is needed to determine if the underlying observed hazards of progression or death for either treatment arm or subgroup stabilise/reduce/converge in the long-term as based on Figure 18 and Figure 19 of the company clarification response, a clear trend cannot be determined. More data are needed from DUO-E to understand if the benefit of SoC+D(+/-O) is potentially being overestimated because the benefits in the SoC arm for each subgroup are potentially underestimated.

The company supplied two scenarios exploring a long-term remission assumption, whereby background mortality rates are applied to patients who are progression-free for longer than a) five years and b) three years in either treatment arm (see Section 5.2.2). The EAG considers that the

scenarios should only be considered illustrative, but they provide committee with the impact on the ICER if survival is improved for the SoC arm of the model. However, the EAG considers that there is substantial uncertainty around the long-term remission scenarios and that as mentioned throughout the report, more mature data are needed from DUO-E to understand the long-term observed trends for PFS and OS to ensure life-time extrapolation of these outcomes are robust.

4.2.3.3 Progression-free survival - dMMR subgroup

The company assessed the standard parametric distributions using visual and statistical fit as well as clinical plausibility of the long-term extrapolations and concluded that none of the distributions fit the observed data well. Instead, the company explored flexible spline models using knots of one, two and three. Figures 21 and 22 of the CS presents the spline extrapolations of PFS for SoC and SoC+D and Table 35 of the CS presents the AIC and BIC statistics.

The EAG notes that the company relied on clinical expert advice provided to the committee for TA963, as well as information from their own clinical experts, to assess the clinical plausibility of long-term extrapolations for PFS for the dMMR subgroup. As mentioned previously, a key assumption underlying the clinical plausibility of the extrapolations was long-term remission after five years without disease progression.

In TA963, the clinical experts and Cancer Drugs Fund (CDF) lead advised that risk of progression is very low after five years progression-free and that based on the trends seen in other dMMR/MSI-H tumour types, most relapses would occur within two years and PFS and OS are likely to plateau between years two and three.[15] Additionally, the CDF lead stated that, "*dMMR/MSI-H cancers respond better to immunotherapy treatments than non-dMMR/MSI-H cancers*".[15] Lastly, the clinical experts for TA963 considered that their own estimates for long-term PFS reflect the company's clinical expert estimates and this information has been used to inform the PFS survival curve selection in the current CS.

Based on visual fit and clinical validation of the survival PFS curves, the company selected the 1-knot spline for SoC and the 2-knot spline for SoC+D. The EAG notes that based on statistical fit (Table 35 of the CS), the company's preferred curves were the lowest ranking of the three splines models explored, but highlights that all models were within five points of each other, indicating similar statistical fit. Figure 11 presents the company's preferred PFS curves. The EAG notes that the shape

of the PFS curves is affected by the general population mortality and OS limits applied in the model (outlined in Section 4.2.3).

Figure 11. Company base case PFS curves for SoC and SoC+D – dMMR

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; PFS, progression-free survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

Table 28 presents a comparison of the landmark estimates from the company-preferred PFS extrapolations with the landmark estimates from TA963. The estimated mean discounted life years in the progression-free health state for SoC and SoC+D was [redacted] years and [redacted] years, respectively.

Table 28. Landmark estimates of PFS – dMMR subgroup

Year	SoC			SoC+D		
	KM data from DUO-E	Estimates from TA963[15]	1-knot spline (company base case)	KM data from DUO-E	Estimates from TA963[15]	2-knot spline (company base case)
1	[redacted]	-	[redacted]	[redacted]	-	[redacted]
2	[redacted]	23.0%	[redacted]	[redacted]	60.0%	[redacted]
3	-	15.0%	[redacted]	-	56.0%	[redacted]
5	-	9.0%	[redacted]	-	46.0%	[redacted]
10	-	7.0%	[redacted]	-	36.0%	[redacted]

Abbreviations: KM, Kaplan-Meier; SoC, standard of care; SoC+D, standard of care with durvalumab

4.2.3.4 EAG critique

The EAG notes that for SoC, the observed PFS data from DUO-E at two years is higher than the clinical expert estimate from TA963 and that the predictions from all the spline models exceed the

TA963 clinical expert estimates (see Table 28). However, the EAG validated the company's base case SoC PFS curve with its clinical experts and they considered the long-term predictions were not unreasonable. As such, the EAG considers the 1-knot spline for SoC PFS to be appropriate.

The EAG's clinical experts did not have experience with using durvalumab but did corroborate the advice given by the CDF lead in TA963, that dMMR patients tend to have better outcomes on immunotherapy. Given the uncertainty around the PFS benefit, the EAG explored the use of the 1-knot spline as an alternative to the company base case choice of the 2-knot spline, for SoC+D PFS (see Figure 12) as it had a better statistical fit and considered that the extrapolation better captured the tail of the KM curve. However, the EAG notes that the end of the KM curve has the greatest uncertainty due to small numbers of events. The results of the EAG's scenario are presented in Section 6.2. The estimated mean discounted life years in the progression-free health state SoC+D was [redacted] years.

For the scenario, the EAG notes that because the estimation of OS remains the same as in the company base case, the total life years remain the same as in the company base case and so in this scenario, patients spend less time in the PF health state and more time in the progression health state. As such, use of the 1-knot spline had a small impact on the incremental QALYs (decreased by 0.09) and increased the ICER from [redacted] to [redacted]. Based on statistical and visual fit, the EAG has included the use of the 1-knot spline for SoC+D PFS in its base case, presented in Section 6.3. Additionally, the EAG explored the company's preferred 2-knot spline in a scenario around the EAG base case.

Figure 12. Comparison of 1-knot spline for both SoC and SoC+D versus 2-knot spline for SoC+D – dMMR

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; PFS, progression-free survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

4.2.3.5 Overall survival - dMMR subgroup

Based on statistical fit, visual fit and clinical validation of the survival OS curves, the company selected the log normal distribution for SoC and SoC+D. Figure 13 presents the company's preferred OS curves. The EAG highlights that background mortality replaces the OS extrapolation from around year 12 onwards, based on the limits in the model described in Section 4.2.3.1.

Table 29 presents a comparison of the landmark estimates from the company-preferred OS extrapolations with compared with KM data from DUO-E. The EAG notes that, based on statistical fit (Table 43 of the CS), the log normal distribution for SoC+D was one of the lower-ranking distributions, but highlights that all models were within five points of each other, indicating similar statistical fit. The estimated mean discounted total life years for SoC and SoC+D was [redacted] years and [redacted] years, respectively.

As described at the beginning of Section 4.2.3, observed OS from DUO-E is extremely immature and as such, the EAG considers that all long-term predictions of OS are subject to a substantial amount of uncertainty. The company attempted to validate their OS extrapolations for SoC against OS estimates considered by the committee for TA963, as well as published estimates of long-term survival based on a trial of carboplatin with paclitaxel for advanced EC (Miller *et al.* 2020) and

another study of outcomes by MMR/MSI-H status for patients with advanced or recurrent EC treated with platinum-based chemotherapy (Chase *et al.* 2023).[40, 41]

In TA963, the clinical experts advising the committee stated that their own estimates of long-term survival would be closer to the estimates provided by the company's clinical experts (presented in Table 29), but noted that, "*there is no long-term experience of people who have benefitted from new immunotherapy treatments*".[15] The EAG notes that the study by Miller *et al.* does not provide OS estimates by MMR subgroup.[40] Additionally, the company noted that the study by Chase *et al.* did not provide information on the distribution of treatments that were included in the estimates for platinum-based chemotherapy but does states that carboplatin with paclitaxel was the most frequently used.[41]

Figure 13. Company base case OS curves for SoC and SoC+D – dMMR subgroup (extracted from the company's economic model)

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab.

Table 29. Landmark estimates of OS – dMMR subgroup

Year	SoC					SoC+D		
	KM data from DUO-E	NICE TA963[15]	Miller *et al.* 2020[40]	Chase *et al.* 2023[41]	Log normal (company base case)	KM data from DUO-E	NICE TA963[15]	Log normal (company base case)
1	[redacted]	-	71.3%	76.0%	[redacted]	[redacted]	-	[redacted]
2	[redacted]	58.0%	46.1%	58.0%	[redacted]	[redacted]	82.0%	[redacted]
3	-	46.0%	35.3%	52.0%	[redacted]	-	76.0%	[redacted]
5	-	30.0%	26.4%	-	[redacted]	-	67.0%	[redacted]
10	-	17.0%	19.5%	-	[redacted]	-	53.0%	[redacted]

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab

Note: The 1-year OS estimate from Chase *et al* was extracted from the paper by the EAG and differ to the estimate presented by the company in Table 44 of the company submission.

4.2.3.6 EAG critique

As mentioned previously, the EAG considers the key issue with the extrapolation of OS in the model is that it is based on immature data from DUO-E, which introduces a substantial amount of uncertainty in the long-term predictions and survival benefit estimated for the SoC+D arm of the model for the dMMR subgroup. Additionally, the EAG highlights that for the SoC arm, a proportion patients would receive subsequent immunotherapy upon disease progression and because of the immaturity of the OS data from DUO-E, the full benefits of subsequent treatment may not be captured in the extrapolations. The EAG considers that the only way to resolve this issue is for further OS data to be collected from DUO-E, but notes that the final OS analysis is planned for 2026.

However, the EAG acknowledges that the company attempted to extensively validate OS estimates for the SoC arm of the model against TA963 and published data as well as with their experts. The company stated that based on OS data from Miller *et al*.,[40] a proportion of patients on carboplatin with paclitaxel can survive beyond 10 years, but the EAG notes that the study did not present data by MMR subgroup. Nonetheless, the EAG's clinical experts considered that the company's long-term OS estimates for SoC were not unreasonable.

However, it is worth noting that while the company has relied on the committee discussion for dostarlimab (TA963) as part of long-term survival validation, the EAG considers this is potentially problematic when comparing the incremental QALY gain of each technology over SoC. In TA963, the company's estimate of incremental QALYs associated with dostarlimab for the dMMR/MSI-H population was 4.26 QALYs, although the committee recognised this estimate was uncertain because data from RUBY-1 were immature (36 months follow-up, 56% PFS maturity and 26% OS maturity at the time of the dostarlimab appraisal).[15] Data for the dMMR subgroup from DUO-E are similarly immature with 32 months follow-up at the April 2023 data cut-off, 41% PFS maturity and 22% OS maturity. The company base case estimate of incremental QALYs for durvalumab in the dMMR subgroup is 5.37 QALYs. For comparison, the hazard ratios (HRs) from RUBY-1 and DUO-E are presented in Table 30.

The EAG conducted exploratory indirect comparisons of SoC+D versus dostarlimab for OS and PFS in the dMMR population (see Section 3.4) and results of the analyses are presented in Table 30. The

EAG's indirect comparisons found that for both PFS and OS the HRs favour treatment with dostarlimab albeit the 95% confidence intervals cross 1.

Table 30. Comparison of PFS and OS hazard ratios from RUBY-1 and DUO-E

Comparison	PFS HR (95% CI)	OS HR (95% CI)
Dostarlimab + carboplatin/paclitaxel vs carboplatin/paclitaxel	0.28 (0.16 to 0.50)	0.30 (0.13 to 0.70)
Durvalumab + carboplatin/paclitaxel vs carboplatin/paclitaxel	0.42 (0.22 to 0.80)	0.34 (0.13 to 0.79)
Durvalumab + carboplatin/paclitaxel versus dostarlimab + carboplatin/paclitaxel*	1.50 (0.63 to 3.55)	1.13 (0.33 to 3.89)

Abbreviations: CI, confidence interval; HR< hazard ratio; OS, overall survival; PFS, progression-free survival.
*EAG analysis using Bucher ITC method. See Section 3.4 for more details.

While the EAG considers that dostarlimab is not a direct comparator in this appraisal as it is recommended for use in the CDF, the EAG considers it to be a useful benchmark for committee decision-making due to the same critical issue of immature PFS and OS. Moreover, the committee for TA963 considered that the benefits of dostarlimab may be overestimated as the benefits of subsequent treatment in the comparator arm may not be fully captured and because data from RUBY-1 are immature.[15] Thus, in TA963 the committee concluded that a preferred approach for OS could not be decided because of the uncertainty in the OS data from RUBY-1.[15]

Therefore, the incremental QALY gain estimated as part of TA963 is not established as definitive and will be subject to change in the managed access review, expected to be published in May 2025 (NICE ID6426).[17] However, the EAG considers that the issues around OS for the appraisal of dostarlimab are also the same for the current appraisal of durvalumab (with or without olaparib) and would rely on additional data from DUO-E to be collected in order to be resolved.

However, the EAG recognises that an alternative approach to the company's base case extrapolation of OS, using the publicly available data the company has presented in their submission could be useful to aid committee decision-making. As such, the EAG investigated the company's alternative standard parametric extrapolations of OS and found that log-logistic extrapolation (Figure 14) produced estimates of OS for SoC+D that are closer to the clinical expert estimates provided in TA963 (see Table 31) and results for the SoC arm are similar to the lognormal distribution. The estimated mean discounted total life years for SoC and SoC+D was [redacted] years and [redacted] years, respectively.

Figure 14. Comparison of lognormal distribution (company base case) versus log-logistic distribution

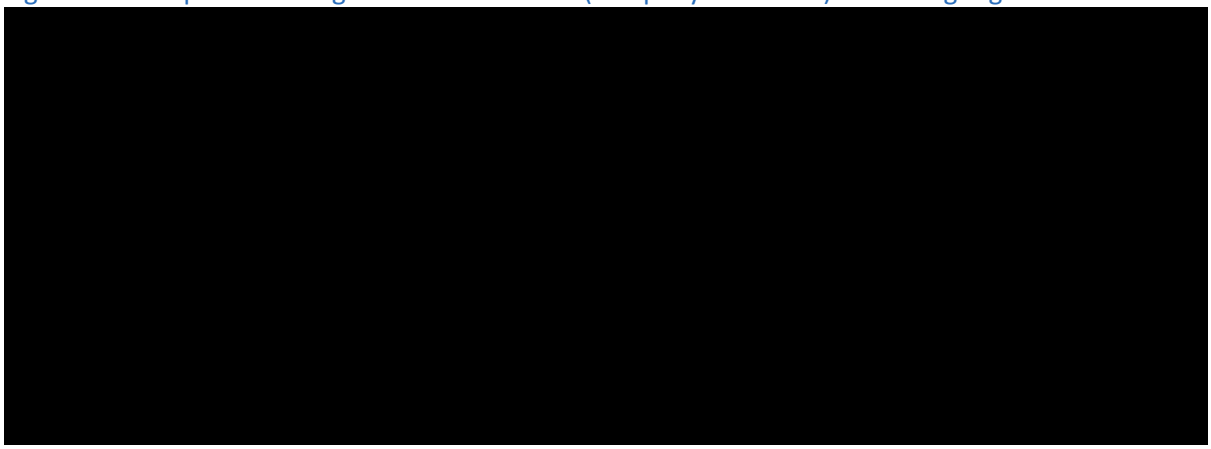


Table 31. Landmark estimates of OS using alternative log-logistic extrapolation – dMMR subgroup

Year	SoC					SoC+D		
	KM data from DUO-E	NICE TA963[15]	Miller *et al.* 2020[40]	Chase *et al.* 2023[41]	Log-logistic	KM data from DUO-E	NICE TA963[15]	Log-logistic
1	[redacted]	-	71.3%	76.0%	[redacted]	[redacted]	-	[redacted]
2	[redacted]	58.0%	46.1%	58.0%	[redacted]	[redacted]	82.0%	[redacted]
3	-	46.0%	35.3%	52.0%	[redacted]	-	76.0%	[redacted]
5	-	30.0%	26.4%	-	[redacted]	-	67.0%	[redacted]
10	-	17.0%	19.5%	-	[redacted]	-	53.0%	[redacted]

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab

Note: The 1-year OS estimate from Chase *et al* was extracted from the paper by the EAG and differ to the estimate presented by the company in Table 44 of the company submission.

The company supplied a scenario exploring the use of the log-logistic extrapolation (see Section 5.2.2) and this increased the ICER from [redacted] to [redacted]. The EAG has included the log-logistic distribution in its base case as an alternative to the company's base case approach. The EAG reiterates that all OS extrapolations are subject to a substantial amount of uncertainty around which extrapolation would reflect clinical reality due to lack of long-term data. In TA963, where the same critical issue was present, the committee could not decide on a preferred approach to OS because of data immaturity. As such, while the EAG has provided an alternative to the company base case, its approach is similarly uncertain. However, the EAG has also included a scenario around its base case exploring the company's preferred lognormal distribution for OS for the dMMR subgroup.

4.2.3.7 *Progression-free survival - pMMR subgroup*

Based on statistical fit, visual fit and clinical validation of the survival PFS curves, the company selected the log-logistic distribution for SoC and SoC+D+O. Figure 15 presents the company's preferred PFS curves. Table 32 presents a comparison of the landmark estimates from the company preferred PFS extrapolations with compared with KM data from DUO-E. The estimated mean discounted life years in the progression-free health state for SoC and SoC+D+O was [redacted] years and [redacted] years, respectively.

Figure 15. Company base case PFS curves for SoC and SoC+D+O – pMMR subgroup (reproduced from Figure 26 of the company submission)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

Table 32. Landmark estimates of PFS – pMMR subgroup

Year	SoC		SoC+D+O	
	KM data from DUO-E	Log-logistic (company base case)	KM data from DUO-E	Log-logistic (company base case)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	-	[redacted]	-	[redacted]
5	-	[redacted]	-	[redacted]
10	-	[redacted]	-	[redacted]

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

4.2.3.8 EAG critique

The EAG considers that the company's base case extrapolation of PFS using the log-logistic distribution is reasonable. During the clarification stage, the company provided details of flexible spline models that were explored (with corresponding scenarios) in the development of the PFS survival analysis for the pMMR subgroup (response to clarification question B2). The company's analysis demonstrated that use of more flexible models to extrapolate PFS for the pMMR subgroup did not offer any meaningful advantages over the standard parametric models that were explored in the main CS. The best fitting spline model only had a minimal impact on the ICER. As such, the EAG is satisfied with the exclusion of the flexible spline models from the survival curve selection process described in the CS.

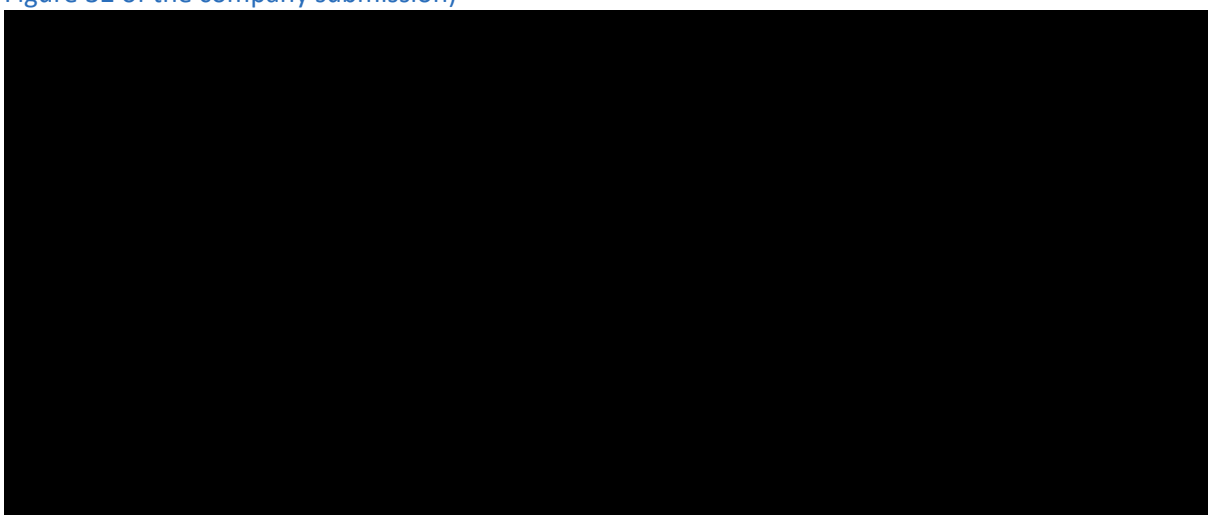
The EAG explored the impact on the ICER of using the company's alternative standard parametric curves but found that the ICER was not sensitive to changes in the extrapolation of PFS and thus considers it not to be a key driver of cost-effectiveness for the pMMR subgroup.

4.2.3.9 Overall survival - pMMR subgroup

Based on statistical fit, visual fit and clinical validation of the survival OS curves, the company selected the log-logistic distribution for SoC and SoC+D+O. Figure 16 presents the company's preferred OS curves. Table 33 presents a comparison of the landmark estimates from the company's preferred OS extrapolations compared with KM data from DUO-E. The EAG notes that, based on statistical fit (Table 47 of the CS), the log-logistic distribution for SoC was one of the lowest-ranking distributions, but highlights that it was within five points of the highest-ranking distribution (Gompertz), indicating similar statistical fit. The estimated mean discounted total life years for SoC and SoC+D+O was [redacted] years and [redacted] years, respectively.

As highlighted throughout Section 4.2.3, observed OS from DUO-E is extremely immature and as such, the EAG considers that all long-term predictions of OS are subject to a substantial amount of uncertainty. Similar to the company's approach to OS for the dMMR subgroup, the company validated their OS extrapolations for SoC against published estimates of long-term survival from Miller *et al.* 2020 and Chase *et al.* 2023, but notes the same issues with the studies as described in Section 4.2.3.5.[40, 41]

Figure 16. Company base case OS curves for SoC and SoC+D+O – pMMR subgroup (reproduced from Figure 32 of the company submission)



Abbreviations: KM, Kaplan-Meier; pMMR, mismatch repair proficient; OS, overall survival; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

Table 33. Landmark estimates of OS – pMMR subgroup

Year	SoC				SoC+D+O	
	KM data from DUO-E	Miller *et al.* 2020[40]	Chase *et al.* 2023[41]	Log-logistic (company base case)	KM data from DUO-E	Log-logistic (company base case)
1	[redacted]	71.3%	78.0%	[redacted]	[redacted]	[redacted]
2	[redacted]	46.1%	57.0%	[redacted]	[redacted]	[redacted]
3	-	35.3%	43.0%	[redacted]	-	[redacted]
5	-	26.4%	-	[redacted]	-	[redacted]
10	-	19.5%	-	[redacted]	-	[redacted]

Abbreviations: KM, Kaplan-Meier; pMMR, mismatch repair proficient; OS, overall survival; SoC, standard of care; SoC+D, standard of care with durvalumab and olaparib.

4.2.3.10 EAG critique

The EAG considers that the key issues that affect the extrapolation of OS for the dMMR subgroup are also applicable to the pMMR subgroup. Namely, that OS from DUO-E is immature and thus the long-term extrapolations of OS for both arms of the model are subject to a substantial amount of uncertainty. Furthermore, because of the immaturity of the OS data, the benefits of subsequent immunotherapy for patients on SoC only may not be fully captured in the company's extrapolations. Therefore, the EAG considers that the only way to resolve this issue is for further OS data to be collected from DUO-E. As mentioned previously, the final OS analysis is planned for 2026.

Nonetheless, as with the dMMR subgroup, the EAG notes that the company attempted to extensively validate OS estimates for the SoC arm of the model against published data as well as with their experts and considered a proportion of patients on carboplatin with paclitaxel can survive beyond 10 years. Additionally, the EAG's clinical experts considered that the company's long-term OS estimates for SoC were not unreasonable.

Therefore, the EAG considers that the company's base case extrapolation of OS using the log-logistic distribution for SoC could be reasonable but adds the caveat that more mature data are needed to understand the impact of subsequent immunotherapy on survival and limit the uncertainty. Moreover, guidance in the DSU TSD 14 recommends that the same type of distribution is used for individual treatment arms of a model.[36] As such, the log-logistic extrapolation of OS for the SoC+D+O arm of the model may not be unreasonable in lieu of any other data to inform long-term estimates of survival associated with durvalumab and olaparib. However, the underlying issue of immature data may make any of the current extrapolations unreliable and so more mature OS data from DUO-E are needed to reduce the uncertainty.

4.2.4 Treatment duration

To estimate the treatment duration for durvalumab in both subgroups and olaparib for the pMMR subgroup, the company extrapolated TTD KM data from DUO-E, using the survival analysis approach outlined in Section 4.2.3.1. However, the company applied a treatment cap of three years that was not included as part of the design of the DUO-E study on extrapolated TTD for durvalumab and olaparib (i.e. patients cannot be on treatment for longer than three years).

The cap on treatment duration contradicts the treatment regimen in DUO-E and the draft Summary of Product Characteristics (SmPCs) for durvalumab and olaparib, which was to treat until disease progression or unacceptable toxicity (no maximum treatment duration). Based on the April 2023 data cut, the median time on treatment from DUO-E for durvalumab in dMMR population was [redacted]. For durvalumab and olaparib in the pMMR subgroup, the median time on treatment from DUO-E was [redacted] and [redacted], respectively. The company referenced stopping rules included for dostarlimab in RUBY-1 (3 years maximum treatment duration) and pembrolizumab in NRG-GY018 (2 years maximum treatment duration), stating that their base case assumption is aligned with other immunotherapies for treating EC.[34, 42]

However, in RUBY-1, the trial protocol stated a maximum treatment duration of three years for dostarlimab and in this is also reflected in the SmPC.[43] Similarly, in NRG-GY018 a stopping rule of two years was included in the trial protocol for pembrolizumab and again is reflected in the SmPC.[44]

The company also stated that they consulted with clinicians who advised that patients would be expected to discontinue immunotherapy within five years (linked to long-term remission), but also that they would have discussions about discontinuing treatment with patients who have a durable response after one to three years as they felt prolonged treatment does not yield additional clinical benefit and these patients likely develop "immunological memory". As such, the company considered their cap on treatment duration in the model maybe implemented in clinical practice. In scenario analysis, the company explored a treatment cap of two and five years, presented in Section 5.2.2. The company did not include any treatment-waning assumptions after patients discontinue treatment but remain progression-free.

4.2.4.1 Time to treatment discontinuation – dMMR subgroup

Based on statistical fit, visual fit and clinical validation of the survival TTD curves, the company selected the gamma distribution for durvalumab. Figure 17 presents the company's preferred durvalumab TTD curve with the three-year cap on treatment. The estimated mean durvalumab treatment duration for the dMMR subgroup was [redacted] years.

Figure 17. Durvalumab time to treatment discontinuation – dMMR subgroup (reproduced from Figure 34 of the company submission)

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; SoC, standard of care; TDT, time to discontinuation of treatment.

4.2.4.2 *Time to treatment discontinuation – pMMR subgroup*

As mentioned previously, the treatment regimen for the pMMR subgroup consists of durvalumab with olaparib added in the maintenance phase of treatment. As such, TTD was modelled for each individual treatment. Treatment duration for durvalumab was modelled from the start of the time horizon as it is given in both the chemotherapy and maintenance phases of treatment. Whereas treatment duration for olaparib is modelled from the maintenance phase onwards (week 18 onwards). The company assumed that at the start of the maintenance phase, [redacted] of progression-free durvalumab patients initiate olaparib, based on data from DUO-E. Please see Section 4.2.6.2 for the EAG's critique on the proportion of patients assumed to start olaparib maintenance treatment for the pMMR subgroup.

Based on statistical fit, visual fit and clinical validation of the survival TTD curves, the company selected the log-logistic distribution for both durvalumab and olaparib. Figure 15 presents the company's preferred durvalumab and olaparib TTD curves with the three-year cap on treatment. The estimated mean durvalumab and olaparib treatment duration for the pMMR subgroup was [redacted] years and [redacted] years, respectively.

During the clarification stage, the EAG queried whether patients would be permitted to continue treatment with either durvalumab or olaparib if they had discontinued one of the treatments in the combination. The company clarified that in DUO-E, if AEs contraindicates further dosing with one of the treatments, patients could discontinue the treatment that is the cause of the AE and continue with the other treatment in the combination. The company anticipates this is how the combination treatment will be used in clinical practice (pending confirmation in the final marketing authorisation).

Figure 18. Durvalumab and olaparib time to treatment discontinuation (reproduced from Figure 37 of the company submission)

Abbreviations: KM, Kaplan-Meier; pMMR, mismatch repair proficient; SoC, standard of care; TDT, time to discontinuation of treatment.

4.2.4.3 EAG critique

The EAG considers that the cap on treatment duration is a key driver of cost-effectiveness in the model as it enforces a limit on the total drug acquisition costs of durvalumab and olaparib in the model (**Key issue 3** in Section 1). Based solely on the treatment regimens in DUO-E and the draft SmPC guidance for durvalumab and olaparib of treat until progression or unacceptable toxicity, the EAG considers that the cap on treatment duration should be removed. As the clinical data informing the model are from DUO-E, efficacy and treatment duration should both match the underlying trial as they are fundamentally interlinked. As such, there would be substantial uncertainty around what the appropriate long-term efficacy should be with a hard cap on treatment duration in place. Furthermore, the company has not explored treatment waning assumptions after the artificial treatment duration cap. Thus, the EAG considers that the benefits of treatment with durvalumab with or without olaparib are potentially not aligned with the costs in the model.

The EAG notes that in TA963, the CDF lead advised that immunotherapies have showed a sustained treatment benefit in other dMMR/MSI-H tumour types but that longer term data are needed.[15] As such, a treatment waning assumption might be considered a secondary issue, compared with the primary issue of immature data from DUO-E.

As discussed throughout this report, more mature data from DUO-E will mitigate the overall uncertainty in the model. For TTD, more mature data in the next 2 years (based on the date of the expected final OS analysis in 2026) is likely feasible and will validate what approach would be appropriate to include in the model.

In lieu of mature TTD data from DUO-E, the EAG proposes that extrapolations of TTD that have a natural decline to zero may be more appropriate. The EAG's clinical experts advised that they would not want to keep patients on treatment in the long-term. Additionally, one of the EAG's experts explained a more cautious approach using "treatment holidays" for patients who are relapse-free for five years.

The EAG assessed the company's standard parametric distributions of TTD for durvalumab for both subgroups, and olaparib for the pMMR subgroup, to identify extrapolations which have a natural decline to zero and clinically plausible mean TTD in addition to a good statistical and visual fit to the observed TTD data from DUO-E. Table 34 outlines the EAG's alternative distributions for TTD for both subgroups, along with landmark estimates for the proportion of patients on treatment at three and five years and associated mean TTD estimates. Figure 19 to Figure 21 presents the alternative extrapolations of TTD alongside the observed KM data from DUO-E.

During the clarification stage, the EAG requested, and the company provided, scenarios exploring the TTD extrapolations outlined in Table 34 and all had a substantial impact on the ICERs (also presented in the Table). The EAG notes that it could not replicate the ICERs the company provided in their response to clarification question B12 and instead the results presented in Table 34 have been produced by the EAG.

Table 34. Alternative TTD extrapolations excluding TTD cap of three years

Subgroup and treatment	Extrapolation	% on treatment				Mean TTD (years)		ICER (£/QALY)
		Durvalumab		Olaparib				
		3 years	5 years	3 years	5 years	Durvalumab	Olaparib	
dMMR subgroup **Company base case ICER = [redacted]**								
Durvalumab	Exponential	[redacted]	[redacted]	-	-	[redacted]	-	[redacted]
	Generalised gamma	[redacted]	[redacted]	-	-	[redacted]	-	[redacted]

	Gamma (company base case)	[redacted]	[redacted]	-	-	[redacted]	-	[redacted]
pMMR subgroup **Company base case ICER = [redacted]**								
Durvalumab + Olaparib	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic (company base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR, mismatch repair deficient; ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; TTD, time-to-treatment discontinuation.

Figure 19. Alternative extrapolations of durvalumab TTD without treatment duration cap – dMMR subgroup

Abbreviations: dMMR, mismatch repair deficient; KM, Kaplan-Meier; SoC, standard of care; TDT, time to discontinuation of treatment; TTD, time to treatment discontinuation.

Figure 20. Alternative extrapolations of durvalumab TTD without treatment duration cap – pMMR subgroup

Abbreviations: KM, Kaplan-Meier; pMMR, mismatch repair proficient; SoC, standard of care; TDT, time to discontinuation of treatment; TTD, time to treatment discontinuation.

Figure 21. Alternative extrapolations of olaparib TTD without treatment duration cap – pMMR subgroup

Abbreviations: KM, Kaplan-Meier; pMMR, mismatch repair proficient; SoC, standard of care; TDT, time to discontinuation of treatment; TTD, time to treatment discontinuation.

For the pMMR subgroup, the EAG considers that the log-logistic may potentially overestimate the proportion of patients in the long-term who are predicted to remain on treatment with durvalumab and olaparib (Table 34). Additionally, the exponential, Weibull and gamma distributions all estimate near identical predictions of treatment duration. Therefore, for the EAG base case for the pMMR subgroup, presented in Section 6.3, the EAG has selected the exponential distribution for durvalumab and olaparib, as the treatment duration for olaparib is slightly longer and therefore estimates that patients are on combination treatment slightly longer.

For the dMMR subgroup, the gamma or the generalised gamma distributions provided the best fits. Additionally, the gamma distribution has the best statistical fit of all the distributions assessed and was the company's base case selection for the extrapolation of durvalumab TTD up to year three. The landmark estimate of the proportion of patients on durvalumab treatment based on the gamma distribution at five years is [redacted]%, which may be considered [redacted] based on clinical opinion, but the EAG notes that more mature data from DUO-E will validate this. However, the EAG notes that the mean estimate of TTD based on the gamma distribution is between [redacted] years, which is aligned with the long-term remission assumption of five years and also reflects the EAG's clinical experts' advice. As such, the EAG has used the gamma distribution for durvalumab TTD in its base case for the dMMR subgroup. Nonetheless, the EAG reiterates that further data collection in DUO-E will mitigate the uncertainty around treatment duration.

Lastly, the EAG notes that its approach to treatment duration means that the inclusion of a treatment waning assumption becomes less of an issue as patients only discontinue treatment because of progression or unacceptable toxicity compared to patients stopping treatment arbitrarily at three years.

4.2.5 Health-related quality of life

Health state utility values (HSUVs) included in the model for both the dMMR and pMMR subgroups are derived from EQ-5D-5L data collected in the DUO-E trial for the intention-to-treat (ITT) population. The company explained that the full trial population was used to estimate utilities as there is no evidence to suggest that health-related quality of life (HRQoL) would differ based on MMR biomarker status and this view was corroborated by the EAG's clinical experts.

During the DUO-E trial, all patients in the ITT population completed the EQ-5D-5L questionnaire at baseline (day one of treatment), every three weeks for the first 18 weeks (chemotherapy treatment

phase), then every four weeks until disease progression (maintenance treatment phase), and at treatment discontinuation. For patients who discontinued treatment for reasons other than disease progression, they were given the EQ-5D-5L questionnaire to complete at the visit where disease progression was confirmed.

As per the NICE reference case, the company mapped the EQ-5D-5L data to EQ-5D-3L using the mapping algorithm by Hernández Alava *et al*. 2020.[13, 35]

A mixed model for repeated measures (MMRM) was used to analyse the utility data from DUO-E. The company explored several combinations of covariates for the model, including: treatment arm (model 1); progression state (model 2); treatment arm + progression state (model 3); and treatment arm + progression state + treatment arm x progression state (model 4). Based on AIC statistics, the company determined that model 2 was the best fit to estimate utilities for the economic model (presented in Table 35). In total, [redacted] observations informed the progression-free (PF) utility estimate, while [redacted] observations informed the progressed disease (PD) estimate.

Table 35. Health state utility values for the economic model – DUO-E ITT population (reproduced from Table 59 of the CS)

Health state	Utility value (95% CI)
PF	[redacted]
PD	[redacted]

Abbreviations: CI, confidence interval; CS, company submission; ITT, intention-to-treat; PD, progressed disease; PF progression-free.

Upon EAG request, the company provided the results of model 2 by MMR status, presented in Table 36. [redacted]

The EAG notes that its clinical experts considered there was no clinical reason why HRQoL would differ from by MMR status, as such, the company's base case approach using values from the ITT population is reasonable.

Table 36. Health state utility values based on model 2 by MMR subgroups (reproduced from Table 19 of the company's clarification response)

Health state	dMMR subgroup	pMMR subgroup
PF	[redacted]	[redacted]
PD	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CS, company submission; dMMR, mismatch repair deficient; ITT, intention-to-treat; PD, progressed disease; PF progression-free; pMMR, mismatch repair proficient.

Utilities in the model were adjusted for age, as per the NICE manual.[13] General population utility values adjusted for age and sex were obtained from the HSE 2014 dataset, as recommended by the DSU.[39] The EAG considers that the general population utility values used by the company are appropriate.

The company applied a utility decrement attributable to AEs in the first cycle of the model to reflect the impact of these events on patients' quality of life. Section 3.3.5 describes the AEs included in the model, derived directly from DUO-E. The company reports that it was unable to directly derive AE utility decrements and duration from the DUO-E trial, and therefore used values reported in a previous single technology appraisal (TA411) and which were also used and accepted by committee in the dostarlimab appraisal (TA963).[15, 20]

The mean durations of adverse events, and utility decrements estimated for patients experiencing adverse events are reported in Table 61 of the CS. The one-off utility decrement applied in the first model cycle for each treatment arm is reported in Table 37 below.

Table 37. Total AE-related utility decrement by treatment arm in the model (obtained from the company's post CQ economic model)

Treatment arm	Total utility decrement due to AEs
SoC	-0.0095
SoC+D	-0.0121
SoC+D+O	-0.0161

Abbreviations: AE, adverse event; CQ, clarification question; CS, company submission; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

4.2.5.1 EAG critique

The EAG considers that the company's approach to estimating HSUVs is reasonable as it measured HRQoL directly from patients in the DUO-E trial using a generic preference-based measure (EQ-5D), following the key components of the NICE reference case.[13] The EAG notes that because the PF utility has been sourced directly from DUO-E, the HRQoL impact from experiencing AEs is likely included in the value. As such, the EAG considers that it may be appropriate to exclude AE disutilities. In the original submission, the company provided a scenario exploring removing AE disutilities and this had minimal impact on the ICER.

The EAG notes that in TA963, utilities were sourced directly from RUBY-1, but AE disutilities were included in both the company and EAG base cases. As such, for consistency with TA963, the EAG maintains the AE disutility impact in its base case but has explored its exclusion as a scenario around the base case, presented in Section 6.3.

4.2.6 Resource use and costs

The following costs were included in the company's model:

- Drug acquisition costs (primary and subsequent treatments);
- Drug administration costs (primary and subsequent treatments);
- Health-state resource use and costs;
- Cost of AEs;
- End-of-life cost.

Drug costs were sourced from the British National Formulary (BNF) or Electronic market information tool (eMIT). Unit costs for health-state resource use were sourced from the NHS Schedule of Reference Costs 2022/2023[45] and PSSRU 2023.[46] When necessary, costs from 2022 or before have been inflated to the current year using the NHS cost inflation indices (NHSCII) published by the PSSRU (2023).[46]

Confidential CAA discounts are available for durvalumab and olaparib of [redacted]% ([redacted] per 500mg vial and [redacted] per 120mg vial) and [redacted]% ([redacted] per 56 tablets), respectively. The CAA discounts for durvalumab and olaparib were used in the economic model and all results are reported in this document include these discounts.

Confidential PAS discounts are available for the subsequent treatments, lenvatinib and pembrolizumab. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.3 for details on the source of the confidential price for each treatment.

4.2.6.1 Drug acquisition costs

Drug acquisition costs for SoC, durvalumab and olaparib were calculated in the model using the dosing regimens from DUO-E (Table 38), drug pack prices (Table 65 in the CS), the mean number of

chemotherapy treatment cycles (Table 39), duration of durvalumab and olaparib using TTD (see Section 4.2.4) and relative dose intensities (Table 41). The company noted that the dosing of carboplatin and paclitaxel was dependent on area under the curve (AUC) of plasma concentration and body surface area (BSA). As such, modelled BSA and AUC has been derived from mean weight, and glomerular filtration rate (GFR) from the DUO-E trial (see Section 2.3.1); assuming each of which were normally distributed.

Table 38. Dosing regimen (reproduced from Table 64 in the CS)

Treatment	Dosing regimen	Source
Carboplatin + paclitaxel (SoC)	Patients received carboplatin (AUC 6 mg/mL/min) and paclitaxel (175 mg/m2) every 3 weeks for 6 cycles.	DUO-E[23]
Durvalumab	Durvalumab 1,120 mg intravenously (IV) every 3 weeks for 6 cycles (chemotherapy phase), followed by maintenance durvalumab 1,500 mg IV every 4 weeks thereafter (maintenance phase).	DUO-E[23]
Olaparib	Olaparib 300 mg tablets taken twice daily, equivalent to a total daily dose of 600mg. (maintenance phase only, assumed from 18 weeks onwards).	DUO-E[23]

Abbreviations: CS, company submission; IV, intravenous; mg, milligram; ml, millilitre; SoC, standard of care.

SoC treatment costs were calculated using the mean number of SoC treatment cycles, derived from the DUO-E trial observed data (Table 39). SoC costs were applied as a one-off cost in the first cycle for all treatment arms.

The drug acquisition cost per administration for durvalumab and olaparib is presented in Table 40. As the company has assumed that durvalumab and olaparib are provided until disease progression or after three years of treatment, whichever occurs earliest, duration of treatment was based on extrapolated TTD, discussed further in Section 4.2.4. The estimated mean durvalumab treatment duration for the dMMR subgroup was [redacted] years. For the pMMR subgroup, the estimated mean durvalumab and olaparib treatment duration was [redacted] years and [redacted] years, respectively.

Table 39. Mean number of chemotherapy cycles and cost by subgroup and treatment arm – DUO-E[23]

Subgroup and treatment arm	Carboplatin	Paclitaxel	One-off cost of chemotherapy
dMMR subgroup			
SoC	5.39	5.39	£654.53
SoC+D	5.34	5.34	£648.41
pMMR subgroup			
SoC	5.55	5.50	£672.28
SoC+D+O	5.55	5.55	£673.76

Abbreviations: dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 40. Drug acquisition cost per administration (reproduced from Table 70 in the CS)

Population	Treatment	Drug acquisition cost per administration	
		Chemotherapy phase	Maintenance phase
dMMR & pMMR	Durvalumab	[redacted]	[redacted]
pMMR	Olaparib*	N/A	[redacted]

Abbreviations: dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

*In the model, the cost per administration of olaparib is the weekly cost of olaparib.

Table 41. Relative dose intensities for durvalumab and olaparib (reproduced from Table 69 in the CS)

Treatment	Relative dose intensity (median)	Source
Durvalumab in SoC+D	[redacted]	DUO-E[23]
Durvalumab in SoC+D+O	[redacted]	DUO-E[23]
Olaparib in SoC+D+O	[redacted]	DUO-E[23]

Abbreviations: SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

In the company's base case, vial sharing for IV drugs has been assumed (i.e. no drug wastage) as the company considers vial sharing for high-cost oncology drugs is common NHS clinical practice to minimise wastage. The company provided a scenario analysis assuming full drug wastage and this is presented in Section 5.2.2.

The total drug acquisition costs estimated for the company's base case for each arm of the model and subgroup for the progression-free health state is presented in Table 42. It should be noted that for olaparib, the company assumed that [redacted]% would initiate treatment at the start of the maintenance phase, based on data from DUO-E.

Table 42. Total drug acquisition costs by treatment arm and subgroup - progression-free health state

Subgroup	SoC	SoC+D (+/- O)
dMMR	£654.53	[redacted]
pMMR	£672.28	[redacted]

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D (+/-O), standard of care with durvalumab (with or without olaparib).

4.2.6.2 EAG critique

A key issue with the estimation of drug acquisition costs, specifically for the pMMR subgroup, is the assumption that [redacted] of pMMR patients in the maintenance phase of treatment initiate olaparib, which the EAG considers potentially underestimates costs (**Key issue 4** in Section 1). The proportion of patients initiating olaparib in the model is based on data from DUO-E, where [redacted] of [redacted] patients (79.1%) randomised to SoC+D+O in the pMMR population initiated treatment with olaparib in the maintenance phase of treatment.

In their clarification response, the company explained the reasons why patients did not initiate treatment with olaparib included disease progression ([redacted] patients) and ineligibility for treatment, such as not meeting maintenance eligibility criteria, discontinuation due to adverse events, patient choice etc. ([redacted] patients). The company also explained that of the SoC+D+O patients that received some form of maintenance treatment ([redacted] patients or [redacted]), [redacted] patients ([redacted]) continued durvalumab monotherapy.

As discussed in Section 2.3.2, the draft SmPC for durvalumab and olaparib for the pMMR population recommends durvalumab in combination with olaparib after a minimum of 4 and up to 6 cycles of treatment durvalumab monotherapy in combination with carboplatin and paclitaxel. Durvalumab monotherapy in the maintenance phase of treatment is not recommended for the pMMR population.

The EAG considers there are two issues with the assumption of the proportion of patients that initiate olaparib in the model:

1. The estimation of treatment duration for olaparib in the model starts from week 18 and not from the start of the time horizon (as confirmed by the company in their clarification response to question B10). As such, the company's use of [redacted]%, which is estimated based on the number of patients at the time of randomisation and the number that initiate olaparib treatment is potentially underestimating costs. As a reminder, olaparib treatment acquisition costs are only applied to patients in the model who are alive and progression-free after week 18. Therefore, the EAG considers that it is more appropriate to estimate a proportion based on the number of patients who received olaparib ([redacted] patients) out of the total number of patients who received durvalumab monotherapy or durvalumab with olaparib ([redacted] patients), which is [redacted]%.

2. In their clarification response, the company explained that it does not expect there to be any wording within the SmPC that excludes the use of durvalumab monotherapy for patients ineligible to receive olaparib in the maintenance phase of treatment. The company does not expect to receive a marketing authorisation for the SoC+D regimen for pMMR patients. However, the company is seeking a NICE recommendation for the pMMR population that is aligned to the marketing authorisation (SoC+D+O), but with flexibility in the recommendation for patients to continue durvalumab monotherapy in the maintenance phase if they are unable to initiate olaparib. The EAG is concerned with this apparent conflict with the company's position and the lack of marketing authorisation for the pMMR population for SoC+D. The EAG highlights this potential issue in the company's base case so that committee are aware of the full implications of a NICE recommendation based on the company's preferred analysis of the pMMR population. That is, it does not appear to wholly align with the anticipated marketing authorisation.

Based on the issues outlined above, the EAG has conducted two scenarios around the proportion of SoC+D+O patients who are alive and progression-free that initiate olaparib, which explores the use of [redacted]% as estimated in issue 1 and 100% initiating olaparib in the maintenance phase to provide the committee with the results that more align with the marketing authorisation for the pMMR subgroup. The EAG acknowledges that there is uncertainty in the results of the second scenario as the model includes survival data from DUO-E that does includes a proportion of SoC+D+O patients who did not receive olaparib in the maintenance phase of treatment ([redacted]%) and so potentially may be underestimating treatment effectiveness for this arm of the model, but the EAG considers this discrepancy is trivial.

Results of the EAG scenarios are presented in Section 6.2. The EAG considers that for its base case it is preferable to include the assumption that [redacted]% of SoC+D+O patients initiate olaparib as it is more appropriate than the company's base case assumption. The EAG's assumption also aligns with the clinical data in the model, but the EAG also explores the use of 100% olaparib use as a scenario around the base case, presented in Section 6.3.

As discussed previously, the EAG considers that the estimation of treatment duration for durvalumab and olaparib in the model is not appropriate based on the treatment regimen included in DUO-E and their draft SmPCs.[2, 3, 26] Please see Section 4.2.4.3 for further discussion of this issue and the EAG's preferred approach.

The EAG's preferred approach to the extrapolation of TTD is to use the gamma distribution without a treatment cap for durvalumab in the dMMR subgroup and the exponential distribution without a treatment cap for durvalumab and olaparib in the pMMR subgroup. Based on the EAG's preferred approach to TTD, the mean treatment duration for durvalumab in the dMMR subgroup is [redacted] years and for the pMMR subgroup is [redacted] years for durvalumab and [redacted] years for olaparib. Total drug acquisition costs for the EAG's preferred base case are presented in Table 43, with results presented in Section 6.3.

Table 43. EAG preferred total drug acquisition costs by treatment arm and subgroup - progression-free health state

Subgroup	SoC	SoC+D (+/- O)
dMMR	£654.53	[redacted]
pMMR	£672.28	[redacted]

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D (+/-O), standard of care with durvalumab (with or without olaparib).

Lastly, the EAG considers that drug wastage should be included in the base case based on advice from its clinical experts who considered that vial sharing does not happen consistently in UK clinical practice. As such, the EAG prefers to include drug wastage for its base case, presented in Section 6.3.

4.2.6.3 Administration costs

Administration costs were applied to IV drugs, with a different cost applied depending on the administration visit (initial vs subsequent attendance) and complexity of administration (Table 44). Chemotherapies were assumed to incur a simple initial administration cost and immunotherapies a complex initial administration cost. No administration cost was assumed for orally administrated treatments.

Table 44. Drug administration costs

Administration type	Unit cost	Source
IV Simple administration – First attendance	£411.99	NHS reference costs 2022/23;[45] Summary: HRG (SB12Z) Deliver simple parenteral chemotherapy at first attendance
IV Complex Administration – First attendance	£486.10	NHS reference costs 2022/23;[45] Summary: HRG (SB13Z) Deliver more complex parenteral chemotherapy at first attendance
IV Subsequent administration	£393.16	NHS reference costs 2022/23;[45] Summary: HRG (SB15Z) Deliver subsequent elements of a chemotherapy cycle

Abbreviations: HRG, health resource group; IV, intravenous; NHS, national health service.

4.2.6.4 EAG critique

The EAG considers that the type of administration and the unit costs are appropriate, consistent with TA963[15] and have been applied correctly in the model.

4.2.6.5 Subsequent treatments

On disease progression, a proportion of newly progressed patients were assumed to receive further lines of treatments applied as a one-off cost upon health state entry, with each MMR subgroup receiving the proportion of subsequent treatments presented in Table 45. The EAG notes that the proportion of subsequent treatments sum to over 100% as patients may receive more than one subsequent treatment.

During the clarification stage, the company updated the proportions of patients on each subsequent treatment as dostarlimab was included in the original submission. However, NICE advised that dostarlimab could not be included as a subsequent treatment for the SoC arm of the dMMR subgroup as it is currently only available to patients through the CDF. As such, based on feedback from their clinical experts, the company has assumed increased usage of pembrolizumab monotherapy, which is approved for use in the dMMR population.[19]

As the DUO-E trial was a multinational trial with no UK sites, the company sought clinical expert opinion to ensure that the assumed proportions of subsequent treatments patients would receive accurately reflected UK clinical practice. The company noted that it was not possible to determine from DUO-E whether subsequent treatments were used in combination or as a monotherapy. Similarly, the company highlighted that rechallenge with immunotherapy is not currently permitted according to Blueteq criteria and lenvatinib is currently only recommended in combination with pembrolizumab at second-line.[12, 47]

Table 45. Subsequent treatment proportions (used in the company's post clarification model)

Treatment	dMMR		pMMR		Source
	SoC	SoC+D	SoC	SoC+D+O	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	UK clinical expert opinion/DUO-E*
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	
Doxorubicin/Doxorubicin hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	

Lenvatinib/Lenvatinib mesilate	[redacted]	[redacted]	[redacted]	[redacted]	
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations D, durvalumab; O, olaparib; SoC, standard of care.

*Subsequent treatment data from DUO-E were provided in Table 5 of the company's clarification response

As with first-line treatment costs, the proportion of patients on each treatment, along with dose per month, price per milligram and the estimated duration of treatment (Table 46) were used to calculate the overall costs for subsequent treatments (Table 47) for each treatment arm and subgroup. The dosing schedule for each subsequent treatment was informed using either the relevant SmPC or clinical trial data. The company assumed an administration cost of £399.92 for intravenous (IV) treatment and oral drugs incurred no administration cost.

A one-off cost of radiotherapy of £3,672 was sourced from National costs and resource requirements of radiotherapy (2024).[48] As a scenario, the company explored a one-off cost of £763 sourced from NHS reference costs 2022/23.[45]

Table 46. Subsequent treatment dosing regimens

Treatment	Dosing regimen	Vial size (mg)/ Tablets per pack	Unit price	Price per mg	Dose per administration (mg)	Number of administrations per monthly cycle	Adjusted dosage per month (mg)	Duration (months)	Source of list price, dosing regimen and duration of treatment
Carboplatin*	Patients received carboplatin (AUC 5 mg/mL/min) every 3 weeks.	150	£20.22	£0.13	750.0	1.45	1087.05	3.20	eMIT[49] SmPC[50] Coleman 2023[51]
Paclitaxel	Patients received paclitaxel (175 mg/m^2) every 3 weeks.	100	£9.13	£0.09	313.3	1.45	454.03	3.20	eMIT[49] SmPC[52] Coleman 2023[51]
Doxorubicin/ Doxorubicin Hydrochloride	The recommended dose is 60-75 mg/m² i.e. as a single dose or in divided doses on 2-3 consecutive days administered with 21 day's intervals.	10	£3.91	£0.39	107.4	1.45	155.67	3.20	eMIT[49] SmPC[53] Coleman 2023[51]
Cisplatin	Single dose of 50 to 120 mg/m^2 every 3 to 4 weeks	100	£29.27	£0.29	90.0	1.45	130.45	3.20	eMIT[49] SmPC[54] Coleman 2023[51]
Pembrolizumab	Pembrolizumab (200 mg) was administered intravenously every 3 weeks	100	£2,630.00	£26.30	200	1.45	289.88	7.20	BNF[55] Makker *et al.* 2022 [KEYNOTE-775][56]
Lenvatinib/ Lenvatinib Mesylate	The recommended dosage is 20 mg orally once daily.	300	£1,437	£4.79	20	30.44	608.75	7.20	BNF[55] Makker *et al.* 2022 [KEYNOTE-775][56]

Abbreviations: AUC, area under the curve; BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information tool; SmPC, summary of product characteristics.

* In Table 74 of the CS, it is reported that AUC 6 mg/mL/min has been assumed as the carboplatin regimen, but in the model, it is AUC 5 mg/mL/min.

Table 47. Subsequent treatment costs (based on Tables 32 and 33 of the company's clarification response)

Subgroup	Treatment arm	Drug acquisition cost (one-off)	Drug administration cost (one-off)	Total cost (one-off)
dMMR	SoC	£46,184	£5,555	£51,740
	SoC+D	£256	£2,464	£2,720
pMMR	SoC	£34,306	£3,905	£38,212
	SoC+D+O	£255	£2,495	£2,750

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

In the company's base case, independent of treatment arm or MMR status, it was assumed that [redacted]% of patients who experienced a non-fatal progression event would receive subsequent treatment, reflecting the proportion of patients with a non-fatal progression event who received at least one subsequent treatment in the DUO-E trial ([redacted] patients). This proportion was validated with the company's clinical experts along with the assumption that the proportion would be the same across treatment arms and MMR status.

During the clarification stage, the company provided, on request by the EAG, the proportion of patients that received at least one subsequent treatment by treatment arm and MMR status (presented in Table 48) and explored these proportions in a scenario, presented in Section 5.2.2. The EAG notes that the numbers informing the proportions in Table 48 are small for each treatment arm in each subgroup and so subject to uncertainty. As such, the company's base case assumption of [redacted]% of the ITT population receiving at least one subsequent treatment is a reasonable simplification.

Table 48. Proportion of patients that received at least one subsequent treatment by treatment arm and MMR status (Table 28 of the company clarification response)

	dMMR subgroup		pMMR subgroup	
	SoC	SoC+D	SoC	SoC+D+O
Number of patients with a non-fatal progression event	[redacted]	[redacted]	[redacted]	[redacted]
N (%) receiving at least one subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

To estimate the proportion of non-fatal progression events in each model cycle (i.e. the proportion of newly progressed patients), the company assumed that a constant proportion of patients transitioning to the PD health state ([redacted]% based on data from DUO-E) had a non-fatal progression event in each model cycle.

4.2.6.6 EAG critique

Overall, the EAG considers that the methods used to calculate subsequent treatment costs reflect those used to calculate initial treatment acquisition costs and are as equally appropriate.

The EAG notes that, based on advice received from its clinical experts, and reflected in the company's original assumptions, many SoC patients in the dMMR subgroup at second-line would receive dostarlimab. However, dostarlimab at this point in the treatment pathway is only recommended for use through the CDF.[20] As such, the use of pembrolizumab monotherapy was artificially increased as consistent advice was received by both the company and EAG's clinical experts that patients on SoC in the dMMR subgroup would receive a subsequent immunotherapy. As such, while the EAG acknowledges that high usage of pembrolizumab monotherapy does not reflect current clinical reality, it is a reasonable assumption to capture the subsequent treatment costs that might be incurred by SoC patients (in the absence of second-line dostarlimab).

With regards to the appropriateness of the proportions of other subsequent treatment use for each treatment arm and subgroup in the model, the EAG considers that the company's approach to adjust data from DUO-E to reflect UK clinical practice is appropriate but notes there is uncertainty around the proportions as no real-world data are publicly available to validate the proportions. Additionally, the EAG is concerned about subsequent immunotherapy usage for the SoC+D and SoC+D+O arms in DUO-E potentially causing bias in the clinical outcomes and this is discussed further in Section 3.2.

Nonetheless, changes to subsequent treatment costs in the model have a greater impact on the SoC arm in each subgroup as these patients effectively "wait" until disease progression to access high-cost immunotherapy treatments. Thus, the EAG does not consider it unreasonable that a high proportion of the total costs in the SoC arm in each subgroup is made up of subsequent treatment costs.

However, a key issue with the estimation of subsequent treatment costs is the estimation of newly progressed patients which incur the one-off cost of subsequent treatment in each cycle of the model

and is a key driver of costs (**Key issue 5** in Section 1). The EAG considers that the company's estimation of newly progressed disease patients, using a constant proportion of [redacted]% (non-fatal progression events from DUO-E) potentially overestimates the proportion of newly progressed patients per cycle.

Additionally, the company's assumption means that in every model cycle there will be newly progressed patients, but in reality, there may be periods of time when the only PFS events are death, especially for patients in long-term remission. As such, costs of subsequent treatments are likely to be overestimated in the model and biased against the comparator, as more patients are estimated to have disease progression on SoC.

While the company has assumed a fixed constant ([redacted]%) of all progression events will be non-fatal, the EAG considers that the number of newly progressed patients per cycle can be calculated directly from the partitioned survival model. To estimate newly progressed patients per cycle using the model survival extrapolations, the EAG considers the following formula might be more appropriate:

$$PD_{new} = (OS_t - PFS_{t)}) - (OS_{t-1} - PFS_{t-1}) * (\frac{OS_t}{OS_{t-1}})$$

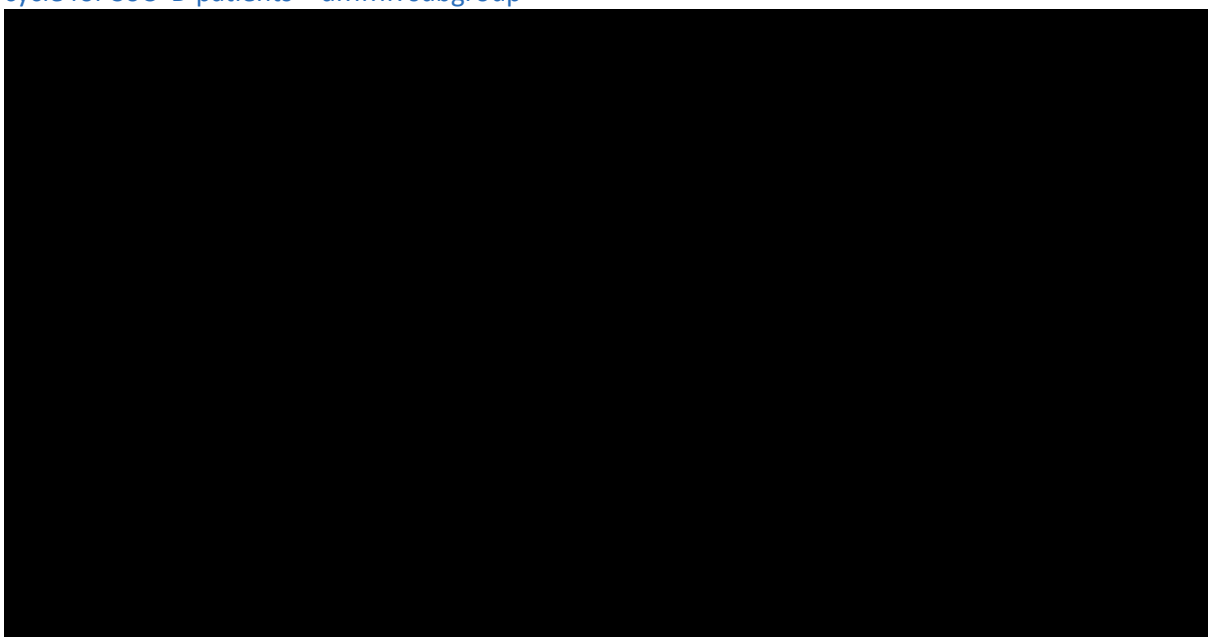
PD_{new} – newly progressed patients between times t and t-1;
PFS_t – progression-free survival at time t
PFS_{t-1} – progression-free survival at time t-1
OS_t – overall survival at time t
OS_{t-1} – overall survival at time t-1

Figure 22 to Figure 25 demonstrates the difference between the company's and EAG's estimation of newly progressed patients on SoC and SoC+D(+/-O).

Figure 22. Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC patients – dMMR subgroup

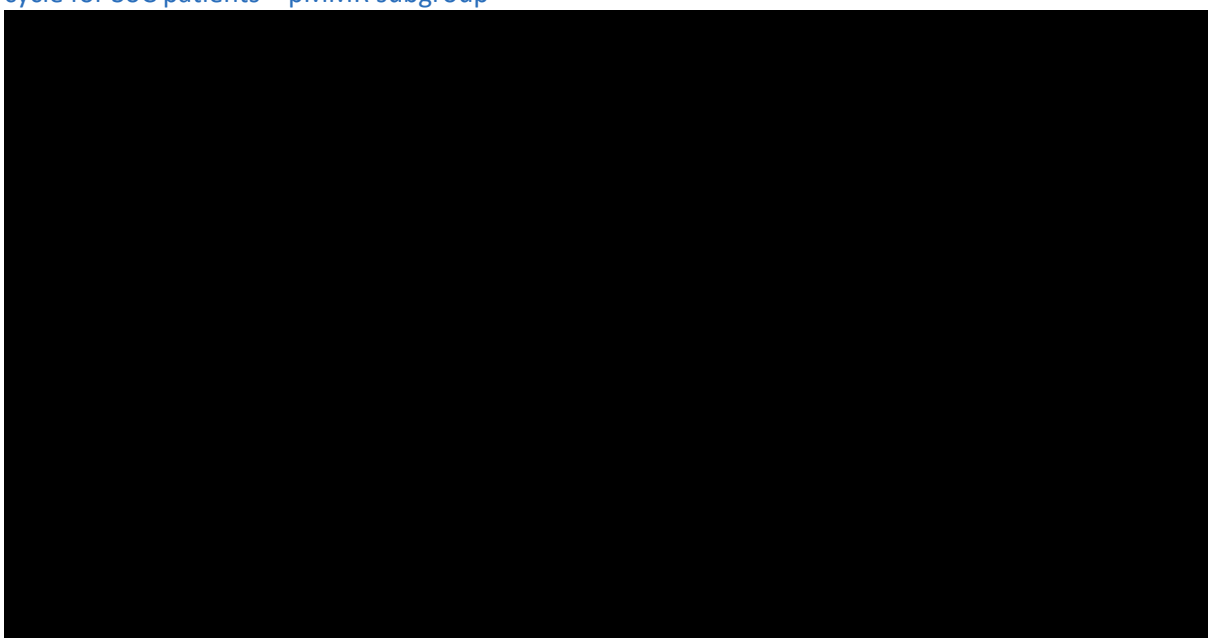
Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; SoC, standard of care.

Figure 23. Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC+D patients – dMMR subgroup



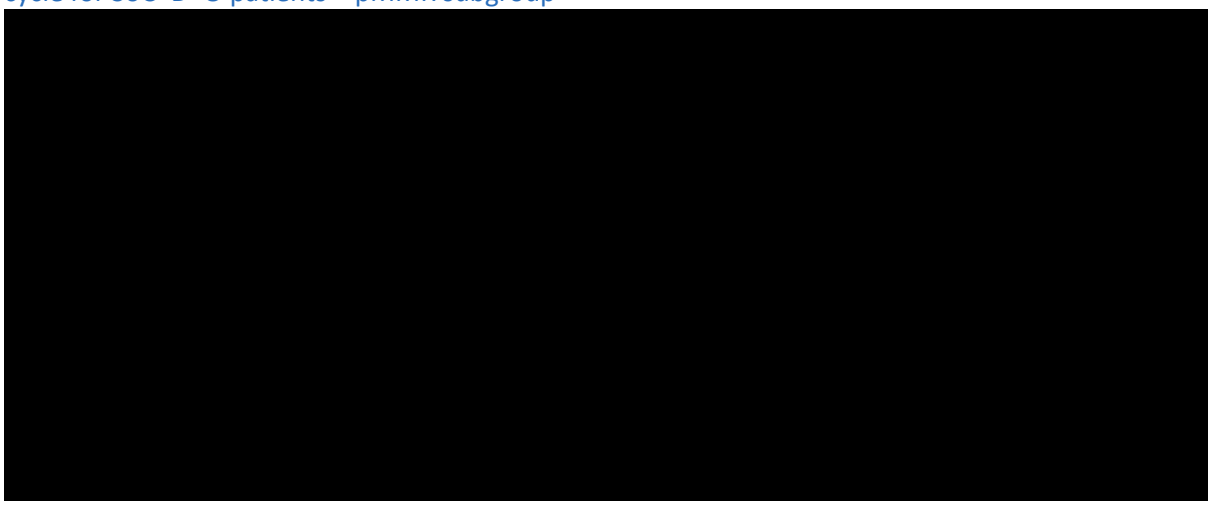
Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; SoC+D, standard of care with durvalumab

Figure 24. Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC patients – pMMR subgroup



Abbreviations: EAG, External Assessment Group; pMMR, mismatch repair proficient; SoC, standard of care.

Figure 25. Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC+D+O patients – pMMR subgroup



Abbreviations: EAG, External Assessment Group; pMMR, mismatch repair proficient; SoC+D+O, standard of care with durvalumab and olaparib.

The EAG acknowledges that its calculation has limitations, in that the OS adjustment includes both patients dying from the PF and PD health state, but it is equivalent to the company's assumption that a fixed proportion of deaths will be from the PF health state. As such, both approaches rely on an implicit assumption around deaths from the PF health state, but the EAG's approach is a useful alternative scenario to explore as it allows changes over time.

During the clarification stage, the EAG requested the company analyses time-to-event data for PFS with disease progression as the only event of interest from DUO-E and explore the use of this in the model or alternatively explore the EAG's calculation as a scenario. The company explained that time-to-progression (TTP) curves would likely mirror PFS as a low number of progression events were fatal. The company also provided data from DUO-E on the percentage of non-fatal PFS events observed over the follow-up to date, presented in Table 49. The EAG notes that the data are for the overall ITT population.

The company considered that the data show that non-fatal progression events over the follow-up of DUO-E to date do not show that this proportion reduces over time albeit the company acknowledges there is uncertainty around this. The EAG considers that if patients achieve long-term remission, then it is not unreasonable to assume that over time PFS will be driven more by fatal events, especially as the mean age of patients from DUO-E is 63 years. However, the EAG agrees there is substantial uncertainty around the long-term trajectory of non-fatal progression that only long-term data from DUO-E can mitigate.

Table 49. Proportion of non-fatal PFS events observed over time in the DUO-E study (Table 11 of the company clarification response)

Time from randomisation	% of PFS that are non-fatal	Non-fatal progression events/ All progression events (cumulative
6	[redacted]	[redacted]
12	[redacted]	[redacted]
18	[redacted]	[redacted]
>18 (total duration of DUO-E follow-up)	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival

The company considered the EAG's request to run a scenario in the model using its alternative calculation of newly progressed patients, but concluded the approach was not valid as for some model cycles a negative proportion was estimated (although the EAG considers a limit can be placed on the calculation such that estimates do not fall below zero). Furthermore, the company estimated that at 30 months (akin to the follow-up of DUO-E) 36-44% of progression events were fatal, which is higher than the [redacted]% estimated in DUO-E, but the EAG in unsure how the company estimated this figure. Instead, the company provided a scenario reducing the constant proportion of non-fatal progression events per cycle to 75% after 60 months and results are presented in Section 5.2.2.

Nonetheless, the EAG implemented its calculation as a scenario and found that for the dMMR subgroup, the ICER increased from [redacted] to [redacted] and for the pMMR subgroup, the ICER increased from [redacted] to [redacted] (see Section 6.2). Given that the EAG's calculation has limitations and that data from DUO-E (although immature) suggests that the majority of progression events are non-fatal, the EAG has not implemented its calculation in its base case but provides it as a scenario around the base case to highlight the impact of a change in this assumption for committee consideration.

As a secondary issue, during the clarification stage, the EAG queried the source of the administration cost (£399.92) used for subsequent treatment as this was not described in the original CS. The company confirmed that the source was from the NHS reference costs 2021/22, SB15Z: Deliver subsequent elements of a chemotherapy cycle.[45] The company acknowledged that a more recent cost from NHS reference costs 2022/23 (£393.16) was used as an administration cost for primary treatment in the model (see Table 44). Inexplicably, the company did not update their base case for the recent cost that was used elsewhere in the model, but instead provided a scenario using the more recent costs. Nonetheless, the EAG has included the most recent cost in its preferred base case to ensure model consistency, presented in Section 6.3.

4.2.6.7 Health state resource use

To inform the costs and patient health state resource use assumptions in the model, the company first conducted an SLR (described in detail in Section 4.1) to identify relevant publications. The SLR identified 19 studies; however, TA963[15] (dostarlimab with platinum-based chemotherapy for treating advanced or recurrent EC with MSI-H or dMMR) was deemed the only relevant and appropriate source and has been used to inform health-state resource use in the model. All other identified studies were considered inappropriate due to either being Canadian or USA based, or due to more appropriate UK sources being available such as publicly available UK databases.

Table 50 presents the health-state resource use, unit costs and frequencies included in the model. Health-state resource use frequency was assumed to differ across the three treatment phases, namely, chemotherapy, maintenance and progressed disease.

Resource use in the chemotherapy and progressed disease phases were informed using NICE TA963 for dostarlimab, while the maintenance phases were informed using routine resource use data from

the DUO-E trial. Health-state costs for the chemotherapy phase were applied for 4.14 months which reflected the average duration of chemotherapy from DUO-E.

Lastly, the company has assumed that resource use does not differ by MMR status and that patients who can be considered in long term remission are discharged from care and incur resource use at the level of SoC patients during the maintenance phase. The EAG notes that the company has assumed that patients are discharged from care if they are still progression free for longer than the maximum treatment duration applied in the model, which is assumed to be three years (see Section 4.2.4 for details on treatment duration).

Table 50. Health-state resource use and costs (per monthly cycle), by treatment arm and health state

Resource type	Unit cost	PF: Chemotherapy stage		PF: Maintenance phase		Progressed disease		Source of unit cost
		SoC	SoC+D (+/- O)	SoC	SoC+D (+/- O)	SoC	SoC+D (+/- O)	
Outpatient visit	£175.17	1.30	1.30	0.35	0.57	0.52	0.52	NHS reference costs 2022/23;[45] Outpatient Care 503
CT scan	£141.52	0.57	0.57	0.22	0.26	0.30	0.30	NHS reference costs 2022/23;[45] Summary: HRG (RD20A, B,C, RD21A, B, C, RD22-27Z) weighted average
Complete blood count	£2.75	1.43	1.43	0.26	0.96	0.39	0.39	NHS reference costs 2022/23:[45] DAPS05
Specialist nurse visit	£118.51	0.48	0.48	0.43	0.30	0.43	0.43	NHS reference costs 2022/23:[45] N10AF and N10AN (weighted average)
GP visit	£49.00	-	-	0.04	0.04	0.04	0.04	PSSRU - Unit Costs of Health and Social Care 2023:[46] GP per surgery consultation lasting 10 mins including direct costs and qualification costs
Cancer antigen test (CA-125)	£30.40	1.43	1.43	0.39	0.96	0.39	0.39	NICE CG122[57] Table A1.10 (Inflated 2010 to 2023 using PSSRU 2023[46] inflation indices)
Thyroid function tests (TSH, T3 & T4)	£4.96	1.43	1.43	0.39	0.96	0.39	0.39	NICE NG145[58] (Inflated 2019 to 2023 using PSSRU 2023[46] inflation indices)
Total cost per monthly cycle	-	**£419.87**	**£419.87**	**£159.92**	**£210.60**	**£203.50**	**£203.50**	-

Abbreviations: NICE, national institute for Healthcare and Excellence; NHS, national health service; PD, progressed disease; PF, progression free; PSSRU, Personal Social Services Research Unit. SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

4.2.6.8 EAG critique

The EAG notes that the heath-state resources included in the model and their frequencies and costs, reflect those included in the model for TA963.[15] When asked to validate these resources, the EAG's clinical experts provided the following opinions:

- Patients on immunotherapy treatments will receive cortisol, kidney and liver function tests while on treatment.
- Patients on immunotherapy will continue to receive outpatient visits every month while still on treatment.
- SoC Patients will not receive thyroid tests while on chemotherapy.
- The resource use frequency for PD durvalumab patients (with or without olaparib) is more likely to be that which has been assumed for SoC patients during the PF maintenance phase.
- The resource use frequency for SoC PD patients is more likely to be that which has been assumed for durvalumab patients during the PF maintenance phase as these patients will now be receiving immunotherapies.

As such, the company was asked to conduct a scenario analysis using the EAG's clinical expert assumptions, with the resources and frequencies adjusted to those presented in Table 47. The company conducted the scenario analysis, but the EAG found that the scenario included thyroid tests for SoC in the PF health states and costs were not exactly the same for SoC PD health state compared with SoC+D(+/-O) for the PF maintenance phase due to slight numerical differences in the numbers. The EAG corrected the company's scenario, and the results had minimal impact on the ICERs (presented in Section 5.2.2).

Table 51. EAG preferred HRCU frequencies

Resource type	PF: Chemotherapy stage		PF: Maintenance phase		Progressed disease	
	SoC	SoC+D (+/- O)	SoC	SoC+D (+/- O)	SoC	SoC+D (+/- O)
Outpatient visit	1.3	1.3	0.35	1	1	0.35
CT scan	0.57	0.57	0.22	0.26	0.26	0.22
Complete blood count	1.43	1.43	0.26	0.96	0.96	0.26
Specialist nurse visit	0.48	0.48	0.43	0.30	0.30	0.43
GP visit	0	0	0.04	0.04	0.04	0.04

Cancer antigen test (CA-125)	1.43	1.43	0.39	0.96	0.96	0.39
Thyroid function tests (TSH, T3 & T4)	0	1.43	0	0.96	0.96	0
Liver function tests	0	1.43	0	0.96	0.96	0
Kidney function tests	0	1.43	0	0.96	0.96	0
Cortisol level tests	0	1.43	0	0.96	0.96	0
Total cost per monthly cycle	**£412.75**	**£426.78**	**£157.98**	**£291.39**	**£291.39**	**£157.98**

Abbreviations: NICE, national institute for Healthcare and Excellence; NHS, national health service; PD, progressed disease; PF, progression free; PSSRU, Personal Social Services Research Unit; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Finally, the EAG's clinical experts considered the company's assumption that resource use for patients treated with immunotherapies would be deescalated to that of chemotherapy patients in the maintenance phase when considered in long term remission was appropriate.

4.2.6.9 Adverse event costs

Costs of AEs were calculated using the frequency, duration (described in Section 3.3.5) and cost of each adverse event (Table 52). Total AE costs per treatment arm were applied as a one-off cost in the first model cycle (Table 53).

Table 52. Adverse event costs

AE	Unit cost	Source
Anaemia	£855.09	NHS reference costs 2022/23; Summary: HRG (SA04G, H, J, K, L): Weighted average of Iron Deficiency Anaemia with CC Score 0-14+
Neutropenia	£1,400.20	NHS reference costs 2022/23; Summary: HRG (SA08G, H, J): Weighted average of other haematological or splenic disorders with CC Score 0-6+
Neutrophil Count Decreased	£941.25	Assumed equal to white cell count decreased
Lymphocyte Count Decreased	£941.25	Assumed equal to neutrophil count decreased
White Cell Count Decreased	£941.25	NHS reference costs 2022/23; Summary: HRG (RN13Z) nuclear medicine infection scan or white cell scan
Hypertension	£720.94	NHS reference costs 2022/23; Summary: HRG (EB04Z) Hypertension
Pulmonary Embolism	£1,110.87	NHS reference costs 2022/23; Summary: HRG (YQ51A, B, C,D, E) : Weighted average of Deep Vein Thrombosis with CC Score 0-12+
Hypokalaemia	£1,845.37	NHS reference costs 2022/23; Summary: HRG (KC05G, H, J, K, L, M): Weighted average of Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-10+

Abbreviations: HRG, health resource group; NHS, national health service.

Table 53. Total AE cost per treatment arm

Treatment arm	Total AE cost (applied as a one-off in first model cycle)
SoC+D	£516.38
SoC+D+O	£650.58
SoC	£464.79

Abbreviations: SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

4.2.6.10 EAG critique

The EAG considers that the adverse event costs included in the model are appropriate and have been applied correctly.

4.2.6.11 End-of-life costs

The company included a one-off terminal care cost applied upon death in the model, which reflects the increase in costs that are assumed to be incurred towards the end of a patient's life. Total end of life costs for cancer were sourced from the end-of-life care section of the PSSRU and are the sum of direct healthcare costs (£8,051) and social care costs (£4,676), leading to a terminal care cost of £12,727.[46]

4.2.6.12 EAG critique

The EAG considers that the end-of-life costs included in the model are appropriate and have been applied correctly.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Confidential commercial access agreement (CAA) discounts for durvalumab ([redacted]) and olaparib ([redacted]) are applied in the company's base case and reflected in the results presented in this report. As confidential prices and PAS discounts are available for platinum-based chemotherapy and subsequent treatments, the External Assessment Group (EAG) has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

5.1.1 dMMR subgroup

Table 54 presents the cost-effectiveness results of the company's updated (i.e. post clarification) base case deterministic and probabilistic analyses for the mismatch repair deficient (dMMR) subgroup. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of 5.00 over SoC along with [redacted] for SoC with durvalumab (SoC+D), generates an incremental cost-effectiveness ratio (ICER) of [redacted]. The net health benefit (NHB) based on the deterministic results using the £20,000 and £30,000 threshold is [redacted] and [redacted], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 54. Updated (post FAC) company base case results – dMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	60,570	3.69	2.72	-	-	-	-
SoC+D	[redacted]	11.34	8.10	[redacted]	7.65	5.37	[redacted]
Probabilistic results							
SoC	60,963	4.18	3.07	-	-	-	-
SoC+D	[redacted]	11.29	8.06	[redacted]	7.10	5.00	[redacted]

Abbreviations: dMMR, mismatch repair deficient; FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

Note: The EAG noted a very minor discrepancy in the estimation of the percentage of durvalumab patients with hypertension and pulmonary embolism in the company's economic model that was provided with the addendum compared

with the clarification response model. The company's clarification response economic model provided a more accurate representation of the AEs and as such, the EAG has used this model to provide updated company base case results inclusive of the updated CAAs for durvalumab and olaparib.

A PSA scatterplot is presented in Figure 26 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 27.

Figure 26. Scatterplot of PSA estimates on a cost-effectiveness plane SoC+D versus SoC – dMMR subgroup

Figure 27. Cost-effectiveness acceptability curve for SoC+D versus SoC at 2L

5.1.2 *pMMR subgroup*

Table 55 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses for the mismatch repair proficient (pMMR) subgroup. The company performed a PSA to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental QALY gain of 0.67 over SoC along with [redacted] for SoC with durvalumab and olaparib (SoC+D+O), generates an ICER of [redacted]. The NHB based on the deterministic results using the £20,000 and £30,000 threshold is [redacted] and [redacted], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 55. Updated (post FAC) company base case results – pMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	54,864	4.57	3.27	-	-	-	-
SoC+D+O	[redacted]	5.46	3.94	[redacted]	0.89	0.67	[redacted]
Probabilistic results							
SoC	55,171	4.59	3.29	-	-	-	-
SoC+D+O	[redacted]	5.49	3.96	[redacted]	0.90	0.67	[redacted]

Abbreviations: FAC, factual accuracy check; ICER, incremental cost-effectiveness ratio; LY, life year; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

Note: The EAG noted a very minor discrepancy in the estimation of the percentage of durvalumab patients with hypertension and pulmonary embolism in the company's economic model that was provided with the addendum compared with the clarification response model. The company's clarification response economic model provided a more accurate representation of the AEs and as such, the EAG has used this model to provide updated company base case results inclusive of the updated CAAs for durvalumab and olaparib.

A PSA scatterplot is presented in Figure 26 and a CEAC is presented in Figure 27.

Figure 28. Scatterplot of PSA estimates on a cost-effectiveness plane SoC+D+O versus SoC – dMMR subgroup

Figure 29. Cost-effectiveness acceptability curve for SoC+D+O versus SoC at 2L

5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagrams presented in Figure 30 for SoC+D versus SoC (dMMR subgroup) and Figure 31 for SoC+D+O versus SoC (pMMR subgroup).

For the dMMR subgroup, the ICER was most sensitive to subsequent IV administration costs, the proportion of patients on subsequent pembrolizumab and outpatient visit costs. For the pMMR subgroup, the ICER was most sensitive to the proportion of patients on subsequent pembrolizumab and subsequent IV administration costs.

Figure 30. Tornado plot – SoC+D versus SoC (dMMR subgroup)

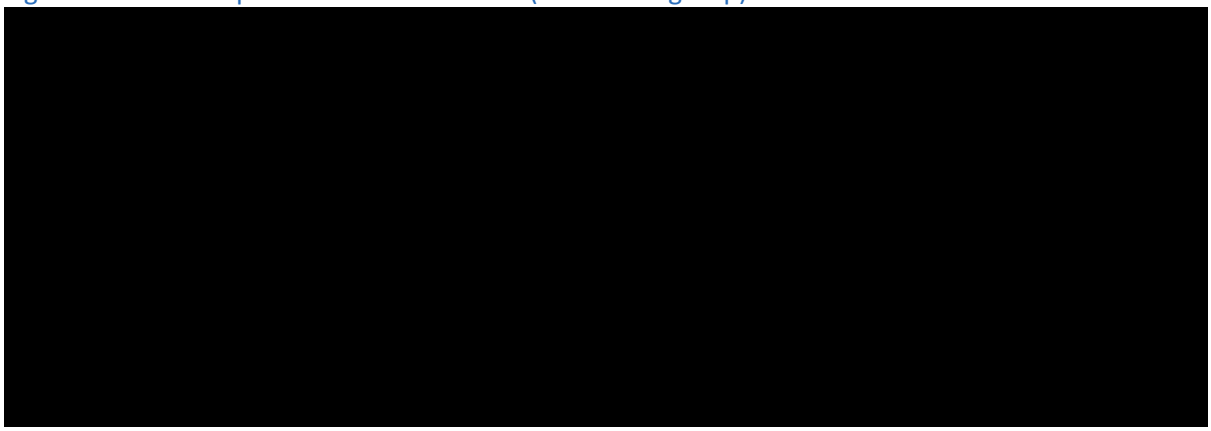
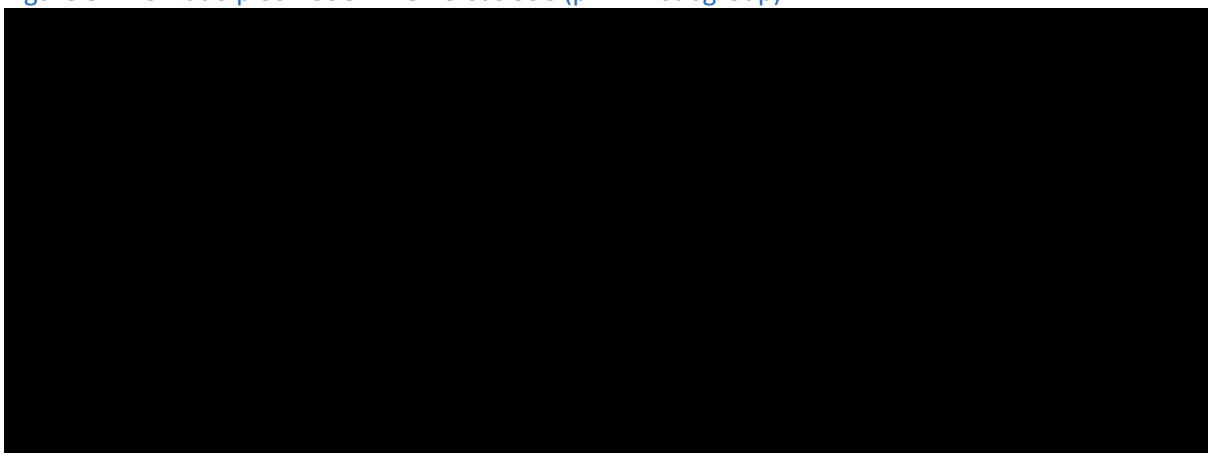


Figure 31. Tornado plot – SoC+D+O versus SoC (pMMR subgroup)



5.2.2 Scenario analysis

The company undertook an extensive series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 56 for the dMMR subgroup and Table 57 for the pMMR subgroup. In addition, the company conducted several additional scenario analyses requested by the EAG, also presented in the tables below.

Table 56. Company scenario analysis – SoC versus SoC+D (dMMR subgroup) (reproduced from Table 96 of the company's additional clarification response)

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	**Company base case**	[redacted]	5.37	[redacted]
1	Time horizon - 25 years	[redacted]	4.96	[redacted]
2	Discount rate - 1.5% for costs and outcomes	[redacted]	6.86	[redacted]
3	PFS SoC+D - Spline, k = 1	[redacted]	5.29	[redacted]
4	PFS SoC - Spline, k = 2	[redacted]	5.15	[redacted]

5	OS: Gamma	[redacted]	4.12	[redacted]
6	OS: Log-logistic	[redacted]	4.6	[redacted]
7	Treatment duration 2 years, parametric curve approach for 1–2 years. Drop to zero at year 2.	[redacted]	5.37	[redacted]
8	Treatment duration 5 years, parametric curve approach for 1–3 years, exponential drop-off 3–5 years	[redacted]	5.37	[redacted]
9	Treatment duration 3 years, Weibull distribution for 1–3 years	[redacted]	5.37	[redacted]
10	Half cycle correction - Excluded	[redacted]	5.37	[redacted]
11	Source for age adjusted utilities - Ara and Brazier (2010)	[redacted]	5.42	[redacted]
12	Drug wastage - Included	[redacted]	5.37	[redacted]
13	Source for health state utilities - NICE TA914[20]	[redacted]	4.94	[redacted]
14	AE disutilities - Excluded	[redacted]	5.38	[redacted]
15	Baseline age - 67.1 (TA963)[15]	[redacted]	4.89	[redacted]
16	Baseline age – 62.5	[redacted]	5.39	[redacted]
17	End of life cost - Excluded	[redacted]	5.37	[redacted]
18	Lifetables - 2020–22	[redacted]	5.35	[redacted]
19	Radiotherapy cost - £763.00	[redacted]	5.37	[redacted]
20	Carboplatin AUC units - 100% AUC 5 units	[redacted]	5.37	[redacted]
EAG requested scenarios				
B3*	PFS capped to OS	[redacted]	5.39	[redacted]
B4	Proportion of non-fatal progression events set to 75% after 60 months	[redacted]	5.37	[redacted]
B6	Broader range of adverse events	[redacted]	5.37	[redacted]
B7	Duration of pulmonary embolism set to 3 months	[redacted]	5.37	[redacted]
B12	TTD - Exponential distribution	[redacted]	5.37	[redacted]
	TTD – Generalised gamma distribution	[redacted]	5.37	[redacted]
	TTD - Gamma distribution	[redacted]	5.37	[redacted]
B17	% of subsequent treatment use by MMR status and treatment arm	[redacted]	5.37	[redacted]
B18	Subsequent pembrolizumab always given with lenvatinib and IO usage assumed to be 70% for SoC – dMMR population only	[redacted]	5.37	[redacted]
B20	Subsequent administrations costs using the latest cost for code SB15Z from NHS references costs (£393.16)[45]	[redacted]	5.37	[redacted]
B21‡	EAG clinical expert resource use assumptions	[redacted]	5.37	[redacted]
B22	Cure point at 3 years	[redacted]	4.62	[redacted]
	Cure point at 5 years	[redacted]	5.08	[redacted]

Abbreviations: dMMR, mismatch repair deficient; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

*After the clarification stage, the company corrected an error with the scenario for B3 and the corrected results are presented in this table.

‡The EAG found errors in the company's scenario (described in Section 4.2.6.8) and provides corrected scenario results in this table.

Table 57. Company scenario analysis – SoC versus SoC+D+O (pMMR subgroup) (reproduced from Table 97 of the company's additional clarification response)

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER
0	**Company base case**	[redacted]	0.67	[redacted]
1	Time horizon - 25 years	[redacted]	0.65	[redacted]
2	Discount rate - 1.5% for costs and outcomes	[redacted]	0.78	[redacted]
3	PFS - Log-normal	[redacted]	0.67	[redacted]
4	OS - Log-normal	[redacted]	0.96	[redacted]
5	OS - Gamma	[redacted]	0.69	[redacted]
6	Treatment duration 2 years, parametric curve approach for 1–2 years. Drop to zero at year 2.	[redacted]	0.67	[redacted]
7	Treatment duration 5 years, parametric curve approach for 1–3 years, exponential drop-off 3–5 years	[redacted]	0.67	[redacted]
8	Treatment duration 3 years, Exponential distribution for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
9	Treatment duration 3 years, Gompertz distribution for 1–3 years for both durvalumab and olaparib	[redacted]	0.67	[redacted]
10	Half cycle correction - Excluded	[redacted]	0.67	[redacted]
11	Source for age adjusted utilities - Ara and Brazier (2010)	[redacted]	0.67	[redacted]
12	Drug wastage - Included	[redacted]	0.67	[redacted]
13	Source for health state utilities - NICE TA914[20]	[redacted]	0.62	[redacted]
14	AE disutilities - Excluded	[redacted]	0.68	[redacted]
15	Baseline age - 67.1 (TA963)[15]	[redacted]	0.66	[redacted]
16	Baseline age – 62.5	[redacted]	0.67	[redacted]
17	End of life cost - Excluded	[redacted]	0.67	[redacted]
18	Lifetables - 2020–22	[redacted]	0.67	[redacted]
19	Radiotherapy cost - £763.00	[redacted]	0.67	[redacted]
20	Carboplatin AUC units - 100% AUC 5 units	[redacted]	0.67	[redacted]
EAG requested scenarios				
B2	PFS: 2-knot spline	[redacted]	0.67	[redacted]
B3	PFS capped to OS	[redacted]	0.67	[redacted]
B4	Proportion of non-fatal progression events set to 75% after 60 months	[redacted]	0.67	[redacted]
B6	Broader range of adverse events	[redacted]	0.67	[redacted]

B7	Duration of pulmonary embolism set to 3 months	[redacted]	0.66	[redacted]
B12	TTD - Exponential distribution	[redacted]	0.67	[redacted]
	TTD - Weibull distribution	[redacted]	0.67	[redacted]
	TTD - Log-logistic distribution	[redacted]	0.67	[redacted]
	TTD - Gamma distribution	[redacted]	0.67	[redacted]
B17	% of subsequent treatment use by MMR status and treatment arm	[redacted]	0.67	[redacted]
B20	Subsequent administrations costs using the latest cost for code SB15Z from NHS references costs (£393.16)[45]	[redacted]	0.67	[redacted]
B21‡	EAG clinical expert resource use assumptions	[redacted]	0.67	[redacted]
B22	Cure point at 3 years	[redacted]	1.09	[redacted]
	Cure point at 5 years	[redacted]	0.70	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

*After the clarification stage, the company corrected an error with the scenario for B3 and the corrected results are presented in this table.

‡The EAG found errors in the company's scenario (described in Section 4.2.6.8) and provides corrected scenario results in this table.

Note: The EAG noted a very minor discrepancy in the estimation of the percentage of durvalumab patients with hypertension and pulmonary embolism in the company's economic model that was provided with the addendum compared with the clarification response model. The company's clarification response economic model provided a more accurate representation of the AEs and as such, the EAG has used this model to provide updated company base case results inclusive of the updated CAAs for durvalumab and olaparib.

5.3 Model validation and face validity check

Section B.3.14 in the company submission outlines the company's approach to the validation of the economic model. Generally, the EAG is satisfied that the company's approach to model validation was robust. However, the EAG did identify one error in the model related to regimen of pembrolizumab, which the company corrected in their post-clarification economic model.

6 Additional economic analysis undertaken by the EAG

6.1 Exploratory and sensitivity analyses undertaken by the EAG

In Section 4 of this report, the External Assessment Group (EAG) describes several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The scenarios that the EAG performed are as follows:

1) Use of the 1-knot spline to extrapolate progression-free survival (PFS) for durvalumab with platinum-based chemotherapy (SoC+D) for the mismatch-repair deficient (dMMR) subgroup – Section 4.2.3.4
    a) Scenario 1 in combination with the use of the log-logistic extrapolation for OS – Section 4.2.3.6.
2) Proportion of patients initiating olaparib is assumed to be [redacted]% (mismatch-repair proficient [pMMR] subgroup) - Section 4.2.6.2.
3) Proportion of patients initiating olaparib is assumed to be 100% on olaparib (pMMR subgroup) - Section 4.2.6.2.
4) The EAG's calculation of non-fatal progression events – Section 4.2.6.6.

The EAG notes that the results of the scenarios, presented in Section 6.2, are deterministic as the company's model requires a substantial amount of time to perform a probabilistic sensitivity analysis (PSA). However, the EAG considers that the company's deterministic and probabilistic results are consistent with each other.

6.2 EAG scenario analysis

Table 58 and Table 59 presents the results of the EAG exploratory analyses described in Section 6.1. Results reported include the company's commercial access agreement (CAA) discount on the list price of [redacted]% for durvalumab and [redacted]% for olaparib.

Confidential PAS discounts are available for lenvatinib and pembrolizumab, which are included in the model as subsequent treatments. As such, the EAG has produced a confidential appendix to the EAG report. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

Table 58. Results of the EAG's scenario analyses – dMMR subgroup

	Results per patient	SoC+D	SoC	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	60,570	[redacted]
	QALYs	8.10	2.72	5.37
	ICER (£/QALY)	-	-	[redacted]
1	1-knot spline for PFS – SoC+D arm only			
	Total costs (£)	[redacted]	60,570	[redacted]
	QALYs	8.01	2.72	5.29
	ICER (£/QALY)	-	-	[redacted]
1a	Scenario 1 + log-logistic extrapolation of OS			
	Total costs (£)	[redacted]	60,405	[redacted]
	QALYs	7.17	2.66	4.51
	ICER (£/QALY)	-	-	[redacted]
4	EAG's calculation of non-fatal progression events			
	Total costs (£)	[redacted]	43,057	[redacted]
	QALYs	8.10	2.72	5.37
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

Table 59. Results of the EAG's scenario analyses – pMMR subgroup

	Results per patient	SoC+D+O	SoC	Incremental value
0	Company base case			
	Total costs (£)	[redacted]	54,864	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]
2	Proportion of patients initiating olaparib assumed to be [redacted]%			
	Total costs (£)	[redacted]	54,864	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]
3	Proportion of patients initiating olaparib assumed to be 100%			
	Total costs (£)	[redacted]	54,864	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]
4	EAG's calculation of non-fatal progression events			
	Total costs (£)	[redacted]	49,563	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred base case for the cost-effectiveness of durvalumab with platinum-based chemotherapy, then with or without olaparib for the treatment of newly diagnosed advanced or recurrent endometrial cancer (EC). The assumptions that form the EAG's preferred base case are listed below.

- EAG scenario 1 - 1-knot spline to extrapolate PFS for SoC+D (dMMR subgroup only).
- Log-logistic distribution to extrapolate overall survival (OS) for the dMMR subgroup.
- Removal of the treatment duration cap and use of the gamma distribution to extrapolate time-to-treatment discontinuation (TTD) for durvalumab in the dMMR subgroup.
- Removal of the treatment duration cap and use of the exponential distribution to extrapolate TTD for durvalumab and olaparib in the pMMR subgroup.
- EAG scenario 2 - proportion of patients initiating olaparib is assumed to be [redacted]% (pMMR subgroup only)
- Inclusion of drug wastage.
- Use of most recent SB15Z cost from NHS reference costs for subsequent treatments administration cost.[45]

Table 60 presents the deterministic EAG base case for the dMMR subgroup and deterministic results for the pMMR subgroup are presented in Table 62. Probabilistic results for the EAG base case are presented in Table 61 for the dMMR subgroup and Table 63 for the pMMR subgroup. Results of the scenarios around the EAG base case (Section 6.3.1) are deterministic as performing PSA in the company's model is time intensive. However, the EAG considers that, based on the base case results, deterministic and probabilistic results are consistent with each other.

Table 60. EAG's preferred model assumptions (deterministic) – dMMR subgroup

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case	-	[redacted]	**5.37**	[redacted]
EAG scenario 1 - 1-knot spline to extrapolate PFS for SoC+D	4.2.3.4	[redacted]	5.29	[redacted]
Log-logistic distribution to extrapolate OS	4.2.3.6	[redacted]	4.51	[redacted]

Removal of the treatment duration cap and use of the gamma distribution to extrapolate TTD for durvalumab	4.2.4.3	[redacted]	4.51	[redacted]
Inclusion of drug wastage	4.2.6.2	[redacted]	4.51	[redacted]
Most recent SB15Z cost from NHS reference costs for subsequent treatments administration cost	4.2.6.6	[redacted]	4.51	[redacted]
EAG preferred base case	**-**	[redacted]	**4.51**	[redacted]

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab; TTD, time-to-treatment discontinuation.

Table 61. EAG base case results – dMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	60,454	3.61	2.66	-	-	-	-
SoC+D	[redacted]	10.08	7.17	[redacted]	6.46	4.51	[redacted]
Probabilistic results							
SoC	61,104	4.16	3.05	-	-	-	-
SoC+D	[redacted]	9.77	6.98	[redacted]	5.61	3.93	[redacted]

Abbreviations: dMMR, mismatch repair deficient; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

Table 62. EAG's preferred model assumptions (deterministic) – pMMR subgroup

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case	**-**	[redacted]	**0.67**	[redacted]
Removal of the treatment duration cap and use of the exponential distribution to extrapolate TTD for durvalumab and olaparib	4.2.4.3	[redacted]	0.67	[redacted]
EAG scenario 2 - proportion of patients initiating olaparib assumed to be [redacted]% (pMMR subgroup only)	4.2.6.2	[redacted]	0.67	[redacted]
Inclusion of drug wastage	4.2.6.2	[redacted]	0.67	[redacted]
Most recent SB15Z cost from NHS reference costs for subsequent treatments administration cost	4.2.6.6	[redacted]	0.67	[redacted]
EAG preferred base case	**-**	[redacted]	**0.67**	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab; TTD, time-to-treatment discontinuation.

Table 63. EAG base case results – pMMR subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	54,932	4.57	3.27	-	-	-	-
SoC+D+O	[redacted]	5.46	3.94	[redacted]	0.89	0.67	[redacted]
Probabilistic results							
SoC	55,394	4.59	3.29	-	-	-	-
SoC+D+O	[redacted]	5.48	3.95	[redacted]	0.88	0.66	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

6.3.1 Scenarios around the EAG base case

The EAG has explored several scenarios around its preferred base case to assess the impact of alternative assumptions on the ICER and these include:

1. Baseline age of 67.1 years. This aligns with the committee's preferred assumption in TA963 – Section 2.3.1.
2. Use of the company's preferred base case extrapolations for PFS and OS in the dMMR subgroup. Specifically, the 2-knot spline for SoC+D PFS and the lognormal distribution for OS – Sections 4.2.3.3 and 4.2.3.5.
3. Exclude AE disutility – Section 4.2.5.1.
4. Proportion of patients initiating olaparib assumed to be 100% on olaparib (pMMR subgroup) - Section 4.2.6.2.

Results of the EAG's scenarios are presented in Table 64 for the dMMR subgroup and Table 65 for the pMMR subgroup.

Table 64. Results of the EAG's scenario analyses around its base case – dMMR subgroup

	Results per patient	SoC+D	SoC	Incremental value
0	EAG base case			
	Total costs (£)	[redacted]	60,454	[redacted]
	QALYs	7.17	2.66	4.51
	ICER (£/QALY)	-	-	[redacted]
1	Baseline age of 67.1 years			
	Total costs (£)	[redacted]	60,429	[redacted]
	QALYs	6.85	2.64	4.21
	ICER (£/QALY)	-	-	[redacted]

2	Company base case extrapolation of PFS and OS			
	Total costs (£)	[redacted]	60,619	[redacted]
	QALYs	8.10	2.72	5.37
	ICER (£/QALY)	-	-	[redacted]
3	Exclusion of AE disutility			
	Total costs (£)	[redacted]	60,454	[redacted]
	QALYs	7.19	2.67	4.51
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: dMMR, mismatch repair deficient; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D, standard of care with durvalumab.

Table 65. Results of the EAG's scenario analyses around its base case – pMMR subgroup

	Results per patient	SoC+D+O	SoC	Incremental value
0	EAG base case			
	Total costs (£)	[redacted]	54,932	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]
1	Baseline age of 67.1 years			
	Total costs (£)	[redacted]	54,810	[redacted]
	QALYs	3.89	3.23	0.66
	ICER (£/QALY)	-	-	[redacted]
3	Exclusion of AE disutility			
	Total costs (£)	[redacted]	54,932	[redacted]
	QALYs	3.96	3.28	0.68
	ICER (£/QALY)	-	-	[redacted]
4	Proportion of patients initiating olaparib assumed to be 100%			
	Total costs (£)	[redacted]	54,932	[redacted]
	QALYs	3.94	3.27	0.67
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; pMMR, mismatch repair proficient; QALY, quality-adjusted life-year; SoC, standard of care; SoC+D+O, standard of care with durvalumab and olaparib.

6.4 Conclusions of the cost effectiveness sections

Generally, the EAG considers the company's submitted cost-effectiveness analysis adheres to the decision problem defined in the NICE final scope.[1] However, the fundamental issue that is driving the uncertainty in the model is the immaturity of the data from DUO-E. At the primary data cut off (April 2023), overall maturity of PFS and OS outcomes in the dMMR subgroup was 40.6% and 21.7%, respectively. For the pMMR subgroup, PFS data were relatively more mature at 66.1% but OS was

immature at 29.2%. Notably, outcome data are more immature for the SoC+D arm of the dMMR subgroup and SoC+D+O arm of the pMMR subgroup of DUO-E. The EAG considers that OS is extremely immature and, that as a result of this, the long-term extrapolations for each treatment arm and each subgroup are subject to a substantial amount of uncertainty. Additionally, long-term trends for non-fatal progression events are uncertain but are needed to accurately estimate subsequent treatment costs (which form a substantial component of total costs for the SoC arms of the model in particular).

Consequently, the EAG considers that the uncertainty around the long-term clinical outcomes assumed in the model can only be overcome by additional data collection in DUO-E. The company has indicated that the final OS analysis from DUO-E is expected in 2026.

Related to the key issue of immature data from DUO-E is the company's assumption that a treatment cap of three years is appropriate for durvalumab and olaparib in the model. The EAG considers that the cap on treatment duration is a key driver of cost-effectiveness in the model as it enforces a limit on the total drug acquisition costs of durvalumab and olaparib that does not relate to the treatment regimens in DUO-E or the draft summary of product characteristics (SmPCs), which are to treat until disease progression or unacceptable toxicity. As such, in lieu of mature data from DUO-E, the EAG considers that a cap on treatment duration should be removed and prefers the use of clinically plausible, full extrapolations of TTD data.

For the pMMR subgroup, an additional complexity around olaparib drug acquisition costs for the SoC+D+O arm of the model was identified by the EAG which may potentially underestimate costs, but also more importantly may cause a disconnect between the treatment regimen in DUO-E and the recommendation the company is seeking from NICE for the subgroup.

The company assumed that [redacted]% of pMMR patients in the maintenance phase of treatment initiated olaparib, based on the number of patients at the time of randomisation and the number that initiated olaparib treatment from DUO-E. The company explained the reasons why patients did not initiate treatment with olaparib included disease progression and ineligibility for treatment, such as not meeting maintenance eligibility criteria, discontinuation due to adverse events, patient choice etc. The company also explained that of the [redacted]% of SoC+D+O patients continued durvalumab monotherapy.

The EAG considers that the company's base case assumption of the proportion of patients initiating olaparib is an underestimate as olaparib treatment acquisition costs are only applied to patients in the model who are alive and progression-free after week 18 and so including patients who have already had disease progression in the calculation is not appropriate. Instead, the EAG considers that is more appropriate to estimate a proportion based on the number of patients who received olaparib out of the total number of patients who received durvalumab monotherapy or durvalumab with olaparib, which is [redacted]%.

More fundamentally, the recommendation the company is seeking for the pMMR subgroup. The company does not expect to receive a marketing authorisation for the SoC+D regimen for pMMR patients. However, the company is seeking a NICE recommendation for the pMMR population that is aligned to the marketing authorisation (SoC+D+O), but with flexibility in the recommendation for patients to continue durvalumab monotherapy in the maintenance phase if they are unable to initiate olaparib. However, the EAG is concerned that the company's base case, and the NICE recommendation the company are seeking for the pMMR population, does not appear to wholly align with the anticipated marketing authorisation.

Given the issues in the cost-effectiveness analysis that are currently unresolvable without further data from DUO-E, the EAG considers that committee may want to consider using a lower ICER threshold for this appraisal to mitigate the fundamental uncertainties in the analysis.

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8 Appendices

8.1 Summary of the EAG critique of the company's SLR

Table 66. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.1	**Appropriate**. The following databases were searched on 13 September 2023 for the original SLR with updates searches conducted on the 15 May 2024: • MEDLINE, including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print; • Embase; • Cochrane Database of Systematic Reviews (CDSR); • Cochrane Central Register of Controlled Trials (CENTRAL); and • Database of Abstracts of Reviews of Effects (DARE) – searched on 13th September 2023 only. In addition, the abstracts of the following oncology conferences were hand searched from 2021 to 2023: • European Society for Medical Oncology (ESMO) Congress; • ESMO-Gynaecological Cancers Congress (ESMO-Gyn); • American Society of Clinical Oncology (ASCO) Annual Meeting; • Society of Gynecologic Oncology (SGO) Annual Meeting; and • International Gynecologic Cancer Society (IGCS) Annual Meeting. Additionally, the following conference proceedings were searched for the SLR update: • The Professional Society for Health Economics and Outcomes Research (ISPOR) International Meeting; and • SGO Annual Meeting 2024. No updated searches were conducted for the ESMO, ASCO and the IGCS congresses as their 2024 meetings had not been held at the time of the update searches for the SLR. In addition, the following trial registries were searched: • ClinicalTrials.gov; and • World Health Organisation International Clinical Trials Registry Platform. The bibliographies of all relevant SLRs and network meta-analyses (NMAs) identified during the SLR were also hand-searched.
Search strategies	Appendix D.1.1	**Appropriate** Searches were broad and appropriately limited by disease stage (advanced and recurrent endometrial cancer) and study design (clinical trials).

		Limits were defined using both keywords and subject heading terms.
Inclusion criteria	Appendix D.1.2	**Appears appropriate** The EAG considers the inclusion criteria to align with the final scope issued by NICE and the decision problem addressed by the company in the CS. The EAG considers it unlikely any studies relevant to the decision problem have been missed although the EAG notes that studies were required to be published in English language.
Screening	Appendix D.1.2	**Appropriate** Title/abstract review and full-text review were completed by two independent reviewers, with a third reviewer resolving any discrepancies.
Data extraction	Appendix D.1.2	**Appears reasonable** Due to the inclusion of a large volume of studies, the company reported that included studies on hormonal therapy were deprioritised and not data extracted. The EAG notes that hormone therapy is not considered to be a comparator by the company. The EAG considers this to be reasonable. Data from the final set of included studies were extracted into a Microsoft Excel® data extraction sheet. Relevant data from each study were extracted by one reviewer and verified by a second independent reviewer. Any discrepancies were resolved by discussion or involvement of a third reviewer.
Tool for quality assessment of included study or studies	Appendix D.3, Table 10 of the CS	**Appropriate** The quality of included randomised controlled trials (RCTs) was assessed using the quality assessment tool developed by the University of York CRD.[59] The quality of included non-randomised interventional studies and observational studies was assessed using the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[60] The EAG performed its own assessment of risk of bias in DUO-E in Section 3.2.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review.

8.2 Baseline characteristics

Table 67. Baseline patient demographics and characteristics in the ITT population of DUO-E (reproduced from CS Table 6)

Characteristic	SoC (N=241)	SoC+D (N=238)	SoC+D+O (N=239)	Total (N=718)
Age (years)				
Mean (standard deviation [SD])	62.1 (10.36)	63.3 (9.82)	62.4 (9.90)	62.6 (10.03)
Median (min–max)	64.0 (31–85)	64.0 (22–84)	63.0 (27–86)	64.0 (22–86)
Age group, years, n (%)				
<65	124 (51.5)	122 (51.3)	135 (56.5)	381 (53.1)
≥65	117 (48.5)	116 (48.7)	104 (43.5)	337 (46.9)
Race, n (%)				
White	143 (59.3)	136 (57.1)	133 (55.6)	412 (57.4)
Asian	73 (30.3)	72 (30.3)	70 (29.3)	215 (29.9)
Black or African American	10 (4.1)	11 (4.6)	14 (5.9)	35 (4.9)
Other	10 (4.1)	8 (3.4)	12 (5.0)	30 (4.2)
American Indian or Alaska Native	0	6 (2.5)	6 (2.5)	12 (1.7)
Native Hawaiian or Other Pacific Islander	2 (0.8)	0	1 (0.4)	3 (0.4)
Not reported	3 (1.2)	5 (2.1)	3 (1.3)	11 (1.5)
Time from initial diagnosis to randomisation (weeks) – newly diagnosed patients				
N	114	113	112	339
Mean (SD)	8.8 (4.49)	9.8 (6.11)	10.1 (14.02)	9.6 (9.17)
Median (min–max)	7.7 (3–29)	8.3 (3–35)	7.6 (3–150)	7.9 (3–150)
Time from initial diagnosis to randomisation (weeks) – recurrent patients				
N	127	125	127	379
Mean (SD)	178.8 (149.43)	166.8 (112.17)	161.3 (131.60)	169.0 (131.90)
Median (min–max)	129.1 (8–804)	132.0 (7–556)	120.9 (24–909)	126.1 (7–909)
Time from recent progression to randomisation (weeks) – recurrent patients				
N	127	124	127	378
Mean (SD)	8.3 (9.98)	8.4 (8.10)	8.0 (5.86)	8.2 (8.13)
Median (min–max)	6.3 (0–87)	6.9 (0–59)	6.9 (1–34)	6.7 (0–87)

Source: DUO-E CSR;[26] Westin *et al.* (2023)[23]

Abbreviations: CS, company submission, ITT, intention to treat; SD, standard deviation; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 68. Disease characteristics in ITT population of DUO-E (reproduced from CS Table 7)

Characteristic/extent, n (%)	SoC (N=241)	SoC+D (N=238)	SoC+D+O (N=239)	Total (N=718)
ECOG performance status				

(0) Normal activity	156 (64.7)	156 (65.5)	166 (69.5)	478 (66.6)
(1) Restricted activity	85 (35.3)	81 (34.0)	73 (30.5)	239 (33.3)
(2) In bed ≤50% of the time	0	1 (0.4)	0	1 (0.1)
Histology type[a]				
Endometrioid	139 (57.7)	141 (59.2)	152 (63.6)	432 (60.2)
Serous	54 (22.4)	58 (24.4)	42 (17.6)	154 (21.4)
Carcinosarcoma	21 (8.7)	12 (5.0)	18 (7.5)	51 (7.1)
Mixed, epithelial	11 (4.6)	9 (3.8)	9 (3.8)	29 (4.0)
Other	6 (2.5)	9 (3.8)	5 (2.1)	20 (2.8)
Clear cell	7 (2.9)	4 (1.7)	8 (3.3)	19 (2.6)
Undifferentiated	3 (1.2)	4 (1.7)	5 (2.1)	12 (1.7)
Mucinous	0	1 (0.4)	0	1 (0.1)
FIGO stage[a]				
Stage I–II	77 (32)	78 (32.7)	73 (30.5)	228 (31.8)
Stage III	42 (17.4)	50 (21.0)	45 (18.8)	137 (19.1)
Stage IV	120 (49.8)	110 (46.2)	120 (50.2)	350 (48.7)
Missing	2 (0.8)	0	1 (0.4)	3 (0.4)
Recurrence of earlier cancer[b]				
Yes	127 (52.7)	125 (52.5)	127 (53.1)	379 (52.8)
No	114 (47.3)	113 (47.5)	112 (46.9)	339 (47.2)
Baseline overall disease classification				
Metastatic[c]	206 (85.5)	201 (84.5)	193 (80.8)	600 (83.6)
Locally advanced[d]	22 (9.1)	25 (10.5)	29 (12.1)	76 (10.6)
Missing	13 (5.4)	12 (5.0)	17 (7.1)	42 (5.8)
MMR status per central laboratory[b]				
Proficient	192 (79.7)	191 (80.3)	192 (80.3)	575 (80.1)
Deficient	49 (20.3)	46 (19.3)	46 (19.2)	141 (19.6)
Unknown	0	1 (0.4)	1 (0.4)	2 (0.3)
Debulking surgery history				
Yes	202 (83.8)	205 (86.1)	207 (86.6)	614 (85.5)
No	39 (16.2)	33 (13.9)	32 (13.4)	104 (14.5)
Unknown	0	0	0	0
Prior chemotherapy				
Yes	51 (21.2)	51 (21.4)	54 (22.6)	156 (21.7)
No	190 (78.8)	187 (78.6)	185 (77.4)	562 (78.3)
Biomarker, n (%)				
PD-L1[e]				
Positive	163 (67.6)	170 (71.4)	150 (62.8)	483 (67.3)
Negative	75 (31.1)	61 (25.6)	82 (34.3)	218 (30.4)

Unknown	3 (1.2)	7 (2.9)	7 (2.9)	17 (2.4)
HRRm				
HRRm	32 (13.3)	26 (10.9)	39 (16.3)	97 (13.5)
Non-HRRm	132 (54.8)	138 (58.0)	141 (59.0)	411 (57.2)
Unknown[f]	77 (32.0)	74 (31.1)	59 (24.7)	210 (29.2)

Footnotes: a Pathology-related disease characteristics were collected at the time of primary diagnosis of disease under investigation; b Mismatch repair status (proficient vs. deficient) was per central laboratory result using the FDA-cleared Class II Ventana MMR IHC panel (based on evaluation of tumour cells from a FFPE tumour tissue sample) and disease status (recurrent vs. newly diagnosed) was as collected on the electronic case report form (eCRF). Two patients with "unknown" MMR status per central laboratory were randomised as "deficient" per interactive voice response (IVRS) based on local testing. Two additional patients were mis-stratified in IVRS (one patient: dMMR per central laboratory was randomised as pMMR per IVRS; one patient: pMMR per central laboratory was randomised as dMMR per IVRS). c Metastatic disease – patient had any metastatic site of disease; d Locally advanced – patient had only locally advanced sites of disease. e The Ventana SP263 PD-L1 assay was used: PD-L1 positive samples were samples with PD-L1 expression with a tumour area positivity score ≥ 1%; PD-L1 negative samples were samples with PD-L1 expression with a tumour area positivity score < 1%; and PD-L1 unknown samples were samples with PD-L1 expression not available either due to a test fail (unevaluable sample or assay failure) or sample slide out of cut-slide stability; f Retrospective testing of HRRm status was by the FoundationOne® CDx tumour tissue next-generation sequencing (NGS) assay (FoundationOne® CDx-P170019/S017). Per data on file, the unknown samples included 26 patients with a failed FoundationOne® CDx assay test, 43 patients who withdrew consent before their sample was shipped for testing, and 141 patients whose HRRm testing could not be performed due to lack of sample availability (including all 36 patients enrolled from Mainland China where testing was not performed due to China Human Genetic Resources regulations).

Source: DUO-E CSR;[26] Westin et al. (2023)[23]

Abbreviations: CS, company submission, ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRRm, homologous recombination repair mutation; ITT, intention to treat; MMR, mismatch repair; PD-L1, programmed cell death ligand 1; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 69. Baseline demographics and patient characteristics in the dMMR and pMMR population (reproduced from Table 13 and Table 18 of the CS)

Characteristic	dMMR population		pMMR population	
	SoC (N=49)	SoC+D (N=46)	SoC (n=192)	SoC+D+O (n=191)
Age (years)				
Mean (SD)	62.4 (10.93)	62.7 (9.04)	62.1 (10.24)	62.7 (10.21)
Median (min–max)	63.0 (34–85)	63.0 (45–84)	64.0 (31–82)	64.0 (27–86)
Age group (years), n (%)				
<65	25 (51.0)	25 (54.3)	99 (51.6)	101 (52.9)
≥65	24 (49.0)	21 (45.7)	93 (48.4)	90 (47.1)
Race, n (%)				
Black or African American	2 (4.1)	0	8 (4.2)	13 (6.8)
American Indian or Alaska Native	0	1 (2.2)	2 (1.0)	1 (0.5)
Asian	15 (30.6)	14 (30.4)	0	6 (3.1)
White	30 (61.2)	29 (63.0)	58 (30.2)	57 (29.8)
Other	0	1 (2.2)	113 (58.9)	104 (54.5)

Not reported	2 (4.1)	1 (2.2)	10 (5.2)	9 (4.7)
Time from initial diagnosis to randomisation (weeks) – newly diagnosed patients				
N	24	20	90	90
Mean (SD)	8.7 (4.23)	8.5 (6.13)	8.8 (4.58)	8.6 (3.88)
Median (min–max)	7.6 (4–22)	6.9 (4–31)	7.7 (3–29)	7.5 (3–23)
Time from initial diagnosis to randomisation (weeks) – recurrent patients				
N	25	26	102	101
Mean (SD)	118.3 (130.35)	147.5 (107.67)	193.7 (150.63)	162.8 (133.19)
Median (min–max)	78.7 (25–543)	114.6 (7–395)	134.9 (8–804)	122.1 (27–909)
Time from recent progression to randomisation (weeks) – recurrent patients				
N	25	26	102	101
Mean (SD)	7.1 (5.28)	7.1 (4.49)	8.6 (10.82)	8.1 (6.28)
Median (min–max)	6.1 (2–28)	5.9 (0–18)	6.6 (0–87)	7.0 (1–34)

Footnote: Disease status (recurrent vs. newly diagnosed) is as collected on the eCRF.
Source: AstraZeneca. Data on File. 2023.[29]

Abbreviations: CS, company submission; dMMR, Mismatch repair deficient; ITT, intention to treat; pMMR, mismatch repair proficient; SD, standard deviation; SoC, standard of care; SoC+D, standard of care with durvalumab; SoC+D+O, standard of care with durvalumab and olaparib.

Table 70. Baseline characteristics of dMMR patients in RUBY and DUO-E trials

Characteristic		RUBY dMMR subgroup		DUO-E dMMR subgroup	
		Dostarlimab (N = 53)	Placebo (N = 65)	SoC (N=49)	SoC+D (N=46)
Median age (range) — yrs		61 (45–81)	66 (39–85)	63.0 (34–85)	63.0 (45–84)
≥65 Yr — no. (%)		23 (43)	35 (54)	24 (49.0)	21 (45.7)
Race	White	44 (83)	56 (86)	30 (61.2)	29 (63.0)
	Black	4 (8)	6 (9)	2 (4.1)	0
	Asian	2 (4)	0	15 (30.6)	14 (30.4)
	American Indian or Alaska Native	0	1 (2)	0	1 (2.2)
	Other	1 (2)	0	0	1 (2.2)
	Unknown or not reported	2 (4)	2 (3)	2 (4.1)	1 (2.2)
ECOG performance category — no./total no. (%)	0	28/52 (54)	39/65 (60)	29 (59.2)	23 (50.0)
	1	24/52 (46)	26/65 (40)	20 (40.8)	23 (50.0)

FIGO stage at diagnosis — no. (%)	I	18 (34)	22 (34)	14 (28.6)	15 (32.6)
	II	3 (6)	5 (8)	2 (4.1)	4 (8.7)
	III	14 (26)	20 (31)	8 (16.3)	10 (21.7)
	IV	14 (26)	15 (23)	24 (49.0)	17 (37.0)
	Unknown	4 (8)	3 (5)	1 (2.0)	0
Recurrent disease n (%)		27 (51)	32 (49)	25 (51.0)	26 (56.5)
Histology type	Endometrioid	44 (83)	56 (86)	41 (83.7)	33 (71.7)

Abbreviations: CS, company submission; dMMR, Mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; SoC, standard of care; SoC+D, standard of care with durvalumab.

8.3 Subgroup results for DUO-E

As detailed in Section 2.3, the EAG is concerned that the dMMR and pMMR populations comprise subgroups of DUO-E and therefore the EAG recommends further subgroup analyses within these populations using the DUO-E data are interpreted with caution. The EAG notes that the company has provided summary forest plots for a range of subgroup analyses conducted in the ITT population for PFS (company response to clarification questions Figure 4 and Figure 5). In addition, the company has provided forest plots for a range of subgroup analyses in the dMMR population for SoC+D compared with SoC and the pMMR population for SoC+D+O for PFS (company response to clarification questions Figure 1).

For the ITT population, across all pre-specified subgroup analyses, HR point estimates (where reported) for PFS were below one and favoured the SoC+D arm for the comparison of SoC+D vs SoC (company response to clarification questions Figure 4) and similarly for the comparison of SoC+D+O arm vs SoC, treatment with SoC+D+O was consistently favoured. The company reported that for the comparison of SoC+D vs SoC, the global interaction test indicated (in addition to the MMR status results) a quantitative interaction involving region, favouring SoC+D with a greater benefit in PFS for patients in the rest of world (RoW) region compared with the Asia region. The company considered this likely to be related to differences in the treatment pathway in Asia compared with the RoW rather than any specific demographic characteristics that would be relevant to the eligible population in UK clinical practice.

The EAG notes that subgroup analyses based on PD-L1 status were requested in the NICE final scope and across both comparisons in the ITT population (SoC+D vs SoC and SoC+D+O vs SoC), a greater PFS benefit was observed for patients with PD-L1+ expression compared to PD-L1 expression. However, the company highlighted that PD-L1 status does not inform current prescribing decisions

and is not routinely tested for in advanced or recurrent EC. Subgroup results for subgroups within the pMMR and dMMR populations can be found in the company response to clarification questions Figure 1; however, the EAG considers these results to be highly uncertain.

8.4 Price sources for treatments included in the confidential appendix

Table 71. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Lenvatinib	Simple PAS
Pembrolizumab	Simple PAS

Abbreviations: PAS, patient access scheme.

Single Technology Appraisal

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

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 16 December 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 ITC versus dostarlimab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, table 2, page 19-20 **And section 3.4, page 70-71** **And section 3.5, page 74** **And section 4.2.3.5, page 90** In their report the EAG discuss an ITC which they have conducted for the DUO-E dMMR SoC+D regimen versus the SoC+dostarlimab regimen in the RUBY-1 trial. The EAG make several statements with regards to this ITC including: • "Limited baseline characteristics were available for RUBY but based on those available the EAG considers them to be broadly comparable to	The company preference is that all mention of the ITC between DUO-E and RUBY-1 should be removed from the report given that it is not in scope for this appraisal and given the fundamental limitations of the EAG analysis. This analysis should have no bearing on decision making and could mislead the committee. If the EAG seek to retain the references to the ITC, then the company suggest that the limitations of this analysis should be more clearly outlined. Suggested amendments include: • Page 71: "Limited baseline characteristics were available for RUBY but based on those available the EAG considers ~~them to be broadly comparable to DUO- E with the exception of race~~ that a number of factors including region (Asia versus	**Baseline characteristics** There are several differences in the baseline characteristics of the DUO-E trial and the RUBY-1 trial which are not mentioned in the EAG report, including: • The relevant patient population from the DUO-E trial is patients with dMMR disease, whereas the approved RUBY-1 population is patients with dMMR and/or MSI-H positive disease. Although there is correlation and a high degree of overlap between these biomarkers, they are not completely equivalent. • Analysis of the DUO-E trial as well as other trials in advanced/recurrent EC trials indicate that there	Thank you for highlighting this inaccuracy. The EAG has amended the text in the EAG report to include details of the additional limitations raised by the company. However, as the company has not provided its "internal analyses adjusting for these variables" for assessment by the EAG, the EAG cannot comment on their robustness or if the company's statement that these "would have a significant impact on the results of any

DUO- E with the exception of race". • "Hazard ratios favour treatment with dostarlimab". • "Dostarlimab is not considered to be a relevant comparator for this appraisal as it is currently only available via the CDF but the EAG presents these results to give context to the assumptions the company has made based on TA963 and also to aid committee in consistency of decision-making".	rest-of-world) and biomarker status (dMMR versus dMMR and/or MSI-high) may be relevant differences. • Page 71: the EAG notes that for both PFS and OS the hazard ratios based on an unadjusted ITC favour treatment with dostarlimab albeit the 95% confidence intervals cross 1. However, the company highlight that exploratory internal analysis indicate that adjusting for patient baseline characteristics would have a significant impact on the results of any such ITC and would not support this conclusion. • Page 20: "In summary, the hazard ratios for both PFS and OS based on an unadjusted ITC favour treatment with dostarlimab, albeit the 95% confidence intervals cross 1. However, the EAG considers the results should be interpreted with caution due to the differences in baseline	may be important treatment effect modifiers in this setting (including region – Asia versus rest-of-world). This has been validated by AZ medical and clinical experts. Internal AZ analyses indicate that adjusting for these variables would have a significant impact on the results of any such ITC and would call into question the EAG conclusion that "hazard ratios favour treatment with dostarlimab". Given that this comparison was not requested as part of the final scope for this appraisal and given that the EAG ITC was not requested during clarification questions, the company has not had an opportunity to provide a more robust adjusted ITC. The company therefore suggest that ideally this ITC should be removed from the EAG report entirely to avoid unduly biasing committee decision-making, or at least that the significant	such ITC" is appropriate.

		characteristics and subgroup nature of the data used in the analyses, including potential significant impacts of region (Asia versus rest-of-world) and biomarker status (dMMR versus dMMR and/or MSI-high). The company highlight that exploratory internal analysis indicate that adjusting for such patient baseline characteristics would have a significant impact on the results of any such ITC and would not support this conclusion.	limitations of the EAG analysis (and resulting conclusions) should receive much greater emphasis within the report. **NICE methods and processes** Although not a factual inaccuracy, the company would also like to highlight that the inclusion of the EAG ITC deviates from the final scope for this appraisal and therefore from standard NICE methods and processes. As acknowledged by the EAG, dostarlimab was not included in the final scope for this appraisal as it is currently reimbursed via the CDF. This informed the company decision to not provide a robust adjusted ITC as part of their submission. Although the EAG state that their report simply presents these results "to give context to the assumptions the company has made", it must be acknowledged that they are not likely to be interpreted in this	

		simplistic light (either by the committee or by clinicians and members of the public once published). By setting the precedent that additional ITCs outside of the agreed appraisal scope can be brought into the NICE process at this stage (without prior consultation with the company) creates difficulties for companies when interpreting the NICE final scope. Companies may be incentivised to provided un-requested ITCs as part of their submissions to "pre-empt" such analyses from being conducted by the EAG, which would create unnecessary complexity in company submissions, and which would undermine the NICE process. The EAG indicate that part of the rationale for conducting this ITC was because the company has referenced committee discussions from the TA963 appraisal to validate long-term survival validation in their economic model. However the	

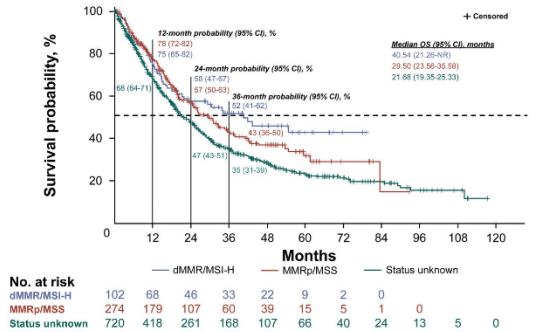
		company would like to reiterate that it is standard practice to review precedent from prior appraisals in similar disease settings to inform survival extrapolations, and that a full ITC is not usually required in each instance where this is done. Therefore, the company reiterate that the inclusion of this ITC in the EAG report is inappropriate both due to the inadequate methodology outlined above, but also due to misalignment with standard NICE methods and processes.	

Issue 2 Uncertainty relating to data immaturity in DUO-E

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, table 2, page 19-20	The company propose that it would be more appropriate to describe the OS data from DUO-E simply as "immature" (i.e. removing the word	Although the company acknowledge that the OS data from the trial is immature, they would like to highlight that the degree of immaturity is not	Not a factual inaccuracy. No change required.

and section 3.3.1.2, page 57 **and section 3.3.2.2, page 61** **and section 3.5, page 71** **and section 4.2.3, page 81** **and section 4.2.3.5, page 88** **and section 4.2.3.9, page 94** **and section 6.4, page 142** Throughout the EAG report the OS data from DUO-E is described as "extremely immature".	"extremely" throughout the EAG report).	particularly unusual or exceptional for a novel treatment in this therapeutic area. The EAG report acknowledges on page 90 that the OS maturity in the dMMR subgroup in DUO-E was similar to that seen in the RUBY-1 trial at the time of its appraisal in TA963. However, throughout the TA963 appraisal documentation OS was described as "immature" rather than "extremely immature". Adopting similar phrasing for the DUO-E and RUBY-1 data is important to avoid unduly influencing committee and clinical perceptions about the relative uncertainty associated with the data for each therapy.	
Section 1.3, table 2, page 19-20 **and section 4.2.3, page 81**	The company propose that this statement is removed throughout the EAG report.	The company understands that as part of the NICE methods and processes, the choice of willingness-to-pay threshold should be made by the committee after a full discussion with all relevant stakeholders at the	Not a factual inaccuracy. No change required.

and section 6.4, page 143 In several places throughout the EAG report, the EAG recommend that “in order to mitigate the fundamental uncertainties in the analysis, the committee may want to consider applying a lower ICER threshold for decision making.”		appraisal committee meeting (as outlined in section 6.1.3 of the NICE methods and processes) and falls outside of the remit of the EAG. Furthermore, as outlined in section 6.2.27 of the NICE methods and processes, the committee may also wish to consider broader factors to inform their choice of threshold, including precedent from prior committee decisions in related appraisals with similar degrees of uncertainty (e.g., TA963 may be considered relevant in this case). Therefore, the company considers it inappropriate for the EAG to make this recommendation, particularly at such an early stage of the appraisal and before broader stakeholder views have been obtained on the true magnitude of decision uncertainty, and this risks unduly biasing committee decision-making.	
Section 4.2.3.9, page 94 The EAG report states that “the estimates from	The company suggest that the EAG report should be amended to either include the original figures outlined in	The company would like to highlight that the figures reported in the company submission come from the	Thank you for clarifying where the data were sourced from in the publication. The

Chase et al. presented in Table 48 of the CS do not match up with the estimates in the publication and the EAG presents the correct data in Table 33”	the company submission (and deleting this phrase entirely). Or alternatively if the EAG would prefer to rely on the values from the table rather than the KM curves, then the EAG report should outline the difference in sources used by the company and the EAG, and any rationale to support their preferred values. The sentence on page 94 could be amended to: • “the EAG highlights that the company submission presented values from the Chase et al, publication based on the Kaplan-Meier plot, whereas the EAG have relied on values presented in data tables within that publication. There are minor differences in the reported values, which may relate to the fact that the KM plot accounts for censoring.”	Chase et al publication Figure 1 for the pMMR subgroup:  1L, first line; dMMR/MSI-H, mismatch repair–deficient/microsatellite instability–high; MMRp/MSS, mismatch repair–proficient/microsatellite stable; OS, overall survival. We can see that the EAG estimates came from Table 1 of the publication, reporting median OS at each timepoint. The company hypothesise that the differences in the values presented in the KM figure and the table could relate to the fact that the KM figure accounts for censoring. As such, the company maintain that the most appropriate figures to use are those from the KM plot.	report has been amended back to the data presented in the CS.

Issue 3 Bias in the clinical outcomes of DUO-E

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Section 1.3, table 3, page 21 The EAG report states that "it is likely that the clinical efficacy of SoC+D and SoC+D+O are overestimated in the economic model and as such the ICER is potentially underestimated."	The company suggest that the word "likely" should be removed from all instances citing potential bias as a result of IO re-challenge that occurred within the DUO-E trial but which does not occur in UK clinical practice. Furthermore, the company recommend that additional text is included in table 3 of the EAG to present a more balanced view of this issues, such as: • The EAG is therefore concerned that the OS estimates from DUO-E may overestimate the clinical efficacy of SoC+D and SoC+D+O when compared with SoC. However, the EAG also acknowledge that there is limited evidence that that IO re-challenge is an efficacious treatment strategy in EC, particularly for patients who progress while receiving first-line	In their report the EAG cite concern that the use of IO re-challenge in the DUO-E trial (but not in UK clinical practice) could bias the clinical outcomes of the study. However, they do not mention the rationale provided by the company in section B.1.3.4 of their submission (and validated by UK clinical experts) that: • Current reimbursement criteria which preclude the routine use of IO rechallenge reflect the insufficient clinical data surrounding the efficacy of this strategy in EC. • In particular, there is a lack of data regarding which patients could benefit from this approach, and it may	Thank you for highlighting this inaccuracy. The EAG has amended the text in Table 3 of the report relating to the clinical efficacy data in the economic model to 'maybe overestimated'.

	immunotherapy (rather than those who responded well to their initial IO, and who had a certain minimum treatment-free interval before relapse).	only be suitable for some patients who responded well to their initial IO, and who had a certain minimum treatment-free interval before relapse (as opposed to patients who progress while receiving first-line immunotherapy). This is supported by studies in other cancer types (such as NSCLC and melanoma). Although the company acknowledge that given this limited evidence-base it is not possible to rule out a potential bias in DUO-E results due to IO re-challenge, the converse is also true, and there is insufficient evidence to say that this is in fact “likely”. Therefore, the company recommend that this phrasing is removed, and that the uncertainty on this topic is presented in a more balanced way.	

Issue 4 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, table 4, page 22 **And section 4.2.2, page 79** **And section 4.2.3.1, page 83** **And section4.2.4, page 96** **and section 6.4, page 142** Throughout the EAG report the EAG refer to the company assumption around treatment duration as a "treatment "cap".	The company suggest that the phrasing of treatment "cap" should be replaced with "maximum treatment duration" throughout the report.	The phrasing of treatment "cap" implies that patients would not be eligible to continue receiving the treatment after the designated timepoint (i.e., that access would be formally restricted to this duration). However, this does not reflect the company intention or expectation. Instead, the maximum treatment duration imposed in the economic model is simply intended to act as a reflection of organic prescribing behaviour which is expected to be seen when the regimen is used in a real-world UK setting rather than in a clinical trial.	Not a factual inaccuracy. No change required.

Section 1.3, table 4, page 22 **And section 4.2.4.3, page 100** Several sections of the EAG report conclude that "more mature TTD data from DUO-E will resolve any uncertainties in the extrapolation of TTD".	The company suggest that this statement should be modified to: "More mature TTD data from DUO-E alongside real-world data on the use of the DUO-E regimen in UK clinical practice (e.g., SACT data) will resolve any uncertainties in the extrapolation of TTD.	Given that the protocol of the DUO-E trial required that treatment should continue until radiologic disease progression, unacceptable toxicity, or other discontinuation criteria were met, it is unlikely that data from the DUO-E trial itself will ever support the company assumption that in real-world UK practice, patients would not be treated indefinitely. This is because clinicians in a clinical trial setting are relatively bound by the trial protocol and may not feel able to make more nuanced treatment decisions based on their broader clinical experience. Therefore, the company highlight that the most useful source of evidence to resolve uncertainty relating to TTD would be UK real world data, such as SACT data.	Not a factual inaccuracy. No change required.

Issue 5 Proportion of patients initiating olaparib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, table 5, page 22-23 In the summary table, the EAG report states that "The company also explained that of the SoC+D+O patients that received some form of maintenance treatment, [redacted] continued durvalumab monotherapy".	Suggest amending to: "The company also explained that a small proportion of pMMR patients in the SoC+D+O arm of DUO-E received durvalumab as monotherapy during the maintenance phase of the trial ([redacted] of all randomised patients)."	The phrasing used by the EAG in the summary box is not entirely clear and could be interpreted to mean that the denominator used to calculate the [redacted]% is the SoC+D+O patients who received some form of maintenance therapy. Instead, the denominator ought to be all randomised patients in the SoC+D+O arm. This is better reflected on page 44 of the EAG report, so the company suggest that similar phrasing is also used in the summary table.	Thank you for highlighting this inaccuracy. The EAG report has been updated accordingly.
Section 1.3, table 5, page 22-23 **And section 4.2.6.2, page 109-110**	Suggest amending to: "the company does not expect there to be any wording within the SmPC that excludes the use of durvalumab	The phrasing used by the EAG does not make it clear that for pMMR patients the treatment intention at the point of treatment initiation would be that such	Thank you for highlighting this inaccuracy. The EAG

and section 6.4, page 143 With regards to the expected marketing authorisation for the DUO-E regimen, the EAG report states that "the company does not expect there to be any wording within the SmPC that excludes the use of durvalumab monotherapy for patients ineligible to receive olaparib in the maintenance phase of treatment.	monotherapy in the maintenance setting for patients who were initially intended to receive the SoC+D+O regimen at the point of treatment initiation, but who subsequently become ineligible to receive olaparib in the maintenance phase of treatment.	patients should receive the full SoC+D+O regimen. Such patients would only receive durvalumab monotherapy in the maintenance setting if they subsequently become ineligible for the olaparib component of the regimen after initiating the treatment regimen (i.e. during the chemotherapy phase).	report has been updated accordingly.
Section 1.3, table 5, page 22-23 **And section 6.4, page 143** The EAG states that "The EAG considers that the company's base case assumption of the proportion of patients initiating olaparib is an underestimate as olaparib	The company believe there is a fundamental flaw in the EAGs methodology in calculating the proportion of patients initiating olaparib treatment. The company suggest that it is not appropriate to apply the [redacted]% to all patients within the olaparib arm of the model. Ideally the company suggest that the EAG should revert to the proportion used in the company base	The EAG have calculated the proportion of patients who should receive olaparib in the model as [redacted]%. This proportion ([redacted]%) is estimated using a subset of the clinical trial data; the proportion of people who have received any treatment in the maintenance phase, which was [redacted] patients ([redacted] olaparib + durvalumab, and [redacted] durvalumab only), of the 191 patients randomized.	The EAG reiterates that the marketing authorisation for the pMMR population is induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC+D+O). As highlighted by the company in their CQ response, the company

treatment acquisition costs are only applied to patients in the model who are alive and progression-free after week 18 and so including patients who have already had disease progression in the calculation is not appropriate."	case ([redacted]%, applied to all patients within the olaparib arm). Alternatively, if the EAG insist on using [redacted]%, they would need to ensure that it is only applied to patients who are progression free at week 18 in the model (although such an approach would also have limitations compared to the company base case). In either case the EAG statement on pages 22 and 143 ought to be deleted and replaced with an alternative statement (which will be dependent on which of the two above options that the EAG which to pursue).	However, the EAG has subsequently applied this [redacted]% to *all* patients in the SoC+D+O arm of the model, rather than just those who are alive and progression-free at 18 weeks. Specifically, the EAG have used the TDT curve specific to patients initiating olaparib (i.e. N=[redacted], [redacted]% of 191 patients in the SoC+D+O arm) and applied this to every patient in the model for SoC+D+O, multiplied by [redacted]%. It is not appropriate to apply this [redacted]% to all patients in the arm, since those experiencing progression prior to the maintenance phase will not have the opportunity to receive any treatment, and therefore will not contribute to this calculation. If the EAG insist on using this proportion, they would need to ensure that it is only applied to patients who are progression free at week 18 in the model (although such an approach	are seeking a recommendation for that aligns with the marketing authorisation. The company is correct that TTD for olaparib does exceed PFS from week 18-77 (representing just over a year of treatment). As such, the EAG's approach may represent a more accurate reflection of the company's marketing authorisation than the company's base case approach. With regards to the company's assertion about the EAG's approach, the EAG did not change the company's base case calculation, but instead changed the input value. As such, the approach to applying the proportion on

		would also have limitations compared to the company base case). The EAG approach creates logical inconsistencies and implausible results within the model: • The EAG calculate that [redacted]% of patients will receive olaparib at week 18, despite only [redacted]% of patients occupying the PF health state at this point of the model (an implausible scenario as per the trial protocol and treatment label). • Therefore, the EAG instead assume that 100% of patients occupying the PF state receive olaparib (since TDT is limited by PFS). This assumption occurs between week 18 and week 77 in the model, since the EAG calculation	olaparib is the same for both the company's and EAG's base case. It is not applied to all patients of the SoC+D+O arm, but only to those patients who are alive and on olaparib maintenance treatment after 18 weeks (as per the company's base case approach). The TTD curve cannot exceed the PFS curve, so the proportion on olaparib (and thus treatment costs for olaparib) are not applied to patients in the progression health state.

		for TDT provides a value in excess of the proportion of patients who are progression-free at these time points. This calculation is a direct contradiction to the EAG's acknowledgement that not all patients in the maintenance phase receive olaparib. The company therefore reiterate that the reporting of this analysis is highly misleading, and well as being methodologically inappropriate and a direct contradiction to the empirical evidence observed in the DUO-E trial.	

Issue 6 Estimation of newly progressed patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, table 6, page 23-24	Suggest amendment to:	The statement made by the EAG does not give enough	Not a factual inaccuracy. No change required.

And section 4.2.6.6, page 117-120 The EAG report states that "The EAG acknowledges that its calculation has limitations, in that the OS adjustment includes both patients dying from the PF and PD health state, but it is equivalent to the company's assumption that a fixed proportion of deaths will be from the PF health state. As such, both approaches rely on an implicit assumption around deaths from the PF health state, but the EAG's approach is a useful alternative scenario to explore as it allows changes over time."	"The EAG acknowledges that its calculation has limitations, in that the OS adjustment includes both patients dying from the PF and PD health state, as well as the fact that the equation generates negative estimates of progression events at certain timepoints, and overestimates the proportion of fatal progression events versus what was observed in the DUO-E trial. ~~but it is equivalent to the company's assumption that a fixed proportion of deaths will be from the PF health state.~~ ~~As such,~~ Both the company and EAG approaches rely on an implicit assumption around deaths from the PF health state, but the EAG's approach is a useful alternative scenario to explore as it allows changes over time."	weight to the significant drawbacks of their suggested formula, as outlined by the company in their response to clarification question B4. The company highlighted in their response that: • The equation estimates a negative number of progression events between months 55 and 294 in the base case analysis (dMMR, SoC trace). • When the equation is used for the dMMR population, the model estimates that, across both treatment arms, 36–44% of progression events are deaths at 30 months (similar to the DUO-E trial period follow-up). This is far higher than observed trial data ([redacted] of	Additionally, the EAG's calculation in the model has a limit such that values cannot fall below 0.

		progression events are deaths). Therefore, the company suggest that these limitations are more clearly outlined in the EAG report.	

Issue 7 Patient access scheme

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Multiple locations Throughout the EAG report durvalumab and olaparib are described as having "patient access schemes (PAS)" in place.	All instances of "patient access scheme" or "PAS" should be replaced by the terminology "commercial access agreement" or "CAA".	The nature of the commercial agreement in place for both olaparib and durvalumab is such that the appropriate terminology is "commercial access agreement" rather than "patient access scheme".	Thank you for highlighting the correction. The EAG report has been updated accordingly.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Multiple locations Throughout the EAG report, phrasing relating to the expected MHRA marketing authorisation has been redacted (as the MHRA approval had not yet been granted)	MHRA approval was received on the 9th of December for both olaparib and durvalumab for the DUO-E indication. Therefore, all phrasing throughout the EAG report relating to the expected marketing authorisation can now be un-redacted. Publicly available SmPCs are expected to be updated imminently.	All phrasing relating to the expected marketing authorisation for both products can now be unredacted. When describing the approved marketing authorisation the following phrasing should be used: **LYNPARZA** Lynparza in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in	Thank you for the update. The EAG report has been unredacted accordingly.

		combination with carboplatin and paclitaxel. **IMFINZI** IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by treatment with: • IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) • IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).	