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:

1. **Draft Guidance Document (DG)** as issued to consultees and commentators

2. **Comments on the Draft Guidance from** AstraZeneca

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. Peaches Womb Cancer Trust

4. **Comments on the Draft Guidance Document from experts:**
   a. Dr Gemma Eminowicz – clinical expert, nominated by NICE
   b. Professor Peter Clark – Cancer Drugs Fund Clinical Lead

5. **External Assessment Group critique of company response to the DG**

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

Draft guidance consultation

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for untreated advanced or recurrent endometrial cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using durvalumab with platinum-based chemotherapy, then with or without olaparib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using durvalumab with platinum-based chemotherapy, then with or without olaparib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 16 April 2025
- Second evaluation committee meeting: 06 May 2025
- Details of membership of the evaluation committee are given in section 5

1 Recommendations

1.1 Durvalumab with platinum-based chemotherapy, then maintenance durvalumab monotherapy, can be used as an option for untreated primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR) in adults who can have systemic treatment.

It should be stopped after 3 years, or earlier if there is disease progression or unacceptable toxicity.

Durvalumab with platinum-based chemotherapy, then maintenance durvalumab monotherapy, can be used if the company provides it according to the commercial arrangement (see section 2).

1.2 Durvalumab with platinum-based chemotherapy, then maintenance durvalumab plus olaparib, should not be used for untreated primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) in adults who can have systemic treatment.

1.3 These recommendations are not intended to affect treatment with durvalumab with platinum-based chemotherapy, then with or without olaparib, that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

dMMR endometrial cancer

Durvalumab with platinum-based chemotherapy, then maintenance durvalumab monotherapy, must be funded in the NHS in England for untreated primary advanced or recurrent endometrial cancer that is dMMR in adults who can have

systemic treatment, if it is considered the most suitable treatment option. Durvalumab with platinum-based chemotherapy, then maintenance durvalumab monotherapy, must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that durvalumab with platinum-based chemotherapy, then maintenance durvalumab monotherapy provides benefits and value for money in adults whose cancer is dMMR, so it can be used routinely across the NHS.

pMMR endometrial cancer

Durvalumab with platinum-based chemotherapy, then maintenance durvalumab plus olaparib, is not required to be funded in the NHS in England for untreated primary advanced or recurrent endometrial cancer that is pMMR in adults who can have systemic treatment. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that durvalumab with platinum-based chemotherapy, then maintenance durvalumab plus olaparib, offers value for money in adults whose cancer is pMMR.

Why the committee made these recommendations

Usual treatment for untreated advanced or recurrent endometrial cancer is platinum-based chemotherapy (from here just chemotherapy) then routine surveillance. This evaluation looked at dMMR and pMMR subpopulations.

For the dMMR subgroup, clinical trial evidence shows that durvalumab with chemotherapy and then maintenance durvalumab alone gives people with endometrial cancer longer before their condition gets worse than just chemotherapy then routine surveillance. Evidence suggests that it also increases how long people

live, but the long-term benefits are uncertain because the study is ongoing and has only followed people for a short time.

In the dMMR subgroup, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So durvalumab with chemotherapy then maintenance durvalumab alone can be used in this group.

In this subgroup, durvalumab should be stopped after 3 years, or earlier if the condition gets worse or there are unacceptable side effects. This reflects how other immunotherapies like durvalumab are used in clinical practice, and how clinical experts said they would use durvalumab.

In the pMMR subgroup, clinical trial evidence shows that durvalumab with chemotherapy then maintenance durvalumab plus olaparib gives people with endometrial cancer longer before their condition gets worse than just chemotherapy then routine surveillance. Evidence suggests that it may also increase how long people live, but the long-term benefits are uncertain because the study is ongoing and has only followed people for a short time.

In the pMMR subgroup, the cost-effectiveness estimates are substantially above the range that NICE considers an acceptable use of NHS resources. So durvalumab with platinum-based chemotherapy then maintenance durvalumab plus olaparib should not be used in this subgroup.

2 Information about durvalumab with platinum-based chemotherapy, then with or without olaparib

Marketing authorisation indication

2.1 Durvalumab (Imfinzi, AstraZeneca) in combination with platinum-based chemotherapy is indicated for ‘the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:

- durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
- durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR)'.

2.2 Olaparib (Lynparza, AstraZeneca) 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 combination with carboplatin and paclitaxel'.

Dosage in the marketing authorisation

2.2 The dosage schedules are available in the summary of product characteristics for durvalumab and the summary of product characteristics for olaparib.

Price

2.4 The list price of durvalumab is £592 for a 120-mg vial and £2,466 for a 500-mg vial (excluding VAT; BNF online accessed March 2025).

2.5 The list price of olaparib is £2,317.50 per 56-pack of 100-mg and 150-mg tablets (excluding VAT; BNF online accessed March 2025).

2.6 The company has confidential commercial access agreements with NHS England. This makes durvalumab and olaparib available to the NHS with a discount, and the discount for olaparib would also have applied to this indication if durvalumab with platinum-based chemotherapy, then durvalumab plus olaparib had been recommended. The size of the discounts are commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Endometrial cancer starts in the lining of the uterus. Symptoms can include vaginal bleeding, pelvic pain, unintended weight loss, nausea and fatigue. People with advanced or recurrent endometrial cancer (meaning it has spread beyond the uterus or returned after treatment) have a poor prognosis. Of this group, only 15% diagnosed at stage 4 live for 5 or more years. The patient experts explained that living with advanced endometrial cancer can also impact on family and carers, and that symptoms can affect the ability to live normally. The patient experts also explained how the possibility of recurrence can cause significant anxiety. The committee concluded that endometrial cancer has a significant effect on life expectancy and quality of life.

Mismatch repair status

3.2 Mismatch repair (MMR) is a system used by cells to correct the mutations in DNA that can cause cancer. Endometrial cancer can be MMR deficient (dMMR; around 25% to 30% of cases) or MMR proficient (pMMR; around 70% to 75% of cases). dMMR tumours are more likely to have high levels of mutation. The higher levels of mutation in dMMR tumours lead to more abnormal proteins being produced, which are recognised by the immune system. dMMR endometrial cancer generally has a better prognosis than pMMR endometrial cancer. The clinical experts explained that dMMR endometrial cancer tends to respond better to immunotherapy, while pMMR endometrial cancer is very heterogeneous. Some pMMR cancers can respond well to treatment while others have particularly poor

prognoses. The clinical experts stated that around a third of people with pMMR cancer have mutations of the tumour protein p53. This is associated with more aggressive endometrial cancers that may benefit more from a first-line PARP inhibitor (olaparib). The committee concluded that, on the whole, dMMR endometrial cancer has a better prognosis and response to immunotherapy than pMMR endometrial cancer. It acknowledged that the presence of p53-mutated disease is an important prognostic indicator in the pMMR subgroup.

Clinical management

3.3 For people with untreated advanced or recurrent endometrial cancer, the only routinely available first-line treatment option is platinum-based chemotherapy followed by routine surveillance. The patient expert explained that going through current treatment has significant psychological impacts because people with endometrial cancer know that outcomes from chemotherapy are poor. Immunotherapy is currently only routinely available as a second-line treatment (dostarlimab is available at first line for dMMR cancer, but only through the Cancer Drugs Fund). The patient expert explained that access to immunotherapy has had a significant impact on life expectancy and quality of life. The patient and clinical experts also highlighted the need for immunotherapy earlier in the treatment pathway, to avoid the need for subsequent treatments or surgery. This is because people's health has often declined at second-line stage and treatments may be harder to tolerate. This means some people are not fit enough for immunotherapy by the time they need a second-line treatment – the clinical expert stated that the attrition rate between first- and second-line treatment is around one third. The patient expert highlighted that this unmet need is particularly high in people with pMMR endometrial cancer. The clinical experts explained that single-agent immunotherapies are well tolerated in all age groups. They added that people who are well enough for chemotherapy would likely be well enough for an add-on immunotherapy, such as durvalumab, and a PARP

inhibitor, such as olaparib (with some exceptions in autoimmune disease). The clinical experts noted that the combination of immunotherapy and a PARP inhibitor as maintenance treatment may cause increased fatigue. But, the patient expert indicated that people would be willing to accept the possible side effects of having these 2 treatments together if there was hope of better outcomes. The committee concluded that platinum-based chemotherapy (specifically, carboplatin and paclitaxel) followed by routine surveillance was the appropriate comparator. It also concluded that there is an unmet need for more effective first-line treatments for people with untreated advanced or recurrent endometrial cancer.

Clinical effectiveness

DUO-E

3.4 DUO-E is an ongoing multicentre, randomised, double-blind, phase 3 trial of durvalumab with paclitaxel and carboplatin then maintenance durvalumab with or without olaparib. The trial included people with untreated advanced (stage 3 or 4) or recurrent endometrial cancer and was split into 3 arms:

- durvalumab plus first-line carboplatin and paclitaxel, then maintenance durvalumab plus olaparib (standard care plus durvalumab and olaparib; n=239)
- durvalumab plus first-line carboplatin and paclitaxel, then maintenance durvalumab plus placebo (standard care plus durvalumab; n=238)
- first-line carboplatin and paclitaxel plus placebo, then placebo maintenance (standard care; n=241).

Treatment continued until disease progression or unacceptable toxicity. Initial treatment was for 18 weeks followed by maintenance treatment. The trial stratified people based on MMR status. But, the EAG noted that the trial population was not randomised specifically to the interventions indicated in the marketing authorisation. That is, to standard care plus

durvalumab in the dMMR population, or standard care plus durvalumab plus olaparib in the pMMR population. So the clinical evidence for this appraisal came from an interim analysis of reported subgroup data for pMMR and dMMR disease from the relevant arms of the trial. The primary outcome was progression-free survival (PFS), with overall survival (OS) as a key secondary outcome. In people with dMMR endometrial cancer, standard care plus durvalumab (n=46) improved PFS (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.22 to 0.80) and OS (HR 0.34, 95% CI 0.13 to 0.79) compared with standard care alone (n=49). In people with pMMR endometrial cancer, standard care plus durvalumab plus olaparib (n=191) improved PFS (HR 0.57, 95% CI 0.44 to 0.73) compared with standard care alone (n=191). But the hazard ratio for OS in this subgroup included 1 (HR 0.69, 95% CI 0.47 to 1.00) and was not statistically significant. The committee concluded that standard care plus durvalumab and standard care plus durvalumab plus olaparib improved PFS in untreated advanced or recurrent dMMR and pMMR endometrial cancer, respectively. It also concluded that standard care plus durvalumab prolonged OS in dMMR endometrial cancer. But it was less certain about how effective standard care plus durvalumab plus olaparib was in prolonging OS in the pMMR subgroup because the hazard ratio was not statistically significant.

Immaturity of DUO-E data

3.5 Follow up in the interim analysis of the DUO-E trial was short. The median follow-up period was 12.6 months in the standard care arm and 15.4 months in the 2 intervention arms. In the primary data cut used to inform clinical efficacy, the data was very immature for the dMMR and pMMR subgroups. In the dMMR subgroup, data maturity for the standard care plus durvalumab arm was 32.6% (15 of 46) for PFS and 15.2% (7 of 46) for OS. In the pMMR subgroup, data maturity for the standard care plus durvalumab plus olaparib arm was 56.5% (108 of 191) for PFS and 24.1% (46 of 191) for OS. The company stated that it was expecting a further

interim analysis in the fourth quarter of 2025, with the final data cut expected in 2026. It also explained that it validated its long-term survival estimates using the committee discussion in the NICE technology appraisal guidance on dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (from here referred to as TA963). But the EAG highlighted that the committee in TA963 had also noted uncertainty in the clinical results and did not agree on a preferred approach for modelling OS. The committee concluded that the short follow up and immaturity of the DUO-E results means that the clinical-effectiveness data is uncertain.

Subsequent immunotherapies

3.6 In DUO-E, a proportion of people having subsequent treatment after disease progression had immunotherapies (the proportions of subsequent treatment use are considered confidential by the company so cannot be reported here). The EAG highlighted that using immunotherapy as a subsequent treatment in the intervention arms does not reflect UK clinical practice. This is because a second immunotherapy is not permitted in NHS commissioning criteria. It also highlighted that subsequent immunotherapy use in the standard care arm differs from UK practice. So, it thought that the clinical efficacy of standard care plus durvalumab, then with or without olaparib, may differ in UK practice compared with the trial. The NHS England Cancer Drugs Fund lead (from here, CDF lead) explained that in clinical practice, immunotherapy rechallenge at second line would not be allowed if a person had already had durvalumab as first-line treatment. The company explained that it would not expect immunotherapy rechallenge in the active treatment arms of DUO-E to have a significant impact on OS. But, it acknowledged that the subsequent immunotherapy use in the standard care arm is different to UK practice and may have a limited impact on outcomes, specifically in the dMMR subgroup. The clinical experts said that they would not typically

expect multiple subsequent immunotherapies to be clinically beneficial. They acknowledged that it was possible for a person to finish a course of immunotherapy and relapse years later, and that subsequent immunotherapy may be beneficial in this scenario. But, this was not captured in DUO-E because of the short follow up (see section 3.5). They also explained that response for second-line single-agent immunotherapy is 45%, and overall at second line 60% to 65% of people would likely have clinical improvement or stable disease. The committee thought that it was unclear whether the costs and efficacy in the model had been appropriately adjusted for the differences in subsequent immunotherapy use. But it concluded that adjustment would require a treatment switching adjustment, which would be difficult and uncertain because of the small size of the subgroups. So, the committee concluded that the differences in subsequent immunotherapy use between DUO-E and NHS practice was an unresolvable uncertainty.

Economic model

Company's modelling approach

3.7 The company used a partitioned survival model with 3 health states: progression free, progressed disease, and death. The committee agreed that the partitioned survival model is a standard approach for estimating the cost effectiveness of cancer drugs and the model structure was appropriate.

Assumptions in the economic model

PFS modelling

3.8 The company explored standard parametric and flexible spline models for the extrapolation of PFS. For the dMMR subgroup, the company selected a 1-knot spline in the standard care arm and a 2-knot spline in the standard care plus durvalumab arm. For the pMMR subgroup, the company selected a log-logistic extrapolation for both standard care arm

and standard care plus durvalumab plus olaparib arm. The EAG agreed with the company's approach in the pMMR subgroup. The EAG preferred a 1-knot spline to model standard care plus durvalumab in the dMMR subgroup. It explained that this aligned with the company's chosen extrapolation in the standard care arm. It also highlighted that the 1-knot spline better captures the tail end of the Kaplan–Meier curve, but acknowledged that this was uncertain because of the immaturity of the data (see section 3.5). But the EAG also noted that the choice of PFS extrapolation had a small impact on the cost-effectiveness estimates. The company explained that the primary endpoint of PFS was already met in the interim analysis and it did not expect to have further data cuts available for PFS. The clinical experts considered that both the company and EAG estimates of PFS in the dMMR subgroup could be reasonable (these estimates are confidential so cannot be reported here). But they thought that the EAG estimates were more plausible. The committee concluded that the following should be used to model PFS:

- a 1-knot spline in both arms of the dMMR subgroup and
- the log-logistic extrapolation in both arms of the pMMR subgroup.

OS modelling

3.9 In the dMMR subgroup, the company's base case used a log-normal extrapolation to model OS in both the standard care arm and the standard care plus durvalumab arm. In the pMMR subgroup, the company preferred a log-logistic extrapolation to model OS in both the standard care arm and the standard care plus durvalumab plus olaparib arm. The EAG thought that the company's extrapolations were reasonable in the pMMR subgroup. But it preferred a log-logistic extrapolation for OS in the dMMR subgroup, applied to both treatment arms. The EAG explained that the overall results for the standard care arm using the log-logistic approach were similar to the company's log-normal approach. Also, the OS estimates for standard care plus durvalumab were closer to OS

estimates from TA963. The EAG acknowledged that the extrapolations for OS were very uncertain because of the immaturity of the data (see section 3.5). But it noted that the choice of OS extrapolation had a small impact on cost-effectiveness results. The company explained that DUO-E is still ongoing and that it would have more data on OS available at the final data cut in 2026. The clinical experts considered that both the company and EAG estimates of OS could be reasonable (these estimates are confidential so cannot be reported here). But they thought that the EAG's estimates for OS at 5 years would be more plausible. The committee concluded that the log-logistic extrapolation should be used to model OS for both arms in the dMMR and the pMMR subgroups.

Cap on treatment duration

3.10 In DUO-E, treatment with durvalumab plus platinum-based chemotherapy, then with or without olaparib, was continued up until disease progression or unacceptable toxicity (see section 3.4). This was reflected in the summary of product characteristics for durvalumab and the summary of product characteristics for olaparib. But in the company's economic model, a maximum treatment duration of 3 years was applied (with time to treatment discontinuation modelled using a gamma extrapolation in dMMR and a log-logistic extrapolation in pMMR, both capped at 3 years). The EAG was concerned that this cap on treatment duration artificially limits costs of the interventions. It was also concerned that a mismatch between treatment duration in DUO-E and in the model introduces substantial uncertainty in long-term efficacy because the model is informed by data from DUO-E. The EAG preferred no cap on treatment duration with time to treatment discontinuation extrapolations tending towards 0. It used a gamma distribution for the dMMR subgroup (in line with the company's preferred extrapolation) and an exponential distribution for the pMMR subgroup (while the company preferred log-logistic). The company explained that assuming a treatment duration cap matches how other immunotherapies are used in endometrial cancer. The

clinical experts confirmed that in NHS clinical practice, other immunotherapies would likely be used up until the point of disease progression or stopped at 2 or 3 years. They said that if there is a sustained response to treatment after 3 years then it would be assumed that further progression events or death do not occur past this timepoint. So, they thought that stopping after 3 years of treatment would be reasonable, regardless of whether olaparib was included in the combination. The committee thought that if progression or death did not occur within 3 years on immunotherapy in line with clinical expert opinion, then stopping the interventions after 3 years would be reasonable. The committee recalled the immaturity of the data from the DUO-E trial (see section 2.8), noting that there was no PFS data for 3 years or more. So there were no efficacy estimates beyond this point. Taking into account the clinical expert opinion that they would stop treatment after 3 years if no progression was observed, the committee considered it appropriate to only include costs of treatment up to 3 years. It concluded that despite some uncertainty, the 3-year treatment duration cap in the company's model was agreed with by clinical experts and is appropriate for decision making. It agreed to implement a 3-year stopping rule in the recommendation, in line with the clinical expert advice.

Olaparib maintenance treatment in pMMR population

3.11 In the economic model, the company and the EAG preferred to assume that different proportions of people with pMMR endometrial cancer have maintenance treatment with olaparib. The company's base case used a proportion informed by DUO-E (the proportion is considered confidential by the company so cannot be reported here). But the EAG explained that the company's proportion is based on DUO-E data at the time of randomisation. The EAG preferred a percentage that reflected the proportion of people in the standard care plus durvalumab plus olaparib arm having maintenance treatment (this proportion is considered confidential so cannot be reported here). The EAG also highlighted that

the company only applied acquisition costs in the model to people who were alive and progression-free after week 18. So, the company's proportion may underestimate acquisition costs of olaparib. The company explained that some people in the standard care plus durvalumab plus olaparib arm in DUO-E did not start maintenance durvalumab because of disease progression or adverse events. Instead these people had durvalumab monotherapy. The EAG was concerned that this did not align with the marketing authorisation, which indicates that at the maintenance stage durvalumab should be used with olaparib. The CDF lead highlighted that in clinical practice, in the maintenance phase people with pMMR disease could stop either durvalumab or olaparib in the event of toxicity. They could then continue with the other treatment. But, people with pMMR disease would need to be eligible for both durvalumab and olaparib at the start of treatment. It would be expected that people would start both durvalumab and olaparib in the subsequent maintenance phase. The clinical experts thought that the EAG's figure was too high and that the company's figure was more plausible. On balance they thought the proportion of people starting olaparib in the pMMR subgroup would likely be somewhere in the middle. The committee concluded that the company's proportion of people starting olaparib in the pMMR subgroup should be used in decision making. This was because by using the DUO-E data to inform the proportion of people starting olaparib in the pMMR subgroup, the costs and effects of olaparib are aligned. But using the EAG's higher proportion would add treatment costs without a corresponding increase in treatment effect. The committee also noted the clinical expert opinion on the anticipated proportion starting olaparib maintenance treatment. The committee acknowledged that there may be some difference between the figure used from the trial and the figure in NHS practice.

Estimation of newly progressed patients per model cycle

3.12 In its base case, the company assumed that a constant proportion of people had a non-fatal progression event in each model cycle based on data from DUO-E (the proportion is considered confidential by the company so cannot be reported here). A one-off cost of subsequent treatment was applied to people moving into the progressed-disease health state. The EAG explained that there may be some periods in the model where death occurs but disease progression does not. So, the company's approach likely overestimates the proportion of newly progressed patients per cycle. The cost of subsequent treatment may also be overestimated in the model because more people are estimated to have disease progression with standard care alone. The EAG proposed a formula-based approach for calculating newly progressed patients per cycle directly from the model, which allows changes in proportion over time. But it acknowledged that this approach had limitations, since the adjustment to OS includes people dying in the progression-free and progressed-disease health states. So the EAG did not use this approach in its base case. But it stated that this approach was equivalent to the company assuming a fixed proportion of deaths from the progression-free health state. The company explained that the percentage of non-fatal progression events in the intention-to-treat population remains constant over time up to the duration of follow up in the interim data cut. But it acknowledged that this proportion may change over time with increased follow up. The company also highlighted that the EAG's scenario leads to a difference in the proportion of fatal events during the trial period because it does not use observed data. It would also lead to negative numbers of progression events in some cycles without the EAG's artificial cap of 0 progression events introduced in this scenario. The committee recognised the merits of the EAG's approach, but acknowledged that the way this was implemented in the model generated implausible results in

some cycles. So it concluded that the company's proportion should be used in decision making.

Other issues with minor impacts on cost effectiveness

3.13 In addition to the key issues discussed in sections 3.8 to 3.12, the EAG also made minor changes to the company's base-case modelling approaches and assumptions (see the EAG report in the committee papers). The additional changes were considered, and it was agreed that the EAG's approaches were reasonable. These were to:

- include drug wastage in the model
- use the most up-to-date costs for subsequent administration of chemotherapy (£393.16, based on 2022/23 NHS reference costs)

The committee concluded that the EAG's additional changes were appropriate and that these only had a minor impact on cost-effectiveness results for both the dMMR and pMMR subgroups.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.14 The cost-effectiveness estimates used by the committee for decision making took into account the available confidential discounts. The exact estimates are confidential and cannot be reported here. For dMMR subgroup, the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) for standard care plus durvalumab in the company's base case were within the range normally considered an acceptable use of NHS resources. In the EAG's base case, the deterministic ICERs for standard care plus durvalumab in the dMMR subgroup were within the range normally considered an acceptable use of NHS resources. But, the probabilistic ICERs were above this range. In the pMMR subgroup, the deterministic and probabilistic ICERs in both the company's and EAG's base cases were substantially higher than the

range normally considered an acceptable use of NHS resources. The size of the ICERs in the pMMR group was largely driven by small incremental quality-adjusted life years (QALYs) in this subgroup.

Committee's preferred assumptions

3.15 For the cost-effectiveness analysis, the committee's preferred assumptions for the dMMR subgroup were:

- using a 1-knot spline extrapolation to model PFS for both arms (see section 3.8)
- using a log-logistic extrapolation to model OS for both arms (see section 3.9)
- using a treatment duration cap of 3 years with a gamma extrapolation (see section 3.10)
- using the company's proportion of newly progressed patients in each model cycle (see section 3.12)
- including treatment wastage and updated costs for subsequent chemotherapy administration (see section 3.13).

The committee's preferred assumptions for the pMMR subgroup were:

- using a log-logistic extrapolation to model both PFS and OS (see section 3.8 and 3.9) for both arms
- using a treatment duration cap of 3 years with a log-logistic extrapolation (see section 3.10)
- using the company's proportion for people starting maintenance olaparib (see section 3.11)
- using the company's proportion of newly progressed patients in each model cycle (see section 3.12)
- including treatment wastage and updated costs for subsequent chemotherapy administration (see section 3.13).

The committee also asked for further analyses in the p53 subgroup since this was highlighted by clinical experts as a key prognostic indicator (see section 3.2).

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted several uncertainties, specifically:

- the long-term clinical benefit of durvalumab plus platinum-based chemotherapy, then with or without olaparib (see section 3.5)
- the generalisability of subsequent treatment use in DUO-E data to NHS clinical practice (see section 3.6)
- the preferred maximum treatment duration of 3 years and implementation of a stopping rule, since this does not align with how the intervention was used in DUO-E (see section 3.10).

Given the level of uncertainty, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained for both the dMMR and the pMMR subgroups. Taking into account its preferred assumptions, the committee noted that:

- for the dMMR subgroup, the ICER was within the range considered a good use of NHS resources
- for the pMMR subgroup, the ICER was substantially higher than the range considered to be a good use of NHS resources.

Other factors

Equality

3.17 The committee considered that the incidence rates and mortality for endometrial cancer are higher in the Black ethnic group compared with White ethnic group. It also considered that incidence of different molecular subtypes of endometrial cancer (including MMR status) varies across ethnic groups. People in Black ethnic groups may also have more aggressive histology and may be more likely to have molecular subtypes with a poorer prognosis. The clinical experts also noted that there is some data suggesting differential responses to immunotherapy across ethnic groups. Race is protected under the Equality Act 2010. The committee considered whether or not this could indirectly discriminate against people in Black ethnic groups. The committee considered that this would be a proportionate means of achieving the legitimate aim of maximising public health. This is because durvalumab plus platinum-based chemotherapy, followed by durvalumab plus olaparib, was not cost effective in the pMMR population.

Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of durvalumab with platinum-based chemotherapy, then with or without olaparib. The committee considered that durvalumab with platinum-based chemotherapy, then with or without olaparib, could be an innovative treatment. It recalled that there are currently no available first-line immunotherapies for endometrial cancer, with the exception of 1 drug currently in the CDF for dMMR disease. The committee also recalled the high unmet need in people with pMMR disease in particular. The committee agreed to take these additional benefits of durvalumab with platinum-based chemotherapy, then with or without olaparib, into account in its decision making.

Conclusions

Recommendations

3.19 The clinical-effectiveness evidence showed that standard care plus durvalumab improved key outcomes in untreated advanced or recurrent endometrial cancer in people with dMMR. The committee concluded that the ICER that included its preferred assumptions was within the range that NICE considers an acceptable use of NHS resources (see section 3.16). So, durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab monotherapy is recommended in the dMMR subgroup. It should be stopped after 3 years, or earlier if there is disease progression or unacceptable toxicity.

3.20 The committee concluded that the ICER that included its preferred assumptions in the pMMR subgroup was substantially above the range that NICE considers an acceptable use of NHS resources (see section 3.16). So, durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab plus olaparib, is not recommended in the pMMR subgroup. Recognising the unmet need in this subgroup, the committee requested data for the p53 mutation subgroup within the pMMR population. It heard from clinical experts that this subgroup within the pMMR population would be expected to greatly benefit from having durvalumab plus olaparib (see section 3.2).

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated primary advanced or recurrent endometrial cancer that is mismatch repair deficient and the healthcare professional responsible for their care thinks that durvalumab with platinum-based chemotherapy followed by maintenance durvalumab monotherapy is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

James Fotheringham
Vice chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Emma McCarthy
Technical lead

Joanna Richardson
Technical adviser

Greg O'Toole and Jeremy Powell
Project managers

Emily Crowe

Associate director

ISBN: [to be added at publication]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Nothing to disclose
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1.	**Executive Summary** AstraZeneca would like to thank NICE for the opportunity to respond to the preliminary recommendations made by the Committee detailed in the draft guidance document (DGD) for durvalumab in combination with platinum-based chemotherapy followed by maintenance durvalumab (SoC + D) for patients with newly diagnosed advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR); and durvalumab in combination with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC + D + O) for patients with newly diagnosed advanced or recurrent EC that is MMR proficient (pMMR). AstraZeneca welcomes the Committee conclusion that SoC + D should be recommended as an option for patients with dMMR EC. Importantly, the availability of this treatment is expected to address a critical medical and patient need, expanding the range of available options and providing a more hopeful outlook for patients with dMMR EC. As the first immunotherapy recommended for routine commissioning in this indication, the availability of SoC + D in the dMMR population also provides certainty for treating clinicians, who will remain able to prescribe this regimen in the long term for their patients who are eligible and are likely to benefit from this therapy. In contrast, AstraZeneca is extremely disappointed in NICE's decision that SoC + D + O could not be recommended as a treatment option for patients with pMMR EC. AstraZeneca were willing to accept all of the Committee-preferred assumptions for the economic analysis of SoC + D + O in people with pMMR EC, including those pertaining to the duration of treatment, the extrapolations of progression-free survival (PFS) and overall survival (OS) and the assumption surrounding the proportion of people starting maintenance olaparib. However, AstraZeneca do not consider a £20,000 willingness-to-pay (WTP) threshold to be appropriate for the appraisal of SoC + D + O, and is concerned with the decision to use the lowest end of the £20,000–£30,000 range available to the Committee. To echo the sentiments of the patient experts and clinicians during Appraisal Committee Meeting (ACM)1, this population has a significant unmet need, driven by the lack of effective first-line (1L) treatments and the poor prognosis for patients; the introduction of SoC + D + O would represent a crucial addition and a step change to the

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	treatment landscape, giving patients and their families more hope for the future. By choosing a threshold of £20,000/quality-adjusted life year (QALY), it is evident that the Committee have overestimated the uncertainty associated with this appraisal, and have not fully recognised the wide-reaching benefits that SoC + D + O will bring to patients and their loved ones. This response will therefore focus on the appropriateness of the £20,000 threshold for this appraisal, by reassuring the Committee regarding the level of uncertainty associated with the incremental cost-effectiveness ratios (ICERs), as well as reiterating the important benefits of SoC + D + O, some of which cannot be quantitively captured in the economic analysis. Furthermore, it will discuss more broadly the challenges posed by the current WTP threshold considered by NICE and the NHS Commercial Framework, which threaten to restrict patient access for therapies requiring commercial flexibility, and which are pertinent to the current appraisal.
2.	**AstraZeneca is concerned that the Committee have overestimated the uncertainty associated with the use of SoC + D + O in patients with pMMR EC** Based on the DGD, it is understood that the primary driver behind the application of a £20,000 WTP threshold for SoC + D + O in the pMMR population is the 'level of uncertainty' that is associated with the ICERs presented. The key areas of uncertainty noted by the Committee when discussing the acceptable ICER are as follows: • The long-term clinical benefit of SoC + D + O; • The generalisability of subsequent treatment use in DUO-E data to NHS clinical practice; • The preferred maximum treatment duration of three years and implementation of a stopping rule. However, as detailed in the following sections, none of the areas of uncertainty in this appraisal have a meaningful impact on the ICER within the pMMR population. As such, AstraZeneca consider that the uncertainty in the appraisal has been overestimated by the Committee and strongly disagree that these areas should contribute to the application of the lower bound WTP threshold within NICE's acceptable £20,000–£30,000 range for this appraisal. ***The long-term benefit of SoC + D + O is associated with no greater degree of uncertainty relative to any other novel oncology intervention***

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	AstraZeneca accepts that, as with almost all oncology appraisals, long-term extrapolations of PFS and OS from DUO-E are subject to some inherent uncertainty. However, it is important to consider this inherent uncertainty in the context of the evidence base and economic model for any given appraisal. To that extent, all of the long-term extrapolations in the model were aligned with extensive clinical expert opinion received from UK-based clinicians, and the chosen extrapolations were deemed appropriate by the External Assessment Group (EAG) and the EAG's clinical experts. Scenario analyses demonstrated that alternative plausible OS extrapolations (log-normal; gamma) and PFS extrapolations (log-normal) explored in scenario analyses had a slight positive impact on the Company ICER, highlighting that the Committee's preferred decision-making ICERs may be conservative. Therefore, for this appraisal specifically, there is no reason to conclude that the extrapolations for SoC + D + O are associated with a particularly high degree of uncertainty relative to any other novel oncology intervention, providing no clear rationale for the use of a £20,000 threshold on this basis. Of particular relevance, it is useful to draw parallels with TA963 (dostarlimab in 1L dMMR EC), given the comparable indication and that uncertainty around long-term outcomes was similarly highlighted as a key issue. In this appraisal, even with the added uncertainty arising from reliance on small sample sizes for the dMMR population (compared with the larger pMMR population relevant to DUO-E), dostarlimab was appraised against a higher £25,000 WTP threshold. ***Subsequent treatment use in DUO-E data to NHS clinical practice is a source of limited uncertainty due to extensive clinical validation received on this topic and the apparent lack of efficacy of immunotherapy rechallenge*** Although the generalisability of subsequent treatment use in the DUO-E trial to NHS clinical practice is noted as a single uncertainty in the DGD, there are two separate aspects to consider: 1. The use of immunotherapy in the SoC arm, whereby according to clinical expert opinion, subsequent immunotherapy use was lower in DUO-E than would be expected in UK practice. 2. The use of immunotherapy re-challenge in the intervention arm (SoC + D + O) in DUO-E – an approach that is not currently permitted in UK clinical practice, but did occur in the DUO-E trial.

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	In both cases, model inputs were adjusted to account for any expected differences between DUO-E and UK clinical practice based on extensive clinical feedback. Model outputs were subsequently validated with UK clinicians to ensure they remained consistent with clinical expectation. The Company therefore consider that the subsequent treatment use in the model is a source of limited uncertainty and should not be considered to meaningfully impact the generalisability of the cost-effectiveness results, as discussed below. With regard to #1, the use of subsequent immunotherapy in the SoC arm is only relevant to the dMMR population and should not be considered a source of uncertainty within the appraisal of SoC + D + O in pMMR EC. The number of patients who received an immunotherapy as a proportion of all patients who received any second-line (2L)+ therapy was [redacted] in the DUO-E trial in the pMMR group, which closely mirrored the feedback received from UK clinicians in relation to expected UK practice [redacted]. The subsequent treatment use in the SoC arm in the pMMR population should therefore be considered to be generalisable to UK clinical practice. AstraZeneca acknowledge that the use of immunotherapy rechallenge in the DUO-E trial within the intervention arm is not reflective of current UK clinical practice. However, there is no evidence to suggest that this rechallenge would have resulted in any meaningful impact to the generalisability of the modelled outcomes for SoC + D + O: • There is no conclusive evidence that demonstrates immunotherapy rechallenge is an effective treatment strategy. Indeed, the current reimbursement criteria preclude multiple rounds of treatment with immunotherapy for precisely this reason – that there is insufficient data to support the effectiveness of this treatment regimen for patients with EC. • Clinical experts consulted by the Company suggested that even if rechallenge might be effective in some patients, it is particularly unlikely to be effective for patients in the DUO-E trial. As per the study protocol, the patients receiving subsequent treatment in DUO-E will have experienced disease progression whilst still receiving active treatment with an immunotherapy. However, clinical experts indicate that immunotherapy rechallenge is most likely to be effective for patients who have experienced a treatment-free interval whilst in PFS, before later experiencing disease progression and receiving subsequent treatment. • This is supported by studies in non-small cell lung cancer and melanoma (discussed further in Section B.3.3.5 of the Company Submission), which highlight the different resistance mechanisms associated with progression during active treatment on an immunotherapy (such as DUO-E) or after a treatment-free interval following immunotherapy use.

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	Consequently, immunotherapy rechallenge was likely to have been associated with limited (if any) success among those who initially received active treatment in DUO-E, particularly among the challenging-to-treatment pMMR population. Of note, it is also important to reiterate that the modelled OS extrapolation for SoC + D + O was aligned with UK clinical expert feedback, and was considered appropriate by the EAG and the EAG's clinical experts. As such, subsequent treatment use and any potential impact on the generalisability of the OS results for SoC + D + O cannot be considered a meaningful source of uncertainty within this appraisal. ***The implementation of a stopping rule in the DGD negates any uncertainty on the treatment duration for SoC + D + O*** AstraZeneca strongly disagree that the treatment duration of SoC + D + O and associated stopping rule should be considered a source of uncertainty in this appraisal at all. This is because the key issue on this topic was whether the three-year maximum treatment duration included in the model would be reflective of UK clinical practice, given that the license for DUO-E permits a treat-to-progression approach (in line with the DUO-E trial). The recommendation of a three-year stopping rule in the DGD therefore effectively negates this uncertainty, by guaranteeing that UK clinical practice will reflect the modelled treatment duration. Notably, emerging evidence on the use of immunotherapy indicates that the benefit of treatment is fully realised in the first 2–3 years, aligning with clinical opinion in ACM1. Therefore, AstraZeneca maintain that patients would experience the full therapeutic benefits of SoC + D + O well within this time period and that this would naturally limit continued use of this treatment in clinical practice beyond three years regardless of a stopping rule. However, NICE's inclusion of a stopping rule resolves any perceived uncertainty on this issue. Implementation of a stopping rule should therefore be considered an effective measure to mitigate any perceived uncertainty on this issue, as opposed to a contributing factor or a justification for the use of the lowest WTP threshold in this appraisal.
3.	**AstraZeneca are concerned that inadequate consideration has been given to the uncaptured benefits and positive broader societal implications associated with the introduction of SoC + D + O in patients with pMMR EC** As per the current NICE methods (Section 6.2.36), Committee conclusions are affected by the following considerations: • If there are strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained

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	• If its decisions have a bearing on broader social considerations and the extent that these are covered by NICE's principles on social value judgements[1] There is compelling evidence which indicates that SoC + D + O is associated with a number of key uncaptured benefits, and would also help to address important health inequalities – one of NICE's principles (Principle 9) and a key pillar of the Health and Social Care Act 2012. Beyond the perceived uncertainties highlighted by the Committee, AstraZeneca are therefore also concerned that the application of the £20,000 WTP fails to capture crucial elements of value associated with the introduction of SoC + D + O and thus may not fully reflect current NICE methods. ***SoC + D + O is an innovative therapy offering significant uncaptured benefits for a patient population with a severe unmet need*** As highlighted in Section 1 and within the DGD itself, the pMMR EC population has a profound unmet need for effective 1L treatment options. These patients, comprising the majority of the overall EC patient population, currently face a very poor prognosis with no innovative therapies currently reimbursed in the 1L setting, and are widely acknowledged to be a challenging-to-treat population. The Peaches Womb Cancer Trust highlighted that patients must currently endure treatment with 'bog standard' chemotherapy, which has limited effectiveness and significant side effects, before being able to access immunotherapy upon disease progression. One patient highlighted *'knowing my only treatment option offered by the NHS would be 'bog standard chemotherapy' as first line filled me with dread and fear'*. By the time that patients are able to access immunotherapy as a 2L treatment, their cancer may have progressed, and/or their health may have worsened, leading to further devasting impacts on their well-being and reducing their ability to tolerate subsequent treatments. As such, 1L treatment may be the only opportunity for many patients to benefit from an immunotherapy. Access to earlier, more effective treatments (such as SoC + D + O) would provide better symptom control, extend the time before cancer progresses, and improve the possibility of a more meaningful and longer life. In the context of this considerable unmet need, it is evident that SoC + D + O – a therapy that has demonstrated substantial efficacy in the pMMR population – is associated with significant uncaptured benefits. As noted in the DGD, SoC + D + O represents an innovative option, being the first licensed regimen to combine immunotherapy with a PARP inhibitor for patients with pMMR EC. Moreover, it would provide hope for patients and their carers who would otherwise face the devastating effects of a disease diagnosis where there are no effective

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	treatment options, helping to address the marked unmet need in this population. These benefits cannot be captured in the economic analysis, but are of vital importance for the Committee to consider – alongside the devastating psychological impact that would stem from a negative recommendation, and the knowledge that an effective treatment exists for pMMR EC, but that patients in the UK are not able to receive it. The DGD suggests that this unmet need and the potential benefits of SoC + D + O might be most pronounced in patients with pMMR and p53. However, it is clear that there is an important unmet need across the entirety of the pMMR population. Furthermore, the DUO-E trial provides compelling evidence regarding the effectiveness of SoC + D + O for all patients with pMMR EC, regardless of p53 status. There is therefore no rationale to consider subgroup analyses based on p53 status. ***SoC + D + O may help address important health inequalities*** AstraZeneca welcomed the Committee's consideration of equality as part of the DGD, but are disappointed with the Committee's final conclusions on this topic, given the substantial evidence base demonstrating that both racial and socioeconomic disparities currently exist for patients with EC in the UK. Importantly, evidence suggests that there may be racial differences in the molecular characteristics of EC across different ethnic groups. Of particular relevance, a recent review identified several molecules and molecular pathways that are present at significantly different levels in EC specimens from Black and White patients.[2] These same inherent racial disparities in the molecular profile of EC have been reported in a separate analysis, which concluded that there were clear differences in the molecular portraits in EC from Caucasian, Black or African American and Asian patients – differences that may have important implications for patient management and prognosis.[3] As previously highlighted as part of the Company Submission (Section B.1.4), people in Black ethnic groups also experience substantially higher uterine cancer incidence and mortality compared to people in White ethnic groups. Data from England and Wales (2012–2019) highlight that the mortality rate for Black ethnic groups is more than double the rate for White ethnic groups. As a result, recommending SoC + D within the dMMR population only may exacerbate existing racial disparities, by limiting access to immunotherapy based on molecular status (and thus indirectly by racial group). Conversely, introducing SoC + D + O may help to reduce these health inequalities, by allowing patients with EC to access effective 1L treatment regardless of their molecular status. Beyond race, the effect of obesity on EC risk is well-established in the literature – 34% of uterine cancer cases in the UK are linked with increased body mass index (BMI).[4] Meanwhile, separate studies have demonstrated that women with a lower income or education are more

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	likely to be obese than those in higher socioeconomic groups,[5, 6] thereby establishing a link between a lower socioeconomic status and EC. Notably, this link is highlighted in the RCOG and BGCS policy statement on gynaecological cancers, which states that EC incidence rates in England are 17% higher in the most deprived quintile compared with the least, emphasising the need for action to be made to address inequalities in cancer incidence.[7] SoC + D + O represents a novel, innovative treatment option which would be available for all patients with pMMR EC, regardless of race or socioeconomic status. The resulting improvements in PFS and OS (among other clinical and humanistic benefits) would therefore reduce the current disparities faced by people in Black ethnic groups or those with a lower socioeconomic status. This represents a key benefit associated with SoC + D + O which cannot be formally captured in the QALY. Importantly, the DGD states that the Committee "agreed to take these additional benefits of durvalumab with platinum-based chemotherapy, then with or without olaparib, into account in its decision making". However, it is unclear the extent to which these have been considered, if at all, given that the consideration of these uncaptured benefits appears to be at odds with the conclusion that £20,000 is the most appropriate WTP threshold for this appraisal. In fact, AstraZeneca notes that when the acceptable ICER is discussed in the DGD in Section 3.16, there is no reference to these uncaptured benefits – this section instead remains focussed solely on the perceived uncertainties, with no consideration of these uncertainties within the broader context of the appraisal.
4.	**This issues in this appraisal illustrate the broader challenges associated with accessing commercial flexibility based on current NICE methods and the NHS Commercial Framework** Importantly, the issues raised in this response reflect broader concerns raised by the wider healthcare industry on the suitability of the current £20,000–£30,000 range that is considered by NICE. The threshold range has remained unchanged since NICE's inception in 1999, raising questions on the relevance of the threshold to the current economic climate and healthcare advancements, and ultimately on whether the existing threshold may unnecessarily restrict patient access to new and effective treatments, inhibit pharmaceutical innovation and undervalue the true benefits of modern therapies. A separate full review of the appropriateness of NICE WTP threshold is therefore required, alongside specific reconsideration of the appropriateness of the £20,000 WTP threshold in this appraisal. Notwithstanding the broader issues highlighted above, AstraZeneca is also concerned that even within the current £20,000–£30,000 range, there has been a downward trend in the ICERs that NICE consider to be acceptable over time. A recent review found that there were 39

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	terminated technology appraisals (or 19 per year) between 2021–2022, versus 48 across the previous 5 years (or 9 per year), meaning that around double the number of appraisals are being terminated annually.[8] Other studies have similarly reported an increasing number of terminated appraisals over the last decade.[9, 10] Whilst there are various factors that may have influenced this increase, increasing pricing pressures are expected to be one contributing factor, potentially driven by a narrowing WTP threshold that NICE are willing to accept and the trend of increasingly – sometimes disproportionately – cautious ICERs selected by Committees.[11] The challenges posed by increasingly adopting the lower threshold range are further compounded for combination therapies where significant access challenges and pricing pressures already exist. This is demonstrated by the EFPIA 2023 report on access to oncology combination therapies in Europe, which found that in England between 2015 and 2021 the availability of approved combination oncology regimens lagged behind availability of all approved oncology products (57% versus 79% respectively). This difference of 22% is much larger than other comparable European markets, with other EU4 markets showing a difference of ≤12%.[12] While the recent Competition and Markets Authority (CMA) position statement represents a step forward in this regard, many combination therapies still face significant access challenges – particularly in cases such as SoC + D + O where both components are innovative. In these cases, commercial flexibilities are particularly valuable, and often essential, for facilitating patient access. However, as per the existing NHS Commercial Framework, such flexibilities can only be accessed once the technology has been appraised "at or below" the lower end of the threshold selected by NICE, resulting in yet a further unwarranted reduction in the threshold that these technologies must meet to achieve access. These broader challenges, combined with the application of the lower bound WTP threshold in this specific appraisal, mean that the barriers to achieving access to SoC + D + O may be insurmountable – an outcome which would deny patients access to an effective treatment offering substantial clinical benefits. AstraZeneca therefore urges the Committee to reconsider their recommendations on the acceptable ICER for this indication, ensuring that the chosen threshold reflects both the limited uncertainty and wide-ranging uncaptured benefits discussed in this response, as well as the implications of the chosen threshold on attaining commercial flexibility for this innovative treatment.
5.	**NICE process and interplay with the NHSE Commercial Framework** [redacted]

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	[redacted]

Insert extra rows as needed

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NICE National Institute for Health and Care Excellence

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Peaches Womb Cancer Trust

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are delighted that NICE has provisionally recommended durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab monotherapy, for use on the NHS in adults with untreated primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR). We have no additional comments on this section of the consultation.
2	We are concerned that NICE has provisionally recommended that durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab plus olaparib, should not be used in adults with untreated primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR). **There is an increasing inequality in access to innovative and effective treatment options on the NHS for patients with advanced or recurrent pMMR endometrial cancer. A significant unmet need continues to exist for these patients in the first-line setting.** The lack of effective first-line treatment options for people with advanced or recurrent pMMR endometrial cancer is devastating. **People with pMMR cancers represent 70-80% of all endometrial cancer cases, meaning that the majority still lack access to effective first-line therapies.** **Patients have told us that this leaves them feeling frustrated, abandoned and hopeless**. They have shared that while their peers with other cancers have at least second- and third-line treatments available, they are left with only what they describe as “bog standard chemotherapy”. These quotes illustrate the despair patients feel from lack of access to innovative technologies: *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.”*

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	"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." *"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."*
3	**We are concerned that there are additional equalities considerations which have not been fully taken into account in NICE's decision-making.** The lack of effective and innovative first-line treatments for people with advanced or recurrent pMMR endometrial cancer is likely to disproportionately impact some racial groups. Not approving the technology for pMMR endometrial cancer is likely to make it more difficult for certain racial groups to access the technology. Whilst the clinical trial data does not delineate into different molecular subtypes beyond pMMR (POLE-mut, NSMP and p53abn), there is evidence that there are racial disparities within the molecular profile of endometrial cancer[1,2]. For example, the p53abn subtype of endometrial cancer is over-represented in Black women. Incidence rates of uterine cancer are higher among individuals of Black ethnicity compared to those of White ethnicity[3]. ONS data shows significant disparities in deaths from endometrial cancer – with Black ethnic groups in the UK being much more likely to die of the disease than other ethnic groups[4]. A review by Illah et al. (2024) has highlighted that Black women are twice as likely to die from endometrial cancer compared with white women, representing one of the worst global inequalities among ethnic groups in cancer[5]. There are multiple drivers of increased mortality in Black women including late diagnosis being more common in those from Black Caribbean and Black African women compared with other groups. Recent data in the UK has shown that African and Caribbean women are twice as likely to be diagnosed at an advanced stage compared with White British women[6]. As Illah et al. (2024) highlight, this "association is so strong

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that Cancer Research UK labelled ethnicity as a 'significant factor' in the stage at diagnosis of EC[7].

Additionally, Black women are more likely to be diagnosed with higher risk endometrial cancer and the most aggressive p53abn subtype, which has the poorest outcomes[8]. Around 15% of all endometrial cancers are p53abn subtype, which is mismatch repair proficient and responsible for 50-70% of deaths from endometrial cancer[9].

Racial inequalities are further compounded by an under-reporting and low quality of reporting of racial characteristics of people diagnosed with endometrial cancer which could mean the full unmet need is not known[10].

The reporting of clinical data at pMMR rather than at further subtypes (POLE, NSMP, p53abn) and our role as a patient organisation (not clinical) means that we are unable to comment on likely efficacy. There are many gaps in existing knowledge on how all these biomarkers show up across different racial groups contributing to health inequality. **We are concerned that racial disparity across all pMMR molecular subtypes has not been taken into NICE's decision-making.**

As above, **we would urge NICE to include greater consideration of equalities impacts that arise from not recommending access for people with pMMR tumours to innovative combined therapies (durvalumab with olaparib).**

Making this treatment available for people with advanced or recurrent endometrial cancer across all subtypes would help address this disparity and improve outcomes for people of all ethnicities.

Please note that the above has been written from a patient advocacy perspective and not a clinical one

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4	We are concerned that the recommendation has not included consideration of downstream treatments for advanced cancer. The likelihood that a large proportion of pMMR patients would be eligible for pembrolizumab with lenvatinib in the second-line setting. Earlier treatment in the first-line with a more effective drug means fewer patients would require pembrolizumab and lenvatinib in the second line. This does not seem to have been taken into account in cost effectiveness considerations.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.

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- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Gemma EMINOWICZ

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I think this summarises the data and justifies the recommendation well

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2	With further follow up data there may be more compelling evidence for this regimen in the MMRp population but I think it is still probably only a subset that get significant enough benefit to warrant the cost
3	
4	
5	
6	

Insert extra rows as needed

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Consultation response from CDF lead- ID6317

Regarding the anticipated use in the NHS of olaparib as maintenance treatment with durvalumab for people with pMMR endometrial cancer:

For pMMR disease, the intent must be at the outset of treatment to use durvalumab with chemotherapy and then use durvalumab with olaparib as maintenance treatment.

For pMMR disease at the outset of maintenance treatment, patients must start both durvalumab and Olaparib.

We expect dose reductions/delays in some patients and these will be delays for durvalumab and dose reductions and/or delays for olaparib. If unacceptable toxicity arises which means that durvalumab or olaparib have to be stopped, then one can be stopped independently of the other.

However, if patients have a true contraindication to starting durvalumab (eg autoimmune disorders) or to starting olaparib (eg the need to continue treatment with a strong CYP3A inducer), then they are disqualified from use of durvalumab and olaparib in this indication. They cannot start maintenance with one without the other.

The SPCs for durvalumab and 0laparib both describe dose delays/reductions/stopping but these are all individual to durvalumab or to olaparib and do not say that both have to be stopped if one is stopped.

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

EAG response to company draft guidance comments

April 2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 169598.

1 Summary of EAG comments on company draft guidance response

In response to the draft guidance (DG) issued by the National Institute of Health and Care Excellence (NICE), the company provided comments on four areas of concern with the committee's considerations for the cost-effectiveness of 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 endometrial cancer (EC) that is mismatch repair proficient (pMMR). However, the company did not provide any new evidence in their response for the committee to consider.

The company's issues with the committee's considerations were as follows:

- Overestimation of the uncertainty in the cost-effectiveness analysis due to:
    - long-term benefits of treatment with durvalumab and olaparib;
    - subsequent treatments used in DUO-E;
    - assumption of a three-year treatment stopping rule.
- Lack of clarity in the consideration of the uncaptured benefits of durvalumab and olaparib.

In the DG, the committee concluded that because there were several areas of uncertainty in the cost-effectiveness of analysis of durvalumab with olaparib for the pMMR subgroup (as outlined above), an acceptable incremental cost-effectiveness ratio (ICER) would be around £20,000 per quality-adjusted life year (QALY) gained. The company disagreed with the committee's use of the lower cost-effectiveness threshold based on the perceived uncertainty in the analysis but acknowledged that [redacted].

The EAG considers that the uncertainty in the long-term benefits of treatment, use of subsequent treatments in both arms of the model and the three-year treatment stopping rule are all interlinked and taken together, contribute to the level of uncertainty the committee outlined in the DG.

In the model, extrapolations of progression-free survival (PFS) and overall survival (OS) are informed by the observed data from DUO-E, which was considered to be immature (please refer to Key Issue 1 of the EAG report for more detail). At the primary data cut off (April 2023), overall maturity of PFS and OS outcomes in the pMMR subgroup was 66.1% and 29.2%, respectively. As such, the EAG considers that OS is extremely immature and, that as a result of this, the long-term extrapolations

for each treatment arm are subject to a substantial amount of uncertainty. The company references TA963 (dostarlimab with platinum-based chemotherapy for treating advanced or recurrent EC with high microsatellite instability or mismatch repair deficiency dMMR/MSI-H) and argues that long-term outcome data are similarly uncertain. The EAG agrees that in TA963, the data maturity from RUBY-1 for the dMMR/MSI-H was similar at 56% for PFS and 26% for OS.

However, the EAG notes that these two appraisals considered two different populations: pMMR (GID-TA11340) and dMMR (TA963). In particular, in the DG for this topic, clinical experts advised that "dMMR endometrial cancer tends to respond better to immunotherapy, while pMMR endometrial cancer is very heterogeneous".[1] Additionally, in reference to the maximum acceptable ICER of £25,000 for dostarlimab in TA963, the committee noted "the durable benefits that have been seen in dMMR/MSI-H populations".

In addition, there are two key assumptions that were included in the model for the current appraisal that are disconnected from the approach taken in DUO-E, which means that PFS and OS observed in the trial may not be reflective of the outcomes that maybe achieved in the NHS for pMMR patients on standard of care (SoC) and those eligible for durvalumab with olaparib:

1. In DUO-E, a proportion of patients on durvalumab and olaparib received subsequent immunotherapy ([redacted]), which would not occur in the NHS. For modelling purposes, subsequent immunotherapy for the SoC+D+O arm was excluded from the estimation of subsequent treatment costs, but any benefits were captured in the extrapolation of OS. Conversely, for the placebo arm of DUO-E, subsequent immunotherapy usage was lower than what would be expected in the NHS. As such, 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 and that the clinical effectiveness of SoC+D+O may be [redacted] in the economic model. As such the ICER is potentially [redacted] (Key Issue 2 of the EAG report) but the magnitude of change in the ICER is uncertain.
2. In DUO-E, treatment was until progression or unacceptable toxicity, which influences the observed PFS, used for the extrapolations in the model (Key issue 3 in the EAG report). However, the committee considered that a stopping rule of three years for treatment with durvalumab and olaparib is appropriate but acknowledged that it does not align with DUO-E and thus considered this to be an area of uncertainty. The company argues that the

treatment stopping rule increases the certainty as continued use of treatment beyond three years would now be limited in NHS practice. However, the EAG considers that the treatment stopping rule only adds certainty to the costs incurred by the NHS but increases the uncertainty around PFS included in the model as patients in DUO-E can receive treatment beyond three years. As such, PFS experienced by patients in the NHS based on a maximum treatment of three years is likely to differ to what was observed in DUO-E, but the extent of the difference is unknown.

The EAG considers that to mitigate the uncertainty caused by the above issues, the committee has implemented the lower threshold in order not to delay a decision for this topic, as is appropriate and outlined in the NICE manual on health technology evaluations.

With regards to the uncaptured benefits of treatment, the company has not provided any new evidence which has not already been considered by committee and reflected in the draft guidance.

2 References

1. National Institue for Health and Care Excellence. Durvalumab with platinum-based chemotherapy, then with or without olaparib, for untreated advanced or recurrent endometrial cancer - Draft Guidance [GID-TA11340], 2025. Available from: https://www.nice.org.uk/guidance/gid-ta11340/documents/draft-guidance. Date accessed: April 2025.