NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

dMMR endometrial cancer

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

pMMR endometrial cancer

1.3 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.

About these recommendations

1.4 These recommendations are not intended to affect treatment with durvalumab with platinum-based chemotherapy, then maintenance

Issue date: June 2025

durvalumab 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. 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, 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 in this population.

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 in this population.

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 endometrial cancer is pMMR.

Why the committee made these recommendations

Endometrial cancer can be dMMR or pMMR based on how well endometrial cells can correct mutations in DNA. Usual treatment for untreated primary advanced or recurrent endometrial cancer is platinum-based chemotherapy (from here just chemotherapy) then routine surveillance.

dMMR endometrial cancer

Clinical trial evidence shows that durvalumab with chemotherapy then maintenance durvalumab alone (monotherapy) gives people longer before their condition gets worse than just chemotherapy then routine surveillance. Evidence suggests that it also increases how long people live, but this is uncertain because the study is ongoing and has only followed people for a short time.

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 for endometrial cancer that is dMMR.

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.

pMMR endometrial cancer

Clinical trial evidence shows that durvalumab with chemotherapy, then maintenance durvalumab plus olaparib, gives people longer before their condition gets worse than just chemotherapy then routine surveillance. Evidence suggests that it also

increases how long people live, but this is uncertain because the study is ongoing and has only followed people for a short time.

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 for endometrial cancer that is pMMR.

2 Information about durvalumab and olaparib

Marketing authorisation indication

2.1 Durvalumab (Imfinzi, AstraZeneca) '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 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

2.3 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 May 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 May 2025).

2.6 The company has confidential commercial access agreements with NHS England. These make durvalumab and olaparib available to the NHS with a discount. 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 sizes 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 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 endometrial cancers can respond well to treatment while others have particularly poor prognoses. The clinical experts stated that around a third of people with pMMR endometrial cancer have mutations in a protein called p53. This is associated with more aggressive endometrial cancers that may respond better to a PARP inhibitor (like olaparib). The committee concluded that, overall, dMMR endometrial cancer has a better prognosis and response to immunotherapy than pMMR endometrial cancer. It acknowledged that the presence of p53 mutations is an important prognostic indicator in the pMMR subgroup. NICE's manual on health technology evaluation notes that the committee will consider:

- which individuals benefit most from the technology, and
- whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness or cost savings.

The committee noted that durvalumab with platinum-based chemotherapy, then maintenance treatment with durvalumab plus olaparib, may be effective for pMMR endometrial cancer with p53 mutations. So, it suggested that it may be appropriate to consider the clinical and cost effectiveness of the treatment in this subgroup. But, in its response to consultation, the company declined to provide p53 subgroup

analyses for the pMMR population. The company explained that the clinical trial (see section 3.4) showed compelling evidence for all people with pMMR endometrial cancer, regardless of p53 status. In the absence of data for the p53 subgroups, the committee was unable to consider this subgroup further.

Clinical management

3.3 For people with untreated primary 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 (see NICE's technology appraisal guidance on pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer and pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency). Dostarlimab is available at first line for dMMR endometrial cancer but, at the time of this appraisal, it was only available through the Cancer Drugs Fund. The patient expert explained that access to immunotherapy has 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 suggested that people would be willing to accept the possible side effects of having these 2 treatments together if there were 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 treatments for people with untreated primary 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 primary 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 plus 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 dMMR and pMMR endometrial cancer 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 confidence interval around the hazard ratio for OS in this subgroup included 1 and was not statistically significant (HR 0.69, 95% CI 0.47 to 1.00). The committee concluded that standard care plus durvalumab and standard care plus durvalumab plus olaparib improved PFS in untreated primary advanced or recurrent dMMR and pMMR endometrial cancer, respectively. It also concluded that standard care plus durvalumab increased OS in dMMR endometrial cancer. But it was less certain about how effective standard care plus durvalumab plus olaparib was at increasing OS in pMMR endometrial cancer because the hazard ratio was not statistically significant.

Immaturity of DUO-E data

3.5 Duration of 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 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 events) for PFS and

15.2% (7 of 46 events) for OS. In the pMMR subgroup, data maturity for the standard care plus durvalumab plus olaparib arm was 56.5% (108 of 191 events) for PFS and 24.1% (46 of 191 events) 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 dostarlimab appraisal (TA963). But the EAG highlighted that the committee in that appraisal 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 mean 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). Overall, the EAG thought that the clinical efficacy reported in the trial may be different to what would be expected in NHS practice. Firstly, 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. 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. The clinical experts agreed that multiple subsequent immunotherapies would likely not 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).

Secondly, the EAG also highlighted that subsequent immunotherapy use in the standard care arm was lower than might be expected in UK clinical practice. The company highlighted that this issue related mainly to the dMMR subgroup. It noted that subsequent immunotherapy use in the standard care arm of the pMMR subgroup was similar to expected use in the NHS. But, it acknowledged that the subsequent immunotherapy use in the standard care arm was different to NHS practice and may have had a limited impact on outcomes. 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 subgroups. So, the committee concluded that the difference in subsequent immunotherapy use between DUO-E and NHS practice was an unresolvable uncertainty with the existing data.

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 the standard care

arm and the standard care plus durvalumab plus olaparib arm. The EAG agreed with the company's approach to extrapolate PFS 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 clinically 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 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 acknowledged that all extrapolations for OS were very uncertain because of the immaturity of the data from DUO-E (see section 3.5). Noting this caveat, the EAG thought that the company's extrapolations for OS could be reasonable in the pMMR subgroup. In the dMMR subgroup, the EAG preferred a log-logistic extrapolation 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 the dostarlimab appraisal (TA963). But it noted that the choice of OS extrapolation had a small impact on cost-effectiveness results for the dMMR subgroup. 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 in the dMMR subgroup 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. For both the dMMR and pMMR subgroups, the committee noted the EAG's concerns about data immaturity from DUO-E. 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 durvalumab 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 the 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 happen 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 happen 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 DUO-E (see section 3.5), noting that there was no PFS data for 3 years or more. So, there were no efficacy estimates beyond this point, and extrapolations were not based on any data from people who were treated for longer than the proposed treatment cap. Because clinical experts had validated both the PFS and OS extrapolations, the committee thought that any treatment waning would be implicitly captured in these validations. It decided that further investigation of treatment waning was not needed. Taking into account the clinical expert opinion that treatment would stop after 3 years if no progression was observed, the committee considered it appropriate to only include costs of treatment up to 3 years. But it also noted the EAG's point that including the treatment cap meant that the trial outcomes would differ from those seen in the NHS, but it was unknown by how much. The committee concluded that despite some uncertainty, the clinical experts agreed with the 3-year treatment duration cap in the company's model and it is appropriate for decision making. The committee agreed to implement a 3-year stopping rule in the

recommendations, with time to treatment discontinuation modelled using a gamma extrapolation in dMMR and a log-logistic extrapolation in pMMR.

Olaparib maintenance treatment in pMMR population

3.11 At the first committee meeting, the proportion of people with pMMR endometrial cancer starting olaparib maintenance treatment was discussed. The company's and the EAG's economic models assumed that different proportions of people with pMMR endometrial cancer have maintenance treatment with olaparib. The company calculated this proportion by dividing the number of people who started olaparib by the total number of people with pMMR endometrial cancer who were randomised to the durvalumab plus olaparib arm of DUO-E (the proportion is considered confidential by the company so cannot be reported here). But the EAG explained that the company's proportion was based on DUO-E data at the time of randomisation, and so does not reflect the proportion of people who would start olaparib maintenance at week 18. The EAG calculated its base-case proportion by dividing the number of people who started olaparib maintenance by the total number of people with pMMR endometrial cancer who had any maintenance treatment in the durvalumab plus olaparib arm of DUO-E (this proportion is considered confidential so cannot be reported here). The company explained that some people in the standard care plus durvalumab plus olaparib arm in DUO-E did not start maintenance olaparib 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, people with pMMR endometrial cancer would need to be eligible for durvalumab and olaparib at the start of treatment with durvalumab plus chemotherapy. It would then be expected that people would start both durvalumab and olaparib in the subsequent maintenance phase. People with pMMR endometrial cancer could then stop either

durvalumab or olaparib in the event of toxicity and continue with the other treatment. Regarding the proportion of people starting olaparib maintenance treatment at week 18, 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 with pMMR endometrial cancer starting olaparib would likely be somewhere in the middle. At the first meeting, the committee concluded that the company's proportion of people with pMMR endometrial cancer starting olaparib should be used in decision making. This was because by using the DUO-E data to inform the proportion of people with pMMR endometrial cancer starting olaparib, 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.

In response to consultation, the CDF lead reiterated that people with pMMR endometrial cancer must start both durvalumab and olaparib in the maintenance phase and cannot start either as monotherapy. This was in line with the marketing authorisations for durvalumab and olaparib. The EAG confirmed that the model applied olaparib costs to people who were progression-free and alive at 18 weeks. These people then stop olaparib in accordance with the olaparib time-to-discontinuation curve from DUO-E. So, the committee concluded that the model should apply costs of olaparib maintenance treatment to all people with pMMR endometrial cancer who are progression-free and alive at 18 weeks.

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 happens but disease progression does not. So, the company's approach likely overestimates the proportion of people with newly progressed disease 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 people with newly progressed disease 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

Acceptable ICER

3.14 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (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. At the first meeting, the committee noted several uncertainties, specifically:

- the long-term clinical benefit of durvalumab plus platinum-based chemotherapy, then maintenance treatment 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.

In its consultation response, the company stated that the committee had overestimated the uncertainty in this appraisal and considered that a threshold of £20,000 per QALY was overly cautious. Regarding the uncertainties, the company raised the following points:

- The short follow up in DUO-E is common in cancer appraisals, the company had clinically validated its long-term OS extrapolations, and the EAG had said the extrapolations in the pMMR subgroup were reasonable.
- In the pMMR subgroup, subsequent treatment use in the standard care arm was similar to that expected in the NHS. Also, subsequent immunotherapy use in the standard care plus durvalumab plus olaparib arm, though not reflective of NHS practice, would be unlikely to be clinically beneficial.
- Implementation of the stopping rule aligns the modelled treatment duration with what would happen in the NHS, and so should not be considered an uncertainty.

At the second meeting, the committee acknowledged the company's response and reassessed each of the uncertainties. It reiterated that:

- The follow up from DUO-E was short, the OS and PFS data were immature, and no statistically significant OS benefit was shown for durvalumab plus olaparib in the pMMR subgroup (confidence interval around the hazard ratio contained 1).

- Subsequent treatment in DUO-E was not generalisable to NHS practice. There was lower subsequent immunotherapy use in the standard care arm than would be expected in the NHS. The committee acknowledged that this was more of an issue in the dMMR subgroup. But, it noted that subsequent immunotherapy use in the pMMR subgroup was still slightly lower than would be expected in the NHS practice. Also, subsequent immunotherapy in the standard care plus durvalumab plus olaparib arm was permitted in DUO-E but would not be permitted in the NHS, and may have extended durvalumab OS. The net result was that the trial may have overestimated standard care plus durvalumab plus olaparib efficacy and underestimated standard care efficacy, but to what extent is unknown.
- The treatment cap might reflect practice and align the modelled costs with those that would be incurred in the NHS. But, it is unclear how it might affect outcomes, and whether the outcomes of DUO-E (which did not include a treatment cap) were generalisable to the NHS.

The committee concluded that the net effect of the 3 uncertainties was to disconnect the modelled outcomes from the DUO-E trial results and from NHS practice. So, the committee remained highly uncertain about whether the model accurately represented expected outcomes in the NHS. The committee also highlighted that it had not been presented with any new data or analyses during consultation. So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained for both the dMMR and the pMMR subgroups.

Company and EAG cost-effectiveness estimates

3.15 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 the dMMR subgroup, the deterministic and probabilistic 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, both the deterministic and probabilistic ICERs for standard care plus durvalumab in the dMMR subgroup were around the upper end of 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 QALYs in this subgroup.

Committee's preferred assumptions

3.16 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 and assuming no treatment waning (see section 3.10)
- using the company's proportion of people with newly progressed disease in each model cycle (see section 3.12)
- including treatment wastage and updated costs for subsequent chemotherapy (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 for both arms (see section 3.8 and 3.9)
- using a treatment duration cap of 3 years with a log-logistic extrapolation and assuming no treatment waning (see section 3.10)

- assuming that all people in the standard care plus durvalumab plus olaparib arm who are alive and progression-free at 18 weeks start olaparib maintenance treatment (see section 3.11)
- using the company's proportion of people with newly progressed disease in each model cycle (see section 3.12)
- including treatment wastage and updated costs for subsequent chemotherapy (see section 3.13).

Taking into account its preferred assumptions, the committee noted that:

- for the dMMR subgroup, the ICER was within the range considered an acceptable use of NHS resources.
- for the pMMR subgroup, the ICER was substantially higher than the range considered an acceptable use of NHS resources.

Other factors

Equality

3.17 At the first meeting, and considering the responses received during consultation, the committee noted that incidence and mortality for endometrial cancer are higher in people from Black ethnic groups compared with people from White ethnic groups. It also noted that incidence of different molecular subtypes of endometrial cancer (including MMR status) varies across ethnic groups. People in Black ethnic groups may also have endometrial cancer with 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 the potential for indirect discrimination would be justifiable as 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 durvalumab with or without olaparib, could be an innovative treatment. It recalled that, at the time of the appraisal, there were no first-line immunotherapies available for endometrial cancer, except for 1 treatment that was in the CDF for dMMR endometrial cancer. The committee also recalled the particularly high unmet need in people with pMMR endometrial cancer. The committee agreed to take these additional benefits of durvalumab with platinum-based chemotherapy, then durvalumab with or without olaparib, into account in its decision making. To do so, it considered whether it should increase its decision-making ICER threshold for the pMMR subgroup. But, on balance, it remained highly uncertain about the clinical effectiveness of durvalumab for pMMR endometrial cancer because of the uncertainties listed in section 3.14. It concluded that an acceptable ICER would be around £20,000 per QALY gained for both the dMMR and the pMMR subgroups.

Conclusions

Recommendations

3.19 The clinical-effectiveness evidence showed that standard care plus durvalumab improved key outcomes in untreated primary advanced or recurrent dMMR endometrial cancer. The committee concluded that the ICER that included its preferred assumptions in the dMMR subgroup was within the range that NICE considers an acceptable use of NHS resources (see section 3.14). 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.

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 3.14). Although recognising a high unmet need in people with pMMR endometrial cancer, the committee remained highly uncertain about whether the model accurately represented expected outcomes in the NHS. So, durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab plus olaparib, is not recommended in the pMMR subgroup.

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 and Tom Palmer

Technical leads

Joanna Richardson

Technical adviser

Greg O'Toole and Jeremy Powell

Project managers

Emily Crowe

Associate director

ISBN: [to be added at publication]