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Draft guidance consultation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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using durvalumab with platinum-based chemotherapy, then with or without olaparib in the NHS in England.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

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