NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Pembrolizumab with carboplatin and paclitaxel 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 pembrolizumab with carboplatin and paclitaxel 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using pembrolizumab in the NHS in England.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: **14 April 2025 5pm**
- Second evaluation committee meeting: **TBC**
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Pembrolizumab with carboplatin and paclitaxel should not be used for untreated primary advanced or recurrent endometrial cancer in adults.

1.2 This recommendation is not intended to affect treatment with pembrolizumab with carboplatin and paclitaxel that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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

Pembrolizumab with carboplatin and paclitaxel is not required to be funded in the NHS in England for untreated primary advanced or recurrent endometrial cancer in adults. It should not be used routinely in the NHS in England.

This is because there is not enough evidence available to determine if pembrolizumab with carboplatin and paclitaxel offers value for money.

Why the committee made these recommendations

People with untreated advanced or recurrent endometrial cancer usually have platinum-based chemotherapy, such as the combination carboplatin and paclitaxel.

Clinical trial evidence shows that adding pembrolizumab to carboplatin and paclitaxel increases how long people have before their condition gets worse compared with carboplatin and paclitaxel alone. It is less certain how pembrolizumab with carboplatin and paclitaxel affects how long people live because the clinical trial has not been long enough and is still ongoing.

There are uncertainties in the economic model. This is because the model combined subgroups from the clinical trial to produce 1 larger population. But the clinical and

cost effectiveness of pembrolizumab with carboplatin and paclitaxel are different in the 2 subgroups and they should be considered separately.

Because of the uncertainties, it is not possible to determine the most likely cost-effectiveness estimates for pembrolizumab with carboplatin and paclitaxel. So, it should not be used.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD), in combination with carboplatin and paclitaxel, is indicated for 'the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for pembrolizumab.

Price

2.3 The list price is £2,630.00 for a 25 mg per 1 ml concentrate for solution for infusion 4-ml vial (excluding VAT; BNF online accessed February 2025).

2.4 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount and it would have also applied to this indication if pembrolizumab with carboplatin and paclitaxel had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by MSD, 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 the 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. Endometrial cancer has a significant effect on both life expectancy and quality of life. People with advanced or recurrent endometrial cancer (meaning that the cancer has spread beyond the uterus or come back after previous treatment) have a poor prognosis; only 15% of people diagnosed at stage 4 live for 5 or more years. The patient experts explained that an endometrial cancer diagnosis is psychologically very challenging. The committee concluded that advanced or recurrent endometrial cancer has a devastating effect on life expectancy and quality of life.

Mismatch repair

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 mismatch repair deficient (dMMR; around 25% to 30% of cases) or 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 that are recognised by the immune system. dMMR endometrial cancer generally has a better prognosis than pMMR endometrial cancer. dMMR tumours also generally have a better response to immunotherapy treatments. The clinical experts explained that some pMMR tumours have biomarkers that are associated with a particularly poor prognosis and are unlikely to respond to treatment. But, some pMMR endometrial cancers can respond well to treatment. The committee concluded that, in general, dMMR endometrial cancer has a better prognosis and response to treatment than pMMR endometrial cancer.

Clinical management

3.3 For people with untreated advanced or recurrent endometrial cancer, the only routinely available treatment option is platinum-based chemotherapy. The patient experts explained that this can cause a sense of hopelessness because chemotherapy is not associated with curing endometrial cancer. They explained that people with endometrial cancer would be willing to accept worse side effects associated with adding immunotherapy to platinum-based chemotherapy if it gave them hope for a cure and potentially avoided the need for further treatment. The patient experts also explained that, if endometrial cancer returns after chemotherapy treatment, the subsequent treatment options can also cause significant side effects. The committee concluded that platinum-based chemotherapy (specifically, carboplatin and paclitaxel) was the appropriate comparator. It also concluded that there is an unmet need for more effective treatments for people with untreated advanced or recurrent endometrial cancer.

Clinical effectiveness

KEYNOTE-868

3.4 KEYNOTE-868 is an ongoing multicentre, randomised, double-blind, phase 3 trial comparing pembrolizumab with carboplatin and paclitaxel followed by pembrolizumab maintenance against carboplatin and paclitaxel and followed by placebo maintenance. Initial treatment was for 18 weeks, followed by maintenance treatment for 84 weeks. Treatment continued until disease progression, unacceptable toxicity or the maximum treatment time was reached, which was approximately 24 months. The primary outcome of the trial was progression-free survival. Overall survival was a secondary outcome. The trial randomised 819 people with previously untreated advanced or recurrent endometrial cancer. A total of 408 people had pembrolizumab with carboplatin and paclitaxel and 411 had placebo with carboplatin and paclitaxel. Each intervention group was split into dMMR (222 people) and pMMR (597

people) subgroups. The results indicated that pembrolizumab with carboplatin and paclitaxel followed by pembrolizumab maintenance was significantly more effective at preventing progression or death than carboplatin and paclitaxel alone in both the dMMR subgroup and pMMR subgroups (the results from each subgroup are considered confidential by the company so cannot be reported here). Overall survival improved in each subgroup in people who had pembrolizumab with carboplatin and paclitaxel, but was not statistically significant in either subgroup. The committee noted that the relatively short follow-up time from the most recent data cut (the exact follow-up time is considered confidential by the company so cannot be reported here) may have affected the statistical significance of the overall survival results. The committee also noted that nobody from the UK was included in the trial, but clinical experts advised that this should not affect the generalisability of the results to NHS clinical practice. The clinical experts advised that stopping treatment after 2 years was appropriate because treatment response had occurred before this point. The committee concluded that pembrolizumab with carboplatin and paclitaxel is an effective treatment for improving progression-free survival in people with untreated advanced or recurrent endometrial cancer, but it was less certain how effective it was at prolonging overall survival. It also concluded that stopping pembrolizumab after 2 years was appropriate, in line with the clinical expert advice and trial evidence.

All-comer population

3.5 The company retrospectively combined the dMMR and pMMR subgroups to produce an ‘all-comer’ population, which it used for most of its analyses. In the all-comer population, pembrolizumab with carboplatin and paclitaxel improved both progression-free survival (the exact improvement in progression-free survival is considered confidential by the company so cannot be reported here) and overall survival (hazard ratio 0.74, 95% confidence interval 0.57 to 0.97). The EAG was concerned about combining results from both subgroups because the analysis was unplanned and retrospective. The company believed that the all-comer

population better fitted the NICE scope and the marketing authorisation, and provided more statistical certainty because of the larger group size. The clinical experts advised that people with dMMR and pMMR endometrial cancer are treated differently in clinical practice because there are different subsequent treatments available for each subgroup. They advised that the groups have large differences in prognosis (see section 3.2) and that the 2 groups are likely to respond considerably differently to immunotherapy and should be considered separately. The committee agreed with the EAG and clinical experts, and concluded that the pMMR and dMMR subgroups should be considered separately.

Economic model

Company's modelling approach

3.6 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 is suitable for decision making.

Assumptions in the economic model

Overall survival modelling

3.7 The company presented overall survival curves for the all-comer population and the dMMR and pMMR subgroups. In each case, it assessed the suitability of curves using visual and statistical methods, and referred to experts to assess the clinical plausibility of the curves. For the all-comer population, the company selected a log-logistic extrapolation for the carboplatin and paclitaxel only group and a 3-knot odds spline for the pembrolizumab with carboplatin and paclitaxel group. For the dMMR subgroup, the company selected an exponential extrapolation for the carboplatin and paclitaxel group and a log-logistic extrapolation for the pembrolizumab with carboplatin and paclitaxel group. For the pMMR subgroup, the company selected a gamma extrapolation for the carboplatin and paclitaxel group and a log-logistic extrapolation for the

pembrolizumab with carboplatin and paclitaxel group. The EAG assessed the suitability of overall survival curves selected for the all-comer population only. It agreed with the company's choice of extrapolation for the carboplatin and paclitaxel arm. But, it was concerned about the choice of extrapolation using the 3-knot odds spline model for the pembrolizumab with carboplatin and paclitaxel arm. It preferred a piecewise log-logistic model with a 9.4-week cut because this was the best fitting model to long-term survival estimates made by the EAG's clinical experts. The committee recalled its preference for analysing the data by MMR subgroup (see section 3.5). The clinical experts also advised that overall survival is likely to be different in the dMMR and pMMR subgroups, as indicated by the clinical trial data (see section 3.4) and the company's overall survival extrapolations by subgroup. The committee noted that the EAG did not assess the suitability of the company's overall survival extrapolations used in its dMMR and pMMR subgroup analyses. So, it did not believe there was enough information to make a judgement on the most suitable overall survival extrapolations for the dMMR and pMMR subgroups. It requested that the EAG assesses the suitability of the company's overall survival extrapolations for the dMMR and pMMR subgroups.

Starting age in the model

3.8 The starting age in the model for the all-comer population was based on the baseline characteristics in KEYNOTE-868. The mean age in KEYNOTE-868 was 65.4 years. The company said that UK clinicians had advised that the KEYNOTE-868 trial population was broadly similar to real-world clinical practice. The EAG believed that the starting age in the model was too low. It said it received advice that a starting age of 70 would be more representative of people with untreated advanced or recurrent endometrial cancer. The EAG preferred to use a starting age of 67.1 years, which was the starting age chosen for the model in NICE's technology appraisal on dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high

microsatellite instability or mismatch repair deficiency. After the first committee meeting, the Cancer Drugs Fund clinical lead presented data on the average age of people with dMMR and pMMR endometrial cancer in the NHS. The data suggested that the median age of people having treatment with dostarlimab (limited to people with dMMR cancer only) was 66 years. The median age of people having treatment with pembrolizumab and lenvatinib at second line (91.6% of whom had pMMR cancer) was 69 years. The committee requested an update to the model that reflects the individual starting ages of people with dMMR and pMMR advanced or recurrent endometrial cancer.

Source of utility values

3.9 Health-related quality of life data was collected in KEYNOTE-868, but the data was not collected using the EQ-5D. The company advised that it had been unable to find a suitable method for converting the data collected in KEYNOTE-868 to EQ-5D data. The company then assessed other sources of health-related quality of life data. It believed that the endometrial cancer subgroup of KEYNOTE-158 was the most suitable source of health-related quality of life data. The company noted that, although it included only people with dMMR cancer and people who had been previously treated, the endometrial cancer subgroup population of KEYNOTE-158 aligned reasonably well with the population of KEYNOTE-868. The resulting utility values were used for the all-comer population and were also used in the company's analysis of the dMMR and pMMR subgroups. The EAG was concerned about the small sample size of the endometrial cancer subgroup in KEYNOTE-158 (the exact population size is considered confidential by the company so cannot be reported here). It noted that the small sample size meant that the data has limited generalisability, is associated with wide confidence intervals, and may under- or overestimate utility values. The EAG was also concerned that the health-related quality of life data was collected only in people with dMMR cancer, and that people with pMMR cancer may have different utility values. At the committee meeting, a clinical expert advised that they

were not aware of any evidence of differences in quality of life between people with dMMR and pMMR cancer. Another clinical expert advised that dMMR cancer would be expected to respond better to immunotherapy, so might have a higher utility value than pMMR cancer, if both respond to treatment. The committee recalled its preference for analysing the data by MMR subgroup (see section 3.5). It believed that the company's choice of source for health-related quality of life data was the most suitable for the dMMR population, but was concerned that it would not adequately represent the pMMR population. So, the committee requested that the company and EAG explore sources for health-related quality of life data in people with pMMR cancer, or justify the use of the KEYNOTE-158 endometrial cancer subgroup health-related quality of life data in the pMMR population.

Treatment effect waning

3.10 Treatment effect waning was not included in the company's base case model. The company said that the mechanism of action of pembrolizumab and the available trial data supported a sustained treatment effect. For the all-comer population, the company provided a scenario including treatment effect waning in overall survival starting 7 years after starting pembrolizumab treatment for people who did not obtain an objective response (24.8% of pembrolizumab with carboplatin and paclitaxel arm). It chose this point based on long-term follow-up in KEYNOTE-006, which showed no treatment effect waning up to 7 years after starting pembrolizumab. The EAG noted the lack of longer-term evidence around treatment effect waning, but also that previous technology appraisals considered it plausible that treatment effect waning began 3 to 5 years after stopping immunotherapy. So, it did scenarios including treatment effect waning in overall survival 5 and 6 years from starting pembrolizumab. The committee recalled its preference for analysing the data by MMR subgroup (see section 3.5). It noted that the treatment effect waning scenarios were done only on the all-comer population and should be repeated separately for the dMMR and pMMR subgroups. The

committee also noted that the impact of adjusting for treatment effect waning on quality-adjusted life years (QALYs) gained was smaller than expected in the all-comer population. It requested a rationale for this. The committee also requested a scenario in the dMMR and pMMR subgroups where treatment effect waning applies to everyone, regardless of response status, in the pembrolizumab with carboplatin and paclitaxel arm.

Resource use

3.11 The company determined resource use in the model by consulting clinical experts and an advisory board, and considering other technology appraisals related to similar cancers. The EAG was concerned that blood tests and outpatient visits appeared to be underestimated in the pembrolizumab with carboplatin and paclitaxel group. It noted that the use of these resources was lower in the pembrolizumab with carboplatin and paclitaxel group than in the carboplatin and paclitaxel group, even though it would be expected that people having pembrolizumab would have more frequent blood tests and outpatient visits. The EAG provided 2 scenarios for resource use. One used estimates from the EAG's clinical experts. The other used resource use from NICE's technology appraisal on dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. The clinical experts agreed that blood test and outpatient visit resource use appeared to be underestimated in the company's base case. They believed that the scenario using estimates from the EAG's clinical experts was most suitable. This is because the frequency of blood tests and outpatient visits (initially every 3 weeks, then every 6 weeks from week 18 while having treatment) aligned with the dosing schedule for chemotherapy followed by maintenance pembrolizumab. The Cancer Drugs Fund clinical lead noted that, in some cases, pembrolizumab is given on a 3-weekly rather than a 6-weekly cycle, and this would be expected to increase the resource use assumed in the EAG's scenario. The committee agreed with the clinical experts and concluded that the

scenario using estimates from the EAG's clinical experts was most suitable, but that this may underestimate the resource used while on treatment.

Subsequent treatments

3.12 Subsequent treatments in the model were calculated as a one-off cost on entry into the progressed disease health state. The company used a weighted average of the proportion of people having each subsequent treatment in KEYNOTE-868, which was then validated and adjusted by clinicians to produce the cost on entry into the progressed disease health state. The company presented the combined treatment mix for the all-comer population, but also provided separate treatment mixes for the dMMR and pMMR subgroups. The EAG noted that it had received advice that it was standard for pembrolizumab with lenvatinib to be given at second line after carboplatin and paclitaxel at first line. It did a scenario analysis where all pembrolizumab monotherapy use was replaced with pembrolizumab with lenvatinib for second-line treatment. The clinical experts explained that pembrolizumab with lenvatinib is available for second line treatment of dMMR or pMMR cancer, but pembrolizumab monotherapy is available as second-line treatment only for people with dMMR cancer. Because of lenvatinib's toxicity, most people with dMMR endometrial cancer would have pembrolizumab monotherapy. They explained that almost everyone with pMMR cancer who had chemotherapy as first-line treatment started pembrolizumab with lenvatinib at second line. But, they also noted that lenvatinib was associated with significant toxicity, so many people have reduced doses of lenvatinib, with some people completely stopping lenvatinib. The Cancer Drugs Fund clinical lead noted that almost everyone with dMMR cancer now has dostarlimab at first line, so would be ineligible for treatment with pembrolizumab monotherapy or pembrolizumab with lenvatinib at second line. But, because dostarlimab is currently funded by the Cancer Drugs Fund, it cannot be considered as part of this appraisal. The committee recalled its preference for analysing the data by MMR

subgroup (see section 3.5). The committee noted that people with dMMR and pMMR cancer would have different treatments. The committee concluded that subsequent treatments should be based on MMR subgroups. It requested that the EAG consider the appropriateness of the company's subsequent treatment mix for the pMMR and dMMR subgroups.

Cost-effectiveness estimates

Committee's preferred assumptions

3.13 The committee's preference was for separate analyses for the dMMR and pMMR subgroups (see section 3.5). The committee requested further analysis of the following key issues by MMR subgroup:

- overall survival extrapolation (see section 3.7)
- starting age in the model (see section 3.8)
- health state utility values (see section 3.9)
- treatment effect waning (see section 3.10)
- subsequent treatment mix (see section 3.12).

The committee noted its preference for the resource use estimates from the EAG's clinical expert. But it would also welcome an analysis that assumes greater resource use for those having treatment in the pembrolizumab with chemotherapy arm aligned with pembrolizumab's treatment schedule (see section 3.11).

Company and EAG cost-effectiveness estimates

3.14 Both the company's and the EAG's base cases were based on the all-comer population. They differed in choice of overall survival extrapolation (see section 3.7) and choice of starting age in the model (see section 3.8). The company also presented subgroup analyses by MMR status. But, the committee noted these analyses did not include health state utility values by MMR subgroup and treatment effect waning was not fully explored. The committee also noted that the EAG did not assess the suitability of

the company's subgroup analyses. So, it agreed that it was not suitable to rely on either the all-comer population analysis or the company's subgroup analyses by MMR status without further consideration and justification for the assumptions included in each subgroup.

Acceptable ICER

3.15 The committee could not identify a plausible ICER because further analyses are needed. The committee could also not determine a preferred ICER threshold for pembrolizumab with carboplatin and paclitaxel for untreated primary advanced or recurrent endometrial cancer.

Other factors

Equality

3.16 The committee noted that endometrial cancer affects people with female reproductive organs. It also noted concerns raised by the company that:

- incidence rates for endometrial cancer are higher among the Black ethnic group than the White ethnic group
- people from the Black ethnic group are more likely than people from other ethnic groups to be
  - diagnosed with higher-risk, non-endometrioid endometrial cancer subtypes
  - given a late-stage diagnosis of endometrial cancer
- the diagnostic method for endometrial cancer (transvaginal ultrasound) is less reliable when fibroids are present and in high-risk, non-endometrioid endometrial cancer tumours, both of which are more common in Black people.

Race and sex are protected characteristics under the Equality Act 2010. The committee noted that these equalities issues could only be addressed by changes in diagnostics, which is not within the remit of this technology appraisal. Because its recommendation does not restrict access to treatment for some people over others, the committee considered these

were not potential equalities issues that could be addressed in this appraisal.

Uncaptured benefits

3.17 The committee discussed whether there were any uncaptured benefits of pembrolizumab with carboplatin and paclitaxel. It did not identify additional benefits of pembrolizumab with carboplatin and paclitaxel that had not already been captured in the economic modelling. So, the committee concluded that all the benefits of pembrolizumab with carboplatin and paclitaxel had been taken into account.

Conclusion

Pembrolizumab with carboplatin and paclitaxel is not recommended

3.18 The committee believed that analyses of pembrolizumab with carboplatin and paclitaxel should be done separately in the dMMR and pMMR subgroups, and that further analysis of key issues by MMR subgroups was needed (see section 3.5). So, it was unable to establish that pembrolizumab with carboplatin and paclitaxel is a cost-effective use of NHS resources. The committee concluded that pembrolizumab with carboplatin and paclitaxel should not be used, within its marketing authorisation, for untreated primary advanced or recurrent endometrial cancer in adults, and that further analysis is needed.

4 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

Radha Todd

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.

George Millington

Technical lead

Albany Chandler

Technical adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

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