NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab with carboplatin and paclitaxel for untreated primary advanced or recurrent endometrial cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Pembrolizumab with carboplatin and paclitaxel can be used, within its marketing authorisation, as an option for untreated primary advanced or recurrent endometrial cancer in adults. It can only be used if the company provides it according to the commercial arrangement.

1.2 Pembrolizumab with carboplatin and paclitaxel should be stopped after 2 years, or earlier if there is disease progression or unacceptable toxicity.

What this means in practice

Pembrolizumab with carboplatin and paclitaxel must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. It should be stopped after 2 years, or earlier if there is disease progression or unacceptable toxicity. Pembrolizumab with carboplatin and paclitaxel must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that pembrolizumab with carboplatin and paclitaxel provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

People with untreated primary 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 it affects how long people live because the clinical trial is still ongoing.

The summary of product characteristics for pembrolizumab recommends that it is given for no longer than 2 years when it is used for untreated primary advanced or recurrent endometrial cancer.

The cost-effectiveness estimates for pembrolizumab with carboplatin and paclitaxel are within the range that NICE considers an acceptable use of NHS resources. So, it can 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 July 2025).

2.4 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on MSD's webpage on responsibility.

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 endometrial cancer that is advanced (has spread beyond the uterus) or recurrent (has 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 a diagnosis of endometrial cancer 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 respond better to immunotherapy. 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 prolonged response and if it potentially avoided the need for further treatment. 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 then maintenance pembrolizumab against carboplatin and paclitaxel then maintenance placebo. 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 suggested

that pembrolizumab with carboplatin and paclitaxel then 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 the 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, summary of product characteristics and trial evidence.

Subgroups

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 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 was a better fit with the NICE scope and the marketing authorisation, and provided more statistical certainty because of the larger group size. The clinical experts advised that 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 that there are biological differences in how dMMR and pMMR endometrial cancer respond to treatment and different subsequent treatments are appropriate for each subgroup. These factors are likely to have an impact on both clinical- and cost-effectiveness estimates. It 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.

Survival modelling

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 the curves using visual and statistical methods and referred to experts to assess the clinical plausibility of the curves. For the dMMR subgroup, the company selected an exponential extrapolation for the carboplatin and paclitaxel only 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 only group and a log-logistic extrapolation for the pembrolizumab with carboplatin and paclitaxel group.

After the first committee meeting, the EAG assessed the suitability of the company's choice of overall-survival extrapolations for each subgroup. The EAG

agreed with the company's choice of overall-survival extrapolations in the dMMR subgroup. But in the pMMR subgroup, it thought a 1-knot hazard spline was more suitable for the carboplatin and paclitaxel group and a 1-knot normal spline was more suitable for the pembrolizumab with carboplatin and paclitaxel group. In response to the draft guidance consultation, the company stated that some people with pMMR endometrial cancer would have a very good long-term response to pembrolizumab with carboplatin and paclitaxel. It stated that this was better reflected by its preferred log-logistic curve than by the EAG's preferred 1-knot normal spline. The EAG noted that the 1-knot normal spline had a better fit to the observed trial data than the log-logistic model and had a stable hazard function in the long term. It also stated that the short follow up in the trial could not be used as evidence for a significant proportion of people having a long-term response to pembrolizumab with carboplatin and paclitaxel. So, the EAG stated that the company's preferred model for the pembrolizumab with carboplatin and paclitaxel group may overestimate survival in the long term.

In response to the draft guidance consultation, the company stated that in the carboplatin and paclitaxel only group, the gamma model had the best statistical and visual fit and matched clinical expert opinion. The EAG noted that the 1-knot hazard spline had a good visual fit. The company and EAG noted that the preferred extrapolations for the carboplatin and paclitaxel only group were very similar.

At the second committee meeting, the clinical expert stated that the EAG's preferred extrapolation for the pembrolizumab with carboplatin and paclitaxel group was most clinically plausible. They explained that it was difficult to assess the carboplatin and paclitaxel only extrapolations because they were so similar. The committee agreed with the clinical expert that the EAG's extrapolation for the pembrolizumab with carboplatin and paclitaxel group was most suitable. It agreed with the EAG that, without longer-term evidence, a more cautious interpretation of the evidence was most appropriate. The committee also thought that the EAG's extrapolation for the carboplatin and paclitaxel only group was most suitable, although it noted there was very little difference between the curves.

Progression-free survival modelling in the dMMR subgroup

3.8 The company presented progression-free survival curves for the dMMR subgroup in its submission. For the pembrolizumab with carboplatin and paclitaxel arm, it selected the generalised gamma extrapolation. The EAG preferred the log-logistic extrapolation for this arm. It explained that the log-logistic curve was more appropriate because the maturity of the data from the trial warranted more cautious extrapolation. The company noted that its experts considered both the EAG's and the company's selections plausible, but the experts' expectation of earlier and flatter plateauing aligned with the company's choice of generalised gamma. The company thought that the EAG's preferred extrapolation was too pessimistic. It highlighted that the clinical experts in NICE's technology appraisal guidance on dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA963) noted that risk of progression was very low after 5 years of progression-free survival. At the second committee meeting, the clinical expert suggested that both curves were plausible.

For the carboplatin and paclitaxel only extrapolation, the company believed that all standard parametric curves had very poor fits to the trial progression-free survival data. So, it selected a 2-piece gamma model with a 27-week cut. The EAG preferred to use the generalised gamma extrapolation. It stated that, because there were limited differences in fit, the company's piecewise approach introduced additional model complexity without enough justification. It thought that, given the maturity of the long-term data, the generalised gamma model provided a more stable and interpretable long-term extrapolation. The company explained that the 2-piece gamma model had a better visual fit to the data than the EAG's preferred extrapolation and was preferred by experts at an advisory board organised by the company. At the second committee meeting, the clinical expert explained that it was difficult to differentiate between the carboplatin and paclitaxel only extrapolations. The committee agreed with the EAG that it was reasonable to cautiously interpret the data because of the trial's limited follow up, and noted the clinical expert's opinion that both approaches were plausible. So, the committee concluded that the EAG's preferred extrapolations for the pembrolizumab with carboplatin and paclitaxel arm and the carboplatin and paclitaxel only arm were appropriate.

Progression-free survival modelling in the pMMR subgroup

3.9 The company presented progression-free survival curves for the pMMR subgroup in its original submission. For the pembrolizumab with carboplatin and paclitaxel arm the company selected a 2-piece generalised gamma model with a 37-week cut. For the same arm, the EAG suggested that spline models showed best fit to the observed trial data and hazards with 2-knot splines had the best visual fit. It selected a 1-knot hazard spline because it had a good visual fit to the trial data and provided a cautious interpretation of uncertain evidence from the trial. The company said that the EAG's preferred extrapolation for the pembrolizumab with carboplatin and paclitaxel arm had a poor visual fit to the observed data, especially in the tail. For the carboplatin and paclitaxel only group the company selected a 1-knot odds spline model. It stated that it had an excellent visual fit and aligned with clinical experts' predictions. The EAG preferred a 2-knot hazard spline. It stated that spline models showed a strong visual fit to the trial data and the 2-knot hazard spline was the best fit to the observed data with a reasonable hazard function. The company suggested that the EAG's extrapolation for the carboplatin and paclitaxel only arm was overly optimistic, with long-term progression-free survival estimates higher than those made by its clinical experts. The company also noted that the curves for each treatment crossed because of the EAG's choice of extrapolations. It suggested that this was implausible because of the higher response rate and observed treatment effect in the pembrolizumab with carboplatin and paclitaxel arm. The EAG believed that the curve crossing was an artefact of uncertain long-term projections and did not undermine the validity of model in the observed trial data.

At the second committee meeting, the NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) agreed with the company that it was implausible that long-term progression-free survival estimates would be higher at any point in the carboplatin and paclitaxel only arm than in the pembrolizumab with carboplatin and paclitaxel arm, as indicated by the curves crossing. The committee agreed that it was appropriate to cautiously interpret the trial data when choosing long-term extrapolations. But, it acknowledged the company's and the Cancer Drugs Fund lead's concerns about the curves crossing when using the EAG's choice of extrapolation. So, the committee requested that the EAG caps the carboplatin and paclitaxel only progression-free survival so that it was never higher than in the pembrolizumab with carboplatin and paclitaxel arm in its chosen extrapolations. The committee concluded that the modified version

of the EAG's extrapolations was most suitable for modelling progression-free survival in the pMMR subgroup.

Other assumptions in the economic model

Starting age

3.10 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 clinical experts 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. The EAG preferred to use a starting age of 67.1 years, which was the starting age chosen for the model in TA963. After the first committee meeting, the Cancer Drugs Fund lead presented data on the average age of people with dMMR and pMMR endometrial cancer in the NHS. The data suggested that the mean age of people having treatment with dostarlimab (limited to people with dMMR cancer only) was 65.4 years. The mean age of people having treatment with pembrolizumab and lenvatinib at second line (91.6% of whom had pMMR cancer) was 67.54 years. The committee requested an update to the model that would reflect the individual starting ages of people with dMMR and pMMR advanced or recurrent endometrial cancer. In response to the draft guidance consultation, the company used the mean age of people having treatment with dostarlimab as its starting age in the model for the dMMR subgroup. The company noted that people having treatment with pembrolizumab and lenvatinib at second line would be, on average, older than people at first line. So, it used the mean age of the pMMR subgroup in KEYNOTE-868 (also 65.4 years) as its starting age in the model for the pMMR subgroup. The EAG accepted the company's updated starting ages in the model because these more closely aligned with the data presented by the Cancer Drugs Fund lead. The committee agreed with both the company and the EAG and concluded that 65.4 years was its preferred starting age in the model for both dMMR and pMMR subgroups.

Source of utility values

3.11 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 thought 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 had previous treatment, 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, because of the small sample size, the data has limited generalisability, is associated with wide confidence intervals and may under- or overestimate utility values. The EAG was also concerned that 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 thought 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 using the KEYNOTE-158 endometrial cancer subgroup health-related quality-of-life data in the pMMR population.

In response to the draft guidance consultation, the company presented evidence that suggested similar utility values between the dMMR and pMMR subgroups. This included a comparison of the all-comer population and pMMR subgroup (which was 84% of the all-comer population) from KEYNOTE-775, which showed similar health-related quality-of-life results between the 2 groups. The company

also provided an analysis from the RUBY study, which showed a slightly higher utility in the overall population than in the dMMR subgroup. It also used utility values from KEYNOTE-B21, which became available after the first committee meeting. KEYNOTE-B21 is a study of people with previously untreated, post-surgical, endometrial cancer. The company thought that the results for the disease-free health state were very similar between the dMMR and pMMR cohorts but noted that it was an earlier stage of cancer. The company also noted that the progressed-disease health state has a lower utility value than the progression-free state, so the impact of lower response rate in the pMMR subgroup is already accounted for in the model. The company noted that, in the long term, the progression-free health state will mostly comprise responders. So, it thought that dMMR utilities should still be reflective of people with pMMR cancer who remain progression free in the long term, because these are also people whose cancer had a good response to treatment. The company used health-related quality-of-life data from the pMMR subgroup in KEYNOTE-B21 to derive utilities for the progression-free health state in the model. The company thought that the disease recurrence health state from KEYNOTE-B21 was largely aligned with the model's progression-free health state. An equivalent of the progressed-disease health state was not available from KEYNOTE-B21, so the company continued to use the value from KEYNOTE-158 for the progressed-disease utility value.

The EAG had several concerns about the company's updated approach. It noted that the dMMR utility values from KEYNOTE-B21 lack face validity, which may question the validity of the pMMR values. The EAG also thought that the people in the disease recurrence health state in KEYNOTE-B21 were not identical to the starting population of KEYNOTE-868, noting that they may have had different previous treatments and have different current treatments. The EAG also preferred not to mix the source of utility values for each health state without good justification. So, it preferred to maintain using KEYNOTE-158 sourced utility values in its base case.

At the second committee meeting, the clinical expert advised that the trial population of KEYNOTE-868 was dissimilar to the KEYNOTE-B21 population. But, they expected dMMR and pMMR utility values to be different because the groups respond differently to treatment. The committee noted the clinical expert's view that dMMR and pMMR utility values are expected to be different. But, it was

reassured by the evidence presented by the company that indicated that, within each health state, utility values between subgroups were similar. It also noted the limited impact on the cost-effectiveness results when using either the company's or the EAG's preferred approach. So, it agreed that using the KEYNOTE-158 utilities for both subgroups in the progression-free and progressed-disease health states was the best available approach for estimating utility values in the model.

Treatment-effect waning

3.12 Treatment-effect waning was not included in the company's base-case model. In response to the draft guidance, the company maintained that treatment-effect waning should not apply. It said that, because pembrolizumab works by modifying the immune system, treatment effect will continue after treatment ends because the immune system will continue to recognise cancer cells. The company also highlighted results from KEYNOTE-868 that showed a longer duration of response for people who had pembrolizumab with carboplatin and paclitaxel than carboplatin and paclitaxel alone. It also explained that the Kaplan–Meier curves for overall survival and progression-free survival separated early in the trial and remained separated during follow up. The company also highlighted evidence from KEYNOTE-024 (pembrolizumab in non-small-cell lung cancer), KEYNOTE-158 (pembrolizumab for previously treated dMMR tumours) and KEYNOTE-006 (pembrolizumab for advanced melanoma). This showed the treatment effect being maintained across disease areas. The company suggested that treatment-effect waning would be better represented using overall-survival extrapolations, which naturally converge. It presented scenarios where this applied. But, its chosen base-case survival curves did not naturally converge. The company also provided scenarios that applied treatment-effect waning from 7 years until 9 years after starting treatment with pembrolizumab. It chose this point to align with assumptions made in NICE's technology appraisal guidance on pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma and pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency. It applied these treatment-effect waning assumptions to everyone in the pembrolizumab with carboplatin plus paclitaxel

arm or only to people in the same arm who did not have a complete response. The EAG suggested that, although it is plausible that treatment effect continues for some time after stopping treatment, it was appropriate to include treatment-effect waning. It noted that there was limited follow up in KEYNOTE-868 and at 36 months there were few people at risk in the pembrolizumab with carboplatin and paclitaxel arm. So, there was insufficient evidence to support a sustained treatment effect. It also noted that the long-term hazards for relative treatment effect were likely to be similar because immunotherapy is available as a subsequent therapy in the comparator arm. The EAG did not think the other studies cited by the company were strong evidence for excluding treatment-effect waning. It noted that KEYNOTE-158 had a small number of people at risk and a maximum follow up of 5 years, so a sustained treatment effect was uncertain. KEYNOTE-158 also included only people with dMMR cancer, so it is not clear whether the duration of effect could be generalised to the pMMR population. The EAG also noted that the other studies cited by the company did not consider endometrial cancer. At the second committee meeting, the clinical expert explained that assumptions about treatment-effect waning in other disease areas were not necessarily generalisable to endometrial cancer. The EAG highlighted that the company's scenarios that included treatment-effect waning with alternative overall survival curves significantly affected the cost-effectiveness results. This suggested that treatment-effect waning was an important driver of uncertainty. The EAG noted a broad precedent for including a gradual treatment waning effect in endometrial cancer, usually between 5 and 7 years and 7 and 9 years after starting treatment with an immunotherapy. The EAG's clinical experts' advice generally aligned with the precedent from previous appraisals. They advised that treatment-effect waning would apply, but 1 expert thought it would apply immediately after 5 years. The EAG included a gradual treatment waning effect that applied from 5 to 7 years after starting pembrolizumab in its base case. At the second committee meeting, the clinical expert advised that treatment-effect waning would apply. They said it was unclear exactly when waning would start, but it was unlikely to be before 5 years, and it would be a gradual effect. The clinical expert advised that treatment-effect waning would apply more to the pMMR population than to the dMMR population, and be linked to a greater proportion with a lack of complete response. The committee considered the clinical expert's input and the evidence available to support a treatment-effect waning assumption. It noted:

- there was limited long-term follow-up data, especially for endometrial cancer,

and the most relevant data from KEYNOTE-868 was immature

- there was added uncertainty with how relative treatment-effect waning should be taken into account when immunotherapies are also available as a second-line treatment for people who have carboplatin and paclitaxel only
- various assumptions around treatment-effect waning had been made in previous appraisals
- the clinical expert had advised it was more likely that treatment-effect waning would occur in people whose cancer had not responded completely to treatment.

Considering all these factors, the committee concluded that it preferred to apply treatment waning gradually from 5 years after starting treatment with pembrolizumab until 7 years after starting treatment with pembrolizumab, and only to people whose cancer did not have a complete response to treatment.

Resource use

3.13 The EAG was concerned that blood tests and outpatient visits in the company's base case in its original submission appeared to be underestimated in the pembrolizumab with carboplatin and paclitaxel group. At the first committee meeting, it provided a scenario for alternative resource-use assumptions, based on clinical expert opinion. The clinical experts agreed that the company's estimates appeared to be too low. The Cancer Drugs Fund 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 that uses estimates from the EAG's clinical experts was most suitable, but this could underestimate the resource used while on treatment.

In response to the draft guidance, the company consulted with experts on resource use in the model. As a result of its consultation and input from clinical experts in the first meeting, the company updated its resource-use assumptions for the pembrolizumab with carboplatin and paclitaxel group. The updated

resource-use assumptions included a blood test and an outpatient visit with each cycle of treatment (every 3 weeks when having chemotherapy and 6 weeks when having only pembrolizumab maintenance therapy). The company noted that the pembrolizumab maintenance phase was explicitly given as every 6 weeks in the summary of product characteristics for the first-line treatment of primary advanced or recurrent endometrial cancer. This was not the case for other indications. The EAG's clinical experts thought the updated resource use estimates were acceptable and probably reflected clinical practice. So, the EAG accepted the company's updated resource-use assumptions. The committee agreed that the company's resource-use assumptions were suitable.

Subsequent treatments

3.14 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. This was then validated and adjusted by clinical experts to produce the cost on entry into the progressed-disease health state. At the first committee meeting, 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 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. The Cancer Drugs Fund lead noted that almost everyone with dMMR cancer now has dostarlimab at first line, so would not be eligible for 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.

In response to the draft guidance consultation, the company consulted more experts on its subsequent treatment mix in the model. The company's experts estimated that 62% to 66% of people with dMMR endometrial cancer and 47% to 51% with pMMR endometrial cancer would have immunotherapy if their cancer

progressed after having carboplatin and paclitaxel at first line. Because the estimates used in the model were similar to the experts' estimates, the company did not change the distribution of people having pembrolizumab monotherapy at second line in the dMMR population in the model. The company noted that pembrolizumab monotherapy was not available for people with pMMR endometrial cancer at second line, although some people with pMMR cancer in KEYNOTE-868 did have it. So, the company redistributed pembrolizumab monotherapy in the pMMR subgroup to all other subsequent treatments equally, which best fit the experts' estimates of subsequent treatment distribution. The company also updated the distribution of other subsequent treatments based on the experts' estimates. The EAG agreed with the company's updated subsequent treatment mix. The committee concluded that the company's updated subsequent treatment mix was appropriate.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.15 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 noted that the survival estimates, especially overall survival, were uncertain because of the relatively short follow-up time of KEYNOTE-868 (see section 3.4). But, it thought that much of this uncertainty was accounted for because it:

- preferred conservative assumptions for:
  - overall-survival modelling (see section 3.7) and
  - progression-free-survival modelling in the dMMR (see section 3.8) and pMMR (see section 3.9) populations, and
- applied treatment-effect waning (see section 3.12).

The committee also noted the unmet need for people with untreated

advanced or recurrent endometrial cancer (see section 3.1). So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.16 The committee's preference was for separate analyses for the dMMR and pMMR subgroups (see section 3.5). The committee's preferred assumptions for the dMMR subgroup were:

- using a log-logistic extrapolation for the pembrolizumab with carboplatin and paclitaxel group and an exponential extrapolation for the carboplatin and paclitaxel only group to model overall survival (see section 3.7)
- using a log-logistic extrapolation for the pembrolizumab with carboplatin and paclitaxel group and a generalised gamma extrapolation in the carboplatin and paclitaxel only group to model progression-free survival (see section 3.8).

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

- to model overall survival using a 1-knot normal spline for the pembrolizumab with carboplatin and paclitaxel arm and 1-knot hazard spline for the carboplatin and paclitaxel only arm (see section 3.7)
- to model progression-free survival using: a 1-knot hazard spline for the pembrolizumab with carboplatin and paclitaxel arm and a 2-knot hazard spline in the carboplatin and paclitaxel only arm, with a cap so the effect is never higher than in the pembrolizumab with carboplatin and paclitaxel arm (see section 3.9).

The committee's preferred assumptions that applied to both subgroups were:

- using a starting age of 65.4 years (see section 3.10)
- utility values derived from KEYNOTE-158 for both the progression-free health state and the progressed-disease health state (see section 3.11)

- treatment-effect waning from 5 to 7 years after starting treatment with pembrolizumab, applied to people whose cancer did not have a complete response to pembrolizumab (see section 3.12)
- using the company's updated resource-use estimates (see section 3.13)
- using the company's updated subsequent treatment mix (see section 3.14).

Cost-effectiveness estimates

3.17 Applying the committee's preferred assumptions to the dMMR population resulted in an ICER below the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Applying the committee's preferred assumptions to the pMMR population also resulted in an ICER below the middle of the range NICE considers a cost-effective use of NHS resources. The exact ICERs cannot be reported here because they include confidential discounts for drugs included for the intervention and second-line treatments in the model.

Other factors

Equality

3.18 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, 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 thought these were not potential equalities issues that could be addressed by this appraisal.

Uncaptured benefits

3.19 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

3.20 The committee noted that, when its preferred assumptions were applied, the cost-effectiveness estimates for both the dMMR and pMMR populations were within what the committee considered a cost-effective use of NHS resources (see section 3.17). So, pembrolizumab with carboplatin and paclitaxel is recommended for untreated primary advanced or recurrent endometrial cancer.

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 and the healthcare professional responsible for their care thinks that pembrolizumab with carboplatin and paclitaxel 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

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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