# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer

## 1 Recommendations

1.1 Pembrolizumab plus lenvatinib is recommended, within its marketing authorisation, for treating advanced or recurrent endometrial cancer in adults:

- whose cancer has progressed on or after platinum-based chemotherapy and
- who cannot have curative surgery or radiotherapy.

Pembrolizumab plus lenvatinib is recommended only if the companies provide them according to the commercial arrangements (see section 2).

**Why the committee made these recommendations**

There is no standard treatment for previously treated advanced or recurrent endometrial cancer. But people would usually have non-platinum-based chemotherapy.

Evidence from a clinical trial suggests that pembrolizumab plus lenvatinib increases the time until the cancer gets worse and how long people live compared with non-platinum-based chemotherapy. But, the results are uncertain because treatments not used in the NHS were used after non-platinum-based chemotherapy in the trial. So, the results may not apply to UK clinical practice.

Pembrolizumab plus lenvatinib meets NICE's criteria to be considered a life-extending treatment at the end of life. There is some uncertainty in the economic



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model about how long the effect of treatment lasts after people stop taking pembrolizumab at 2 years. But the cost-effectiveness estimates are within the range considered acceptable for an end of life treatment. So, pembrolizumab plus lenvatinib is recommended.

# 2 Information about pembrolizumab with lenvatinib

## Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD), in combination with lenvatinib (Lenvima, Eisai), is indicated for 'the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation'.

## Dosage in the marketing authorisation

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

## Price

2.3 The price of pembrolizumab is £2,630 per 100 mg per 4-ml vial (excluding VAT; BNF online accessed October 2022). The price of lenvatinib is £1,437 per 30 4-mg or 10-mg capsules (excluding VAT; BNF online accessed October 2022). The companies have commercial arrangements. These make pembrolizumab and lenvatinib available to the NHS with discounts. The sizes of the discounts are commercial in confidence. It is the companies' responsibility to let relevant NHS organisations know details of the discounts.

# 3 Committee discussion

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



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## New treatment option

### People with advanced or recurrent endometrial cancer would welcome a new treatment option that is well tolerated

3.1 Endometrial cancer has a devastating impact on life expectancy and quality of life. Recurrent or advanced endometrial cancer has a reported prognosis of 12 months or less and 5-year net survival rates of about 20%, compared with 89% for non-recurrent disease. Physical symptoms can be debilitating and include bleeding, pain, discomfort, reduced appetite, nausea and fatigue. There can also be long-term physical effects after treatment affecting quality of life, including ongoing pain, discomfort and incontinence. Patient experts emphasised the devastating impact of the disease on a person's quality of life. The impact is not just limited to physical health, but also mental health and wellbeing. Repeated intimate examinations can psychologically affect sexual function and intimacy, and lead to distance in relationships. People also experience reduced confidence going to social events because of tiredness, access to a toilet and fear of urinary leakage. Limited mobility and pain resulting in being unable to leave home or work (or work less than full-time) can lead to additional concerns and anxiety about finances. Patient experts highlighted the impact of feeling vulnerable while having chemotherapy, such as the fear of neutropenic sepsis. They also noted how it limits normal activities like seeing family and friends, because of the need to be near a hospital in case of a crisis. The lack of available treatment options other than chemotherapy can lead to a lack of hope for the future and fear of relapse. A patient expert described the importance of hope with the availability of a treatment that could offer a longer and fuller life. The committee heard that since taking pembrolizumab their quality of life had improved dramatically with them being able to take part in sports, have an active social life again and focus on their career. The committee concluded that people with advanced or recurrent endometrial cancer would welcome a new treatment option.



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## Current clinical management

### There is no standard second-line treatment for advanced or recurrent endometrial cancer

3.2 The marketing authorisation for pembrolizumab with lenvatinib states that it is indicated for use after platinum-based chemotherapy. The committee noted that this could be when a person has advanced or recurrent disease after having neoadjuvant or adjuvant platinum-based chemotherapy, or has had platinum-based chemotherapy as first-line treatment for advanced disease. Clinical experts noted that there are no standard second-line treatment options for endometrial cancer when it has progressed or recurred. Options depend on the time interval from previous chemotherapy, previous response and toxicities to chemotherapy, and patient preference. After neoadjuvant platinum-based treatment, people could then have retreatment with platinum-based doublet chemotherapy. Clinical experts noted that possible options include carboplatin with paclitaxel (as retreatment), but they stated that retreatment with platinum-based chemotherapy is infrequently used in the advanced setting. This is because many people do not want to go through hair loss and risk neutropenic sepsis again and some people would be too frail at this point to have chemotherapy again. Pegylated doxorubicin, and weekly paclitaxel monotherapies, are more commonly used as second-line chemotherapies. The clinical experts noted that the response rate with current second-line chemotherapy is only 10% to 15%. One of the clinical experts stated that weekly paclitaxel may have a slightly higher response rate, but overall the 2 drugs have similar efficacies and are used equally, noting that neither option was good. The EAG highlighted that dostarlimab (see NICE technology appraisal guidance on dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency, from now TA779) was recently appraised but could not be considered as a comparator because it was recommended for use in the Cancer Drugs Fund. Hormone therapy, such



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as high-dose progesterone, may be considered if chemotherapy cannot be tolerated, but it is usually part of palliative care or a 'holding measure' to improve wellbeing for people who are more unwell or less fit. The company noted that best supportive care, which had been included in the scope as a comparator, is used for people not well enough for active treatment so is not a relevant comparator. The EAG noted that people for whom active treatment is suitable may choose best supportive care, but noted that the aims are different so excluding this as a comparator is appropriate. The committee acknowledged that platinum-based chemotherapy retreatment may be the relevant comparator when neoadjuvant platinum-based chemotherapy was used in the previous 12 months. However, it noted the comments from the clinical experts about the minimal use in this setting and noted that the company's scenario has a minor impact on the cost-effectiveness estimates. The committee concluded that there is no standard second-line treatment for advanced or recurrent endometrial cancer after platinum-based chemotherapy. But, for the purposes of this appraisal, doxorubicin or paclitaxel monotherapy are appropriate comparators.

## Clinical evidence

### Key evidence for pembrolizumab with lenvatinib comes from the KEYNOTE-775 trial, which is generalisable to the NHS

3.3 The company presented evidence from the KEYNOTE-775 trial, an open-label randomised controlled trial in advanced or recurrent endometrial cancer that had progressed after platinum-based chemotherapy in adults who could not have surgery or radiotherapy. The trial compared pembrolizumab plus lenvatinib (n=411) with treatment chosen by physicians (either paclitaxel or doxorubicin monotherapy; n=416). The trial stratified people by mismatch repair status, with about 16% with mismatch repair deficiency (dMMR) or high microsatellite instability, and 84% with proficient mismatch repair (pMMR). The EAG noted, based on clinical input, that people in UK clinical practice are likely to be older and weigh



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more (and therefore need larger doses of pembrolizumab) than those in the trial. But it noted that both changes had a relatively small impact on the incremental cost-effectiveness ratio (ICER), particularly weight. The company disagreed with the EAG that higher age and weight would be seen in UK practice. It cited 2 real-world evidence studies that reported only a slightly greater age than people in KEYNOTE-775 from the UK (none of these proportions can be reported here because they are marked as confidential by the company). The first study, ECHO, is a retrospective multicentre chart review of advanced or recurrent endometrial cancer that has progressed after a previous systemic therapy commissioned by the company. The number of people included is marked as confidential by the company. The second is Heffernan (2022; n=999), a retrospective review of the English National Cancer Registration and Analysis Service covering people whose cancer progressed to second-line chemotherapy (meaning those who had previous neoadjuvant platinum-based chemotherapy were not included). The clinical experts explained that people in the trial were a bit younger than in clinical practice, but because the drug combination is suitable for older people and those with a poor performance status, it was unlikely to affect the generalisability of the treatment to clinical practice. They noted that the age reported in the real-world studies was more representative of UK clinical practice. The committee acknowledged that there are often some differences between people selected for trials and those in clinical practice because of stringent selection criteria. The committee concluded that the trial was generalisable to NHS clinical practice for the purposes of this appraisal.

## Pembrolizumab plus lenvatinib improves overall and progression-free survival compared with doxorubicin or paclitaxel monotherapy

3.4 The primary endpoints in the trial were progression-free survival and overall survival. The company presented evidence from an interim data cut (October 2020) from KEYNOTE-775 in its original submission. At technical engagement the company presented the results from the final data cut (March 2022) but was not able to incorporate the final data cut in



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the economic model in time for the first committee meeting. In response to consultation on the draft guidance, the company incorporated the final data cut in the model. The final data cut had median 14.7 months follow up. Progression-free survival reached 7.3 months in the pembrolizumab plus lenvatinib arm compared with 3.8 months in the paclitaxel or doxorubicin monotherapy arm. This resulted in a statistically significant improvement in progression-free survival for pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy (hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.48 to 0.66). At the final data cut, overall survival was 18.7 months with pembrolizumab plus lenvatinib compared with 11.9 months with paclitaxel or doxorubicin monotherapy. This resulted in a statistically significant improvement in overall survival for pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy (HR 0.65, 95% CI 0.55 to 0.77). The committee concluded that pembrolizumab plus lenvatinib improved both overall and progression-free survival compared with doxorubicin or paclitaxel monotherapy.

## Pembrolizumab plus lenvatinib may be better in dMMR disease than in pMMR disease but there is not enough evidence to conclude this

3.5 The trial had stratified people based on MMR status and reported separate results for pMMR and dMMR disease from the interim data cut. The EAG noted a differential result by MMR status, with the dMMR population having a better response. For the dMMR group, the HR for overall survival was 0.37 (95% CI 0.22 to 0.62) compared with 0.68 (95% CI 0.56 to 0.84) in the pMMR group. Progression-free survival was 0.36 (95% CI 0.23 to 0.57) in the dMMR group compared with 0.60 (95% CI 0.50 to 0.72) in the pMMR group. The EAG acknowledged that the trial was not powered to explore differences and there was limited follow up, so it considered these subgroup analyses exploratory. However, the EAG's clinical expert noted that prognosis and treatment likely differs between these groups. They also noted that there was no separate cost-effectiveness analyses or model functionality to explore a scenario



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examining these groups separately. While the EAG noted that the impact on the ICER was unknown, pembrolizumab plus lenvatinib may have a lower ICER in dMMR because of the improved overall survival hazard ratio compared with the pMMR group. The company highlighted that it is not clear if the results are clinically or statistically meaningful because the trial was not powered for subgroups; the focus should be on the whole population as per the scope and the marketing authorisation. The company noted that there was a benefit of pembrolizumab plus lenvatinib over doxorubicin or paclitaxel monotherapy in both groups and that there was unmet need in both groups. It also noted that requiring mismatch repair status for treatment may limit access if biopsy or testing is delayed. The clinical experts noted that dMMR cancer may be more likely to relapse after surgery, but that the treatments offered have not differed until the recent guidance on dostarlimab for dMMR disease. They noted that some people with dMMR disease may have dostarlimab (though this is through the Cancer Drugs Fund; see section 3.2) so there is currently more unmet need for the pMMR group. The committee noted that, because dostarlimab is not recommended for routine commissioning, dostarlimab and pembrolizumab plus levantinib cannot be compared for this appraisal. The committee concluded that the study was not powered to consider subgroups based on MMR status and that the treatment pathways for routinely commissioned treatments for both subgroups are the same. It further concluded that both subgroups have had benefit from pembrolizumab plus lenvatinib compared with doxorubicin or paclitaxel monotherapy.

## Economic model

### The model structure is suitable for decision making

3.6 The company used a partitioned-survival economic model that included 3 health states: progression-free, progressed disease and death. The time horizon was 40 years with a 1-week cycle length. There was a 24-month stopping rule for pembrolizumab, as in KEYNOTE-775. The EAG



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considered that the model structure was reasonable. The committee concluded that the model structure was generally appropriate.

## A one-knot spline model for extrapolating progression-free and overall survival is appropriate

3.7 The company originally considered standard parametric and 2-piece parametric curves for the extrapolation of overall and progression-free survival. However, the EAG noted that the hazards were not well tracked with these curves, and that the breakpoint was arbitrary and not determined in an appropriate way. The EAG felt that the company should have considered more sophisticated flexible models (such as cubic splines) because they may better fit the evidence and better track the hazards from the trial. The committee agreed that more sophisticated curves may have a better fit. This was particularly important given the uncertainty and substantial impact on the ICER of the overall survival extrapolation curve and treatment waning assumption. In response to consultation, the company used more flexible spline models and selected the one-knot spline model using an odds scale for the extrapolation of both overall and progression-free survival in both arms over time. The EAG considered the company's new approach to be more defensible and that the results had greater credibility. However, it noted that the justification for the placement of the knot was not clear, which leads to some uncertainty. At the committee meeting, the company advised that it used the default placement for the knot applied by the statistical package used. The EAG noted that the odds scale appears appropriate for the extrapolation of overall survival for the pembrolizumab plus lenvatinib arm, but all extrapolations predicted higher than observed hazards at the end of the observation period. The EAG did an additional scenario using a 2-knot spline for the comparator arm but this had minimal impact on the ICER. The EAG expressed some concerns about the extrapolation of progression-free survival, noting that a comparison of survival estimates was not provided between models for progression-free survival. It also noted that spline models fit the comparator arm better than the



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pembrolizumab plus lenvatinib arm and odds scale models better fit the pembrolizumab plus lenvatinib arm, but this was less clear for the comparator. The EAG would have liked to test alternative types of models but the company model only allows for the odds scale to be used. The committee concluded that, given the EAG scenarios having minimal impact on the ICER, the one-knot spline model was an appropriate choice for the extrapolation of both overall and progression-free survival in both arms.

## Adjusting for the relative treatment effect to account for people having non-NHS treatments after paclitaxel or doxorubicin monotherapy gives the most optimistic estimate of the benefits of the technology

3.8 At the first committee meeting, the committee noted that the impact of having immunotherapies as subsequent therapy after paclitaxel or doxorubicin monotherapy in KEYNOTE-775 on the resulting effect estimate had not been explored. In its response to consultation, the company noted that a proportion of people who had paclitaxel or doxorubicin monotherapy had later switched to pembrolizumab plus lenvatinib or other PD1/PD-L1 or VEGF/VEGFR inhibitor therapies not available in this line in the UK. The proportion cannot be reported here because the company considered it to be confidential. It noted that the trial estimates therefore likely overestimate overall survival for paclitaxel or doxorubicin monotherapy and so underestimate the benefit of pembrolizumab plus lenvatinib compared with the comparator. The company explored different treatment switching methods, noting that all methods improve the benefit of pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy. However, it considered the two-stage estimation (TSE) method to be the least biased and used the adjusted data resulting from using this method in its updated base case. The EAG noted that the committee did not request treatment switching in its preferred base case as the company had done, it just noted that it had not been explored. The EAG noted that the company preferred the TSE



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method without recensoring, but the reason for excluding recensoring was not stated. However, the EAG acknowledged that differences in the hazard ratios are small and that the more conservative result (with a lower treatment estimate) was chosen. The EAG noted that the TSE method assumes the same treatment effect for all treatments after switching. But, that may not be appropriate because there were a variety of treatments that people switched to after paclitaxel or doxorubicin monotherapy and they may have different effectiveness. The EAG considers that the true effect likely lies between the adjusted and unadjusted values. The committee also noted that the TSE method uses a new baseline at progression, assuming all those who progressed have the same prognostic factors. However, the committee agreed that it is unlikely that all will have the same prognostic factors at the new baseline. It also noted that switching does not necessarily happen immediately after progression. The company had reported the time to progression (the exact value is marked as confidential by the company so cannot be reported here). The committee considered that this could have an impact in the model. The company responded that current treatment has limited impact on overall survival, so people are unlikely to benefit from subsequent therapies if their disease has not responded to current first-line treatments. It also noted that adjusting for specific treatments is more complicated. The committee agreed that a result that was adjusted for treatment switching was likely to be less biased than an unadjusted result but was also likely to be an overly optimistic assumption. So, it concluded that the true result was likely to be between the adjusted and unadjusted values.

### It is appropriate to assume some treatment waning in the model

3.9 KEYNOTE-775 used a 2-year stopping rule for pembrolizumab while lenvatinib was continued until clinical progression. The company's model assumed a continuing treatment effect after pembrolizumab is stopped at 2 years with no treatment effect waning for the duration of the model's 40-year time horizon. At the first committee meeting, the committee concluded that it preferred the EAG scenario that included treatment



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waning from years 3 to 5 after starting treatment, but would prefer to see alternative treatment waning scenarios. In response to consultation, the company maintained its position that treatment waning was not appropriate because there is no evidence to substantiate a treatment effect waning. But it explored several scenarios with waning of different proportions of patients from years 5 to 7 after starting treatment. The company argued that there is no evidence of treatment effect waning in KEYNOTE-775, noting that both data cuts show a sustained longer-term benefit of pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy. It noted that the biological rationale of no waning is supported by the fact that pembrolizumab and lenvatinib work synergistically. It considered that lenvatinib may continue to benefit people when pembrolizumab stops by helping to shift tumour environment to immune-stimulatory state by inhibiting VEGFR and FGFR. The company's clinical experts confirmed that some people will have a durable response. The company also reported that a small proportion of people in KEYNOTE-775 were still taking lenvatinib at the last recorded time point of 3 years after starting treatment. The company cited several studies noting that waning was implausible and inappropriate. It noted that multiple pembrolizumab trials in other disease areas (melanoma and non-small cell carcinoma) with 5-year follow up showed a sustained treatment effect. Hazard plots of pembrolizumab from 2 trials in melanoma showed no structural difference in hazards between the trial that had 2-year stopping criteria and the trial that had no stopping criteria. The company also noted long-term durability of the treatment effect for CTLA4 agents in advanced melanoma from year 3 up to year 10 and stated that these work similarly to PD-1 agents. So, the company considered that a similar plateau would likely occur with pembrolizumab plus lenvatinib in this population. It also noted a plateau for overall survival in KEYNOTE-146, the longest-term data of the treatment in this population, with 30% survival reported at 5 years. KEYNOTE-146 was a multicentre, open-label arm phase 1b/2 basket trial of people with selected solid tumours who had



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pembrolizumab plus lenvatinib. It included 108 women with pre-treated endometrial cancer with a median follow-up 34.7 months (95% CI 30.9 to 41.2). The company also noted that in the recent appraisal of the same drug combination in renal cell carcinoma, waning was not included as a preferred assumption. The committee acknowledged that this was because no scenarios incorporating waning had been presented to that committee and its conclusion was not that no waning had been accepted but that treatment waning was plausible but uncertain. The EAG for that topic had acknowledged that there is uncertainty in the long-term treatment effect of pembrolizumab and, because lenvatinib continues after pembrolizumab stops, it is not possible to plausibly separate out any potential waning of treatment effect. The EAG for this topic noted that there is some evidence to support some duration of effect after stopping pembrolizumab, but it is not sufficient to conclude that there is no waning over time. It noted that it is difficult to generalise findings from studies in different disease areas to advanced or recurrent endometrial cancer because previous treatments, patient characteristics and disease severity differed. The EAG noted that the modelled 5-year overall survival for pembrolizumab plus lenvatinib in KEYNOTE-775 showed some evidence of a sustained response (the exact value cannot be reported because it is considered confidential). But this was lower than the 30% response reported in KEYNOTE-146. It also noted that there was uncertainty in the survival rate reported in KEYNOTE-146 because there was considerable censoring and few patients at risk at 28 months. Clinical experts considered that the treatment effect of pembrolizumab plus lenvatinib was likely durable, but it must be assumed that there would be some treatment waning. NHS England's clinical lead noted that it is not appropriate to apply conclusions made for renal cell carcinoma to this appraisal. This is because tyrosine kinase inhibitors (TKI) are in routine commissioning for that disease but, for this indication, it is the first time a TKI would be seen in an established role. The committee noted that waning scenarios had not been explored in the renal cell carcinoma appraisal and so the



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conclusion in the renal cell carcinoma appraisal was not applicable to this appraisal. It agreed that this assumption should be explored based on evidence for this specific technology appraisal. The committee concluded that there was unlikely to be a continuing effect with no waning so it preferred some treatment waning in the model.

### There is likely to be a period with a sustained treatment effect before waning starts

3.10 The committee acknowledged that levantinib could continue for some people for a period of time after pembrolizumab had been stopped. But it noted that data presented showed that only a small proportion of people were still on levantinib at 3-year follow up. It noted that it was unclear how lenvatinib alone (or the synergistic effect of both) could impact a continued benefit from the immunotherapy after it had been stopped. But the committee agreed that it was likely there was a period with a sustained treatment effect before waning was likely to start. So, the committee re-considered its previously preferred assumption of waning from year 3 to 5 after starting treatment as likely to be pessimistic (this was the EAG's preferred assumption, which was consistent with waning assumptions preferred by NICE in other immunotherapies). However, it was difficult to conclude an appropriate time when waning would start. The committee noted that the company's 3 scenarios examining waning from year 5 (the maximum follow up of KEYNOTE-146) to year 7 after starting treatment had been applied to 60%, 70% and 80% of people. The committee acknowledged that there may be some people who have a durable response to treatment. But it agreed that the company's approach was unusual and it was likely that a more appropriate methodology such as a mixture cure model would be needed when taking this approach. The committee therefore agreed to consider all patients in any waning scenario. It concluded that the company's scenario of waning at 5 to 7 years after starting treatment was plausible. But it used the EAG's scenario of all patients waning at 5 to 7 years after starting treatment for decision making because it considered waning of all patients.



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## Using progression status to derive utilities is appropriate

3.11 The company used a time to death approach to derive utilities in the model. The EAG preferred an approach of deriving utilities using progression status because it is more consistent with the model structure. It considered that the company's approach 'divorced health-related quality of life from disease status' in the model. The company noted that the time to death approach is becoming more common and allows finer gradations in utility because it distinguishes between multiple health states not just 2. It considered that the limited utility assessments in immunotherapy trials after disease progression means that the time to death approach is more comprehensive because it captures patient utilities across the full spectrum of the disease, including being close to death. The committee noted that the dostarlimab appraisal (TA779) used a time-to-death utility approach but included disease progression as a covariate to predict utility. The committee noted that the company's approach in this appraisal limits the amount of information informing health states. So while the approach may provide more granular information than the progression status approach, the increased uncertainty in the utility estimates obscures differences between each of the time-to-death categories. In response to consultation, the company updated its base case and used an approach similar to that taken for TA779, except it used 6 time to death (TTD) categories (less than 30 days, 30 to 89 days, 90 to 179 days, 180 to 269 days, 270 to 359 days, 360 days and longer) for both the pre- and post-progressed health states rather than the 2 time to death categorise used in TA779 (TTD less than 180 days and TTD 180 days and longer). The EAG noted that the committee concerns about data required and associated uncertainty are still relevant. The EAG conducted a scenario using the approach used in TA779, which made a small to moderate impact on the ICER. The committee appreciated the company trying an alternative method to incorporate progression status. The committee was unclear of the reason for the cut-offs for the 6 TTD categories chosen by the company. The committee and clinical expert looked at the utilities



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estimated using the company's approach for the health states by the 6 TTD categories. They concluded that it was difficult to know which method was most appropriate given the information that was provided from the company on its scenarios. The committee maintained its conclusion from the first committee meeting that the EAG's approach to deriving utilities using progression status is more appropriate.

### People included in the model should be slightly older than reported in KEYNOTE-775 but younger than used by the EAG

3.12 As discussed in section 3.3, clinical experts felt KEYNOTE-775 was generalisable to UK clinical practice. But, they felt that the average age would be slightly higher than that used by the company and less than that used by the EAG. The experts thought that the most accurate age was likely be around 67, which is between the trial and EAG's estimate and is close to what was reported in the real-world studies. While changing age in the model did not have a very large influence on the results, the committee felt that it was appropriate to include the more applicable average age in the model, as reported in ECHO. Both the company and EAG incorporated a mean age of 67 in their revised base cases. The committee concluded that the age now used in the model is most appropriate.

## End of life

### Pembrolizumab with lenvatinib meets the end of life criteria

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Life expectancy for people with previously treated advanced or recurrent endometrial cancer is typically less than 24 months. The company noted that, at the interim data cut, the paclitaxel or doxorubicin monotherapy arm of KEYNOTE-775 reported mean survival of 11.4 months at the interim data cut and 11.9 months at the final data cut. It also noted that survival was less than 12 months in both



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ECHO (the exact value is confidential so cannot be reported) and Heffernan (2022), in which median survival was 10.3 months. This was consistent with the company's model (the exact value is confidential so cannot be reported) as well as the clinical expectations reported to the company of life expectancy being less than 12 months. The EAG noted that survival in the EAG base-case model was around 24 months. But it received clinical input that average life expectancy was plausibly less than 24 months so was satisfied it met this criterion. Pembrolizumab with lenvatinib appears to extend life longer than 3 months. The company noted that, at both the interim and final data cuts, the pembrolizumab with lenvatinib arm extended life by 6.9 months over the paclitaxel or doxorubicin monotherapy arm. This was consistent with the company's modelled mean survival which cannot be reported here because it is marked as confidential. The EAG noted that clinical input it received supports a survival gain of at least 3 months for both dMMR and pMMR. The committee concluded that pembrolizumab with lenvatinib meets the end of life criteria.

## Cost-effectiveness estimates

### The most plausible ICER is less than £50,000 per QALY gained

3.14 The company's updated base-case deterministic and probabilistic ICERs for pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy were less than £50,000 per QALY gained. This was when confidential commercial arrangements for pembrolizumab, lenvatinib and other treatments in the model were included, so the exact ICERs cannot be reported here. However, the company's base case did not incorporate all the committee's preferred assumptions, including:

- applying waning from years 5 to 7 after starting treatment (3 to 5 years after treatment with pembrolizumab stops; see section 3.9)
- using progression status to derive utilities (see section 3.11).



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The committee concluded that the most plausible ICERs using its preferred assumptions were generated from the EAG's scenarios. It was between the EAG's scenario adjusted for treatment switching and the EAG's scenario unadjusted for treatment switching (see section 3.8). The committee noted that these were less than £50,000 per QALY gained.

## Innovation

### It is uncertain whether pembrolizumab with lenvatinib meets NICE's criteria for an innovative treatment

3.15 NICE defines innovation as a 'step-change' in treatment with benefits not accounted for in the modelling. The company stated that there is uncaptured value because there is no standard care and very few treatment options for people with previously treated advanced or recurrent endometrial cancer. It noted that there were no NICE appraisals for endometrial cancer until recently (dostarlimab, TA779). The dostarlimab appraisal only covers a small proportion of people with dMMR disease, as well as only being recommended in the Cancer Drugs Fund. The company noted that prevalence is higher in older people but many people are of working age, and most people with advanced or recurrent disease have expected survival of around 12 months after diagnosis. The company cited the government's Women's Health Strategy that prioritises improving screening and increasing survival rates for gynaecological cancers, including endometrial cancer, for at least 5 years after diagnosis. Clinical experts considered this treatment to be a 'game changer' and a 'huge step change' for people with endometrial cancer who otherwise have limited treatment options. One expert noted that conversations with people with endometrial cancer have changed substantially with this treatment from very difficult discussions to ones of hope. They noted that the response rate with current second-line chemotherapy is only 10% to 15% so the much better response with pembrolizumab and lenvatinib has a real tenable and meaningful difference. The clinical experts also noted that the treatment has shorter treatment duration, less frequent



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administration, very little monitoring, and no additional testing or unusual concomitant medication. A patient expert explained that they had many activities of daily living back, which make life worth living. At the second committee meeting, patient experts explained that the impact on people faced with chemotherapy or palliative care is not captured in the trials: the chance to live a life and thrive, not just survive. In response to consultation the company reiterated that it considered the combination innovative, noting the synergistic effect of pembrolizumab plus lenvatinib. During the second committee meeting, the company explained that the benefits associated with this technology exceed those directly modelled, noting that there are improvements that are not likely captured in the EQ-5D questionnaire. A clinical expert noted that the duration of response is more remarkable with this treatment over the comparator. However, the committee noted that these can be directly modelled because duration of response is captured in the model. The committee also felt that the benefits noted by experts would be captured in the domains included on the EQ-5D questionnaire. The committee concluded that the technology likely reflects a step-change in treatment, but did not identify any benefits not captured by the company's economic modelling.

## Equality

### There are no equalities issues

3.16 Patient experts noted that there are 2 groups disadvantaged by age and sex. Most people with endometrial cancer have been through the menopause and many have obesity which may be associated with comorbidity and disability. Patient experts noted that, for these people, pembrolizumab with lenvatinib is a kinder treatment than chemotherapy, with a shorter infusion time and fewer side effects affecting quality of life. People who have not been through the menopause are often diagnosed at an advanced stage because healthcare professionals may not recognise symptoms in younger people and because there is no clear guidance about referral for people under 55 years. These people are let



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down by the health services so deserve access to the best available treatments to allow them to life a longer and more normal day-to-day life. Patient experts also highlighted that the ease of use of pembrolizumab plus lenvatinib compared with chemotherapy could benefit disabled people or people with a lower socioeconomic status. They explained that this is because pembrolizumab plus lenvatinib can be administered in local hospitals, so people would not have to travel to tertiary centres, which may be difficult and expensive. The committee acknowledged these issues, which had also been raised by stakeholders, and agreed that improving outcomes for people with endometrial cancer was important. However, the committee considered that because it was assessing pembrolizumab with lenvatinib for all groups raised its decision would not disadvantage any protected group.

## Conclusion

### Pembrolizumab with lenvatinib is recommended

3.17 The committee concluded that the most plausible ICERs are within the range usually considered a cost-effective use of resources when the end of life criteria are met. So, pembrolizumab with lenvatinib is recommended for treating previously treated advanced or recurrent endometrial cancer.

James Fotheringham
Chair, appraisal committee
May 2023

# 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 appraisal within 3 months of its date of publication.



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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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement 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 recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

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 advanced or recurrent endometrial cancer and the doctor responsible for their care thinks that pembrolizumab with lenvatinib is the right treatment, it should be available for use, in line with NICE's recommendations.



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# 5 Appraisal committee members and NICE project team

## Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

## NICE project team

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

**Heather Stegenga**
Technical lead

**Joanna Richardson, Eleanor Donegan**
Technical advisers

**Thomas Feist**
Project manager

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