NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pembrolizumab with lenvatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: November 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using pembrolizumab with lenvatinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 23 November 2022

Second appraisal committee meeting: 10 January 2022

Details of membership of the appraisal committee are given in section 4

1 Recommendations

1.1 Pembrolizumab plus lenvatinib is not recommended, within its marketing authorisation, for treating advanced or recurrent endometrial cancer in adults who have disease progression on or after platinum-based chemotherapy and who cannot have surgery or radiotherapy.

1.2 This recommendation is not intended to affect treatment with pembrolizumab plus lenvatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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.

Clinical evidence shows that pembrolizumab plus lenvatinib increases the time until the cancer gets worse and how long people live compared with non-platinum-based chemotherapy.

There is uncertainty in the economic model about how long people live in the long-term with pembrolizumab plus lenvatinib. The model also assumes that the effect of pembrolizumab plus lenvatinib continues for a person's lifetime after treatment stops, which is unlikely. Both these issues significantly affect the cost-effectiveness estimates. It is also difficult to know what the most likely estimates are because the most recent trial data has not been included. So, pembrolizumab plus lenvatinib is not 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 (simple discount patient access schemes). These make pembrolizumab and lenvatinib available to the NHS with discounts and it would have also applied to this indication if the technologies if they had been recommended. 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 review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

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.

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 ERG 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

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 ERG noted that best supportive care may not always be limited to those for whom active treatment is not suitable (that is, people for whom active treatment is suitable may choose best supportive care). But it 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 NHS clinical practice

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 ERG noted, based on clinical

input, that people in UK clinical practice are likely to be older and weigh more than those in the trial, but noted that both changes had a relatively small impact on the incremental cost-effectiveness ratio (ICER), particularly weight. The company disagreed with the ERG 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). However, the company reported that they did not have time to incorporate the final data cut in the economic model. The interim data cut had median overall survival follow up of 11.4 months; the final data cut had median 14.7 months follow up. Progression-free survival reached 7.2 months in the pembrolizumab plus lenvatinib arm compared with 3.8 months in the paclitaxel or doxorubicin monotherapy arm for the interim data. These values were 7.3 and 3.8 months, respectively, in the final data cut. 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). The additional follow-up data from the final data cut supports the interim analysis for progression-free survival, with the HR being unchanged (HR 0.56; 95% CI 0.48 to 0.66). At the interim data cut, overall survival was 18.3 months with pembrolizumab plus lenvatinib compared with 11.4 months with paclitaxel or doxorubicin monotherapy. These values were 18.7 and 11.9 months, respectively, at the final data cut. This resulted in a statistically significant improvement in overall survival for pembrolizumab plus lenvatinib compared with paclitaxel or doxorubicin monotherapy (HR 0.62, 95% CI 0.51 to 0.75). The data from the final data cut supported the conclusions about the relative impact of the treatment estimated from the interim data although the statistically significant improvement in overall survival decreased slightly (HR 0.65, 95% CI 0.55 to 0.77). The committee concluded that lenvatinib plus pembrolizumab 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 ERG 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 ERG 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 ERG'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 examining these groups separately. While the ERG 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 more unmet need for the pMMR group. However, it is possible that pembrolizumab plus lenvatinib is better than dostarlimab in the dMMR population, but there is no evidence to conclude this. 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 ERG considered that the model structure was reasonable. The committee concluded that the model structure was generally appropriate.

A Kaplan–Meier plus log logistic curve is preferred for extrapolating overall survival using interim data, but final data may change this conclusion

3.7 The company considered standard parametric and 2-piece parametric curves for the extrapolation of overall and progression-free survival. It selected the Kaplan–Meier plus log logistic model for the extrapolation of pembrolizumab plus lenvatinib over time. While the ERG considered other models should be explored (see section 3.8), it agreed based on clinical expert input that this curve is plausible. For the extrapolation of overall survival for the paclitaxel or doxorubicin monotherapy arm, the company selected the Kaplan–Meier plus exponential curve based on visual assessment, statistical fit, validation with clinical experts and external published data. The company validated its curve choice using 2 real-world evidence studies: ECHO and Heffernan (2022). The ERG was concerned with this extrapolation. It noted that the chosen curve for pembrolizumab plus lenvatinib tracks a decline in hazards, but the curve the company chose for the paclitaxel or doxorubicin monotherapy arm did not track the decline in hazards that happened later than for pembrolizumab plus lenvatinib. Also, the exponential extrapolation assumes constant hazards, which does not appear appropriate based on the hazards presented from the data. Based on clinical input, the ERG considered the company's extrapolation of the paclitaxel or doxorubicin monotherapy arm to be

overly pessimistic, and that this meant that the gap between extrapolated arms was larger than is clinically plausible. The ERG was concerned that both supportive studies had relatively short follow-up durations, no more than the median 27.4 months in Heffernan (2022). There was very little detail reported about the ECHO study and its methods. Also, the population was older and had worse health than the population in the KEYNOTE-775 trial, which meant that survival might be lower in clinical practice than in the trial. The ERG considered the Heffernan (2022) study to be of better quality. It noted that it is larger but also highlighted that the median survival was half of what was reported in the KEYNOTE-775 trial: 8.3 months with carboplatin and 6.6 months with paclitaxel compared with 11.9 months from the final data cut for the paclitaxel or doxorubicin monotherapy arm of KEYNOTE-775. This may be because of the trial's patient selection or extra monitoring in the trial, which may have resulted in overestimating survival in both arms. Also, this could be because Heffernan (2022) only included people whose cancer progressed to second-line chemotherapy who may have a worse prognosis than people who had previous neoadjuvant platinum-based chemotherapy. The ERG noted that any impact on the ICER was unclear and it was difficult to analyse this because the curves for each treatment arm were modelled independently. Of the 2-piece approaches, the ERG preferred the Kaplan–Meier plus log logistic extrapolation curve for its base case. It noted that the ICER was very sensitive to different scenarios it explored for overall survival extrapolations. The clinical experts considered the ERG's choice of extrapolation of the paclitaxel or doxorubicin monotherapy arm to better reflect what they saw in clinical practice, but it may be an overestimate. The clinical experts thought that an extrapolated curve having some people surviving longer (that is, the company's choice of extrapolation) may be more appropriate for some people with low volume disease because they had recent previous neoadjuvant chemotherapy. The committee considered that it was not unusual for a trial to have better outcomes than real-world evidence because of patient

selection, but that this would impact both arms so the impact should not be considered for one arm only. The committee noted that the difference in results when using different extrapolation curves needs exploring. The committee concluded that the ERG's preferred model for the paclitaxel or doxorubicin monotherapy arm was more appropriate when using the interim data in the model, but it is unclear how the final data would change the curve fitting for both arms. Having the additional 18 months of data from the trial incorporated in the model may allow the committee to have more certainty in extrapolation curve choice.

Alternative flexible models may be needed

3.8 As noted in section 3.7, the company considered standard parametric and 2-piece approaches to extrapolation. But, it considered the 2-piece approaches to have a better visual fit, statistical fit to trial outcomes and underlying hazards and felt that both internal and external validity (and plausible extrapolations for survival) were met. However, the ERG was concerned that the 2-piece approach was insufficient, noting that the hazard functions were not well tracked and that the breakpoint was arbitrary and not determined in an appropriate way. The ERG felt that more sophisticated flexible models should have been considered by the company (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. It also noted that the impact of having immunotherapies as subsequent therapy in the comparator arm on the effect estimate had not been explored. The committee concluded that exploring different flexible models may be needed, because of the uncertainty and substantial impact on the ICER of the overall survival extrapolation curve and treatment waning assumption (see section 3.7 and section 3.9).

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. The company cited that the mechanism of immunotherapy, the 'immunotherapeutic effect', and evidence from both the KEYNOTE-775 and KEYNOTE-146 trials supports the maintenance of effect after stopping treatment. It noted that there is no evidence to substantiate a treatment effect waning, so this was not explored by the company. KEYNOTE-146 was a multicentre, open-label arm phase 1b/2 basket trial of people with selected solid tumours who had treatment with 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 reported that long-term overall survival in KEYNOTE-146 showed a durable and sustained treatment effect beyond the 2-year treatment in the form of a plateau with 30% survival reported at 5 years. The ERG considered that 5-year survival was likely to be lower in clinical practice because there was considerable censoring and few patients at risk at 28 months in KEYNOTE-146. The ERG's clinical expert noted that there is little data on the effect of waning but that it was reasonable to assume some gradual waning after treatment and that some people's cancer will relapse. The ERG noted that NICE's recent appraisal for dostarlimab (TA779) included treatment waning. The ERG included a scenario with waning from 2 to 5 years showing that the results were highly sensitive to this, but did not include waning in their base case because of the lack of data supporting the assumption. Clinical experts considered that the treatment effect of pembrolizumab with lenvatinib was likely durable, but it must be assumed that there would be some treatment waning. The company further cited 2 supportive appraisals of pembrolizumab monotherapy showing an ongoing treatment benefit. Both the ERG and the NHS England clinical lead noted that the appraisals cited by the company were in different disease areas and it is unclear how endometrial cancer would respond. In the appraisal for advanced melanoma after disease progression with ipilimumab (see NICE

technology appraisal guidance on pembrolizumab for treating advanced melanoma after disease progression with ipilimumab) there was no stopping rule for pembrolizumab so it would not make sense to have treatment waning. The trial used in the appraisal in non-small-cell lung cancer (see NICE technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) required people to have tumours expressing at least 50% PD-L1. NHS England's clinical lead noted that people in that trial had cancer that was more likely to respond. So the approach to treatment waning in that appraisal may not be generalisable or applicable to disease that has not been pre-selected as being likely to respond. The committee also heard that all other appraisals for pembrolizumab included treatment waning, although there were differing waning effects used, with waning occurring from over 1 year to up to 5 years after stopping treatment. The committee agreed that there was unlikely to be a continuing effect with no waning so preferred some treatment waning in the model. The company noted that the final data cut was not likely to answer the question about long-term treatment waning because there was not enough longer follow up. However, the committee considered that having the longer-term data with a flexible fit curve to the updated data may help determine when waning occurs. It noted that overall survival in the final data cut of KEYNOTE-775 shows 30% survival at 3 years, whereas the KEYNOTE-146 trial showed the same proportion at 5 years. The committee agreed that it preferred the ERG's scenario that included treatment waning over 3 years after stopping treatment with pembrolizumab, but the impact of alternative treatment waning assumptions would be helpful. The committee concluded that it would prefer to see alternative treatment waning scenarios in a model that incorporates the final data cut.

Using progression status to derive utilities is appropriate

3.10 The company used a time to death approach to derive utilities in the model. The ERG 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 ERG noted that the company's model produced counterintuitive results when a scenario was applied that varied the progression-free survival curve while maintaining the same overall survival curve. This impacted costs but not quality-adjusted life years. The ERG's approach to use progression status increases the ICER but only minimally. 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. They 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. The committee concluded that the ERG'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 ERG

3.11 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 ERG. The experts thought that the most accurate age was likely be around 67, which is between the trial and ERG'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. It concluded that it would prefer to see that as the assumption for age in the model rather than the company's or ERG's assumptions.

End of life

Pembrolizumab with lenvatinib meets the end of life criteria

3.12 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 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 ERG noted that survival in the ERG base-case model was around 24 months. But they received clinical input that average life expectancy was plausibly less than 24 months so were 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 ERG 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 cost-effectiveness estimate is unknown, further analyses including data from the final data cut is needed

3.13 Having agreed the end of life criteria had been met, the committee noted that it preferred most of the assumptions used by the ERG in the scenario, including the ERG's base case with treatment waning. However, the committee did not agree with the ERG's assumption of using the mean age of 75 in the model and agreed that the mean age of 67 better reflected the age of people in clinical practice (see section 3.11). When the confidential patient access schemes for pembrolizumab, lenvatinib and subsequent treatments were applied to the ERG's scenario, which included waning, the ICERs would not be within the range considered a cost-effective use of NHS resources. However, the committee noted the uncertainty in how the use of the final data cut in the model may impact the choice of extrapolation and the assumptions around waning. As a result, the committee concluded that the most plausible cost-effectiveness estimate was currently unknown and further analyses, including the data from the final data cut, was needed for decision making.

Innovation

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

3.14 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 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 has changed substantially with this treatment from a very difficult discussion to one 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 meaningful difference. The clinical experts also noted that the treatment has shorter treatment duration, less frequent administration, very little monitoring, 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. The committee concluded that the technology likely reflects a step-change in treatment, but did not identify benefits not captured by the company's economic modelling.

Equality

There are no equalities issues

3.15 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 fail to recognise symptoms in younger people and because there is no clear guidance about referral for people under 55 years. These people are let

down by the health services so deserve access to 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 with lenvatinib compared with chemotherapy could benefit disabled people or people with a lower socioeconomic status. They explained that this is because pembrolizumab with 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 pembrolizumab with lenvatinib for all groups raised and felt its decision would not disadvantage any protected group.

Conclusion

Pembrolizumab with lenvatinib cannot be recommended because further analyses are needed for decision making

3.16 The committee recognised that there was a high unmet need for people with previously treated advanced or recurrent endometrial cancer. It agreed that pembrolizumab with lenvatinib improved progression-free and overall survival in these people. However, it did not have a plausible cost-effectiveness estimate to use in its decision making. The committee requested to see analyses that reflect its preferred assumptions (see section 3.13) and which also address the following:

- Including results from the final data cut (March 2022) in the model, ideally exploring more sophisticated flexible models, to allow the committee to see how this may affect the choice of extrapolation for both arms and the justification of waning in the model (see sections 3.7 to 3.9).
- The impact of different treatment effect waning scenarios on the ICER (see section 3.10).

The committee therefore concluded that it could not recommend pembrolizumab with lenvatinib for people with previously treated advanced or recurrent endometrial cancer.

James Fotheringham
Chair, appraisal committee
November 2022

4 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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