NICE National Institute for Health and Care Excellence

NICE guidance

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

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 Dostarlimab is recommended for use within the Cancer Drugs Fund as an option for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency in adults who have had platinum-based chemotherapy. It is recommended only if the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect treatment with dostarlimab 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 with high microsatellite instability or mismatch repair deficiency. People are usually offered further chemotherapy, which has limited effectiveness, so there is an unmet need for an effective treatment for this population.

Clinical trial evidence suggests that dostarlimab increases the time until the cancer gets worse and how long people live. However, this is uncertain because the trial is ongoing and dostarlimab has not been directly compared with other treatment options. Indirect comparisons of dostarlimab with other treatments are highly uncertain because of differences between the included studies.

Dostarlimab has the potential to be cost effective, but more long-term evidence is needed to address the clinical uncertainties. So, dostarlimab cannot be recommended for routine use in the NHS.

More data from the dostarlimab trial would help address uncertainties about its clinical effectiveness. Dostarlimab is therefore recommended for use in the Cancer Drugs Fund so that more data can be collected.

2 Information about dostarlimab

Marketing authorisation indication

2.1 Dostarlimab (Jemperli) is indicated as 'monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of dostarlimab is £5,887.33 per 500 mg vial. The company has a commercial arrangement. This makes dostarlimab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by GlaxoSmithKline, 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.

The condition and current treatment

Chemotherapy is standard of care for previously treated advanced or recurrent endometrial cancer with high MSI or MMR deficiency

3.1 Clinical experts explained that there are different subtypes of endometrial cancer and that endometrioid carcinoma is the most common. People with advanced or recurrent endometrial cancer who have already had platinum-based chemotherapy have an extremely poor prognosis. Advanced or recurrent endometrial cancer is also associated with a range of debilitating symptoms including deteriorating physical functioning and health-related quality of life. Around 23% of people with endometrial cancer have the subtype with high microsatellite instability (MSI) or DNA mismatch repair (MMR) deficiency biomarkers. Most people with advanced or recurrent endometrial cancer with high MSI or MMR deficiency that has progressed during or after treatment with a platinum-containing regimen will have further lines of chemotherapy. There is no standard care for second-line treatment. People usually have either paclitaxel or doxorubicin, or combination chemotherapy. A small number may have hormone therapy. The committee concluded that there is a range of different treatment options available to people after having platinum-based chemotherapy.

People with the condition have a poor prognosis

3.2 The company evidence submission described a range of studies that showed poor prognosis for people with advanced or recurrent endometrial cancer after platinum-based chemotherapy. The clinical

experts also noted recently reported results from the KEYNOTE-775 trial that were not referred to in either the company's evidence submission or the ERG's report. This trial compared pembrolizumab plus lenvatinib with paclitaxel or doxorubicin monotherapy in people who have advanced endometrial cancer with MMR deficiency and who have had platinum-based chemotherapy. The committee heard that for people in the chemotherapy arm, median progression-free survival was 3.7 months and median overall survival was 8.6 months. The committee agreed that KEYNOTE-775 was a useful source of comparator data for this population (see section 3.7). It concluded that people with the condition have a poor prognosis with current clinical management.

There is high unmet need for people who have had previous treatment

3.3 The patient experts explained that existing treatments for previously treated advanced or recurrent endometrial cancer have limited effectiveness. Chemotherapy can also have considerable adverse effects that impact quality of life, including fatigue, pain, nausea, hair loss and itching. The clinical and patient experts explained that dostarlimab is associated with fewer serious adverse events than chemotherapy and would therefore offer a considerable improvement in quality of life. The patient experts emphasised that quality of life is very important to people with advanced or recurrent endometrial cancer because of their poor prognosis. Standard chemotherapy can take up to a day to be administered in hospital whereas dostarlimab takes approximately 30 minutes, which is much less burdensome for people having treatment. The patient experts noted that people with the condition would welcome more effective and targeted treatments that extend survival and improve quality of life, but also those with a lower treatment burden than standard chemotherapy. The committee agreed that the second-line treatment options provide limited survival benefit and are associated with adverse events that negatively impact quality of life. The committee concluded that people with previously treated advanced or recurrent endometrial cancer have high unmet clinical need.

Clinical evidence

The main clinical evidence comes from a single-arm study

3.4 Clinical-effectiveness evidence for dostarlimab came from the GARNET trial, an ongoing phase 1, open-label, single-arm, multicentre study of the efficacy and safety of dostarlimab. GARNET includes 129 people with recurrent or advanced endometrial cancer with high MSI or MMR deficiency who have progressed during or after platinum-based chemotherapy. The primary endpoints are objective response rate and duration of response. Secondary endpoints include progression-free survival, overall survival, health-related quality of life and safety. The results of GARNET are confidential and cannot be reported here. The company consider that dostarlimab shows a good objective response rate, and improves progression-free and overall survival in people who have a poor prognosis. The committee was aware that paclitaxel monotherapy is the only second-line chemotherapy treatment that has consistently shown a response rate of more than 20%, less than half the objective response rate shown by dostarlimab. However, the committee noted that this evidence was not from people with the MMR deficiency or high MSI biomarkers, that is, the subpopulation of interest. Clinical and patient experts noted that dostarlimab appears to be well tolerated and associated with a manageable adverse event profile similar to other currently licensed anti-programmed cell death ligand 1 (PD-L1) treatments. Adverse events related to treatment were generally low grade, and discontinuation because of treatment-related adverse events was uncommon. The committee concluded that data from GARNET is very immature. It also concluded that the lack of a biomarker-matched comparator arm makes it difficult to compare dostarlimab with current treatments for this specific subpopulation of people with endometrial cancer.

The real-world evidence subgroup from registry data is not a robust comparator for GARNET

3.5 The company's systematic literature review of comparator treatments identified some observational studies, but patient characteristics and

Kaplan–Meier survival data were poorly reported in these studies. The studies were therefore not suitable for robust indirect treatment comparisons. The company identified a real-world evidence (RWE) cohort from retrospective linked patient-level health data from 2013 to 2018, available through the National Cancer Registry Analysis System (NCRAS). A subgroup of registry patients was identified as 'GARNET-like'. They had advanced or recurrent endometrial cancer that progressed after 1 platinum-based doublet chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The company considered that this subgroup matched the inclusion criteria of people in GARNET, although information on high MSI or MMR deficiency status was not available. Registry patients had a wide range of chemotherapy regimens. The company considered the RWE study to be the primary evidence to evaluate the comparative efficacy of dostarlimab. This was because of its large sample size, the close alignment to the patient characteristics in GARNET, and the real-world representation of current clinical management for this population. The ERG agreed that using the RWE is a pragmatic approach to resolving the lack of comparative data in the existing literature. However, it raised concerns about how generalisable the subgroup of people identified in the RWE as 'GARNET-like' are to people in GARNET, because:

- There was no information on biomarkers in the NCRAS dataset, so it was uncertain how many of the subgroup could be expected to have endometrial cancer with high MSI or MMR deficiency.
- Although people with an ECOG performance status of 2 or more were excluded from the RWE subgroup, there was no status recorded for almost half of the people included.
- There were considerable differences in histology between GARNET and the RWE study. This included a much higher proportion of people with endometrioid disease in GARNET, which is associated with a more favourable prognosis than other histological subtypes.

- People in GARNET had more prior lines of treatment than the RWE subgroup. This is because GARNET included people who had 1 or more previous treatments, but people in the RWE subgroup only had 1 treatment.

  Clinical experts explained that the differences in ECOG performance status would not cause substantial bias because they represent a relatively small difference between patient prognoses at this stage in the treatment pathway. They noted that differences in the number of lines of previous therapy was likely to be a key prognostic factor to consider when matching the 2 populations. The committee noted the ERG opinion that differences between the GARNET and RWE subgroup would cause any indirect treatment comparison to be highly uncertain. The committee agreed that the RWE represents a pragmatic approach to the problem of inadequate comparator studies. However, any indirect treatment comparisons using the RWE could not be robust. This is because of concerns over matching the 2 populations and the unknown prevalence of high MSI or MMR deficiency in the RWE subgroup. The committee also noted that there is often a discrepancy between evidence from clinical trials compared with RWE, which can have lower observed efficacy for a wide range of reasons. The clinical experts also noted that randomised trial data, when available, was considered preferable to RWE. This was particularly relevant because the trial and RWE were not matched for several factors, including MMR deficiency and MSI status. The committee concluded that evidence from the RWE subgroup was not a robust comparator for GARNET.

The company's naive comparison suggests dostarlimab improves survival, but this is highly uncertain

3.6 The company's naive comparison with the GARNET-like subgroup from the RWE registry predicted that dostarlimab has better progression-free survival and overall survival outcomes than current care in the UK. This data is academic in confidence and cannot be reported here. The committee concluded that endometrial cancer with high MSI or MMR deficiency is more likely to respond to immunotherapy than the treatments used in current clinical management. However, the benefit of dostarlimab remained highly uncertain because of the limited follow up and lack of a comparator arm in GARNET.

Evidence from KEYNOTE-775 is a more relevant comparator

3.7 The committee recalled that the clinical experts had described the recent reporting of KEYNOTE-775 (see section 3.2). This trial compared pembrolizumab plus lenvatinib with paclitaxel or doxorubicin monotherapy in people who have advanced endometrial cancer with MMR deficiency and who have had platinum-based chemotherapy. The committee discussed whether the chemotherapy arm of KEYNOTE-775 represents the most relevant comparator data for dostarlimab, because the evidence for dostarlimab came from a single-arm trial (see section 3.4). The clinical experts emphasised that the KEYNOTE-775 population is biomarker-matched to people in the dostarlimab trial. They also emphasised that KEYNOTE-775 is a randomised controlled trial rather than a real-world registry. It would therefore be a more reliable comparator for the dostarlimab single-arm trial. The committee agreed with the clinical experts and concluded that KEYNOTE-775 may provide a better source of comparative data for the cost-effectiveness analyses of dostarlimab.

Indirect treatment comparisons

Matching-adjusted indirect treatment comparisons suggest that dostarlimab improves survival, but these are highly uncertain

3.8 To investigate the impact of any remaining differences between the 2 populations, the company also did a matching-adjusted indirect comparison (MAIC) of overall survival between GARNET and the UK RWE subgroup. The company did a targeted literature review to identify a range of prognostic variables typically associated with survival in people with endometrial cancer, which were validated by a panel of clinical experts. Cox regression models were also used to investigate the prognostic value of each potential matching variable. Based on these results, 2 MAIC scenarios were constructed:

- Scenario 1, based on the prognostic variables identified by clinical expert opinion, including histology (non-endometrioid and unknown versus endometrioid) and the number of lines of prior platinum-based therapy for advanced or recurrent disease (0 or 1 versus 2 or more).

- Scenario 2, based on the matching variables found to be statistically significant based on regression analyses, including ethnicity (black, other and unknown versus white), stage at diagnosis (stage 3 or 4 versus stage 1 or 2), histology (non-endometrioid and unknown versus endometrioid) and prior surgery (yes versus no).

  The results are marked as academic in confidence and cannot be reported here. Both matching scenarios showed that the median overall survival, as well as the percentage of people alive at months 6, 12 and 18, was greater with dostarlimab than current clinical management. The hazard ratios for overall survival showed that dostarlimab statistically significantly reduced the risk of death compared with current clinical management. The company considered that the similarity of the overall survival results between the unadjusted GARNET population and both matched scenarios showed minimal differences between the GARNET and RWE GARNET-like populations. However, the ERG considered that systematic differences remained between the 2 cohorts because of the methodological issues associated with data collection, case definition and selection. This particularly included the complicated screening processes used to identify the final RWE subgroup. The ERG noted that these systematic biases are difficult to recognise and quantify, and cannot be adjusted for by statistical methods. The committee agreed with the ERG about the limitations of the MAIC scenarios and the validity of the results. The committee also recalled its reservations about whether RWE would be an adequate proxy for a control arm of a randomised controlled trial comparing dostarlimab with conventional care in this population. The company also did a series of MAICs comparing GARNET with individual studies of some comparator chemotherapy treatments identified in the literature. This was to provide additional evidence to support the results from the primary MAICs between GARNET and the RWE study. However, the ERG cautioned that these MAICs were also severely limited because the studies had small sample sizes, and patient characteristics and prognostic variables were poorly reported. In particular, the lack of data on previous anticancer treatments was a key limitation because this is an important prognostic variable, based on clinical expert opinion. The ERG suggested that analyses from a more homogeneous subgroup, such as people with endometrioid disease, would help mitigate these concerns. The committee agreed that the company's MAICs (scenarios 1 and 2) could not be considered a robust source of evidence because of the high levels of uncertainty in matching the cohorts. The committee concluded

that better data was needed to inform a robust analysis of comparative efficacy between dostarlimab and comparator treatments.

Exploratory analysis is also uncertain, but the overall evidence suggests that dostarlimab is more effective than current care

3.9 At the technical engagement stage, the company provided an additional MAIC analysis that was based on more homogenous cohorts of people with the endometrioid subtype from GARNET and the RWE study. This was provided to explore the effect of closer population matching on the comparative efficacy of dostarlimab. The company considered the similar hazard ratios for the endometrioid-only cohorts and MAICs show only minor imbalances between the full RWE subgroup and GARNET populations. However, the ERG considered it more likely that the MAICs had not adequately adjusted for the remaining imbalances between the 2 endometrioid cohorts. While the endometrioid subgroup data mitigated one of the major differences between GARNET and RWE, the ERG noted that substantial differences in patient characteristics remained, even within this more homogeneous subgroup of patients. Key differences included ECOG performance status, International Federation of Gynaecology and Obstetrics stage, disease grade, number of prior platinum-based therapies for advanced or recurrent disease, and prior surgery for advanced or recurrent endometrial cancer. The net effect of excluding people who do not have the endometrioid subtype was a smaller estimated survival advantage for dostarlimab compared with comparator treatments. The ERG explained that while the endometrioid-only analysis may have removed histological type as a source of uncertainty, the comparisons still likely had a substantial degree of uncertainty. The MAIC for this subgroup did not adequately address these issues. Therefore, the relative effectiveness of dostarlimab estimated from the endometrioid-only subgroup is still associated with a high level of uncertainty and may be over-estimated. The committee agreed with the ERG that the endometrioid-only subgroup supplementary analysis had reduced some bias but was still highly uncertain because of remaining differences between the 2 populations (see section 3.5). The committee noted that the endometrioid-only MAIC suggested that closer matching resulted in reduced comparative efficacy of dostarlimab. It also noted that this further underlines the need for

better evidence to produce more robust conclusions about the comparative effectiveness of dostarlimab. The committee concluded that dostarlimab had a biologically plausible reason for being more effective than conventional care, and the analyses presented tend to support this. However, the magnitude of any benefit remained highly uncertain because of the single-arm trial and major shortcomings in the comparator evidence.

Economic model

The company's model is appropriate for decision making

3.10 The company used a partitioned-survival economic model that included 3 health states: pre-progression, post-progression and death. The committee concluded that the model was generally appropriate and consistent with the models used in other appraisals for endometrial cancer.

Survival extrapolation

There is high uncertainty in the extrapolation of overall survival because of the immaturity of trial data

3.11 The company independently fitted parametric models to dostarlimab (GARNET) and standard of care (the GARNET-like RWE cohort) in the base case cost-effectiveness analysis. It considered independent parametric models to be a more robust approach because of differences in the mechanisms of action between dostarlimab and the different chemotherapy options that are current clinical management. The company noted that treatment response to immunotherapy differs from the response to chemotherapy, including the possibility of a delayed response and longer-term treatment benefits after treatment discontinuation. The company's process for selecting the most appropriate curve for overall survival for dostarlimab was to:

- explore the visual fit of parametric models by presenting them superimposed onto the Kaplan–Meier analysis
- adjust the parametric model for the waning of treatment effect and so it does not exceed the overall survival of the general population

- select an adjusted parametric model that best reflects and conforms to the predictions of the company's clinical expert advisory panel.

  The overall survival extrapolations appeared to provide a good fit to the observed Kaplan–Meier data for the duration of the data collection in the trial. The company selected the generalised gamma extrapolation for overall survival with dostarlimab beyond the trial data because it gives the most clinically plausible long-term extrapolations and is more closely aligned with the clinical expert feedback. The lognormal model was considered to give the next most clinically plausible long-term extrapolations after the generalised gamma model, and it also had the lowest sum of Akaike and Bayesian information criteria. However, the company asserted that the lognormal model is not clinically plausible. This is because when treatment waning was applied, the lognormal curve substantially underestimated the predicted numbers of people alive at 5, 10, 15 and 20 years compared with the clinical expert estimates. The ERG explained its concerns about relying on clinical experts' opinions on the expected overall survival for people having dostarlimab. It explained that the clinical predictions should probably be regarded as informed speculation because of the widely varying estimates from individual clinicians. It is possible that consulting more, or different, clinicians could result in a considerably different mean estimate. The ERG explained that it considered the company's preferred generalised gamma curve to be overly optimistic because it predicted survivors well beyond 30 years, which does not seem clinically plausible. The ERG preferred the Weibull curve because the company expert responses could be biased by the elicitation methods used, and therefore too high to assess how reasonable the adjusted curves were. The company did not accept the ERG's preference for the Weibull curve. It suggested that the shape of the hazard function produced by that model was inappropriate for the treatment effect associated with immunotherapies such as dostarlimab. But the ERG further explained that all models under consideration were associated with substantial uncertainty because of the lack of data. The visual fit of all models to the Kaplan–Meier data was relatively poor because the plot did not reach a median, exhibited several changing trajectories and had a long flat tail. The clinical experts explained that the Weibull curve preferred by the ERG appeared to be somewhat pessimistic. This is because it predicted lower overall survival than might be expected from immunotherapies in other clinical indications, which can have a prolonged treatment effect and a shallowing curve over time. Defining exactly where plateauing of the curve begins and

how long it is maintained is uncertain, but this is very difficult to predict with any certainty given the limited duration of follow up in the trial. The ERG thought that longer-term overall survival was uncertain because the trial follow up was too short and there are not enough participants. It also thought that there were too few overall survival events relative to the number of participants to accurately predict future survival. The committee noted that longer follow up could partially mitigate this problem. The ERG also explained that after technical engagement, the company reconsidered its preferred treatment waning effect. Implementing this in the model substantially reduced the differences in results between the company's preferred generalised gamma model and the ERG's preferred Weibull model. But the ERG still considered that the generalised gamma was likely to be over optimistic. The ERG noted that the lognormal curve represented a middle value between the generalised gamma and the Weibull curve. But ultimately, the considerable uncertainties meant that there was not a strong case for selecting one extrapolation in preference to another. The committee noted the ERG's concerns over the relative plausibility of the models and concluded that the immaturity of the data limits selecting the most appropriate extrapolation for overall survival for dostarlimab.

Key assumptions in the economic model

The effect of treatment waning is uncertain, but the ERG's more conservative approach is currently preferred

3.12 The committee noted that the implementation of treatment waning in the economic model was closely related to the issue of extrapolating survival appropriately (see section 3.11). The company adjusted its implementation of treatment waning in the model after ERG feedback at technical engagement, but the ERG explained that it did not agree with this adjusted implementation. The values preferred by the company and the ERG are confidential and cannot be reported here. The ERG expressed its concern that there was little evidence to support the assumptions used by the company, particularly for the maintenance of full treatment effect for an extended duration beyond treatment discontinuation. The clinical experts explained that there is a broad clinical consensus that there is some retention of the full benefits from immunotherapy after stopping treatment. But, they noted that there is no

good evidence on when waning of this benefit is likely to start. The company evidence submission referenced previous technology appraisals for other immunotherapies with the same mechanism of action as dostarlimab, such as nivolumab and pembrolizumab. In these, NICE had previously accepted a treatment effect duration of between 3 to 5 years when people stop having the immunotherapy after 2 years. However, the ERG maintained that there is no evidence to support that this will also be the case in this population. It preferred the waning of treatment effect to begin immediately at treatment discontinuation, with declining effect over a longer period of time until the chance of dying is the same between dostarlimab and current clinical management. The committee noted how the type of waning approach substantially impacts how the parametric overall survival models extrapolate survival in the economic model (see section 3.11) so recalled that this shows how choice of waning method is driving the overall survival model in the economic analysis. The committee acknowledged the high degree of uncertainty because of the lack of data to support the maintenance of full treatment effect after stopping treatment. Implementing the ERG's preferred treatment waning assumptions in the model would increase the company's corrected base case incremental cost-effectiveness ratio (ICER) from £38,363 to £43,028 per quality-adjusted life year (QALY) gained for dostarlimab compared with current clinical management. The committee concluded that the more conservative approach preferred by the ERG is favoured, given the immaturity of the data and high degree of uncertainty, although this could be mitigated with longer trial follow up.

The percentage of people on treatment at key time points is uncertain

3.13 GARNET did not contain a stopping rule for dostarlimab. To obtain estimates of time to treatment discontinuation (TTD), the company presented a panel of clinical experts with the number remaining at risk instead of the Kaplan–Meier TTD curve. This resulted in a range of estimates for the percentage of people expected to remain on treatment at a specific timepoint in the economic model. These values and the timepoint are confidential and cannot be reported here. The ERG explained that the modelled TTD curve bears no resemblance to the numbers remaining on treatment that were presented to the experts. The

ERG further explained that by presenting the number remaining at risk, data cut-off is effectively treated as a discontinuation event, and this incorrect assumption would seriously bias the presentation and experts' estimates. Unbiased overall survival and progression-free survival estimates adjusted for the TTD and treatment stopping rules would usually require consideration of the TTD and stopping rules. The ERG also questioned why the TTD and stopping rules elicitation exercise was done after the overall survival and progression-free survival elicitation exercise. The ERG suggested that while the range of TTD estimates could be considered as a likely minimum for the proportion of people remaining on treatment at that timepoint, they should not be used as averages. The ERG preferred a more conservative value that was towards the upper end of the range provided by the company's elicitation exercise. Implementing this value in the model would increase the company's corrected base case ICER for dostarlimab compared with current clinical management from £38,363 to £41,354 per QALY gained. The committee noted the ERG's view that the company TTD and stopping rules elicitation exercise was poorly constructed, and that its results are unreliable. The committee concluded that the more conservative value preferred by the ERG is appropriate given the high degree of uncertainty.

End of life

Dostarlimab meets the end of life criteria

3.14 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. It recalled that KEYNOTE-775 showed poor life expectancy for people with previously treated recurrent or advanced endometrial cancer with high MSI or MMR deficiency (see section 3.2). The committee noted that overall survival was immature in GARNET but has been modelled by the company and ERG. Both the company and ERG agree that dostarlimab appears to meet the end of life criteria for people with recurrent or advanced endometrial cancer that has progressed during or after platinum-based chemotherapy. However, the ERG cautioned that there is uncertainty around the survival estimates

because GARNET's data is immature and there are many issues with comparator data and longer-term outcomes beyond 2 years. The committee concluded that dostarlimab likely meets the end of life criteria.

Results of the cost-effectiveness analysis

Dostarlimab is not recommended for routine use in the NHS

3.15 The committee noted that the company's base case ICER for dostarlimab compared with current clinical management increased to £38,363 per QALY when model errors identified by the ERG were corrected in the economic model. Although this ICER falls within the range that NICE considers to be cost effective for treatments at the end of life, it does not take into account the committee's preferences for amendments to the company model. Given the immaturity of GARNET data, uncertainty about long-term survival, absence of a matched trial population for current clinical management and reliance on a different real-world population, the committee agreed with the ERG's more conservative preferences. This included the ERG's modelling of both treatment waning and treatment discontinuation for dostarlimab. For extrapolation of overall survival, the committee agreed with the ERG that there is not enough evidence to prefer either the Weibull or generalised gamma curves. It also agreed that the true survival of people having dostarlimab lies within a wide range of possibilities. Using the ERG's preferred assumptions but with the company's choice of generalised gamma for overall survival for dostarlimab gave an ICER of £49,454 per QALY gained. The same assumptions with the ERG's alternative choice of the Weibull curve for overall survival for dostarlimab gave an ICER of £61,306 per QALY gained. The committee however noted that the choice of overall survival extrapolation was dependent on having confidence in the overall treatment comparison between dostarlimab and the comparator treatments. The committee agreed that the data from GARNET was too immature. It also agreed there was too much uncertainty in the MAICs to be confident about the robustness of any of the ICERs produced by the company's economic model. The committee concluded that dostarlimab could not be recommended for routine commissioning.

Cancer Drugs Fund

Dostarlimab is recommended for use in the Cancer Drugs Fund

3.16 Having concluded that dostarlimab could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced or recurrent endometrial cancer with high MSI or MMR deficiency after platinum-based chemotherapy within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum):

- The company expressed an interest in dostarlimab being considered for funding through the Cancer Drugs Fund.
- The committee noted that GARNET is still ongoing, with the next data cut expected in early 2022, and agreed that additional survival data is needed to reach a decision on the cost effectiveness of dostarlimab.
- Clinical evidence from KEYNOTE-775 (see section 3.2) would provide a better source comparator data for future cost-effectiveness analyses of dostarlimab. This is because it would overcome many of the problems associated with matching the GARNET and the RWE study populations that impacted the robustness of the company's indirect treatment comparisons.

  The committee considered that further data collection in the Cancer Drugs Fund could address some of the uncertainty in the company's estimates. It recalled that using the ERG's preferred assumptions but with the company's choice of generalised gamma for overall survival for dostarlimab gave a plausibly cost effective estimate of £49,454 per QALY gained. The committee concluded that dostarlimab met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended dostarlimab for use within the Cancer Drugs Fund as an option for people with advanced or recurrent endometrial cancer with high MSI or MMR deficiency after platinum-based chemotherapy, if the conditions in the managed access agreement are followed. When the guidance is next reviewed, the company should use the committee's preferred assumptions as set out in section 3.12 and section 3.13, unless new evidence indicates otherwise.

Innovation

Some benefits of dostarlimab have not been captured in the QALY

3.17 The company considered dostarlimab to be an innovative treatment. The clinical experts agreed that this treatment represents a step change for people who have advanced or recurrent endometrial cancer with high MSI or MMR deficiency and who have few effective options after platinum-based chemotherapy. The benefits for people having treatment includes 1 factor not captured in the QALY estimate, which is the added value of a treatment that needs a shorter hospital visit than chemotherapy.

Other factors

3.18 No equality or social value judgement issues were identified.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has advanced or recurrent endometrial cancer and the doctor responsible for their care thinks that dostarlimab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. 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 the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Recommendations for data collection

5.1 Proposals for further data collection in the Cancer Drugs Fund include further evidence on:

- overall survival
- progression-free survival
- time to treatment discontinuation, and
- the comparative effectiveness.

6 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.

Luke Cowie
Technical lead

Eleanor Donegan
Technical adviser

Shonagh D'Sylva
Project manager

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Accreditation