NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer

Technology appraisal guidance
Published: 13 December 2023

www.nice.org.uk/guidance/ta939

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

This guidance replaces TA885.

1 Recommendations

1.1 Pembrolizumab plus chemotherapy with or without bevacizumab is recommended as an option for treating persistent, recurrent or metastatic cervical cancer in adults whose tumours express PD-L1 with a combined positive score of at least 1. It is recommended only if:

- pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if the cancer progresses, and
- the company provides it according to the commercial arrangements.

1.2 This recommendation is not intended to affect treatment with pembrolizumab plus chemotherapy with or without bevacizumab 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

This rapid review considers new evidence that has become available on pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer since the publication of NICE's technology appraisal guidance TA885.

Standard care for persistent, recurrent or metastatic cervical cancer includes chemotherapy with or without bevacizumab. Evidence from a clinical trial shows that, compared with standard care, pembrolizumab plus chemotherapy with or without bevacizumab increases the time it takes for the cancer to get worse. It also suggests that it increases how long people live. In this trial, people had pembrolizumab for up to 2 years.

Pembrolizumab plus chemotherapy with or without bevacizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. When taking this into account, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, pembrolizumab plus chemotherapy with or without

bevacizumab is recommended.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, Merck Sharp & Dohme) plus chemotherapy with or without bevacizumab is indicated for 'the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS $\geq$ 1'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £2,630.00 per 100 mg/4 ml concentrate for solution for infusion vial (excluding VAT; BNF online accessed October 2023).

2.4 The company has a commercial arrangement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Sharp & Dohme and a review of this submission by the external assessment group (EAG). See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Cervical cancer is defined as persistent when it does not respond to treatment, recurrent when it has returned after treatment and metastatic when it has spread beyond the cervix to other places in the body. The committee noted that persistent, recurrent or metastatic cervical cancer has a poor prognosis and leads to a substantial disruption to quality of life. There are limited effective treatment options available for this type of cancer. The main aim of treatment is to relieve symptoms and improve quality of life, and to extend life if possible. The committee concluded that there is a high disease burden for people with persistent, recurrent or metastatic cervical cancer. It also concluded that a treatment which can prolong life but also improve quality of survival by managing symptoms would be welcome.

Clinical effectiveness

Updated clinical data

3.2 The clinical evidence was based on KEYNOTE-826, a phase 3, double-blind randomised placebo-controlled trial in people with recurrent, persistent or metastatic cervical cancer. KEYNOTE-826 compared pembrolizumab plus chemotherapy with or without bevacizumab against placebo plus chemotherapy with or without bevacizumab as a first-line treatment. In line with the marketing authorisation, the company presented efficacy data for people whose tumours express PD-L1 with a combined positive score (CPS) of at least 1. In the original

NICE technology appraisal guidance on pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer (from now TA885), the committee considered the interim analysis from the trial. For this rapid review, the company provided data from the final analysis of KEYNOTE-826. This included 17 months of additional follow-up data, with median overall survival in the pembrolizumab group now reached. There was a clinically meaningful and statistically significant benefit for the pembrolizumab group compared with the placebo group for both progression-free survival (PFS) and overall survival (OS). Median PFS was 10.5 months in the pembrolizumab group and 8.2 months in the placebo group (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.47 to 0.71). This was a slight improvement on the hazard ratio from the interim analysis (HR 0.62, 95% CI 0.50 to 0.77). Median OS was 28.6 months in the pembrolizumab group and 16.5 months in the placebo group. (HR 0.60, 95% CI 0.49 to 0.74). This was also a slight improvement on the interim analysis (HR 0.64, 95% CI 0.50 to 0.81). The EAG commented that all reported endpoints from the final analyses were similar to the results from the interim analyses. It noted that the treatment effect sizes were generally similar in size, with greater precision because of the additional observed events. The committee concluded that the more mature data from KEYNOTE-826 was consistent with the interim analysis and strengthened the clinical evidence for pembrolizumab.

Generalisability

3.3 The EAG questioned whether the trial data was generalisable to the NHS. It highlighted that clinical expert advice presented by the company estimated that people who have standard care could expect to live for 3 to 15 months. But median OS in the placebo arm in KEYNOTE-826 was 16.5 months. Also, some people in the trial had subsequent immuno-oncology treatments that are not available on the NHS. The committee accepted that the subsequent treatments may have extended survival. It also considered that the difference in survival may have been because people in clinical trials tend to be fitter than people in clinical practice. The company said that clinical expert opinion had confirmed that the trial results were generalisable to the NHS population. The Cancer Drugs Fund lead said that real world outcomes often do not match those seen in clinical trials. There are several reasons for this (for example, people with additional health complications are typically excluded from trials). But he said there were no

particular concerns about generalisability for this appraisal. He also noted that having a fitter trial population would lead to better outcomes in both arms of the trial, not just the pembrolizumab arm. The committee was reassured that the OS outcomes in the placebo group of KEYNOTE-826 were consistent with those previously seen in GOG 240. This was a randomised phase 3 trial in people with persistent, recurrent or metastatic cervical cancer. The committee concluded that the results from KEYNOTE-826 were broadly generalisable to the NHS and appropriate for decision making.

Economic model

Company's modelling approach

3.4 The company presented a 3-state Markov state transition model to estimate the cost effectiveness of pembrolizumab plus chemotherapy compared with chemotherapy (both with or without bevacizumab). The 3 health states were PFS, progressed disease and death. In TA885, the company explained that there was not enough OS data for people whose cancer responded to treatment. So, the data on OS was not mature enough to accurately model long-term survival, particularly in people whose cancer responded completely. Taking these factors into account, the committee for TA885 agreed that a state transition model (STM) was more appropriate than a partitioned survival model (PSM). This was because an STM uses a structural link between PFS and OS rather than directly extrapolating OS data. But the committee noted that the appropriate model structure may change when there was more data. In its submission for this rapid review, the company said that the OS data still did not fully reflect the survival benefit for people whose cancer responded well to treatment. So, its base case still used the STM. At the EAG's request, the company also provided a PSM. But the EAG acknowledged that the results generated by the PSM were not clinically plausible. The EAG said that the most logical extrapolations resulted in an unrealistic crossing of OS and PFS curves. This was because OS data was too immature to capture the plateau trend seen in the PFS curve. But the EAG noted that the cost-effectiveness results produced using a PSM remained relatively robust and were unlikely to be a key driver of uncertainty. The committee agreed that, given the implausible results generated by the PSM, the STM was still the

most appropriate modelling approach. But it acknowledged the remaining uncertainty about the long-term benefits of pembrolizumab, particularly among people whose cancer responds well to treatment.

Extrapolation of PFS and OS

3.5 In TA885, the committee noted that the long-term projections for PFS were highly uncertain. Given the structural link between PFS and OS in the model structure (see section 3.4), this also drove uncertainty in the long-term projections for OS. It noted that these uncertainties may be reduced when there was longer follow-up data from KEYNOTE-826. The final analysis has provided this data, and the company said that the range of appropriate extrapolation curves for PFS has been narrowed, so reducing this uncertainty. The company's base case selected a 3-knot hazard model, which gave similar estimates to those previously used in TA885. The company also examined 1-knot and 2-knot models in sensitivity analyses. The EAG was 'generally satisfied' with the company's extrapolation approach, agreeing there was a good visual and statistical fit to the updated data. But it noted that much of the modelled incremental benefit associated with pembrolizumab was in the extrapolated portion of the survival curves. So, it thought that some uncertainty remained about the long-term survival benefit with pembrolizumab, particularly among people whose cancer responds well to treatment. The committee concluded that the company's extrapolation of the survival curves was appropriate, noting that some uncertainty remained.

End of life

3.6 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 its conclusion from TA885 that the end of life criteria had been met. The committee considered the updated data from the final analysis of KEYNOTE-826. It noted that the extension to life for people with recurrent, persistent or metastatic cervical cancer having pembrolizumab plus chemotherapy with or without bevacizumab was substantially greater than 3 months compared with standard care. It also noted that most people in the placebo arm of KEYNOTE-826 lived for less than 24 months. By 24 months,

60.6% of people had died, and median OS was 16.5 months. The EAG noted that the modelled mean OS in the standard care arm had increased from 24.7 months to 31.8 months since the interim analysis. It questioned whether, given this increase, the end of life criteria were still met. The company said that the reason for the mean being higher was that the cancer in some people responded very well to treatment. But it was clear that most people with persistent, recurrent or metastatic cervical cancer live for less than 24 months. The committee considered that the control arm of KEYNOTE-826 provided strong evidence on life expectancy and that the results were consistent with those from GOG 240 (see section 3.3). It also noted the appeal outcomes of NICE's technology appraisal guidance on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy and NICE's technology appraisal guidance on tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma. In the appeal for avelumab, the panel concluded that end of life criteria could apply even if some measures of life expectancy were over 24 months. It said that a totality of the data and analysis should be taken account of when considering whether the criteria are met. In the appeal for tafasitamab, the panel acknowledged the influence of stakeholder views in the appeal judgements, noting that clinicians typically use medians rather than means when discussing life expectancy with patients in clinic. The committee concluded that OS for the standard care arm was 'normally less than 24 months' and that the end of life criteria had been met.

Cost-effectiveness estimates

Acceptable ICER

3.7 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee accepted that the amount of uncertainty had been reduced since TA885 because of the additional 17 months of follow-up data. But it noted that

there was still uncertainty about the long-term survival benefit of pembrolizumab, particularly among people whose cancer responds well to treatment (see section 3.5). The committee considered the remaining uncertainty and the greater weight given to QALYs at the end of life (see section 3.6). It concluded that the maximum acceptable ICER would be substantially below £50,000 per QALY gained.

Company and EAG cost-effectiveness estimates

3.8 The committee's preferred assumptions from TA885 were implemented into the company's base case for this rapid review. They included a treatment effect waning from 3 years to 5 years after stopping pembrolizumab with a 2-year stopping rule. The company's base-case ICER for pembrolizumab plus chemotherapy compared with placebo plus chemotherapy (both with or without bevacizumab), and ICERs from scenario analyses exploring key assumptions, were all substantially below the acceptable level of £50,000 per QALY gained (see section 3.7). Because of confidential commercial arrangements for pembrolizumab, bevacizumab and postprogression therapies, the ICERs are confidential and cannot be reported here. The EAG was satisfied with the company's analyses and did not provide any additional scenarios. Because the ICERs were below the agreed level, the committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab could be recommended for routine use.

Conclusion

Recommendation

3.9 The committee concluded that the more mature data from KEYNOTE-826 had strengthened the clinical evidence for pembrolizumab plus chemotherapy with or without bevacizumab. The most plausible ICERs were within the range usually considered a cost-effective use of resources when the end of life modifier was applied. So, pembrolizumab plus chemotherapy with or without bevacizumab is recommended as an option for treating persistent, recurrent or metastatic

cervical cancer in adults whose tumours express PD-L1 with a CPS of at least 1.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has persistent, recurrent or metastatic cervical cancer and the doctor responsible for their care thinks that pembrolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Radha Todd
Chair, technology appraisal committee A

NICE project team

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

Alex Sampson
Technical lead

Zoe Charles
Technical adviser

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