NICE National Institute for Health and Care Excellence

NICE guidance

Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency

Technology appraisal guidance
Published: 20 September 2023

www.nice.org.uk/guidance/ta914

Your responsibility

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

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

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

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

Contents

1 Recommendations

1.1 Pembrolizumab is recommended as an option for treating tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults with:

- advanced or recurrent endometrial cancer that has progressed during or after a platinum-based therapy, who cannot have curative surgery or radiotherapy
- unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after 1 therapy
- colorectal cancer after fluoropyrimidine combination therapy, only if they cannot have nivolumab with ipilimumab.

  It is only recommended 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 arrangement.

1.2 This recommendation is not intended to affect treatment with pembrolizumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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

For previously treated endometrial, gastric, small intestine and biliary cancer with high MSI or MMR deficiency in adults, usual treatment at the time of the evaluation was chemotherapy. For people with previously treated colorectal cancer with high MSI or MMR deficiency, usual treatment is nivolumab with ipilimumab, or chemotherapy if they cannot have nivolumab with ipilimumab. Pembrolizumab would be offered as an alternative to chemotherapy for all of these indications.

Pembrolizumab has not been compared directly with chemotherapy in clinical trials. When compared indirectly, the results suggest that people having pembrolizumab live for longer and have longer before their cancer gets worse than people having chemotherapy, although these results are uncertain.

When considering the condition's severity, its effect on quality and length of life, and the uncertainty in the clinical evidence, the most likely cost-effectiveness estimates for pembrolizumab in all the types of cancer are within the range that NICE considers an acceptable use of NHS resources. So, it is recommended.

2 Information about pembrolizumab

Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD) as monotherapy is indicated for treating high microsatellite instability (MSI) or mismatch repair (MMR) deficient tumours in adults with:

- 'unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy'
- 'advanced or recurrent endometrial carcinoma, 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'
- 'unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price is £2,630.00 for a 25 mg per 1 ml concentrate for solution for infusion vial (excluding VAT; BNF online accessed June 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 MSD, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need

3.1 The marketing authorisation for pembrolizumab for treating tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency specifies 5 tumour sites: colorectal, endometrial, gastric, small intestine and biliary (see section 2.1). The company submission highlighted that the NICE guidance for treating small intestine and biliary cancer is limited, but for colorectal, endometrial and gastric cancers the guidance is well established. The committee heard from 2 patient experts in association with AMMF – The Cholangiocarcinoma Charity who represented people with biliary cancer. They explained that the incidence of biliary cancer is increasing every year, with many younger adults being diagnosed. They said that often, diagnosis is late because of a lack of awareness at primary care level and because many symptoms are vague and can easily be attributed to other causes. This leads to many people receiving a terminal diagnosis because the cancer is inoperable. The patient experts said that people with biliary cancer have an unmet need for effective treatments, molecular profiling, and centres of expertise, because many of them never see healthcare professionals with specialist knowledge. They stated that after diagnosis, many families struggle to understand why the treatment options are so limited, particularly when more targeted treatments such as immunotherapies are available for other cancers. The clinical expert supported this, explaining that from their experience there is an unmet need for immunotherapies for the gastrointestinal tumour sites (colorectal, gastric, small intestine and biliary). They also noted that the published real-world evidence is limited because of the small numbers of people with these cancers. The committee acknowledged that the evidence would be limited by the small population numbers, and that for many people with cancer in these sites there is an unmet need for new and effective treatment options

such as targeted therapies. It concluded that it would take these factors into account in its decision making.

Clinical management

Testing

3.2 High MSI is determined by a positive polymerase chain reaction (PCR) test, and MMR deficiency is determined by a positive immunohistochemical staining (IHC) result. Testing for these biomarkers is not routinely available in the NHS for all of the tumour sites in the marketing authorisation. NICE diagnostic guidance states that IHC testing should be offered to people diagnosed with colorectal cancer (see NICE's diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer) and endometrial cancer (see testing strategies for Lynch syndrome in people with endometrial cancer). But no routine IHC testing is available for gastric, biliary or small intestine cancers. The NHS England Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund lead) said that a test would become available for the remaining subgroups if pembrolizumab was recommended. The committee concluded that routine testing would be needed for all 5 tumour sites if this technology was recommended, and that the modelling of testing costs was appropriate.

Treatment pathway

3.3 Chemotherapy is the first-, second- and subsequent-line treatment option for high MSI or MMR deficient tumours in adults with metastatic gastric, small intestine or biliary cancer, and advanced or recurrent endometrial cancer. In the second-line setting, dostarlimab is also available through the Cancer Drugs Fund (see NICE's technology appraisal guidance on dostarlimab for previously treated advanced or recurrent endometrial cancer with high MSI or MMR deficiency). NICE recently recommended pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. But because it was not recommended for routine use at the time of the evaluation, it was not considered a comparator for pembrolizumab. For metastatic colorectal

cancer with confirmed high MSI or MMR deficiency, first-line treatment is pembrolizumab (see pembrolizumab for untreated metastatic colorectal cancer with high MSI or MMR deficiency). For colorectal cancer with unknown MSI and MMR status, or if there is disease progression that needs a fast response, first-line treatment is chemotherapy. If high MSI or MMR deficiency is confirmed, second-line treatment in most cases is nivolumab and ipilimumab (see nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high MSI or MMR deficiency). For people unable to have nivolumab and ipilimumab, for example because of autoimmune-related comorbidities or patient fitness, chemotherapy is the second- and third-line treatment option. Regorafenib is available after other available therapies (see regorafenib for previously treated metastatic colorectal cancer).

Comparators

3.4 For all tumour sites, the company positioned pembrolizumab as an alternative to second-line chemotherapy. For colorectal cancer, the company's decision problem excluded 3 of the comparators listed in the NICE scope: nivolumab with ipilimumab, irinotecan, and raltitrexed. The company proposed that pembrolizumab would be a treatment option for the small proportion of people who do not have first-line pembrolizumab, and who cannot or do not want to have second-line nivolumab with ipilimumab after first-line chemotherapy. It accepted that nivolumab with ipilimumab is preferred in clinical practice because it would be more effective than pembrolizumab. So, it aimed to position pembrolizumab for people with metastatic colorectal cancer who cannot or do not want to have nivolumab with ipilimumab. The clinical expert supported this positioning, saying that nivolumab with ipilimumab would be the preferred second-line treatment, but that sometimes, second-line doublet immunotherapy is not desirable because of the increased risk of toxicities. The clinical expert also said that pembrolizumab would be valuable as a second- or subsequent-line option because it would be superior to any current chemotherapy options. The EAG agreed that pembrolizumab would only be offered to people for whom nivolumab with ipilimumab is unsuitable. But it highlighted that no evidence had been presented for pembrolizumab compared with any colorectal comparator specific to people with tumours with high MSI or MMR

deficiency who cannot or do not want to have nivolumab with ipilimumab. The company said that for this very small population, in current practice, chemotherapy is the only treatment option. The Cancer Drugs Fund lead supported this and said that only around 35 people per year are expected to have nivolumab with ipilimumab for colorectal cancer with high MSI or MMR deficiency. This number is small because pembrolizumab is already available as a first-line therapy and people can only have a checkpoint inhibitor at 1 point in the treatment pathway. The company stated that irinotecan and raltitrexed were excluded based on clinical feedback that they are rarely used in practice unless other treatments are contraindicated. The clinical expert and Cancer Drugs Fund lead both confirmed that irinotecan and raltitrexed monotherapy are rarely used in clinical practice. The committee agreed that chemotherapy was the only relevant comparator in the positioned subgroup of people unable to have nivolumab with ipilimumab. The committee concluded that chemotherapy was the appropriate comparator in all 5 tumour sites.

Clinical effectiveness

Clinical trials

3.5 The company's clinical evidence for pembrolizumab came from 2 phase 2, single-arm, non-randomised, open-label trials, in people aged 18 years and over.

- KEYNOTE-158 included people with advanced high MSI or MMR deficient endometrial cancer (n=83), gastric cancer (n=51), small intestine cancer (n=27) or biliary cancer (n=22), after at least 1 previous treatment had not worked.
- KEYNOTE-164 included people with previously treated locally advanced unresectable metastatic high MSI or MMR deficient colorectal carcinoma (n=124) after at least 1 previous treatment had not worked.

  The trials assessed pembrolizumab (200 mg) administered intravenously every 3 weeks. The primary outcome was the objective response rate, based on Response Evaluation Criteria In Solid Tumours (RECIST) criteria version 1.1 as assessed by independent central radiological review. Key secondary outcomes

included overall survival, progression-free survival, duration of response and safety and tolerability.

Generalisability

3.6 The characteristics of the people in the trials were compared with UK population data, which was not specific to people with tumours with high MSI or MMR deficiency. The EAG stated that there were large differences in ethnicity. In response to technical engagement, the company provided subgroup analyses by ethnicity, and reported that there was no meaningful difference in objective response rate (primary outcome) between ethnicities. It said that there was also no evidence to suggest that ethnicity is a treatment effect modifier, which means that pembrolizumab is not expected to be more effective in some ethnicities than others. The clinical expert also said that there is no known biological reason for there to be a difference in pembrolizumab effectiveness between ethnicities. The committee acknowledged that there were ethnicity differences between the trial and UK population data but concluded that the trial was sufficiently generalisable for decision making.

Indirect treatment comparison

3.7 There was no evidence directly comparing pembrolizumab with the relevant comparators for any tumour site, within the specific high MSI or MMR deficient population. The company tried various methods to estimate the relative treatment effects of pembrolizumab and the comparators for each tumour site. This included indirect treatment comparisons, matching-adjusted indirect comparisons, and fitting independent parametric survival models to comparator evidence sources. The proportional hazards assumption was not met for each tumour site and the company noted the limitations of unadjusted indirect treatment comparisons and unanchored matching-adjusted indirect comparisons. So, neither was used in the company's economic analyses. Instead, it fitted independent parametric survival curves to comparator pseudo-individual patient data with the most clinically plausible extrapolations chosen for use in the model. The company acknowledged that this method was also not ideal because it used non-randomised

data with no adjustment for confounding. The EAG noted that there were serious limitations in all approaches used to estimate the relative treatment effects. The committee recognised that uncertainty is often associated with single-arm trials and small populations. It concluded that there was considerable uncertainty in the relative treatment effects, and it would take this into account in its decision making (see section 3.14).

High MSI or MMR deficiency status in the comparator populations

3.8 The comparator evidence was not specific to a high MSI or MMR deficient population in most tumour sites. The company explained that there was a lack of available chemotherapy data in the high MSI or MMR deficient populations. But it said that using data from a population with cancer and unknown MSI and MMR status was likely to result in a conservative estimate of relative efficacy. Evidence suggests that having high MSI or MMR deficiency is a negative prognostic factor (a variable that predicts worse outcomes), so the comparator response to chemotherapy would be worse. To support this, the company provided evidence from clinical trials (KEYNOTE-061, ZEBRA, KEYNOTE-158 and KEYNOTE-775). This evidence suggested that compared with tumours without high MSI, people with high MSI tumours have a worse prognosis when having treatment with chemotherapy, and better outcomes when having treatment with pembrolizumab. The committee was aware that in NICE's technology appraisal guidance on nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high MSI or MMR deficiency, the committee concluded that high MSI or MMR deficiency is associated with a poorer prognosis and a greater risk of death. The company's clinical experts agreed that these mutations have a worse prognosis but a better response to immunotherapy. The committee recognised that the lack of comparator data in the target population is unresolvable, and concluded that it was plausible that high MSI or MMR deficient tumours are associated with a worse prognosis but may respond better to immunotherapy.

Economic model

Company's modelling approach

3.9 The company used a multi-cohort partitioned survival model to estimate the cost effectiveness of pembrolizumab compared with the relevant comparators in each tumour site. Similar to standard oncology partitioned survival models, there were 3 health states: pre-progression, post-progression and death. It separately modelled each of the 5 tumour sites, and then aggregated the results into an overall solid tumour outcome that was weighted by tumour site prevalence, based on epidemiological calculations. The company stated that if pembrolizumab was cost effective for the individual tumour sites and the overall indication, then the weighting calculation did not determine cost effectiveness. Although both types of results were provided, the EAG questioned the appropriateness of aggregating the results because of the potential heterogeneity across the tumour sites. The committee considered the approach taken for previous solid tumour technologies (see NICE's technology appraisal guidance on entrectinib for treating NTRK fusion-positive solid tumours and larotrectinib for treating NTRK fusion-positive solid tumours). The committee was aware that these evaluations had histology-independent marketing authorisations, which included any solid tumour with the specific biomarker. In comparison, this evaluation has 5 specified tumour populations with high MSI or MMR deficiency status (see section 2.1). The committee concluded that it was appropriate to consider the tumour sites individually.

Bayesian hierarchical modelling

3.10 In the company's base case, it modelled the efficacy of pembrolizumab using Bayesian hierarchical modelling (BHM) for overall survival and progression-free survival outcomes. BHM represents a middle ground between assuming that pembrolizumab is equally effective in all tumour sites, and assuming each tumour site responds differently to pembrolizumab (such as fitting separate parametric survival models). The EAG acknowledged the advantages of the BHM approach allowing information to be borrowed between tumour sites when sample sizes are

small. The committee agreed that BHM is a useful approach but recognised that it relies on assuming that the tumour sites are sufficiently similar. It was concerned that BHM had not previously been applied to time-to-event data, and the methodology had not been peer reviewed. The committee also noted that the differences in observed survival outcomes indicated substantial heterogeneity between the individual tumour sites, which may introduce bias. The company provided scenario analyses that used partitioned survival modelling. The committee agreed that it was helpful to have both survival approaches available. It was aware that the choice of survival modelling approach had only a minor impact on the cost-effectiveness results and concluded that although neither the BHM nor partitioned survival modelling approach was ideal, both were plausible and would inform its decision making.

Subsequent treatments

3.11 The company assumed that the same proportion of people whose cancer progressed in the model would have subsequent treatments, regardless of the initial line of therapy (pembrolizumab or chemotherapy). The proportion, frequency and duration of subsequent treatments were based on KEYNOTE-158 and KEYNOTE-164. The EAG highlighted the lack of evidence provided to show that subsequent treatment proportions would be the same for the comparators, and questioned the generalisability of the modelled subsequent treatments to UK clinical practice. To understand the influence of subsequent treatments on the cost-effectiveness estimates, the EAG did some scenario analyses, which had a moderate impact on the results. The committee recognised that not all of the modelled subsequent treatments may reflect UK clinical practice because the trial was not done in the UK. But it concluded that this would not have a large impact on the incremental cost-effectiveness ratio (ICER).

Treatment effect waning

3.12 The company's base case included pembrolizumab treatment for a maximum of 2 years followed by a treatment effect waning assumption 7 to 9 years from the start of treatment. The company chose this

because it had observed Kaplan–Meier data up to 6 years. The committee noted that the duration of clinical trial follow up was considerably longer than it has typically seen for immunotherapies with a 2-year stopping rule in place. So, the committee concluded that applying the treatment effect waning from 7 to 9 years was a reasonable and potentially conservative assumption based on the data provided for this particular indication.

Severity

3.13 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. After technical engagement, the company and EAG aligned their base cases to apply a 1.2 severity weighting to the QALYs in the colorectal, endometrial, gastric, and small intestine tumour sites and a 1.7 severity weighting to the biliary cancer QALYs. This was based on the proportional QALY shortfall estimates that were calculated using health state utility values. The company highlighted that if the comparator QALYs in the gastric and small intestine tumour sites reduced by a small amount, the highest severity modifier (1.7) could be achieved. It presented evidence that showed how the model may overestimate these QALYs. But the EAG noted that the severity estimates could be over or underestimated given the lack of evidence in the correct high MSI and MMR deficient population. The committee concluded that a severity weight of 1.2 should be applied to the colorectal, endometrial, gastric and small intestine tumour site QALYs, and a severity weight of 1.7 should be applied to the biliary tumour site QALYs.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.14 After technical engagement, the company and EAG base cases were aligned. The probabilistic base-case ICER for most tumour sites was below £20,000 per QALY gained (the exact ICERs cannot be reported here because of confidential commercial discounts). The committee considered the base-case ICERs, and all of the scenario analyses provided by the company and EAG. It acknowledged the uncertainties in the evidence alongside the unmet need for an immunotherapy in these populations and the rarity of this condition, particularly in the tumour sites with ICERs above £20,000 per QALY gained.

Other factors

Equality

3.15 The committee did not identify any equality issues.

Innovation

3.16 The committee considered if pembrolizumab was innovative. It did not identify additional benefits of pembrolizumab not captured in the economic modelling. So, the committee concluded that all additional benefits of pembrolizumab had already been taken into account.

Conclusion

Recommendation

3.17 The committee recognised that solid tumours with high MSI or MMR deficiency are very rare. It acknowledged the uncertainties in the evidence alongside the rarity of this condition and the unmet need for an immunotherapy for these populations (see section 3.1). The committee

noted that if pembrolizumab was recommended, biomarker testing for small intestine, gastric and biliary cancer would need to be made available for routine commissioning (see section 3.2). The committee considered that for metastatic colorectal cancer, pembrolizumab should only be available for people for whom nivolumab with ipilimumab is unsuitable (see section 3.4). It agreed that a severity weight of 1.2 should be applied to the colorectal, endometrial, gastric and small intestine tumour site QALYs, and a severity weight of 1.7 should be applied to the biliary tumour site QALYs (see section 3.13). After including the comparators' confidential commercial discounts, the cost-effectiveness estimates for all tumour sites were below £30,000 per QALY gained. To reflect the modelling, which was in line with the clinical trial, pembrolizumab should be stopped at a maximum of 2 years of uninterrupted treatment. So, pembrolizumab is recommended for treating high MSI or MMR deficient tumours in adults with previously treated biliary, colorectal, endometrial, gastric or small intestine cancer.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 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 a high microsatellite instability (MSI) or mismatch repair (MMR) deficient tumour that is:

- advanced or recurrent endometrial cancer that has progressed during or after

treatment with a platinum-containing therapy, when curative surgery or radiotherapy is unsuitable

- unresectable or metastatic gastric, small intestine, or biliary cancer that has progressed during or after at least 1 therapy
- unresectable or metastatic colorectal cancer after previous fluoropyrimidine combination therapy, when nivolumab with ipilimumab is unsuitable

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 D.

Committee members are asked to declare any interests in the pembrolizumab 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

Stephen Smith
Chair, technology appraisal committee D evaluation committee

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.

Cara Gibbons
Technical lead

Lorna Dunning and Caron Jones
Technical advisers

Kate Moore and Louise Jafferally
Project managers

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