NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer

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

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

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

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

Issue date: October 2020

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

After consultation:

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

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

The key dates for this appraisal are:

Closing date for comments: 25 November 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Nivolumab is not recommended, within its anticipated marketing authorisation, for treating unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults after fluoropyrimidine and platinum-based therapy.

1.2 This recommendation is not intended to affect treatment with nivolumab 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

Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma is usually first treated with fluoropyrimidine and platinum-based therapy. Then if the cancer progresses, it is treated with a taxane (docetaxel or paclitaxel).

Clinical trial evidence suggests nivolumab does not improve how well the disease responds or how long people live without their disease progressing compared with taxane treatment. In the trial, the rate of death in the first 3 months of treatment was higher with nivolumab than with taxanes, even though the trial excluded people with a life expectancy of less than 3 months. After that, evidence suggests people live for longer with nivolumab compared with taxane treatment, but clear evidence of long-term survival after 3 months is needed.

Because of the uncertainty in the clinical evidence, there is substantial uncertainty about the most appropriate estimates for costs associated with nivolumab. New data based on further follow up from the trial (up to 36 months) has just become available to the company, but the effect on cost-effectiveness estimates is unknown.

Nivolumab meets NICE's criteria to be considered a life-extending treatment at the end of life. However, the most likely cost-effectiveness estimates are above what

NICE normally considers an acceptable use of NHS resources. So, nivolumab is not recommended for routine use.

Nivolumab is not recommended for use within the Cancer Drugs Fund because it is unlikely to be cost effective at its current price (even if the uncertainty about its effectiveness is reduced).

2 Information about nivolumab

Anticipated marketing authorisation indication

2.1 On 15 October 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product nivolumab. The CHMP adopted a new indication as follows: Nivolumab (Opdivo, Bristol-Myers Squibb) as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based combination chemotherapy.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics.

Price

2.3 Nivolumab is available in 3 different sizes as a concentrate for solution for infusion vials. The cost varies according to vial size: £439 (40 mg per 4 ml), £1,097 (100 mg per 10 ml) and £2,633 (240 mg per 24 ml) (excluding VAT; BNF online, accessed October 2020). The cost for 1 dose of treatment is £2,633 (240 mg per 24 ml).

The company has a commercial arrangement. This makes nivolumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 (section 5) considered evidence submitted by Bristol-Myers Squibb, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 3 issues were resolved during the technical engagement stage, and agreed that:

- The model time horizon (issue 7, see technical report page 8) used by the company in the economic model of 40 years was sufficient to capture data for everyone having nivolumab or taxanes.
- Nivolumab is likely to improve overall survival by at least 3 months (issue 13, see technical report page 14), meeting the second criteria for end-of-life treatment.
- The approach used to calculate the cost of monitoring response to treatment (issue 12, see technical report page 13) was appropriate.

Clinical need

People would welcome a new treatment option

3.1 The clinical experts explained that people with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma whose disease has progressed after fluoropyrimidine and platinum-based combination therapy have a poor prognosis and no curative treatment options. It disproportionately affects people from lower socioeconomic backgrounds and smoking and alcohol consumption are risk factors. The taxanes paclitaxel and docetaxel are standard treatment for most people and weekly or 3-weekly hospital visits are needed for infusions. People often feel unwell and may experience debilitating fatigue and loss of appetite. Many people find the weekly or 3-weekly treatment regimens

difficult to tolerate because of the associated adverse events. Frequent blood tests are needed to monitor neutropenia. The NHS England clinical lead noted that taxanes have limited efficacy and people are often not well enough to have third-line treatment if taxanes do not control the disease. People who are unable to tolerate taxane chemotherapy have best supportive care, which has no effect on disease progression. Older people are less likely to tolerate chemotherapy, and about 40% of people diagnosed with squamous oesophageal cancer are over 75. The committee recognised the unmet need for a treatment with lower toxicity than chemotherapy, which provides long-term benefit and improves quality of life. The clinical expert explained that if people are not well enough to tolerate taxane therapy they are unlikely be well enough to tolerate nivolumab. Although immunotherapy is generally better tolerated, it still carries risks, notably immune-related side effects. The committee concluded that patients and clinicians would welcome an effective treatment that is better tolerated, particularly if it offers an option of further third-line treatment after disease progression.

Trial design

The ATTRACTION-3 study is appropriate for estimating clinical effectiveness

3.2 The company's clinical evidence came from ATTRACTION-3. This included people with unresectable oesophageal squamous cell carcinoma whose disease was refractory or were intolerant to combination therapy with fluoropyrimidine and platinum-based drugs, and who had a life expectancy of at least 3 months. People were monitored every 6 weeks and assessed using RECIST 1.1 criteria. They could continue treatment after first disease progression in both treatment groups, based on the investigators' judgement. The clinical expert explained that immunotherapies are associated with pseudo-progression, which is a distinct radiological pattern of apparent progression from baseline that is not confirmed with subsequent assessment. For this reason, if there is

evidence of progression but the person feels well, they usually continue having nivolumab for another cycle and then radiological progression is assessed at the next monitoring appointment. The committee concluded that ATTRACTION-3 was an appropriate source of clinical data and could be used for estimating clinical effectiveness.

Clinical evidence

The results from ATTRACTION-3 are generalisable to people in the NHS

3.3 ATTRACTION-3 was done in the US, Europe and Asia. Of the people included in the study, 96% were of Asian family origin, and two-thirds of these people were of Japanese family origin. Oesophageal squamous cell cancer is more prevalent in Asia than in Western countries. The clinical expert commented that although the trials were mainly done in Asia, there is no difference in the underlying biology of oesophageal squamous cell cancer compared with people in the UK. Also, treatment is similar because of consensus in the management of advanced oesophageal cancer. The company accepted that the population in the clinical trial was generally younger and fitter (with an Eastern Cooperative Oncology Group performance status of 0 to 1) than the population seen in NHS practice. The committee agreed with the clinical expert and concluded that the clinical trial was broadly generalisable to people with advanced oesophageal squamous cell cancer in the UK.

Nivolumab improves overall survival but disease progresses faster in the first 3 months of treatment

3.4 Nivolumab is associated with a difference in median overall survival of 2.58 months compared with the combined taxane therapy arm (median overall survival 10.91 months for nivolumab, 8.38 months in the taxane arm). However, median progression-free survival was slightly lower for nivolumab (1.68 months compared with 3.35 months), as was the overall response rate (19.3% compared with 21.5%). More people had disease progression with nivolumab than with taxanes, and most of the overall

survival benefit from nivolumab was after progression. The committee questioned why the benefit was predominantly seen after progression rather than before, which is what would be expected if nivolumab had the potential to be curative. It discussed whether this could be because of people having nivolumab after disease progression and it slowing progression, a carry-over effect after stopping nivolumab into the progression phase, or because people remained well enough for follow-on therapies at progression. The committee concluded that it was unclear why the survival benefit mainly happened after disease progression.

People are at more risk of dying having nivolumab in the first 3 months

3.5 Results up to 24 months for overall survival were provided by the company and analysed by the ERG. At 2 months and 4 months, people having nivolumab had worse overall survival than people having taxanes. However, from 6 months onwards overall survival was higher for nivolumab compared with taxanes (the data cannot be reported here because the company submitted it as academic in confidence). The clinical expert explained that this pattern in overall survival is commonly found with immunotherapies. This is because of the delay in benefit as the immune system is activated, while chemotherapy immediately acts on the cancer cells. The higher death rate in the first 3 months seen with nivolumab was particularly concerning because people in ATTRACTION-3 were expected to survive at least 3 months. The NHS England clinical lead suggested that people generally have worse performance scores in the NHS than in the trial. In clinical practice, it is possible to distinguish between people who are and are not likely to tolerate nivolumab therapy. The company stated that an additional dataset for 36 months was now available for overall survival, progression-free survival and time on treatment. NICE, the ERG and the committee have not had an opportunity to review this and so it could not be taken into account for decision making. Based on the available data, the committee concluded that nivolumab improves overall survival despite a greater death rate in the first 3 months.

Adverse events

Nivolumab is better tolerated than taxanes, but immunotherapies can cause significant side effects

3.6 Fewer patients experienced drug-related adverse events in the nivolumab group compared with taxanes in the clinical trial (the data cannot be reported here because the company submitted it as academic in confidence). The clinical experts agreed that nivolumab is better tolerated than taxanes, and that taxane therapy can be associated with long-term adverse events, such as neuropathy of the hands and feet. The NHS England clinical lead noted that nivolumab is also associated with rare but potentially life-threating gastrointestinal, renal, endocrine and hepatic adverse events. The clinical expert commented that there are standard guidelines for managing immunotoxicity associated with treatments like nivolumab, which are well managed in clinical practice. The committee concluded that nivolumab is better tolerated than taxanes, but immunotherapies can cause significant immune-related side effects.

Comparator

Taxane chemotherapy is the relevant comparator

3.7 The clinical trial compared nivolumab with a combined taxane arm (paclitaxel and docetaxel). The clinical experts and NHS England clinical lead agreed that there is a class effect for taxanes, both in efficacy and side-effect profile. Best supportive care was not considered to be a relevant comparator, because people who are not well enough to tolerate taxane therapy are unlikely to benefit from nivolumab. The committee concluded that the relevant comparator for nivolumab therapy is taxane chemotherapy.

Cost effectiveness

There is uncertainty over the method of extrapolating overall survival

3.8 The company used a semi-parametric approach to model overall survival to capture the changing risk of death over time with nivolumab treatment. Kaplan−Meier curves from the trial were used in both groups up to 2.99 months. Then parametric extrapolation was used based on a log-logistic distribution in the nivolumab arm and an exponential distribution in the taxane arm. The ERG used the Kaplan−Meier curves with a cut-point at 5.75 months and then used a generalised gamma extrapolation for both arms. It chose a later point at which to switch from the Kaplan−Meier curves to parametric extrapolation so that this was at a point after the overall survival curves crossed, and also to maximise the use of clinical data from the trial. The ERG also commented that the choice of extrapolation method should be informed by visual fit to the Kaplan−Meier curve, goodness-of-fit statistics and clinical plausibility. It considered that a generalised gamma distribution gave a better visual fit to observed data in both groups. The company's method assumed a constant risk of death for taxanes and a high initial risk of death that reduced in the long term for nivolumab. The committee considered that the company's model was not a good fit to the currently available Kaplan–Meier curves and was likely to overestimate the overall survival benefit with nivolumab. At the meeting, the company made the committee aware of a later data cut providing estimates for overall survival up to 36 months. However, this could not be taken into account because the NICE technical team, ERG and committee did not have an opportunity to review it before the meeting. The committee considered that the most recent survival data may resolve some of the uncertainty about the most appropriate methods of extrapolation. It concluded that there is uncertainty over the optimal method of extrapolating overall survival.

No adjustment was made to efficacy or additional costs of third-line therapy

3.9 In the clinical trial, patients were able to continue initial treatment (see section 3.2) and have subsequent treatment (surgery, radiotherapy or pharmacotherapy) after disease progression. The proportion of people having subsequent therapy after progression was similar in both the nivolumab and taxane groups. However, more people in the nivolumab arm continued having their initial treatment compared with the taxane arm. The clinical expert explained that nivolumab may be continued after disease progression until the next scheduled scan confirms that the disease has progressed, but treatment would be stopped when progression was confirmed. However, because it is better tolerated than taxanes, more people would be able to have further active treatment after nivolumab than after taxanes. The committee considered the opportunity for active third-line treatment to be an important consideration for patients. It concluded that nivolumab would be more likely to be continued in the short term after progression than taxanes, as seen in the trial. It is not possible to tell whether any differences between the third-line treatments in ATTRACTION-3 and the NHS would affect the relative effectiveness of nivolumab in the NHS compared with the trial.

Utility values

Using different utilities after progression in the nivolumab and taxane arms is not adequately justified

3.10 The company estimated the utilities before and after progression using a statistical model fit to EQ-5D data from the clinical trial, with missing values imputed under the assumption that they were missing at random. Nivolumab had a higher utility before progression than taxanes because of its more favourable safety profile (the data cannot be reported here because the company submitted it as academic in confidence). The company model assumed a higher utility after progression for nivolumab

compared with taxanes because of the continued benefit of nivolumab. The committee considered it plausible for the utility before progression for nivolumab to be higher than the taxane arm, based on differences in tolerability and adverse events. But it noted that the difference was greater in the company's analysis compared with the ERG's analysis, which used values from an alternative statistical model fit by the company that did not include imputation of missing values. The clinical expert explained that it often takes people 6 months to recover from the adverse effects of chemotherapy. The NHS England clinical lead advised that if nivolumab increased the use of third-line treatments, a constant utility after progression was not plausible. The committee concluded that a differential utility before progression was reasonable, but the company had not given adequate justification for a long-term difference in utility after progression.

Costs

The company's method for estimated medical resource use costs is not adequately justified, eMIT should be the source for treatment costs

3.11 The company used the Monthly Index of Medical Specialities list price of taxanes and subsequent treatment for their economic model. Section 5.5.2 of NICE's guide to the methods of technology appraisals recommends using electronic market information tool (eMIT) prices because this is the most reflective source of average prices paid by NHS trusts. The committee concluded that eMIT should have been used to estimate the costs of treatment. This would increase the company base-case model incremental cost-effectiveness ratio (ICER) to £53,459 per quality-adjusted life year (QALY) gained.

The company's model underestimates the cost of inpatient treatment

3.12 The company estimated the cost of each episode of hospitalisation at £534.07 based on an average of 1 bed day per person. The ERG did not consider this method appropriate, instead using the cost of full length of

hospitalisation without adjusting for the length of stay. This increased the cost of hospitalisation to £3,379.73. The committee noted that this remains an uncertainty that has a substantial effect on the ICER. It concluded that the company had not given adequate justification for the estimation of hospital costs based on the duration of stay of 1 bed day.

The range of plausible ICERs is above what is considered cost effective

3.13 The committee noted that the company base-case ICER (including eMIT costs for taxanes) was £53,459 per QALY gained. There were several modelling uncertainties remaining, including the extrapolation of overall survival, progression-free survival and time on treatment. All of these could be affected by evidence from the 36-month data cut. The ERG base-case analysis included different assumptions for overall survival, time on treatment, utility values before and after progression, and medical resource use costs. This gave a cumulative ICER of £125,984 per QALY gained. Using the data available so far, the ICER may be between £53,459 (company base case with eMIT taxane prices) and £125,984 (ERG base case) per QALY gained. The committee concluded that nivolumab could not be recommended as a cost-effective use of NHS resources. It noted that the lowest ICER is also above what is considered plausibly cost effective for consideration in the Cancer Drugs Fund.

End of life

Nivolumab 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. The committee considered whether nivolumab meets the end-of-life criteria for people with unresectable, advanced or recurrent oesophageal cancer who have had fluoropyrimidine and platinum-based therapy. The company and ERG both agreed based on their analyses that life expectancy in this population is less than 24 months. The committee concluded that nivolumab was indicated for

people with a short life expectancy. The observed median overall survival benefit with nivolumab of 2.5 months was extrapolated. This gave an expected overall mean survival benefit of 7.8 months in the company's base-case model and 4.0 months in the ERG model. The committee considered it likely that the extension to life criterion was met but would like to see the effect of the 36-month data on modelled survival benefit.

Conclusion

Nivolumab is not recommended given the uncertainty in clinical and cost-effectiveness data

3.15 Data from the clinical trial shows that nivolumab offers improved survival benefit compared with taxanes in the long term, but not the short term. The committee has not seen the most recent results for overall survival, progression-free survival and time on treatment. Further justification and supporting evidence is needed for methods of extrapolation, differential utility after progression between treatment arms and hospitalisation costs. The most plausible ICER is currently likely to range between £53,459 (company base case with eMIT taxane prices) and £125,984 per QALY gained (ERG base case). Based on the current evidence, nivolumab is not cost effective for routine use or inclusion in the Cancer Drugs Fund.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam

Chair, appraisal committee

October 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

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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.

Farhaan Jamadar
Technical lead

Eleanor Donegan
Technical adviser

Jeremy Powell
Project manager

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