NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

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 combination with fluoropyrimidine- and platinum-based combination chemotherapy 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 2021

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 combination with fluoropyrimidine- and platinum-based combination chemotherapy 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: 11 November 2021

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 Nivolumab with platinum- and fluoropyrimidine-based combination chemotherapy is not recommended, within its anticipated marketing authorisation, as an option for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more.

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

There are no curative treatment options for HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more. The usual treatment is palliative chemotherapy. Most people have platinum- and fluoropyrimidine-based chemotherapy with capecitabine plus oxaliplatin (XELOX) or fluorouracil plus oxaliplatin with folinic acid (FOLFOX).

Clinical trial evidence shows that nivolumab with XELOX or FOLFOX increases the length of time before gastric, gastro-oesophageal junction or oesophageal adenocarcinoma gets worse compared with XELOX or FOLFOX alone. Evidence also shows that people live longer if they have nivolumab with XELOX or FELOX compared with XELOX or FOLFOX alone.

Nivolumab meets NICE's criteria to be considered a life-extending treatment at the end of life. But, the company’s economic model is not suitable for decision making because it includes assumptions which overestimate how long people live after

treatment and its survival estimates are not supported by clinical trial evidence. Also, the model is not suitable for exploring how different assumptions about people's long-term survival affect the cost-effectiveness estimates. This means that it is not possible to determine whether nivolumab is cost effective. So, nivolumab is not recommended.

2 Information about nivolumab

Anticipated marketing authorisation indication

2.1 On 16 September 2021, 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 (Opdivo, Bristol Myers Squibb). The CHMP adopted a new indication as follows: Nivolumab 'in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of nivolumab is £439 per 40 mg/4 ml concentrate for solution for infusion vial; £1,097 per 100 mg/10 ml concentrate for solution for infusion vial; and £2,633 per 240 mg/24 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed August 2021).

2.4 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 considered evidence from a number of sources. See the committee papers for full details of the evidence.

The condition

Gastric, gastro-oesophageal junction and oesophageal adenocarcinoma have a poor prognosis and a large impact on quality of life

3.1 The patient experts explained that gastric, gastro-oesophageal junction and oesophageal adenocarcinoma significantly impact quality of life. They explained that major symptoms include difficulty swallowing and malnutrition, which can lead to severe fatigue, weight loss and the need to use a feeding tube. These symptoms can be both painful and distressing, limiting people's ability to live normally and participate in social events. Diagnosis is often at an advanced stage, and around 40% of all new cases are diagnosed in people aged 75 and over. Gastric, gastro-oesophageal junction and oesophageal adenocarcinoma is more common in men than women, although the patient experts report increasing numbers of younger people and women are being diagnosed. The committee concluded that advanced gastric, gastro-oesophageal junction and oesophageal adenocarcinoma have a poor prognosis and a large impact on quality of life.

People would welcome a new treatment option

3.2 The patient and clinical experts explained that there are no curative treatment options for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. Standard first-line treatment for people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and no significant comorbidities is

palliative chemotherapy. NICE's guideline on oesophago-gastric cancer: assessment and management in adults recommends dual therapy with fluorouracil or capecitabine plus cisplatin or oxaliplatin, or triple therapy with epirubicin. The clinical experts explained that dual therapy regimens are preferred and that most people would have capecitabine and oxaliplatin (XELOX). This is because oxaliplatin is better tolerated than cisplatin and has a shorter infusion time. People have XELOX for 3 weeks (capecitabine is an oral medicine). Some people may be offered fluorouracil with oxaliplatin and folinic acid (FOLFOX). People have FOLFOX every 2 weeks (fluorouracil is an intravenous medicine). People having FOLFOX treatment need more hospital visits compared with people having XELOX. The patient and clinical experts agreed that there is unmet clinical need in this population. Nivolumab is an immunotherapy and has a different mechanism of action to chemotherapy. The committee concluded that patients and clinicians would welcome a new effective treatment for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

XELOX is the key comparator for this appraisal

3.3 The company suggested that XELOX and FOLFOX were the relevant comparators for this appraisal. The evidence research group (ERG) agreed with this approach and noted that most people would have XELOX because it is more convenient and cheaper than FOLFOX. Clinical experts also confirmed the company's approach and noted that dual chemotherapy regimens have similar efficacy. The committee concluded that XELOX was the key comparator for this appraisal.

Clinical evidence

Nivolumab plus chemotherapy improves progression-free survival and overall survival compared with chemotherapy alone

3.4 CheckMate 649 (n=1,581) was an open-label randomised multicentre trial (including 38 patients from 5 UK centres) that compared nivolumab plus XELOX or FOLFOX with XELOX or FOLFOX alone. It included people with untreated and unresectable, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma who had an ECOG performance status of 0 to 1. People with known HER2-positive status and untreated central nervous system metastases were excluded from the study. The primary outcomes were progression-free survival and overall survival in people whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more (n=955). July 2020 results were based on a minimum follow up of 12.1 months and showed that:

- nivolumab plus chemotherapy improved progression-free survival compared with chemotherapy alone (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.56 to 0.81)
- nivolumab plus chemotherapy improved overall survival compared with chemotherapy alone (HR 0.71, 95% CI 0.59 to 0.86).

The committee noted that this data was mature (meaning that more than half the trial population had progressed disease or died over the period of follow up). After technical engagement, the company provided some data from a longer follow up. The committee noted that this data confirmed the July 2020 results (the data is academic in confidence and cannot be reported here). The committee concluded that adding nivolumab to platinum- and fluoropyrimidine-based combination chemotherapy improved progression-free survival and overall survival compared with chemotherapy alone.

CheckMate 649 data is generalisable to NHS clinical practice

3.5 The ERG heard clinical advice suggesting that the trial population was younger and fitter than people seen in NHS clinical practice with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma who have an ECOG performance status of 2 and an average age between 70 and 75. Additional UK data reported that people seen in the NHS had an average age between 64 and 66 (Cancer Research UK and Royal Marsden Hospital Trust data). The clinical experts explained that average age of the trial population is expected to be lower than the average age of the NHS population with this condition. They agreed there is no evidence that treatment would be less effective in older people and stated that treatment should be based on patient fitness and comorbidities, regardless of age and performance status. The company noted that the trial age is aligned with UK data sources and that there is limited evidence to suggest outcomes differ between ECOG performance status scores. The committee concluded that CheckMate 649 data is generalisable to NHS clinical practice.

Long-term remission and cure

Some people may have long-term remission, but their life expectancy may be shorter than the general population

3.6 The company considered that CheckMate 649 suggested that hazard of progression or death in people whose disease had not yet progressed decreases over time and plateaus at 30 months. The company proposed that people who had no disease progression 30 months or more after starting treatment were in 'long-term remission'. The company's estimates of the risk of dying in people with long-term remission were the same as the general population. The ERG noted that this meant the company assumed that people whose cancer had not progressed by 30 months after starting treatment were cured and had the same lifespan as the general population. The company considered that other evidence showing

long-term survival in some people supports this assumption, for example COUGAR-02, ATTRACTION-2, Chau 2009 and Royal Marden Hospital data. The ERG considered that none of the long-term evidence supported the cure assumption. The number of people in CheckMate 649 at 30 months was too low for conclusions about cure to be made. The clinical experts agreed that long-term data supporting a cure assumption does not exist. However, the clinical and patient experts explained that long-term survival is likely for some people because this has been seen with other immunotherapy treatments. The clinical expert said that about 4% of people could be expected to achieve long-term remission with chemotherapy and that they expect nivolumab could double the number to 8%. The NHS England clinical lead noted that disease in long-term remission can relapse, but this is uncommon. The clinical experts said that people in long-term remission have a low burden of disease and their quality of life is good. However, their fitness is unlikely to return to pre-treatment levels because of long-term toxicities with chemotherapy, such as irreversible neuropathy. They expected the mortality rate in people with long-term remission to be higher than that of the general population because they previously had advanced cancer and cytotoxic chemotherapy. The committee concluded that some people are likely to have long-term remission but it was unclear if they were cured. The committee further concluded that people in whom disease did not recur would still be expected to have a shorter life expectancy than people who have not had this type of advanced cancer and chemotherapy.

The company's economic model

The company's model is not suitable for decision making

3.7 The company used a cohort-based semi-Markov model with 4 states: pre-progression, progressed disease, long-term remission and death. The model used CheckMate 649 individual patient data for progression-free survival (blinded independent central review). All people in the pre-

progression state at 30 months entered the long-term remission state and were assumed to have the same risk of dying as the general population and were effectively assumed to be cured (see section 3.6). The ERG explained that the company's model was unnecessarily complicated and differed from the 3-state partitioned survival models often used in NICE appraisals of cancer treatments. The model did not use overall-survival data directly, even though this was as mature as the progression-free survival data used to derive overall-survival estimates. The company modelled overall survival indirectly by using blinded independent central review progression-free survival data from CheckMate 649. The ERG explained that the company's model survival estimates were higher than the overall survival seen in the trial. Because the company's model did not correspond with the CheckMate 649 data, the ERG stated that the model long-term survival estimates and cost-effectiveness results lack reliability. The ERG suggested that a 3-state partitioned survival model could use the survival data from CheckMate 649 directly. The committee agreed the model lacked face validity because the modelled survival estimates did not match the survival estimates over the time that data was available. The committee noted that the survival data was mature (see section 3.4) and should be used in the model. It agreed with the ERG that 3-state partitioned survival models are suitable and noted that the inclusion of the long-term remission state in its current format (see section 3.8) makes the model unsuitable. The committee concluded that the company's model is not suitable for decision making.

Cure modelling

Assumptions around cure need to be explored

3.8 The committee had already concluded that while the company's cure assumption was not supported by the available evidence, some people may have prolonged remission of their cancer. The proportion of people whose cancer could be considered cured had not been fully explored. The

model also did not allow for a potentially higher long-term mortality even if the disease did not recur. The committee concluded that assumptions around cure need to be explored in a revised company model.

Other assumptions and inputs in the economic model

Utility values, model baseline age and adjustments for missed doses are appropriate for decision making

3.9 After technical engagement both the company and ERG made several changes and agreed on the following assumptions and inputs:

- applying the company's new adjustment of costs for chemotherapy and nivolumab for missed doses
- setting model mean baseline age to 64.15 years based on Cancer Research UK data instead of CheckMate 649 data
- using the company's utility values based on CheckMate 649 data.

The Checkmate 649 data that was used to inform utility values cannot be reported here because the company has stated it is academic in confidence. The clinical experts agreed with the company's and ERG's approach. The committee concluded that the utility values, model baseline age and adjustments for missed doses used in the model were appropriate for decision making.

The cost of PD-L1 CPS testing needs to be included

3.10 The company did not include the cost of PD-L1 CPS testing in its results. PD-L1 CPS testing is not routinely done in people with advanced HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. The clinical experts explained that PD-L1 CPS testing needs to be included in clinical pathways to avoid delayed access to PD-L1-specific treatments. The NHS England clinical lead confirmed that PD-L1 CPS testing needs to be implemented for this population and that the testing cost needs to be included in the cost-effectiveness results. The

committee concluded that the company needs to include the cost of PD-L1 CPS testing in its cost-effectiveness estimates.

Cost-effectiveness estimates

No plausible cost-effectiveness estimates can be determined

3.11 The deterministic cost-effectiveness results include nivolumab's confidential discount (see section 2.4) and do not include the cost of PD-L1 CPS testing (see section 3.10). The company's base case resulted in incremental cost-effectiveness ratios (ICERs) of £37,229 per quality-adjusted life year (QALY) gained compared with XELOX and £40,659 per QALY gained compared with FOLFOX. The ERG removed the long-term remission health state from the company's base case (see section 3.7), which resulted in ICERs of £71,014 per QALY gained compared with XELOX and £77,329 per QALY gained compared with FOLFOX. The company did not present any scenario or sensitivity analyses for its base case in people with a PD-L1 CPS of 5 or more. The committee had already concluded that the company's model is not suitable for decision making (see section 3.7) and therefore no plausible cost-effectiveness estimates could be determined.

A new model is needed to provide more robust overall-survival estimates and to model long-term remission appropriately

3.12 The committee recognised that a new effective treatment is needed for HER2-negative untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (see section 3.2). However, because the company's model lacked face validity and did not use mature survival data (see section 3.7 and 3.8), the committee concluded that a new model is needed. The committee agreed that the new company's model should:

- Be a 3-state partitioned survival model that directly uses overall-survival data (see section 3.7). Mixture cure modelling approaches may

be acceptable if adequately justified and the impact of any assumptions is explored with sensitivity analyses (see section 3.8).

- Be populated with the most recent data from CheckMate 649 (not July 2020 data currently used in the model; see section 3.4).
- Update all data included in the model to reflect the marketing authorisation population (see section 2.1).
- Include costs of PD-L1 CPS testing (see section 3.10).

The committee further noted that the key comparison would be with XELOX and that probabilistic, scenario and sensitivity analyses should be provided (these are currently not available, see section 3.10).

End of life

End of life criteria are met

3.13 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 considered whether nivolumab with platinum- and fluoropyrimidine-based combination chemotherapy meets the end of life criteria for people with untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more. The company and ERG both agreed, based on their analyses, that life expectancy in this population is less than 24 months. The observed median overall-survival benefit with nivolumab plus XELOX or FOLFOX in Checkmate 649 was larger than the additional 3-month extension to life needed by the criteria (the data cannot be reported here because the company submitted it as academic in confidence). The committee concluded that nivolumab met the end of life criteria.

Equalities

There are no equality issues relevant to the recommendations

3.14 No equality or social value judgement issues were identified.

Conclusion

Nivolumab is not recommended for routine use

3.15 The committee did not consider the company's model was appropriate for decision making, because it included implausible assumptions about how long people live, and the modelled survival estimates were not supported by the available clinical trial data. It also was not possible to use the model to explore the effect of alternative assumptions about people's survival on the cost effectiveness. No plausible cost-effectiveness estimates could be determined. This means that nivolumab cannot be recommended for treating advanced or metastatic HER2-negative gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more.

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
September 2021

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.

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.

Marcela Haasová and Cara Gibbons
Technical leads

Mary Hughes
Technical adviser

Thomas Feist
Project manager

ISBN: [to be added at publication]