NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer

Technology appraisal guidance
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www.nice.org.uk/guidance/ta876

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 Nivolumab with chemotherapy is recommended, within its marketing authorisation, as an option for the neoadjuvant treatment of resectable (tumours at least 4 cm or node positive) non-small-cell lung cancer (NSCLC) in adults. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Standard care for NSCLC that can be surgically removed (resectable) is surgery. Sometimes chemoradiotherapy before (neoadjuvant) or chemotherapy after (adjuvant) surgery is also used.

There is no clinical trial evidence directly comparing neoadjuvant nivolumab plus chemotherapy with standard care but an indirect comparison suggests it is more effective.

The cost-effectiveness estimates for neoadjuvant nivolumab with chemotherapy compared with standard care are within the range NICE normally considers an acceptable use of NHS resources. So, neoadjuvant nivolumab with chemotherapy is recommended.

2 Information about nivolumab with chemotherapy

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) with chemotherapy is indicated for 'the neoadjuvant treatment of resectable (tumours ≥ 4 cm or node positive) non-small cell lung cancer in adults'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for nivolumab is £439.00 for a (10 mg/ml) 4-ml vial (excluding VAT; BNF online, accessed January 2023).

2.4 The company has a commercial arrangement. This makes nivolumab 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 Bristol-Myers Squibb, a review of this submission by the external assessment group (EAG), and submissions from stakeholders. See the committee papers for full details of the evidence considered.

The condition

Unmet need

3.1 Standard care for resectable non-small-cell lung cancer (NSCLC) is surgical resection. Treatment options in addition to surgery are limited. Neoadjuvant chemoradiotherapy or adjuvant chemotherapy may be considered with the aim of improving long-term outcomes. Some people choose not to have adjuvant chemotherapy because of the associated serious adverse events and some may not be fit enough to tolerate it after surgery. The patient organisation submission highlighted that the 5-year survival rate after surgical resection with curative intent is about 50%, with relapses in distant sites. It explained that symptoms of recurrent NSCLC, such as breathlessness, cough and weight loss, are often difficult to manage without active treatment. It also highlighted that neoadjuvant treatment is well established in other cancers, such as breast cancer, as a promising approach for prolonging survival and increasing the chance of cure for people with potentially resectable NSCLC. A professional organisation submission highlighted that NSCLC has a very poor prognosis in the UK. It explained that only a small proportion of people have NSCLC that can be cured at an early stage and a substantial proportion have recurrence. So, it is important that new treatment options are made available to ensure the best chance of cure. This submission noted that nivolumab plus chemotherapy increases the potential of good outcomes for the small proportion of people who have potentially curable NSCLC. There are limited treatment options for resectable NSCLC after surgery, and outcomes with available treatments are poor. Also, there is a need for a new treatment option, particularly in the neoadjuvant setting. The committee concluded that there is an unmet need for treatments for resectable NSCLC, and neoadjuvant nivolumab plus chemotherapy would be welcomed.

Comparators

3.2 In its submission, the company compared neoadjuvant nivolumab plus chemotherapy with neoadjuvant chemoradiotherapy, surgery alone and adjuvant chemotherapy. The company highlighted that surgery alone represents the active monitoring comparator as per the NICE scope. It further explained that, in its economic model, people in the neoadjuvant chemoradiotherapy arm had chemotherapy plus radiotherapy then surgery. Some people had adjuvant treatment. In the surgery alone arm, people had surgery and did not have neoadjuvant or adjuvant treatment, but had monitoring after surgery. In the adjuvant chemotherapy arm people had surgery and a subsequent course of chemotherapy. The EAG noted that the comparators included in the company's economic evaluation were in line with the NICE scope and representative of NHS clinical practice. The committee concluded that the comparators included in the company submission were appropriate.

Clinical effectiveness

CheckMate-816 trial evidence

3.3 The clinical-effectiveness evidence for neoadjuvant nivolumab plus chemotherapy came from CheckMate-816. This is an ongoing phase 3, multicentre, randomised, open-label, clinical trial. It is comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant chemotherapy alone in adults with resectable stage 1B to 3A NSCLC. In the interim analysis 1 (October 2021), there was a median follow up of 29.5 months. Results from this analysis showed that neoadjuvant nivolumab plus chemotherapy improved event-free and overall survival. They also showed that the odds of pathological complete response were higher compared with neoadjuvant chemotherapy alone. The EAG highlighted that its clinical advice suggested that NSCLC disease stage is the main prognostic factor. It did subgroup analyses for disease stage, which showed that neoadjuvant nivolumab plus chemotherapy was less effective for stage 1B to 2 NSCLC than for stage 3 NSCLC. The result was less precise for stage 1B to 2 NSCLC, indicating that the analysis was underpowered. The EAG noted that more people in CheckMate-816 had cisplatin-based chemotherapy than

carboplatin-based chemotherapy, consistent with clinical advice it had received. But clinical advice also suggested carboplatin-based chemotherapy could be paired with nivolumab. Clinical advice to the EAG further suggested that cisplatin plus vinorelbine would be the most commonly used chemotherapy regimen in the UK. But this combination was only used in the neoadjuvant chemotherapy alone arm of CheckMate-816. The EAG considered that, when assessed in the overall population, neoadjuvant nivolumab plus chemotherapy is more effective for stage 1B to 3A resectable NSCLC compared with neoadjuvant chemotherapy alone. It also thought that, although neoadjuvant nivolumab plus chemotherapy may be less effective for the stage 1B to 2 NSCLC subgroup (compared with the stage 3A NSCLC subgroup), its effectiveness in the overall resectable stage 1B to 3A NSCLC population is more relevant. The committee concluded that neoadjuvant nivolumab plus chemotherapy is more effective for stage 1B to 3A resectable NSCLC compared with neoadjuvant chemotherapy alone.

CheckMate-816 generalisability

3.4 The EAG noted that CheckMate-816 has not recruited anyone from the UK, and that about 50% of people in the study had an Asian family background. So, it considered that generalisability of the trial to NHS clinical practice is questionable. The EAG also noted that the characteristics of the North American and European family background subgroups from CheckMate-816 may be more applicable to NHS clinical practice. The EAG's subgroup analyses by family background showed that neoadjuvant nivolumab plus chemotherapy was less effective in the North American and European populations compared with the Asian population. In CheckMate-816, 59.1% of people in the neoadjuvant nivolumab plus chemotherapy arm and 63.0% of people in the neoadjuvant chemotherapy alone arm had thoracotomy. Also, 16.8% of people in the neoadjuvant nivolumab plus chemotherapy arm and 25.2% in the neoadjuvant chemotherapy alone arm had pneumonectomy. But clinical advice to the EAG suggested that minimally invasive surgery is more common in NHS clinical practice. In CheckMate-816 only 29.5% of people in the neoadjuvant nivolumab plus chemotherapy arm and 21.5% in the neoadjuvant chemotherapy alone arm had minimally invasive surgery. Clinical advice to the EAG also suggested that pneumonectomy is now very uncommon for NSCLC resection in NHS clinical practice. So, the EAG considered that the main resection types used in

CheckMate-816 may not reflect NHS clinical practice. But it is unclear if resection type is associated with different recurrence rates and health-related quality of life. The EAG considered that all other baseline characteristics were well balanced between treatment arms in CheckMate-816. The committee acknowledged that there were differences in demographics between the trial and NHS clinical practice, and noted that neoadjuvant nivolumab plus chemotherapy is less effective in some subgroups. But it considered that the trial is likely representative of NHS clinical practice and that most baseline characteristics between the CheckMate-816 treatment arms were well balanced. So, the committee concluded that clinical evidence from CheckMate-816 was uncertain but suitable for decision making.

Indirect comparison

3.5 There was no evidence directly comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant chemoradiotherapy, surgery alone or adjuvant chemotherapy. So, the company presented an indirect treatment comparison informed by network meta-analyses. These provided comparative effectiveness evidence for neoadjuvant nivolumab plus chemotherapy compared with all the relevant comparators and neoadjuvant chemotherapy alone. The primary outcomes assessed in the network meta-analyses were event-free survival and overall survival. The secondary outcomes assessed were time to locoregional recurrence (TTLR), time to distant metastasis, pathological complete response and safety. The results of the network meta-analyses showed that neoadjuvant nivolumab plus chemotherapy was more effective at improving survival outcomes compared with neoadjuvant chemotherapy alone, neoadjuvant chemoradiotherapy, surgery alone and adjuvant chemotherapy. Results for secondary outcomes were considered confidential by the company, so cannot be reported here. The EAG noted that some studies in the network meta-analyses only included people with an Asian family background, while about 50% of people in CheckMate-816 had an Asian family background. Also, it noted that, although its clinical advice suggested disease stage is the main prognostic factor, only CheckMate-816 included stage 1B to 3A NSCLC. Subgroup analyses conducted by the EAG contained data that the company considered confidential, so cannot be reported here. Despite the differences between the studies included in the network meta-analyses, it was considered that the company had sufficiently

responded to the EAG's requests at the clarification stage to explore these uncertainties. It was also decided that little more could be done to further address the uncertainties. So, the network meta-analyses were deemed sufficient, and the results considered acceptable for decision making. Because the marketing authorisation for nivolumab plus chemotherapy is not restricted by disease stage, the results of the network meta-analyses for neoadjuvant nivolumab plus chemotherapy for the overall resectable stage 1B to 3A NSCLC population were considered appropriate. The committee concluded that neoadjuvant nivolumab plus chemotherapy is more effective than all the relevant comparators.

Survival extrapolation

3.6 The parametric models used to extrapolate time to any progression (TTaP) and TTLR beyond CheckMate-816 follow up played an important role in determining the efficacy of the intervention. There is considerable uncertainty around the extrapolation of the TTaP and TTLR curves. The company's and EAG's approaches to modelling long-term TTLR and event-free mortality was uncertain. But both were considered plausible and produced cost-effectiveness estimates that were well below NICE's cost-effectiveness threshold. The committee concluded that the optimal approach to modelling survival was uncertain.

Economic model

Model structure

3.7 The company presented a 4-state semi-Markov model to estimate the cost effectiveness of neoadjuvant nivolumab plus chemotherapy compared with neoadjuvant chemoradiotherapy, surgery alone and adjuvant chemotherapy. The 4 health states were event-free, locoregional recurrence, distant metastasis and death. The model used a lifetime horizon and a cycle length of 3 weeks. The model assumed distant metastasis was an absorbing state and applied a one-off cost, and life-year and quality-adjusted life-year (QALY) pay-off upon transitions to the distant metastasis health state. Utility values in the locoregional recurrence

state were assumed to be lower than in the event-free state and lower still in the distant metastasis state. A short-term disutility was included to reflect grade 3 and grade 4 adverse events associated with adjuvant treatment during the first cycle of the model. The EAG noted the model structure was consistent with previous economic models for lung cancer. It considered the approach to modelling the distant metastasis state was pragmatic, reduced the complexity of the model and was consistent with previous NICE technology appraisals for lung cancer. The committee concluded that the company's model was appropriate based on the available evidence for this appraisal.

Cure assumption

3.8 In its economic model, the company applied a 'cure assumption'. The EAG considered that there was no convincing clinical evidence to support how the cure assumption had been modelled. It was noted that there is generally a consensus among clinical experts that cure occurs between years 5 and 8. But there is no consensus on the rates of cure, and the empirical evidence to support this assumption is lacking. The company's and the EAG's scenario analysis removing the cure assumption only had a small effect on the cost-effectiveness results. The committee concluded that the cure assumption applied was uncertain.

Utility values

3.9 The health-state utility values used in the cost-effectiveness model were associated with a degree of uncertainty. This was mainly because the utility values for both the event-free and locoregional recurrence health states were higher than what would be expected in a population with NSCLC. Other minor issues included:

- using overall rather than treatment-specific utilities from CheckMate-816
- using linear mixed models when analysing non-linear EQ-5D-3L data
- the age-sex adjustment process implemented in the model.

But these issues would be difficult to resolve given the lack of evidence. The EAG presented 4 scenarios to explore this uncertainty. The committee concluded that, given the available evidence, the uncertainty had been sufficiently explored.

Retreatment restrictions

3.10 In its model, the company applied immuno-oncology therapy retreatment restrictions for people who had neoadjuvant nivolumab plus chemotherapy as their initial treatment and whose NSCLC progressed within 6 months. These people were not considered eligible for further immuno-oncology treatment. Data from CheckMate-816 was used to adjust the distribution of treatment in the distant metastasis health state to account for the proportion of people in the neoadjuvant nivolumab plus chemotherapy arm who had an event while on treatment. So, these people were not eligible for further treatment with immuno-oncology therapy for 6 months, and their treatments were redistributed across the remaining treatment options. The EAG considered there was uncertainty in the proportion of people ineligible for retreatment with immuno-oncology therapy and the timelines of these restrictions. But it noted that the company had done a scenario analysis with retreatment restriction extended to 12 months, and that the percentage of those not considered for further immuno-oncology retreatment was increased. A further scenario analysis was done by both the company and the EAG in which the retreatment restriction was not included. The EAG did additional scenario analyses by assuming the distribution of chemotherapies in the distant metastasis health state were the same for immuno-oncology and non-immuno-oncology treatments. It was noted that further evidence on the distribution of chemotherapies used for immuno-oncology and non-immuno-oncology treatments in the distant metastasis health state would help address this uncertainty. The committee concluded that the application of retreatment restrictions in the economic model was uncertain.

Cost-effectiveness estimates

Results

3.11 When commercial arrangements for nivolumab plus chemotherapy and all the comparators were included, the company's and EAG's base-case incremental cost-effectiveness ratios (ICERs) compared with neoadjuvant chemoradiotherapy, surgery alone and adjuvant chemotherapy were all below £20,000 per QALY gained. The exact ICERs are considered confidential and cannot be reported here. Outstanding areas of uncertainty were considered, including:

- long-term survival modelling beyond CheckMate-816 trial follow up (see section 3.6)
- application of a cure assumption (see section 3.8)
- utility values for event-free and locoregional recurrence health states (see section 3.9)
- application of retreatment restrictions (see section 3.10).

The committee considered that key uncertainties had been explored sufficiently by both the company and EAG. It noted that almost all of the ICERs remained within the range that is normally considered by NICE as a cost-effective use of NHS resources. So, the likelihood of decision error in this appraisal was assessed to be minimal. The committee concluded that neoadjuvant nivolumab plus chemotherapy for neoadjuvant treatment of resectable NSCLC is likely to be a cost-effective use of NHS resources.

Other factors

Equality issues

3.12 No equality issues were identified. NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.13 It was considered whether neoadjuvant nivolumab plus chemotherapy is innovative. No additional benefits of nivolumab plus chemotherapy were identified that were not captured in the economic modelling. So, the committee concluded that all additional benefits of neoadjuvant nivolumab plus chemotherapy had already been taken into account.

Conclusion

Recommendation

3.14 All the ICERs considered were in the range normally considered by NICE to be a cost-effective use of NHS resources. So, nivolumab plus chemotherapy is recommended for the neoadjuvant treatment of resectable NSCLC.

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 non-small-cell lung cancer and the doctor responsible for their care thinks that nivolumab with chemotherapy 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 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

Stephen Smith
Chair, technology appraisal committee D

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.

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