NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy

Technology appraisal guidance
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Your responsibility

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

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

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

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

Contents

This guidance replaces TA483.

1 Recommendations

1.1 Nivolumab is recommended as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC) in adults after chemotherapy, only if:

- it is stopped at 2 years of uninterrupted treatment, or earlier if their disease progresses and
- they have not had a PD-1 or PD-L1 inhibitor before.

It is recommended only if the company provides nivolumab according to the commercial arrangement.

Why the committee made these recommendations

The treatment pathway for locally advanced or metastatic squamous NSCLC starts with a PD-1 or PD-L1 inhibitor or chemotherapy. Nivolumab would be used after chemotherapy. In line with clinical practice, nivolumab is a treatment option for people who have not had a PD-1 or PD-L1 inhibitor.

Evidence was collected in the Cancer Drugs Fund for people with advanced or metastatic squamous NSCLC having up to 2 years of nivolumab treatment in the NHS. The key clinical trial shows that people who have nivolumab live longer than those who have docetaxel, which is the most appropriate comparator. There is uncertainty about how long people should have nivolumab for, but evidence suggests that there is continued benefit when treatment is stopped at 2 years.

Nivolumab meets NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimates for nivolumab compared with docetaxel are likely to be within what NICE considers to be an acceptable use of NHS resources. Therefore, it is now recommended in the NHS after chemotherapy for people who have not had a PD-1 or PD-L1 inhibitor before, if it is stopped at 2 years.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) has a marketing authorisation in the UK for 'the treatment of locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy in adults'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of nivolumab is £2,633 per 240 mg per 24-ml vial (excluding VAT; BNF online, accessed March 2020). 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 appraisal committee considered evidence submitted by Bristol-Myers Squibb, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected after time in the Cancer Drugs Fund (CDF) to address uncertainties identified during the original appraisal. Further information about the original appraisal can be found in the committee papers. As a condition of the CDF funding and the managed access arrangement, the company was required to collect updated efficacy data from the CheckMate 017 study for people with advanced squamous non-small-cell lung cancer (NSCLC). In addition, data were collected on nivolumab for people with squamous NSCLC after chemotherapy in the NHS through the CDF using the Systemic Anti-Cancer Therapy (SACT) dataset.

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

- the progression-free survival curve using the hybrid exponential extrapolation underestimated observed progression-free survival, so the spline 1-knot-hazard gave a better fit and was appropriate to model progression-free survival
- it was appropriate to consider the full population regardless of PD-L1 expression.

The committee recognised that there were remaining areas of uncertainty in the analyses presented (see technical report, table 2, page 17) and took these into account in its decision making. The committee discussed the following issues, which were outstanding after the technical engagement stage:

- choice of parametric models to predict overall survival
- the 2-year stopping rule for nivolumab and the continued duration of treatment benefit if nivolumab is stopped at 2 years.

Clinical need

People with treated advanced squamous NSCLC value having nivolumab as a treatment option

3.1 People who have treatment with nivolumab see it as an effective treatment option that is generally well tolerated. The committee considered patient accounts of living with squamous NSCLC. Patient concerns were not only about their own health and wellbeing, but included the effect that living with cancer may have on their family members. The committee noted that some patients had experienced anxiety and distress because of the 2-year stopping rule used in the original guidance. This was because they did not want to stop benefiting from treatment. Patients wanted treatment options to be personalised to their needs and be reassured that effective care would be available after a treatment had stopped if needed. The clinical expert submission suggested that in clinical practice, nivolumab would be used in people who had not had a PD-1 or PD-L1 inhibitor before. The committee concluded that people with previously treated squamous NSCLC value having nivolumab as a treatment option.

Docetaxel alone is the most appropriate comparator

3.2 In the original appraisal, docetaxel monotherapy was considered the most relevant comparator. The committee was aware that since its publication, pembrolizumab and atezolizumab have been recommended for previously treated locally advanced or metastatic NSCLC (see NICE's technology appraisal guidance on atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy and pembrolizumab for treating PD-L1-positive NSCLC after chemotherapy). There have also been changes to treatment options for untreated disease (see NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic NSCLC). The CDF clinical lead confirmed that the treatment pathway had changed and because immunotherapies were now available for untreated disease, nivolumab was not used as often for previously treated disease. In line with NICE's methods guide for technology appraisals, the original scope was not changed for this CDF review. This meant that pembrolizumab and atezolizumab could not be considered comparators

because they were recommended after the original guidance was published. Therefore, the committee concluded that docetaxel alone was the most appropriate comparator for this CDF review.

Clinical effectiveness

Nivolumab is clinically effective compared with docetaxel alone for people with squamous NSCLC after chemotherapy

3.3 There were new data from CheckMate 017, which is an open-label randomised trial. It included adults with squamous NSCLC, whose disease had progressed during or after treatment with 1 platinum combination chemotherapy. The committee noted that there were 135 patients in the nivolumab arm and 137 patients in the docetaxel arm. Patients were randomised to have either nivolumab (3 mg per kg, the recommended dose in the summary of product characteristics at the time) or docetaxel. The hazard ratio using 5-year data from CheckMate 017 showed nivolumab was associated with a statistically significant improvement in overall survival compared with docetaxel (the exact data are confidential and cannot be reported here). The committee concluded that nivolumab was clinically effective compared with docetaxel alone for people with squamous NSCLC after chemotherapy.

Results from CheckMate 017 are generalisable to the NHS in England

3.4 The committee was aware that as well as new data from CheckMate 017, there were new SACT data. These were collected from 348 people who had nivolumab in the CDF, with a median follow up of 487 days (with a range of 5 months to 20 months). The median treatment duration was 3.5 months. The overall survival estimates using the SACT data were similar to CheckMate 017 data. The committee concluded that results from CheckMate 017 were generalisable to the NHS in England.

Dosing

The new dosage of nivolumab was not used in CheckMate 017 but is unlikely to have a large effect on clinical- and cost-effectiveness results

3.5 At the time of the original appraisal, the recommended dose of nivolumab in its summary of product characteristics was 3 mg per kg every 2 weeks, but this has since changed to 240 mg every 2 weeks. The company assumed that the new dose had the same clinical effectiveness as the previously recommended dose of 3 mg per kg. The committee understood that there were no clinical-effectiveness data using the new dosage. The CDF clinical lead advised that the dose change for nivolumab had been accepted by the regulatory body and was already being used in clinical practice in the NHS in England. The committee concluded that although it had not seen clinical-effectiveness evidence for the new dosage, it was unlikely to have had a large effect on the clinical- and cost-effectiveness results.

Economic model

The company's economic model is suitable for decision making

3.6 The updated model used the same approach as the original appraisal. The model had 3 health states: progression-free disease, progressed disease and death. Health-state occupancy over time was informed by overall survival and progression-free survival curves fitted to data from CheckMate 017. The company modelled nivolumab using clinical-effectiveness data for the 3 mg per kg dose, but applied the costs of the currently recommended flat dose of 240 mg every 2 weeks. The committee considered that this approach was appropriate and concluded that the company's model was suitable for decision making.

Modelling overall survival and progression-free survival

The company's spline hazard 1-knot model is appropriate for progression-free survival

3.7 In the previous appraisal, the committee considered that the most appropriate method of extrapolation was applying an exponential curve after the trial data split at 2.2 months (hybrid exponential). This method reduced the influence of data collected before the first radiological assessment on the long-term extrapolation. But, the hybrid exponential extrapolation did not fit well with the long-term data in CheckMate 017 and consistently underestimated observed progression-free survival. The company fitted several models to the updated 5-year progression-free survival data from CheckMate 017 for both treatment arms and preferred the spline 1-knot normal curve for its base-case analysis. At technical engagement, it was agreed that extrapolation of progression-free survival using the spline hazard 1-knot model was appropriate in both the nivolumab and docetaxel treatment arms. The committee concluded that the company's spline hazard 1-knot model was clinically plausible.

The company's spline hazard 2-knot model is appropriate for overall survival

3.8 The committee and the company agreed that the 5-year data suggested that the generalised gamma distribution (preferred by the committee in the original appraisal) was likely to underestimate overall survival. The company fitted several models to the updated 5-year overall survival data from CheckMate 017 for both treatment arms and preferred the spline 2-knot hazard model for its base-case analysis. The ERG stated that overall survival may be plausibly modelled using the spline 2-knot hazard, the spline 1-knot hazard or the Gompertz models. The committee recognised that the 5-year data gave greater certainty in survival extrapolation, noting that overall survival estimates did not change to a large extent with the 3 plausible choices of extrapolation models. However, the additional follow-up data were for a population of people who had nivolumab without a stopping rule in place. So, the committee also took into account the

percentage of people from CheckMate 017 who continued having treatment over the time horizon of the 5-year follow-up data. The committee concluded that it was clinically plausible to model overall survival using the spline 2-knot hazard model to extrapolate the 5-year data.

Stopping rule and continued treatment effect

It is likely that nivolumab's survival benefit continues after it is stopped

3.9 The company preferred to include a 2-year stopping rule for nivolumab and assumed that the overall survival benefit would accumulate over the patients' lifetimes. At technical engagement, a professional organisation commented that it is clinically plausible that the immune system could be 'reset'. This means benefit from treatment could be maintained for years after nivolumab is stopped. The committee understood that the summary of product characteristics approved nivolumab while clinical benefit is seen or until treatment is no longer tolerated. The committee considered CheckMate 003, a single-arm study that included 129 patients with squamous or non-squamous NSCLC, of whom 54 had squamous disease. It included people who had between 1 and 5 previous treatments, whose disease had progressed after at least 1 platinum- or taxane-based chemotherapy, and who had stopped nivolumab treatment after 1.8 years. The company explained that data from CheckMate 003 showed that of 16 people who survived for 5 years and had no therapy after stopping nivolumab, 12 (75%) were still progression free. The committee agreed the study had evidence that supported the continued treatment effect but noted there was uncertainty because of the mixed population and small sample size (only 18 of the 129 patients with NSCLC had squamous NSCLC and a 3 mg per kg dose). The committee considered if data from CheckMate 153 would be informative. CheckMate 153 is an ongoing study investigating the effect of a maximum of 1-year treatment with nivolumab, but it was not reported within the company submission. The company explained that findings of CheckMate 153 were similar to CheckMate 003 and showed survival benefit after the 1-year stopping rule. The committee concluded that although there was uncertainty about how long people should have nivolumab, survival benefit was likely to continue for at least

3 years after treatment had stopped.

The 2-year stopping rule for nivolumab is appropriate

3.10 The company preferred to include a 2-year stopping rule for nivolumab. The committee recalled that CheckMate 017 did not specify a stopping rule and questioned if it was appropriate for the 2-year stopping rule to remain. The ERG explained that there was no robust evidence to show the optimal duration of treatment with nivolumab. The committee recalled its earlier conclusion that it is plausible that a survival benefit from nivolumab would continue after it is stopped at 2 years. The committee also recalled that some patients experienced anxiety and distress because their treatment was stopped at 2 years (see section 3.1). The company suggested that this was not the experience of all patients and some may welcome a break from treatment. The CDF clinical lead explained that a 2-year stopping rule for immunotherapies such as nivolumab was commonly being used in clinical practice for squamous NSCLC in the NHS in England. The committee concluded that a 2-year stopping rule for nivolumab was appropriate because it was likely the benefit would continue after it is stopped. Also, there was no new evidence to show that continuing for longer gave additional benefit.

When nivolumab is stopped at 2 years, it is acceptable to assume an additional survival benefit for at least 3 more years

3.11 In its base-case analysis, the company preferred to assume that if nivolumab is stopped at 2 years, patients will continue to accumulate a lifetime survival benefit after that point. But, the committee was not convinced that the company's preferred lifetime survival benefit was plausible. In the original guidance, a 3-year continued benefit after stopping nivolumab was accepted. The committee recognised that 5-year data were now available from CheckMate 017. But, it noted that there was no new robust evidence on the duration of the continued benefit after stopping nivolumab that would change the assumption accepted in the original guidance. It was aware that removing the stopping rule and changing the duration of treatment benefit had a large effect on the cost-effectiveness results. It considered plausible durations of treatment benefit and believed that the cost-effectiveness estimate preferred by the company was likely to be

optimistic. This was because a lifetime treatment effect was not supported by the evidence. The committee considered that a cost-effectiveness estimate based on 2 years of treatment and 3 years of continued benefit after treatment had stopped was likely to be conservative. This was because treatment effect was unlikely to stop immediately after 5 years. It also considered alternative treatment waning scenarios presented by the company during technical engagement, for which the modelling approach was adapted so that treatment benefit did not suddenly stop at a given time point. The exact treatment benefit duration was not known. The committee's preferred assumption was that if nivolumab was offered for 2 years of uninterrupted treatment, it was likely that its survival benefit would continue for 3 or more years after being stopped.

End of life

Nivolumab meets the end-of-life criteria

3.12 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. In the original appraisal, the data showed that life expectancy for people with NSCLC was less than 24 months and that nivolumab extended life by at least 3 months. The committee noted that no evidence had been identified to change this conclusion. So, the committee concluded that nivolumab meets the end-of-life criteria and can be considered a life-extending treatment at the end of life.

Cost effectiveness

The most plausible ICER is within what NICE considers an acceptable use of NHS resources

3.13 The company's preferred incremental cost-effectiveness ratio (ICER) for nivolumab compared with docetaxel alone for people with squamous NSCLC was £35,710 per quality-adjusted life year gained. This included a 2-year stopping

rule for nivolumab and continuing to accumulate a lifetime survival benefit after stopping treatment, which the committee did not feel was plausible. Using the committee's preferred assumptions of 2 years of treatment and 3 years of continued benefit once treatment had stopped, the most plausible ICER was likely to be below £40,168. This scenario was modelled using the company's preferred assumptions, including a spline 2-knot hazard extrapolation for overall survival. Given that end-of-life criteria was met, the committee concluded that this was within what NICE considers a cost-effective use of NHS resources.

Other factors

3.14 No equality or social value judgement issues were identified.

Conclusion

Nivolumab is recommended for routine commissioning for people with advanced squamous NSCLC after chemotherapy

3.15 Considering new evidence from CheckMate 017, SACT data and the committee's preferred assumptions, all plausible cost-effectiveness estimates were within what is considered a cost-effective use of NHS resources when the end-of-life criteria were applied. Nivolumab was therefore recommended for use in the NHS as an option for treating locally advanced or metastatic squamous NSCLC in adults after chemotherapy, only if:

- it is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses and
- they have not had a PD-1 or PD-L1 inhibitor before.

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 clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement 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 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 appraisal document.

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 advanced squamous non-small-cell lung cancer and the doctor responsible for their care thinks that nivolumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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 C.

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.

Adam Brooke and Vicki Pollit
Technical leads

Alexandra Filby
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Update information

April 2021: We removed recommendation 1.2 because it's not needed.

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