NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

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

- their tumours are PD-L1 positive, and
- 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 (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for nivolumab for locally advanced or metastatic PD-L1 positive non-squamous NSCLC (NICE technology appraisal guidance 484).

The treatment pathway for locally advanced or metastatic non-squamous NSCLC starts with a PD-1 or PD-L1 inhibitor or chemotherapy. Nivolumab would be used after chemotherapy.

Evidence collected in the Cancer Drugs Fund is for people with PD-L1 positive disease having up to 2 years of nivolumab treatment in the NHS. The key clinical trial shows that people with PD-L1 positive tumours 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 shows 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 an acceptable use of NHS resources. Therefore, it is now recommended in the NHS for people with PD-L1 positive tumours who have not had a PD-1 or PD-L1 inhibitor before, when it is stopped at 2 years.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers Squibb) has a marketing authorisation 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 (simple discount patient access scheme). 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 (section 6) considered evidence submitted by Bristol-Myers Squibb and 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 057 study. In addition, data were collected on nivolumab for people with PD-L1 positive disease in the NHS through the CDF using the Systemic Anti-Cancer Therapy (SACT) dataset.

The committee recognised that there were remaining areas of uncertainty in the analyses presented (see technical report, table 3, page 23) and took these into account in its decision making. The committee discussed the following issues, which were outstanding after the technical engagement stage:

- the appropriate comparator
- parametric models to predict overall survival and progression-free survival
- utility values
- 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 previously treated advanced non-squamous non-small-cell lung cancer (NSCLC) with PD-L1-positive tumours value nivolumab as a treatment

3.1 Non-squamous NSCLC is often diagnosed late in life and causes debilitating and distressing symptoms. The clinical expert submission explained that overall survival for lung cancer in the UK is poor, but the introduction of immunotherapies such as nivolumab means people can live longer. The committee was aware that patients and professionals want treatments that are effective, minimally disruptive, and improve quality of life. It 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 benefitting from treatment. The clinical expert submission suggested that in clinical practice nivolumab would be used when people had not had a previous PD-1 or PD-L1 inhibitor. The committee concluded that people with locally advanced or metastatic non-squamous NSCLC with PD-L1 positive tumours would value nivolumab as a treatment option.

Docetaxel alone is the most appropriate comparator

3.2 In the original appraisal, docetaxel monotherapy, nintedanib plus docetaxel for people with adenocarcinoma and best supportive care were considered relevant comparators. 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 non-small-cell lung cancer after chemotherapy and pembrolizumab for treating PD-L1-positive non-small-cell lung cancer 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 non-small-cell lung cancer and pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer). The CDF clinical lead from NHS England 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. The company only submitted cost-effectiveness analyses comparing nivolumab with docetaxel alone because it stated that neither best supportive care nor nintedanib and docetaxel are commonly used in clinical practice. Clinical advice to the

ERG also suggested that nintedanib plus docetaxel is not commonly used to treat non-squamous NSCLC, and at technical engagement, a professional organisation advised that less than 5% of people have this combination. Furthermore, the CDF clinical lead explained that nintedanib plus docetaxel is not commonly used because it is associated with a wide range of side effects. The committee was concerned that the company had not presented cost-effectiveness estimates comparing nivolumab with nintedanib plus docetaxel, which was considered a relevant comparator in the original appraisal. However, it understood that this was because changes to the treatment pathway after publication of the original appraisal mean it is now very unlikely to be used in clinical practice in the NHS in England. The committee agreed that best supportive care was also very unlikely to be used after chemotherapy. It 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 PD-L1 positive non-squamous NSCLC after chemotherapy

3.3 As well as new data from the CheckMate 057 and CheckMate 003 studies, there were new SACT data available for this review. This was collected from 43 people who had nivolumab in the CDF between September 2017 and December 2018. CheckMate 057 is an open-label trial that included 582 adults with non-squamous NSCLC, whose disease had progressed after previous platinum-based chemotherapy and who had not previously had a PD-1 or PD-L1 inhibitor. 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. There were 122 patients with PD-L1 positive disease (PD-L1 on at least 1% of tumour cells) in the nivolumab arm and 123 patients with PD-L1 positive disease in the docetaxel arm. For the PD-L1 positive subgroup, the hazard ratio using 5-year data from CheckMate 057 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 understood that 1-year overall survival reported in the SACT data (43%, 95% confidence interval: 28% to 58%) was considerably lower than that in the nivolumab arm of the trial (for which the exact data are confidential and cannot be reported here). However, the SACT data were limited by their small sample size and short follow up. The committee agreed that data from the CheckMate 057 trial were the most robust and were suitable for assessing the clinical effectiveness of nivolumab. It concluded that nivolumab was clinically effective compared with docetaxel alone for people with PD-L1 positive non-squamous NSCLC after chemotherapy.

Dose of nivolumab

The new dosage for nivolumab was not used in CheckMate 057 but is unlikely to have a large effect on the clinical and cost-effectiveness results

3.4 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. This has since changed to 240 mg every 2 weeks. The company assumed that the new dose has the same clinical effectiveness as the previously recommended dose. 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 was not considered important because it had been accepted by the regulatory body and was already being used in clinical practice in the NHS. The committee concluded that although it had not seen clinical-effectiveness evidence for the new dosage, it was unlikely to have a large effect on the clinical and cost effectiveness of nivolumab.

Economic model

The company's economic model is suitable for decision making

3.5 The company's 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 survival curves from CheckMate 057, but the committee only considered data for the relevant subgroup (PD-L1 of at least 1%). The company modelled nivolumab using clinical-effectiveness data for the 3 mg per kg dose but applied the costs of 240 mg every 2 weeks, and the committee considered this approach appropriate. It concluded that the company's model was suitable for decision making.

Modelling overall survival and progression-free survival

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

3.6 The company fitted several models to the updated 5-year progression-free survival data from CheckMate 057 for both treatment arms. It preferred the spline 1-knot normal curve for its base-case analysis. The ERG considered the company's model to be a good fit to the observed Kaplan−Meier data. The committee concluded that the company's spline 1-knot normal model was appropriate.

The company's log-normal model for overall survival and scenario analysis using a spline 3-knot model for nivolumab are both plausible

3.7 The company also fitted several models to the updated 5-year overall survival data from CheckMate 057 for both treatment arms. It preferred the log-normal curve for its base-case analysis. The company explained that the log-normal curve was selected based on statistical fit to the trial data, but it did not provide a good visual fit to the middle or tail of the observed data for the nivolumab arm. The company reasoned that this could underestimate long-term survival and so provided a scenario

analysis using a spline 3-knot hazard curve to model survival for the nivolumab arm. The ERG suggested that the spline 3-knot hazard model gave a better visual fit to the data, but because the CheckMate 057 data were mature the choice between alternative plausible distributions was unlikely to have a large effect on the cost-effectiveness results. The committee considered the company's models for overall survival. It accepted that for nivolumab, the spline 3-knot hazard curve gave a slightly better visual fit to the observed Kaplan−Meier data than the log-normal curve, but noted that both curve fits were similar. Using the spline 3-knot hazard curve to model overall survival for nivolumab improved its cost-effectiveness results. The committee concluded that the company's base-case log-normal model for overall survival, and scenario analysis using a spline 3-knot hazard model for nivolumab, were both clinically plausible.

Stopping rule and continued treatment effect

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

3.8 The company asserted that people who had nivolumab would continue to accumulate further survival benefit after nivolumab was stopped. In response to technical engagement, 1 professional organisation considered it clinically plausible that nivolumab could 'reset' the immune system and that its benefit could last for years after it was stopped. The company advised that data from CheckMate 003 showed that, out of 16 people who survived for 5 years and had no therapy after stopping nivolumab, 12 (75%) still did not have progressed disease. CheckMate 003 is a single-arm study of 129 patients with squamous or non-squamous NSCLC, of whom 19 had non-squamous disease and had 3 mg per kg of nivolumab. It included people who had between 1 and 5 previous therapies and disease progression after at least 1 platinum or taxane-based chemotherapy, and who stopped nivolumab after 1.8 years. The company also explained that only a small proportion of people were still on treatment with nivolumab after 5 years in CheckMate 057 in the PD-L1 positive subgroup (the exact data are confidential and cannot be

reported here). However, an overall survival benefit was seen compared with docetaxel (see section 3.3). The CDF clinical lead agreed that the long-term data from CheckMate 003 and CheckMate 057 suggested a continued survival benefit after treatment was stopped. Data from CheckMate 003 were limited because:

- it included a mixed population and only 19 people had non-squamous NSCLC and had the recommended 3 mg per kg dose of nivolumab
- after 4 years, the number of patients that remained in the trial was too small to detect the risk of an event
- the results were not specific to people with PD-L1 positive disease.

The committee recognised the limitations of CheckMate 003, but accepted that it was biologically plausible that nivolumab's survival benefit continued after treatment was stopped. It concluded that nivolumab is likely to provide a continued survival benefit after it is stopped.

The 2-year stopping rule for nivolumab is appropriate

3.9 The company preferred to include a 2-year stopping rule for nivolumab. The ERG explained that there was no robust evidence to show the optimal duration of treatment. The company did not submit any data from CheckMate 153, an ongoing study investigating the effect of a maximum of 1-year treatment with nivolumab. The committee understood that the summary of product characteristics approved nivolumab to be used as long as clinical benefit was observed or until treatment was no longer tolerated, and that no stopping rule was used in CheckMate 057. It agreed that there was uncertainty about how long people should have nivolumab for, based on the updated CheckMate 057 and 003 data. The CDF clinical lead explained that a 2-year stopping rule for immunotherapies such as nivolumab was commonly used in clinical practice in the NHS. Some patients experienced anxiety and distress because of having treatment stopped at 2 years (see section 3.1). At the committee meeting, the company suggested that this was not the experience of all patients and

some might welcome a break from treatment. The committee was aware that removing the 2-year stopping rule had a large effect on the cost-effectiveness results. It concluded that a 2-year stopping rule for nivolumab was appropriate because it is likely there is a continued survival benefit. Also, there was no new evidence to show that continuing treatment 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

3.10 In its base-case analysis, the company preferred to assume that if nivolumab is stopped at 2 years, it will provide a lasting, lifetime survival benefit. The ERG reiterated that the duration of any continued treatment effect is unknown. The company agreed that this is uncertain. It provided 2-way sensitivity analyses increasing the duration of additional benefit and the proportion of patients who experience it. Evidence from CheckMate 003 showed a continued survival benefit after stopping nivolumab, so the committee considered it clinically plausible that benefit could last for years after it was stopped (see sections 3.8 and 3.9). However, it was not convinced that the company's preferred lifetime survival benefit was plausible. Also, it had not seen evidence to favour any of the company's 2-way sensitivity analyses. The committee was aware that in the original guidance a 3-year continued benefit after stopping nivolumab was accepted. It recognised that 5-year data were now available from CheckMate 057, but there was no new robust evidence on the overall duration of the continued benefit. So, the assumption accepted in the original guidance had not changed. The committee concluded that the exact duration of treatment benefit was unclear, but it was likely to be at least 3 years after treatment had stopped.

Health-related quality of life

A post-progression utility value of 0.569 is appropriate

3.11 The company's base-case analysis used a post-progression utility value of 0.688, based on the updated 5-year EQ-5D data from CheckMate 057. However, the committee understood that a decline in the EQ-5D completion rate meant that post-progression values may be influenced by selection bias. This is because it is likely that responses were increasingly provided by relatively healthy patients in the trial. In the original guidance, the committee's preferred post-progression utility value (0.569) was based on the midpoint between 0.480 (based on van den Hout, 2006, a Dutch study of people having palliative radiotherapy for NSCLC) and 0.657 (based on 3-year EQ-5D data from CheckMate 057 with a disutility for end-of-life care applied). The committee was aware that the post-progression values used in technology appraisals for NSCLC were based on time to end of life, with values declining from 0.68 to 0.32 in NICE's technology appraisal guidance for pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy, and from 0.68 to 0.35 in NICE's technology appraisal on atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. The company advised that NHS practice has moved on since the van den Hout study, giving better quality of life. The committee considered that the updated utility values from CheckMate 057 would still be influenced by the same selection bias as in the original data. It also agreed that while NHS practice has moved on since 2006, the midpoint value of 0.569 is higher than the van den Hout study's 0.480. Also, the relevant patients still have advanced or metastatic NSCLC at the end of life. The committee agreed that it had not heard any robust evidence to change the assumption accepted in the original guidance. Therefore, it concluded that it was appropriate to use the 0.569 utility value for progressed disease from the original appraisal.

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 PD-L1 positive NSCLC was less than 24 months and that nivolumab extended life by at least 3 months. The committee did not hear any robust evidence to change this conclusion. Therefore, it concluded that nivolumab met the end-of-life criteria and could be considered a life-extending treatment at the end of life.

Cost effectiveness

The most plausible incremental cost-effectiveness ratio (ICER) is within what NICE considers an acceptable use of NHS resources

3.13 The company's preferred ICER compared with docetaxel alone for people with PD-L1 positive non-squamous NSCLC was £33,191 per quality-adjusted life year (QALY) gained. No cost-effectiveness results were reported that compared nivolumab with nintedanib plus docetaxel. The comparison of nivolumab and docetaxel included a 2-year stopping rule for nivolumab, but did not include the committee's other preferred assumptions of:

- a spline 3-knot hazard as a plausible alternative curve to model overall survival (see section 3.7)
- a continued survival benefit of 3 years after nivolumab is stopped at 2 years (see section 3.10)
- a post-progression utility value of 0.569 (see section 3.11).

Using its preferred assumptions, the committee noted that the most plausible ICER was between £44,169 (spline 3-knot hazard curve) and £44,547 (log-normal curve) per QALY gained. It concluded that this was

within the range that 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 PD-L1 positive advanced non-squamous NSCLC after chemotherapy

3.15 New evidence was considered from CheckMate 057, CheckMate 003, CDF SACT data and the committee's preferred assumptions. All estimates of cost effectiveness for nivolumab compared with docetaxel alone were below what is considered to be a cost-effective use of NHS resources when the end-of-life criteria were applied. Nivolumab is therefore recommended for use in the NHS as an option for treating locally advanced or metastatic non-squamous NSCLC after chemotherapy in adults, only if:

- their tumours are PD-L1 positive, and
- 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(6) 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 non-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 Review of guidance

5.1 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.

Stephen O'Brien
Chair, appraisal committee
September 2020

6 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.

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