NICE National Institute for Health and Care Excellence

NICE guidance

Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer

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

1 Recommendations

1.1 Nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy is not recommended, within its marketing authorisation, for untreated metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations.

1.2 This recommendation is not intended to affect treatment with nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy 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

Standard care for untreated metastatic NSCLC that has no EGFR or ALK mutations is usually immunotherapy plus platinum-doublet chemotherapy. People have different treatments depending on their PD-L1 tumour proportion score and whether they have squamous or non-squamous NSCLC.

Clinical trial evidence suggests that people who have nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy (nivolumab combination) live longer than those who have platinum-doublet chemotherapy alone. Nivolumab combination has only been compared indirectly with other treatments. The results of these indirect comparisons of nivolumab combination with atezolizumab plus bevacizumab, carboplatin and paclitaxel (atezolizumab combination), pembrolizumab monotherapy, and pembrolizumab plus pemetrexed and platinum chemotherapy are uncertain. It is also uncertain how long the effect of nivolumab combination lasts.

The cost-effectiveness estimates for nivolumab combination compared with platinum-doublet chemotherapy, atezolizumab combination and pembrolizumab monotherapy are higher than what NICE considers an acceptable use of NHS resources. The cost-effectiveness estimates compared with pembrolizumab plus pemetrexed and platinum chemotherapy are uncertain because of problems with the analysis.

There is no additional data that could be collected through the Cancer Drugs Fund or from clinical trials that could resolve the uncertainty. So, nivolumab combination is not recommended for routine use or through the Cancer Drugs Fund.

2 Information about nivolumab with ipilimumab and chemotherapy

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) plus ipilimumab (Yervoy, Bristol Myers Squibb) and 2 cycles of platinum-based (platinum-doublet) chemotherapy has a marketing authorisation for 'the first-line treatment of metastatic non-small-cell lung cancer in adults whose tumours have no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation'.

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 May 2021). The list price of ipilimumab is £15,000 per 200 mg per 40-ml vial (excluding VAT; BNF online, accessed May 2021). The company has commercial arrangements for nivolumab and ipilimumab. These make nivolumab and ipilimumab available to the NHS with discounts, which would have applied to this indication if the technology had been recommended. The size of the discounts is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discounts.

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 responses from stakeholders. See the committee papers for full details of the evidence.

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

- the populations in the clinical trials generally reflected people who would have treatment in NHS clinical practice (issue 2, see ERG report page 17)
- the company's indirect treatment comparisons at technical engagement were acceptable for decision making, despite some differences between the trials in patient characteristics and trial design (issue 3, see ERG report page 18)
- the CheckMate-227 data should be incorporated into the indirect treatment comparisons (issue 4, see ERG report page 19)
- nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy (nivolumab combination) was likely to have similar efficacy across subgroups, including people aged 75 and over, people who have never smoked, and people with liver or bone metastases (issue 5, see ERG report page 20)
- the duration of treatment for atezolizumab plus bevacizumab, carboplatin and paclitaxel (atezolizumab combination) should be based on the observed data from the IMPower150 trial (issue 11, see ERG report page 27)
- docetaxel should be removed as a subsequent therapy for people having first-line platinum-doublet chemotherapy (issue 15, see ERG report page 30).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented, and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- whether the decision problem should be split into 3 separate subgroups based on histology (non-squamous or squamous non-small-cell lung cancer [NSCLC]) and PD-L1 tumour proportion score (TPS; issue 1, see ERG report page 16)

- whether different curves should be used to model overall survival and progression-free survival for nivolumab combination in these 3 subgroups (issue 8, see ERG report, page 23)
- what composition of platinum-doublet chemotherapy best reflects NHS clinical practice (issues 6 and 7, see ERG report, pages 21 to 23)
- whether survival for people having platinum-doublet chemotherapy should be modelled using the CheckMate-9LA data up to 13 months and the CheckMate-227 data thereafter, or using the CheckMate-227 data alone (issue 9, see ERG report, page 25)
- how long the effect of treatment with nivolumab combination lasts (issue 10, see ERG report, page 26)
- whether the utility values should be based on progression status or time to death (issue 12, see ERG report, page 28)
- whether the adjustment for relative dose intensity should be applied to the cost of the drug, or the expected required treatment dose (issue 13, see ERG report, page 29)
- what proportion of people have subsequent anticancer therapy after their first-line treatment (issue 14, see ERG report, page 29)
- whether nivolumab combination meets the criteria for end of life treatments (issue 16, see ERG report, page 31)
- whether nivolumab combination meets the criteria to be considered for use within the Cancer Drugs Fund (issue 17, see ERG report, page 32).

Clinical need and management

Nivolumab combination is another option for untreated, metastatic NSCLC

3.1 The clinical experts explained that immunotherapy with platinum-doublet chemotherapy (chemo-immunotherapy) is standard care in the NHS for untreated metastatic NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. Most people having chemo-immunotherapy stop treatment before 2 years because

their disease progresses or there are tolerability issues, and few survive in the long term. The clinical experts considered that nivolumab combination is likely to have similar efficacy to other first-line chemo-immunotherapy combinations. Limiting the duration of chemotherapy to 2 cycles may reduce renal toxicity and allow platinum-doublet chemotherapy to be offered again as a later-line therapy. The side effects of long-term immunotherapy are usually mild but can sometimes be considerable, needing specialist management. The clinical experts noted that combining 2 immunotherapies is likely to cause more immune-related toxicities than current regimens with only 1 immunotherapy. The committee concluded that nivolumab combination offers another treatment option for untreated metastatic NSCLC with no EGFR or ALK mutations, which may have advantages for some people.

Treatment and prognosis differ based on histology and PD-L1 status, and subgroups based on these should be considered separately

3.2 The clinical experts explained that:

- current treatment is based on histology (non-squamous or squamous NSCLC) and PD-L1 TPS, in line with NICE guidance
- prognosis may differ by histology and PD-L1 TPS, and outcomes tend to be worse for people with squamous NSCLC.

The ERG considered that the population with untreated metastatic NSCLC who have no EGFR or ALK tumour mutations should be split into 3 subgroups, according to the treatments currently available:

- non-squamous NSCLC, with PD-L1 TPS below 50%
- squamous NSCLC, with PD-L1 TPS below 50% and
- NSCLC of either histology, with PD-L1 TPS at least 50%.

The committee concluded that it was appropriate to consider the 3 subgroups identified by the ERG separately.

The comparators are appropriate, but pembrolizumab plus pemetrexed and platinum chemotherapy is also relevant for non-squamous NSCLC

3.3 The committee heard that, in line with NICE's technology appraisal guidance on pembrolizumab with pemetrexed and platinum chemotherapy for non-squamous NSCLC and pembrolizumab with carboplatin and paclitaxel for squamous NSCLC, these combinations are widely used in NHS clinical practice. When the scope for this appraisal was developed, pembrolizumab plus pemetrexed and platinum chemotherapy was recommended for use within the Cancer Drugs Fund. So, it was not included as a comparator in line with NICE's position statement on handling comparators and treatment sequences in the Cancer Drugs Fund. However, it is now recommended for routine commissioning, and is therefore an appropriate comparator for non-squamous NSCLC. NICE's technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel is being reviewed, but this technology is still recommended for use within the Cancer Drugs Fund while the review is ongoing. It is therefore not an appropriate comparator. The committee understood that, in line with the scope, the following comparators were included in the cost-effectiveness analysis:

- platinum-doublet chemotherapy for all 3 subgroups, including optional pemetrexed maintenance for people with non-squamous NSCLC
- atezolizumab combination for the subgroup with non-squamous NSCLC and PD-L1 TPS below 50%
- pembrolizumab monotherapy for the subgroup with either histology and PD-L1 TPS at least 50%.

The committee agreed that these comparators were appropriate. However, it concluded that pembrolizumab plus pemetrexed and platinum chemotherapy became a relevant comparator for non-squamous NSCLC. So it should be included in the analysis to reflect established NHS practice (see section 3.7).

Clinical effectiveness

CheckMate-9LA does not include all the relevant treatments used in NHS clinical practice

3.4 The main clinical effectiveness evidence for nivolumab combination came from CheckMate-9LA. This is an ongoing open-label phase 3 randomised controlled trial, comparing nivolumab combination with standard platinum-doublet chemotherapy. For people with non-squamous NSCLC, platinum-doublet chemotherapy was pemetrexed plus either cisplatin or carboplatin, with optional pemetrexed maintenance therapy. For people with squamous NSCLC, platinum-doublet chemotherapy was paclitaxel plus carboplatin. The committee was aware that CheckMate-9LA included adults with untreated recurrent or metastatic NSCLC (with no EGFR or ALK mutations) with an Eastern Cooperative Oncology Group performance status of 0 or 1. The trial included people regardless of PD-L1 status. CheckMate-9LA did not include these comparators used in NHS clinical practice:

- atezolizumab combination and pembrolizumab plus pemetrexed and platinum chemotherapy (for non-squamous NSCLC and PD-L1 TPS below 50%)
- pembrolizumab monotherapy (for NSCLC of any histology and PD-L1 TPS at least 50%)
- pembrolizumab plus pemetrexed and platinum chemotherapy (for non-squamous NSCLC).

The committee acknowledged that, because there was no head-to-head evidence with these comparators, indirect treatment comparisons were needed to assess the relative effectiveness of nivolumab combination.

Nivolumab combination improves overall and progression-free survival compared with standard chemotherapy

3.5 An interim analysis of CheckMate-9LA showed a statistically significant difference in overall and progression-free survival in favour of nivolumab combination compared with standard platinum-doublet chemotherapy. At

the most recent data cut (March 2020), median overall survival was 15.6 months for nivolumab combination and 10.9 months for standard chemotherapy (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.55 to 0.80). Median progression-free survival was 6.7 months for nivolumab combination and 5.0 months for standard chemotherapy (HR 0.68, 95% CI 0.57 to 0.82). Some people having nivolumab combination in CheckMate-9LA had either immunotherapy or a therapy targeted against EGFR, ALK or vascular endothelial growth factor as a subsequent therapy. This did not represent NHS clinical practice, because people would not have immunotherapy again or a targeted therapy on disease progression. The clinical experts stated that this was unlikely to have had a large effect on treatment outcomes. But it meant that the survival of people having nivolumab combination may have been overestimated in CheckMate-9LA. The committee concluded that nivolumab combination was clinically effective compared with standard chemotherapy.

Indirect treatment comparisons

Most of the company's indirect treatment comparisons are acceptable for decision making, despite uncertainty

3.6 The company did indirect treatment comparisons because there were no head-to-head trials comparing nivolumab combination with pembrolizumab monotherapy and atezolizumab combination. The company considered that the proportional hazards assumption (that is, the relative risk of an event is fixed irrespective of time) was not met. It therefore used fractional polynomial models to estimate time-varying hazard ratios. The committee noted that this approach meant that there was a lot of uncertainty with the indirect treatment comparisons. For the indirect comparison with pembrolizumab monotherapy in the subgroup with PD-L1 TPS at least 50%, the company used the data from the full intention-to-treat (ITT) population from CheckMate-9LA. For the comparison with atezolizumab combination for the subgroup with non-squamous NSCLC and PD-L1 TPS below 50%, the company used the data from the relevant subgroup of CheckMate-9LA. The results of the indirect comparisons are confidential and cannot be reported here. At technical engagement, it was agreed that the CheckMate-227 data

should also be included in the indirect treatment comparisons. CheckMate-227 is an ongoing open-label phase 3 randomised controlled trial in a similar population to that in CheckMate-9LA. It includes a nivolumab plus ipilimumab treatment arm and a platinum-doublet chemotherapy treatment arm, both stratified by PD-L1 TPS. The most recent data cut from CheckMate-227 (February 2020) had a minimum follow up of 37.7 months compared with 12.7 months for CheckMate-9LA. The committee noted that some of the company's indirect treatment comparison results had wide confidence intervals and were uncertain, but concluded that they were acceptable for decision making.

The indirect treatment comparison with pembrolizumab plus pemetrexed plus platinum chemotherapy is not suitable for decision making

3.7 At the first meeting, the committee concluded that pembrolizumab plus pemetrexed and platinum chemotherapy was now widely used in the NHS. It was approved for routine use after the initial scope for this appraisal, and became a relevant comparator for the subgroup with non-squamous NSCLC and PD-L1 TPS below 50% (see section 3.3). So, the company updated its indirect treatment comparison at consultation. It found that nivolumab combination was more effective than pembrolizumab plus pemetrexed and platinum chemotherapy in this subgroup. The ERG was concerned because:

- the updated indirect treatment comparison excluded pembrolizumab monotherapy as a comparator

- there was no evidence for pembrolizumab monotherapy compared with pembrolizumab plus pemetrexed and platinum chemotherapy in the subgroup with non-squamous NSCLC and PD-L1 TPS at least 50%.

  The ERG explained that the updated analysis included an additional trial for pembrolizumab plus pemetrexed and platinum chemotherapy. This affected both the nivolumab combination arm and the atezolizumab combination arm. It increased the life years gained for nivolumab combination but reduced the life years gained for atezolizumab combination. The additional trial increased the incremental difference in life years gained, which the ERG was unable to validate. The committee discussed the unexpected results of the comparison of nivolumab combination with pembrolizumab plus pemetrexed and platinum chemotherapy; particularly that a shorter duration of treatment resulted in a longer duration of benefit for this pembrolizumab combination. The ERG considered that the modelling for this comparison was not robust enough for decision making. The company explained that KEYNOTE-598 (a trial of pembrolizumab with either ipilimumab or placebo for people with untreated metastatic NSCLC) had a short follow up (about 12 months), with heavy censoring around that time. But for the nivolumab combination trials, there was separation of the curves around 12 months. However, the committee was aware that KEYNOTE-598 was stopped because adding ipilimumab to the immunotherapy showed no incremental survival benefit. Also, the company's indirect treatment comparison comparing progression-free and overall survival for nivolumab combination with pembrolizumab for the subgroup with non-squamous and squamous NSCLC with PD-L1 TPS at least 50% favoured single-agent immunotherapy, as in KEYNOTE-598. But the difference was not statistically significant. The committee recalled that the clinical experts expected similar outcomes for the nivolumab combination and other first-line chemo-immunotherapy combinations (see section 3.1) in clinical practice. This contradicted the findings in the company's analysis, in which nivolumab combination dominated (was more effective and less expensive) the pembrolizumab combination. The committee had several concerns about the company's comparative efficacy and modelling results, which suggested that overall survival was better with nivolumab combination than with many other options. The committee noted that there was a lot of uncertainty with the fractional polynomial indirect treatment comparison (see section 3.6). It recalled a direct comparison in KEYNOTE-198 showing that pembrolizumab plus ipilimumab was no better than pembrolizumab alone for non-squamous

metastatic NSCLC. It also recalled previous trial evidence (KEYNOTE-024, CheckMate-026) which suggested that nivolumab monotherapy was inferior to pembrolizumab monotherapy for untreated NSCLC. So, the committee considered that the modelled outcomes did not seem realistic. The committee concluded that the company's indirect treatment comparison of nivolumab combination with pembrolizumab plus pemetrexed and platinum chemotherapy was not robust enough for decision making.

Adverse events

Nivolumab combination is likely to be less well tolerated than other chemo-immunotherapy combinations

3.8 The clinical experts explained that immunotherapy is generally well tolerated but is associated with some rare but unpleasant, and potentially serious, adverse events. These were likely to be more common for nivolumab combination (2 different immunotherapies) than current chemo-immunotherapy combinations (only 1 immunotherapy). The company did not agree, so at consultation provided further evidence using data from CheckMate-227. It explained that:

- adverse events from chemotherapy are less frequent with nivolumab combination, which includes only 2 cycles of chemotherapy

- adverse events with nivolumab combination tend to occur early in treatment and, if managed effectively, reduce with later cycles.

  The company provided adverse event results over time from an indirect treatment comparison of nivolumab combination and pembrolizumab plus chemotherapy. This showed no statistically significant differences in the odds of having adverse events leading to discontinuation of any drug in the combination. This was true for grade 3 to 5 and grade 1 to 5 adverse events. However, the ERG could not comment because details of the indirect treatment comparison were not available. The committee considered that it would be helpful to understand which drugs in the combinations are most frequently discontinued. It was unclear how the company's evidence on treatment-related adverse events over time should be interpreted, because some people would stop treatment for other reasons. The committee understood that clinicians are experienced in recognising and managing serious adverse events, and established toxicity management algorithms are in place. It concluded that nivolumab combination was likely to be less well tolerated than other chemo-immunotherapy combinations, so more specialist management would be needed for serious adverse events.

The company's economic model

The company's model structure is acceptable for decision making

3.9 The company used a 3-state partitioned survival model to estimate the cost effectiveness of nivolumab combination compared with platinum-doublet chemotherapy, atezolizumab combination and pembrolizumab monotherapy. People were able to move to different health states; from pre-progression to post-progression and death and from post-progression to death. The ERG agreed with the company's model structure, noting that it was consistent with previous appraisals. For people having nivolumab combination and people having standard platinum-doublet chemotherapy, the company used the results from CheckMate-9LA to model overall and progression-free survival for the first 13 months. The results from CheckMate-227 were used after this point because longer-term data was available (see section 3.6). Survival curves were modelled for the ITT population and applied for everyone,

regardless of histology and PD-L1 TPS. Relative risks from the indirect comparisons were then applied to the nivolumab combination data to estimate overall and progression-free survival for atezolizumab combination and for pembrolizumab monotherapy. The committee concluded that the company's model structure was acceptable for decision making. But it noted the uncertainty about whether it was appropriate to use the same survival curves for everyone (see section 3.11).

Including a 2-year stopping rule is acceptable

3.10 The company included a 2-year treatment stopping rule in its model. The maximum possible duration for nivolumab combination in CheckMate-9LA was 24 months, and this was also stated in the summary of product characteristics. The committee understood that implementing a 2-year stopping rule was consistent with other NICE technology appraisal guidance on untreated NSCLC. It also reflected how nivolumab combination would be used in clinical practice. The committee concluded that a 2-year treatment stopping rule, in line with the clinical- and cost-effectiveness evidence, was acceptable.

Modelling survival

The company's analyses modelling survival for histology and PD-L1 subgroups separately are appropriate for decision making

3.11 The committee considered whether it was appropriate to use the same overall and progression-free survival curves across all 3 subgroups, based on the ITT data from CheckMate-9LA and CheckMate-227 (see section 3.9). The company took this approach because it believed there was a consistent efficacy benefit across subgroups in CheckMate-9LA, including those based on PD-L1 and histology. However, the ERG noted that the CheckMate-9LA and CheckMate-227 results suggested there were differences in the absolute and relative efficacy of nivolumab combination across some of the subgroups. Clinical advice to the ERG was that people whose NSCLC has a higher PD-L1 TPS generally have greater benefit with anti-PD-L1 immunotherapies. The company

considered that using the ITT data was more appropriate than the subgroup data, because the subgroups were not prespecified and included smaller numbers of people. The company also noted that the lack of external clinical data available to validate the subgroup curves placed greater reliance on clinical opinion. Also, it considered that by combining 3 different mechanisms of action, nivolumab combination was not expected to have the same efficacy differences by histology or PD-L1 TPS as other immunotherapies. The committee considered that because it had agreed to separate the population into 3 subgroups (see section 3.2), it was appropriate to reflect this heterogeneity in the data used to generate the survival curves. It also noted that applying separate survival curves based on the subgroup data had a considerable impact on the cost-effectiveness results. The committee agreed that there was uncertainty about the validity of applying survival curves derived from the ITT data across all the subgroups. It concluded that survival curves should be modelled separately for each subgroup. So, in its updated base case after consultation, the company modelled the survival curves separately for each subgroup, based on the 1-year data cut for CheckMate-9LA and 3-year data cut for CheckMate-227. The company highlighted that CheckMate-9LA not was not stratified or powered for analyses of combined histology and PD-L1 subgroups. The committee concluded that the company's analyses modelling overall survival data for histology and PD-L1 subgroups separately were appropriate for decision making.

Survival for people having platinum-doublet chemotherapy should be modelled using the CheckMate-227 data alone

3.12 The ERG noted that median overall survival for people having platinum-doublet chemotherapy was longer in CheckMate-227 than in CheckMate-9LA. This could have been because fewer people had subsequent therapy in CheckMate-9LA than in CheckMate-227. The ERG considered that the proportion of people having subsequent therapy after platinum-doublet chemotherapy in CheckMate-9LA was lower than in NHS clinical practice. It was therefore concerned that using the CheckMate-9LA data to estimate survival for the first 13 months (see section 3.9) may have underestimated survival for people having platinum-doublet chemotherapy. The ERG did a scenario analysis in

which survival for people having platinum-doublet chemotherapy was modelled using the CheckMate-227 data alone. In this, the relative efficacy of nivolumab combination was taken from the indirect treatment comparison. However, the ERG preferred to retain the company's original approach of using the CheckMate-9LA data followed by the CheckMate-227 data for its base case. This was because it used the same data sources for people having nivolumab combination and people having platinum-doublet chemotherapy. The committee noted that in NICE's technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel for squamous NSCLC, it was estimated that around 50% of people having first-line chemotherapy have immunotherapy after disease progression. The clinical experts noted that this may be an underestimate based on the proportion of people switching from chemotherapy to pembrolizumab in the KEYNOTE-024 trial. KEYNOTE-024 was an open-label phase 3 randomised controlled trial, comparing pembrolizumab with chemotherapy for untreated metastatic NSCLC. At consultation, the company said that it preferred its original approach, in line with the nivolumab combination arm (CheckMate-9LA data used up to 13 months, then conditional survival from CheckMate-227 applied). Because CheckMate-9LA was the registration trial, the company felt it was the most appropriate to estimate survival for people having platinum-doublet chemotherapy. It would preserve the benefits of comparing between arms of the randomised controlled trial. The ERG found that the model predicted 5-year survival of 10.5% for platinum-doublet chemotherapy using CheckMate-227 alone, and 9% in the approach using CheckMate-9LA and CheckMate-227. This was consistent with previous appraisals. The committee understood that around 28% of people had subsequent immunotherapy after first-line chemotherapy in CheckMate-9LA, compared with around 41% in CheckMate-227. It considered that the rate of subsequent immunotherapy in CheckMate-227 was likely closer to that in NHS clinical practice. The committee concluded that survival for people having platinum-doublet chemotherapy should be modelled using the CheckMate-227 data alone.

A treatment effect lasting 3 to 5 years after starting treatment is appropriate and consistent with previous appraisals

3.13 The company's base case included a lifetime treatment effect with nivolumab combination. The company justified this using pooled data from 4 clinical trials of nivolumab for previously treated NSCLC, which showed that nivolumab had a long-term survival advantage over docetaxel. The ERG noted that a lifetime treatment effect was inconsistent with previous technology appraisals for NSCLC. For those, a treatment effect lasting from 3 to 5 years after starting treatment had been accepted. The ERG also considered the pooled data used by the company to be of limited relevance. This was because the data was from trials of nivolumab as a monotherapy in a population who had previous treatment, and survival outcomes were only reported to 4 years. The ERG preferred a scenario with a treatment effect lasting 5 years after stopping treatment. This was modelled by setting the mortality rate as equal to that of platinum-doublet chemotherapy from this timepoint onwards. The committee understood that the assumption around the duration of treatment effect had a considerable impact on the cost-effectiveness results. It agreed that, although it was biologically plausible for the treatment effect to continue after stopping treatment with nivolumab combination, its duration was uncertain. The clinical experts explained that there was insufficient evidence to suggest the treatment effect of nivolumab combination lasted longer than for other immunotherapies. The committee concluded that a treatment effect lasting 3 to 5 years after starting treatment was appropriate for decision making, for consistency with previous immunotherapy appraisals in NSCLC.

There is no evidence to support a treatment effect duration of longer than 3 to 5 years

3.14 At consultation, the company's updated base case used a 5-year treatment effect after stopping treatment. This was more optimistic than what the committee preferred at the first meeting, which was a treatment effect lasting 3 to 5 years after starting treatment (see section 3.13). The company acknowledged the misunderstanding, but explained that a treatment effect of 5 years after stopping would be a

conservative assumption. It explained that the new CheckMate-227 data would support an additional benefit over other chemo-immunotherapy combinations, particularly the number of people whose disease maintained a response at 3 years. However, this new data did not arrive in time to be incorporated into its analyses. The committee recalled the plausible treatment effect duration for single-agent immunotherapy plus platinum-doublet chemotherapy and noted that strong evidence would be needed to accept a longer duration. It considered that there was no evidence that nivolumab combination had a longer treatment effect duration than pembrolizumab plus platinum-doublet chemotherapy. So, a more favourable assumption could not be made for nivolumab combination. The committee concluded that its preferred assumption for nivolumab combination was still a treatment effect lasting 3 to 5 years after starting treatment.

Health-related quality of life

The ERG's approach of using progression-based utility values is preferred

3.15 The ERG explained that the company's time-to-death approach for including utility values was not appropriate. This was because in previous technology appraisals in which this approach had been accepted, health-related quality-of-life data had only been collected for up to 30 days after stopping treatment. This meant that the utility value for the post-progression state may have been overestimated, because the full effects of progression may not yet have been evident. However, in CheckMate-9LA, health-related quality-of-life data was collected until death, and there were many observations (1,004) contributing to the post-progression health state. In contrast, there were only 114 observations contributing to the utility value for 4 weeks or less to death in the company's approach. The ERG also had concerns with using time to death to determine health-related quality of life. A time-to-death approach meant that people entering the model had a different health-related quality of life depending on the treatment arm they were assigned to. The ERG preferred a progression-based approach, using utility values derived from the EQ-5D data collected in CheckMate-9LA.

The clinical experts explained that quality of life may not immediately decline after disease progression. The committee was also aware that progression-based utility values may be overestimated because there were fewer observations in people with more severe disease. However, it agreed with the ERG that utility values based on disease progression were more appropriate for decision making, given the large amount of data captured after progression. At consultation, the company maintained that the time-to-death approach was an appropriate way to include utility values. But it accepted the use of health state utility values in line with the committee's preferred assumption.

Composition of platinum-doublet chemotherapy

Separate chemotherapy regimen distributions should be used for each subgroup to reflect differences in clinical practice

3.16 To calculate the costs associated with platinum-doublet chemotherapy, the company based the distribution of chemotherapy regimens on the CheckMate-9LA data. It applied the same assumption for everyone having platinum-doublet chemotherapy, regardless of histology or PD-L1 TPS. The ERG considered that the distribution of chemotherapy regimens in CheckMate-9LA may not reflect NHS clinical practice. For example, some people with squamous NSCLC were modelled as having pemetrexed, which they would not have in practice. It noted that there were differences in drug and administration costs between chemotherapy regimens, which meant that the costs calculated from the company's distribution may not have been representative. The ERG preferred to apply a specific distribution of chemotherapy agents for each subgroup (see section 3.2), including different proportions of people having pemetrexed maintenance therapy. It took these distributions from reported UK market share information in:

- NICE's technology appraisal guidance on pembrolizumab with pemetrexed and platinum chemotherapy for non-squamous NSCLC (TA557) and

- NICE's technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel for squamous NSCLC (TA600).

  At technical engagement and with clinical input, the company revised the proportion of people having each chemotherapy regimen but continued to apply a single weighted distribution for everyone. The clinical experts explained that the most widely used chemotherapy regimens in clinical practice differed by histology. Carboplatin plus either gemcitabine or vinorelbine were the most common combinations for people with squamous NSCLC, but pemetrexed was preferred for people with non-squamous NSCLC. The committee considered that these differences should be reflected in the composition of platinum-doublet chemotherapy in the economic model. It concluded that the ERG's approach of applying separate distributions of chemotherapy regimens for each subgroup was more appropriate for decision making.

Subsequent therapy

The proportion of people having subsequent therapy should be based on the CheckMate-227 data

3.17 In the company's model, 31% of people having nivolumab combination as their first-line treatment had subsequent therapy, based on the CheckMate-9LA data. The same assumption was used for people having pembrolizumab monotherapy and atezolizumab combination. In the model, 40% of people having platinum-doublet chemotherapy as their first-line treatment had subsequent therapy. The ERG noted that the data on the rates of subsequent therapy from CheckMate-9LA was immature, and likely an underestimate. The rates from CheckMate-227 were higher (45% for people having nivolumab combination as first-line treatment, and 61% for people having platinum-doublet chemotherapy). The ERG considered that the CheckMate-227 rates were more in line with those seen in NHS clinical practice. They were also based on more mature data. Also, using the CheckMate-227 data was consistent with the approach used for modelling long-term survival. At technical engagement, the company accepted that the rates of subsequent therapy in CheckMate-9LA may be lower than expected in a clinical trial, but considered that they reflected NHS clinical practice. The committee

recalled its earlier conclusion that the proportion of people having subsequent therapy in the clinical trials was likely lower than in NHS clinical practice (see section 3.12). Therefore, it concluded that the higher rates from CheckMate-227 better reflected clinical practice and should be used in the model.

Relative dose intensity

The difference between the company and the ERG's relative dose intensity adjustments has minimal impact on the cost-effectiveness results

3.18 Relative dose intensity is the percentage of the prescribed dose of a treatment that people take. The company applied the relative dose intensities to the cost of the drug, after this had been estimated from the number of vials needed based on the treatment dose in the marketing authorisation. The ERG considered it more appropriate to apply the relative dose intensities to the expected treatment dose, and then calculate the number of vials and associated drug costs from these adjusted numbers. Because this may not necessarily reduce the number of vials, the ERG was concerned that the company may have underestimated the drug costs. The committee concluded that the relative dose intensity likely lay between the company's and the ERG's assumptions. However, it noted that this had minimal impact on the cost-effectiveness results.

End of life

Nivolumab combination is likely to meet the end of life criteria for squamous NSCLC with PD-L1 TPS below 50%

3.19 The committee considered the advice about life-extending treatment for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It understood that, at the first meeting, the company and the ERG agreed that nivolumab combination did not meet the criteria for end of life treatments for:

- non-squamous NSCLC and PD-L1 TPS below 50% or
- NSCLC of either histology and PD-L1 TPS at least 50%.

For the subgroup with squamous NSCLC and PD-L1 TPS below 50%, both the company's and the ERG's base cases predicted a mean overall survival of around 24 months for people having platinum-doublet chemotherapy. The clinical experts stated that the life expectancy for this subgroup was likely to be less than 2 years, even with immunotherapy. The company and the ERG estimated that the mean life extension for nivolumab combination in this subgroup was more than 3 months compared with platinum-doublet chemotherapy. The committee was satisfied that nivolumab combination was likely to meet the criteria for end of life treatments in the subgroup with squamous NSCLC and PD-L1 TPS below 50%.

The end of life criteria are not met for all other populations covered by this appraisal

3.20 At consultation, the company presented evidence to support that the end of life criteria should apply across all the populations in this appraisal. This included a retrospective study using data from the Flatiron database, for people with stage 3B or stage 4 NSCLC who had chemo-immunotherapy (over 98% had pembrolizumab plus chemotherapy). The reported median overall survival for people with squamous and non-squamous NSCLC was shorter than in the KEYNOTE-407 and KEYNOTE-189 trials. However, the ERG considered it uncertain whether the Flatiron evidence reflected the population who would have nivolumab combination for untreated, metastatic NSCLC in the NHS. This was because people in the Flatiron dataset had poorer performance status, were older, and were more likely to have unstable brain metastases. Also, they had treatment in the US, which has different treatment patterns to the UK. The company contrasted the real-world Flatiron evidence with real-world evidence for nivolumab as second-line treatment for NSCLC. It explained that outcomes in clinical practice (from the Systemic Anti-Cancer Therapy Dataset) were similar to those seen in the randomised controlled trials. The committee recalled that in NICE's technology appraisal guidance on pembrolizumab with pemetrexed and platinum chemotherapy for non-squamous NSCLC, the committee did

not accept that the end of life criteria were met. The ERG noted that there was little long-term observational evidence on whether having nivolumab first line would extend survival by 3 months in clinical practice. It considered that efficacy might decline in practice (similar to the clinical trial) when people with more severe disease have nivolumab. Also, survival may not be extended by 3 months for people with severe disease. But the ERG noted that this was uncertain and not supported by evidence. The Cancer Drugs Fund clinical lead explained that real-world outcomes for chemo-immunotherapy seem to reflect what is seen in trials. This is because people must be well enough to have chemo-immunotherapy, which has additional selection considerations for clinicians, compared with immunotherapy alone. The committee considered that the evidence presented by the company only showed that the end of life criteria could plausibly be met for the subgroup with squamous NSCLC and PD-L1 TPS below 50%. It recalled that mean survival was preferable to median survival for decision making around end of life criteria for chemo-immunotherapy. The committee concluded that the criteria were not met for all other populations covered by this appraisal.

Cost-effectiveness results

Nivolumab combination is not cost effective in any subgroup

3.21 The committee recalled that its preferred assumptions were:

- considering 3 separate subgroups based on histology and PD-L1 TPS (see section 3.2)
- applying separate survival curves for each subgroup (see section 3.11)
- modelling survival for people having platinum-doublet chemotherapy using the CheckMate-227 data alone (see section 3.12)
- a treatment effect lasting 3 to 5 years after starting treatment (see section 3.13 and section 3.14)
- utility values based on disease progression rather than time to death (see section 3.15)

- applying separate platinum-doublet chemotherapy distributions for each subgroup, using UK market share data from TA557 and TA600 (see section 3.16)
- subsequent treatment rates based on the CheckMate-227 data (see section 3.17).

The cost-effectiveness results are commercial in confidence because they included the discounts from commercial access agreements and patient access schemes for atezolizumab, pembrolizumab, bevacizumab and pemetrexed maintenance.

- For the subgroup with squamous NSCLC and PD-L1 TPS below 50%, the incremental cost-effectiveness ratios (ICERs) for nivolumab combination compared with platinum-doublet chemotherapy were above what is normally considered a cost-effective use of NHS resources for end of life treatments (£50,000 per quality-adjusted life year [QALY] gained).
- For the subgroup with non-squamous NSCLC and PD-L1 TPS below 50%, the ICERs for nivolumab combination compared with both atezolizumab combination and platinum-doublet chemotherapy were above the upper end of the range normally considered a cost-effective use of NHS resources (£30,000 per QALY gained). Although nivolumab combination dominated (was more effective and less expensive) pembrolizumab plus pemetrexed and platinum-doublet chemotherapy, the analysis was not considered robust enough for decision making and the modelled outcomes did not seem realistic.
- For the subgroup with NSCLC of either histology and PD-L1 TPS at least 50%, nivolumab combination was more costly and less effective than pembrolizumab monotherapy (that is, it was dominated by pembrolizumab). Compared with platinum-doublet chemotherapy, the ICERs were above £30,000 per QALY gained.

The committee concluded that the cost-effectiveness estimates for nivolumab combination were mostly higher than what NICE normally considers a cost-effective use of NHS resources.

Other factors

3.22 No relevant equalities issues were identified.

3.23 The company stated that nivolumab combination was innovative because it was the first dual immunotherapy licensed for NSCLC. However, the clinical experts explained that they did not consider the treatment to be innovative because the important step change had already been made by the earlier immunotherapies. The committee concluded that there were no additional benefits associated with nivolumab combination that had not been captured in the economic analysis.

Conclusion

Nivolumab combination is not recommended for routine use in the NHS

3.24 Nivolumab combination is more clinically effective than standard chemotherapy, and is likely to have similar efficacy to other chemo-immunotherapies. The committee agreed that the most plausible ICERs for nivolumab combination compared with platinum-doublet chemotherapy, atezolizumab combination and pembrolizumab monotherapy were mostly higher than what NICE normally considers a cost-effective use of NHS resources. The results comparing nivolumab combination with pembrolizumab plus pemetrexed and platinum chemotherapy did not seem realistic, and that analysis was not considered robust enough for decision making. Therefore, it concluded that nivolumab combination could not be recommended for routine use as an option for untreated metastatic NSCLC with no EGFR or ALK mutations.

Nivolumab combination is not recommended for use in the Cancer Drugs Fund

3.25 Having concluded that nivolumab combination could not be recommended for routine use, the committee then considered if it could be recommended within the Cancer Drugs Fund. The committee

discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund technology appraisal process and methods guide (addendum). The company had expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund. At consultation, the company provided the most up-to-date overall survival results for CheckMate-9LA compared with CheckMate-227, for subgroups with:

- non-squamous NSCLC and PD-L1 TPS below 50%
- all types of non-squamous NSCLC
- squamous NSCLC with PD-L1 TPS below 50%
- all types of squamous NSCLC.

The company considered this data to be commercially sensitive so it cannot be shown here. The company explained that additional data for both these trials would reduce uncertainty, increase confidence in the analyses, and allow long-term outcomes across currently approved chemo-immunotherapy regimens to be compared. The ERG considered that, because the new data was not included in the new indirect treatment comparisons, the long-term efficacy of nivolumab combination compared with other chemo-immunotherapy combinations was uncertain. Also, any long-term outcomes data collected in the Cancer Drugs Fund would be affected by subsequent treatments that people had in CheckMate-9LA, which are not used in UK practice. The ERG emphasised that even if data for nivolumab combination was collected in the Cancer Drugs Fund, the maximum duration of treatment benefit that could be seen would be 5 years from the start of treatment. This would be in line with the upper limit of the committee's preference. At the first meeting, the key uncertainty around lifelong duration of benefit (that is, cure in some people) was thought to be unresolvable with up to 2 years of further data collection. The committee understood that CheckMate-9LA and CheckMate-227 were ongoing, and further data would become available. However, the committee agreed that this would likely be insufficient to reduce the uncertainty affecting the cost-effectiveness results, particularly the duration of the treatment effect. The committee concluded that nivolumab combination did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

4 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 D.

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.

Amy Crossley, Charlie Hewitt and Thomas Paling
Technical leads

Caron Jones
Technical adviser

Kate Moore
Project manager

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Accreditation