

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations

Technology appraisal guidance

Published: 18 May 2022

www.nice.org.uk/guidance/ta789

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	4
2 Information about tepotinib.....	5
Marketing authorisation indication	5
Dosage in the marketing authorisation	5
Price.....	5
3 Committee discussion	6
A new targeted treatment	6
Population and subgroups.....	7
Comparators	8
Clinical effectiveness	9
The company's economic model	15
End of life	19
Cost-effectiveness estimates	21
Other factors	22
4 Implementation.....	23
5 Appraisal committee members and NICE project team	24
Appraisal committee members	24
NICE project team	24

1 Recommendations

- 1.1 Tepotinib is recommended, within its marketing authorisation, as an option for treating advanced non-small-cell lung cancer (NSCLC) with METex14 skipping alterations in adults, only if the company provides tepotinib according to the [commercial arrangement](#).

Why the committee made these recommendations

Standard care for advanced METex14 skipping NSCLC is usually chemo-immunotherapy. 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 a clinical benefit for tepotinib. It has been indirectly compared with other treatments in 2 ways, but the results of both are uncertain.

Tepotinib meets NICE's criteria to be considered a life-extending drug at the end of life for people who have had previous treatment, but not for people who have not had previous treatment.

For both groups, the cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. So, tepotinib is recommended.

2 Information about tepotinib

Marketing authorisation indication

- 2.1 Tepotinib (Tepmetko, Merck) is indicated for 'the treatment of adult patients with advanced non-small-cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for tepotinib](#).

Price

- 2.3 The list price of tepotinib is £7,200 for 60×250-mg tablets. The company has a [commercial arrangement](#). This makes tepotinib 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 Merck, 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.

A new targeted treatment

People with METex14 skipping NSCLC would welcome a new oral treatment option that is well tolerated

- 3.1 There is no defined treatment pathway specific to METex14 skipping non-small-cell lung cancer (NSCLC) because there are no targeted treatments available in the UK. People with METex14 skipping NSCLC are offered the same standard care as people with NSCLC without this specific oncogenic biomarker. These treatments include chemotherapy (such as platinum-doublet chemotherapy), immunotherapy (such as pembrolizumab) and combinations of chemotherapy and immunotherapy (chemo-immunotherapy). The clinical experts explained that people with METex14 skipping NSCLC have a poorer prognosis than people without this biomarker. They tend to be older than people with other oncogenic-driven NSCLC, and so treating this population can be challenging because of comorbidities and overall frailty. The clinical experts further explained that this population would benefit from the favourable side effect profile of tepotinib compared with chemotherapy and chemo-immunotherapy. In addition, these people would benefit from the reduced treatment administration burden offered by an oral therapy that does not need day-unit attendance, as is the case for chemotherapy and chemo-immunotherapy. The clinical experts stated that, if recommended across its marketing authorisation, tepotinib would likely be offered as a first-line treatment for people with METex14 skipping NSCLC confirmed by genomic testing. They clarified that testing for METex14 skipping mutations is variable across the UK. Because of this, clinicians would continue to use other first-line treatment options until the mutation is confirmed. Tepotinib may therefore be used at other points in the

treatment pathway, in line with its marketing authorisation, but the number of people who have already had treatment is expected to reduce when genomic panel testing is nationally available. The committee agreed that there is a clear unmet need in this patient population. It concluded that people with METex14 skipping NSCLC would welcome a new oral treatment option that is well tolerated.

Population and subgroups

Untreated and treated subgroups should be considered separately

- 3.2 In its original evidence submission, the company base-case population comprised all people with METex14 skipping NSCLC regardless of whether or not they had already had treatment. The NICE scope stated that the population should be addressed according to specific subgroups, if possible. These subgroups were defined as previous treatment (treated or untreated), histology (squamous or non-squamous), and level of PD-L1 expression. This was because the comparators differed according to these subgroups. The company explained that the base case in its original evidence submission did not consider subgroups by treatment line or histology because, given the small number of people with METex14 skipping NSCLC, using all patients across treatment lines allowed for a larger data set for the indirect comparisons. The company considered that anyone with this condition would be offered tepotinib regardless of PD-L1 expression or histology. In addition, clinical experts consulted by the company considered that the clinical-effectiveness results for tepotinib in the overall population should be generalisable regardless of histology. The ERG agreed that the data limitations made it difficult to present results for true subgroups, such as histology and PD-L1 status. But it stressed that by presenting results for the overall population, the company had grouped together people who would be eligible for different comparator treatments. The committee agreed that the treatments recommended by NICE for NSCLC differ based on treatment line (untreated or treated), histology (squamous or non-squamous), and PD-L1 tumour proportion score (below 50%, or 50% and above). By grouping together people on the basis of having METex14 skipping NSCLC only, the company's base-case analysis potentially

masked any variation in treatment effect and cost effectiveness between people who would have different comparator treatments. The committee acknowledged the practical difficulties faced by the company, but did not consider that the company's approach was appropriate. At the first meeting, the committee concluded that it would prefer to consider the cost-effectiveness results for previously treated and untreated disease separately. The company provided this analysis for the second committee meeting (see [section 3.9](#) and [section 3.13](#)).

The majority of the available evidence is for untreated non-squamous NSCLC with METex14 skipping alterations

- 3.3 The clinical experts explained that most METex14 skipping NSCLC is of non-squamous histology. The committee noted that the evidence was primarily for that histology. It recalled that tepotinib, if recommended across its marketing authorisation, would mostly be offered to people with untreated METex14 skipping NSCLC (see [section 3.1](#)). At consultation, the company acknowledged that untreated non-squamous NSCLC with METex14 skipping alterations was the key treatment population for this appraisal. However, it highlighted that previously treated and squamous NSCLC with METex14 skipping alterations are also important, as outlined by clinical expert feedback in its evidence submission. The committee agreed that the previously treated and squamous groups should be considered fully, in line with the marketing authorisation. It understood that the evidence for these groups is limited, and that the majority of available evidence is for untreated non-squamous NSCLC with METex14 skipping alterations.

Comparators

Chemo-immunotherapy is the most relevant comparator for untreated non-squamous NSCLC with METex14 skipping alterations

- 3.4 In its original evidence submission, the company did not compare tepotinib with the specific comparators outlined in the NICE scope. Instead, it compared tepotinib with 2 grouped treatment classes:

chemotherapy and immunotherapy. This was because of the limited data available to model specific comparator treatments (see [section 3.7](#)). The company did not include chemo-immunotherapy as a comparator in the overall population. The clinical experts explained that this did not reflect UK clinical practice, where chemo-immunotherapy is the most commonly used treatment. The Cancer Drugs Fund clinical lead agreed that people with untreated non-squamous METex14 skipping NSCLC would usually have either immunotherapy (pembrolizumab monotherapy) or chemo-immunotherapy (pembrolizumab with pemetrexed and platinum chemotherapy), depending on their PD-L1 tumour proportion score. The company agreed and, for the second meeting, provided new analyses for the comparators relevant to UK clinical practice (see [section 3.9](#)), presented separately for the untreated and treated populations. This included a comparison with pembrolizumab plus pemetrexed and platinum as its new base case for the untreated group. Recalling its preference for analyses presented separately for untreated and treated populations (see [section 3.2](#)), the committee concluded that the company had made all efforts to provide the most relevant analyses for specific populations, including chemo-immunotherapy as the most relevant comparator for untreated non-squamous NSCLC with METex14 skipping alterations.

Clinical effectiveness

The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice

- 3.5 The evidence for tepotinib comes from the VISION clinical trial. This is an ongoing, single-arm, open-label, phase-2 trial including people with advanced (locally advanced or metastatic) NSCLC with METex14 skipping alterations or MET amplification. The primary outcome of the trial is objective response rate. Secondary outcomes include duration of response, progression-free survival, overall survival and health-related quality of life. A total of 152 people with METex14 skipping alterations were enrolled into cohort A. Cohort C is a confirmatory cohort recruited at a later time point, enrolling 123 additional people with METex14

skipping alterations. Cohort B enrolled people with MET amplification, and so this cohort is not relevant to the appraisal. The trial recruited people from Asia (23%), North America (26%) and Europe (51%), but not from any UK centres. The clinical experts noted that the response rate in VISION was higher than would be expected with current standard treatments. From the February 2021 data cut-off, using cohort A, the objective response rate in the overall population was 46.7% (95% confidence interval [CI] 38.6 to 55.0), and was slightly higher in people having first-line treatment (50.7%) than in those having second-line treatment (43.4%). The median progression-free survival was 10.8 months (95% CI 8.3 to 12.4), and the median overall survival was 19.1 months (95% CI 15.2 to 22.1), with results being consistent across first- and second-line treatment. The committee noted that the median overall survival was higher in the previously treated group, which is counter to expectations. However, it agreed that VISION suggests that tepotinib is clinically effective. It also noted that the distribution of subsequent treatments in VISION meant that the results may not be generalisable to NHS clinical practice (see [section 3.14](#)). The committee felt that a randomised controlled trial should have been conducted or planned as a confirmatory study, as this would considerably reduce many sources of uncertainty. It did not agree with the company that this was impractical because of low numbers of patients with METex14 skipping NSCLC, because it has been done in other similar populations with comparable population sizes. The committee concluded that basing the evidence on 1 single-arm study meant that there was substantial uncertainty in the data for tepotinib. This was particularly because the survival data was immature, and the lack of comparative data made assessing comparative effectiveness challenging.

Using the data from cohort A plus cohort C has little effect on the results, but is preferable

- 3.6 In its original evidence submission, the company used the data from cohort A exclusively for its cost-effectiveness analysis. This was because the patient-level data from cohort C was only available shortly before the submission date. The committee noted that the Kaplan–Meier plots for progression-free survival and overall survival based on cohort A were almost identical to those based on cohort A plus cohort C. The company

emphasised that the patient characteristics and outcomes were very similar for cohort A compared with cohort A plus cohort C. It did not expect that any minor differences, such as a small improvement in median overall survival and lower median time on treatment for cohort A plus cohort C compared with cohort A, would make much difference to the cost-effectiveness results. The company considered that any differences resulting from using cohort A plus cohort C would likely favour tepotinib. The ERG agreed that the differences were likely inconsequential. However, because overall survival was slightly better for cohort A plus cohort C than for cohort A alone, using this data could slightly increase the likelihood that tepotinib would be cost effective. At the first meeting, the committee agreed that using the data from cohort A was acceptable, and that using the data from cohort A plus cohort C would have little effect on the results. However, it concluded that if the data from cohort A plus cohort C could be used in the cost-effectiveness analysis, then this would be preferable. The company provided this new analysis during consultation, and the committee concluded that this approach was preferable.

The company did indirect treatment comparisons to establish the relative efficacy of tepotinib

- 3.7 Because VISION is a single-arm trial, indirect treatment comparisons were needed to establish the relative efficacy of tepotinib. There was no comparator clinical trial data in METex14 skipping NSCLC, so in its original evidence submission the company developed a real-world cohort from patient-level data specifically for NSCLC with this genetic biomarker. The company took this data from 3 non-interventional studies it had done: NIS-0015, NIS-0035 and COTA. Further data from people with METex14 skipping NSCLC was available from a [study by Wong et al. \(2021\)](#), which the company also used. NIS-0015 comprised complete data on 39 people with MET mutations from a US electronic medical records database. NIS-0035 comprised data on 86 people with MET mutations from electronic medical records from a variety of countries, but not from the UK. COTA comprised 202 complete patient records with at least 1 data point from a real-world database from the US and Canada. Wong et al. was a retrospective review of treatments and outcomes for 41 people with METex14 skipping mutations in Canada. Because patient

numbers were too small to compare tepotinib with all the individual comparators in the NICE scope, the company did indirect treatment comparisons of tepotinib with 2 grouped treatment classes: chemotherapy and immunotherapy. Very few people had chemo-immunotherapy in the real-world cohort. So, the company estimated survival for people with untreated METex14 skipping NSCLC having chemo-immunotherapy by applying hazard ratios from KEYNOTE-189 to the chemotherapy survival curves derived from its real-world cohort (see [section 3.12](#)). KEYNOTE-189 was a trial of pembrolizumab plus chemotherapy compared with chemotherapy alone in people with advanced non-squamous NSCLC without epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations. The company noted that its approach of using grouped comparators had been used in previous submissions to NICE in NSCLC and other oncology indications. It applied the same inclusion and exclusion criteria as used in the VISION trial to the real-world patient data, to form a comparable dataset. The company used propensity scoring to achieve a balance of patient characteristics between tepotinib and the 2 grouped comparators, and to adjust for possible confounding. Data from 66 people who had chemotherapy and 51 people who had immunotherapy was available to conduct the indirect treatment comparisons. The ERG agreed that propensity scoring was the most appropriate method to adjust the indirect treatment comparisons. The committee noted that the company's real-world cohort did not include any people from the UK. The clinical experts explained that the treatments received, and subsequent treatments, did not match the treatments that are used in the UK. This was particularly the case for the low number of people having chemo-immunotherapy in the real-world cohort.

The company's original indirect treatment comparison results are highly uncertain

- 3.8 The results of the indirect treatment comparisons showed that tepotinib had a statistically significant progression-free survival benefit compared with both chemotherapy and immunotherapy. Tepotinib did not have a statistically significant overall survival benefit compared with either chemotherapy or immunotherapy. The clinical experts considered that

the overall survival results from the indirect treatment comparisons did not reflect what would be expected in clinical practice, particularly for chemotherapy. The committee agreed that the results of the indirect treatment comparisons were inconsistent and counter to expectations, with chemotherapy sometimes appearing to be more effective than immunotherapy. This could be partially explained by a lack of generalisability to the UK population, because of the mix of comparator treatments and because people in VISION and from the matched comparator cohort were fitter than would be seen in UK clinical practice. The indirect treatment comparisons were also based on small sample sizes, and may not have been robust for other unknown methodological reasons. However, the committee considered that this cast doubt on the extent of improved overall survival compared with chemotherapy or immunotherapy. The clinical experts and Cancer Drugs Fund clinical lead suggested that the company could consider basing the indirect treatment comparisons on data from comparator trials in people without specific oncogenic biomarkers. This may be more robust because it would allow larger comparator patient numbers. At the first committee meeting, the committee agreed that these analyses may have value, but acknowledged that there would be uncertainty because the comparator trial populations would be different to that of tepotinib. The company reiterated its view that the original indirect treatment comparisons were in the correct METex14 skipping NSCLC population and should be considered. But it agreed to provide new indirect treatment analyses using data from comparator trials in people without specific oncogenic biomarkers for the second committee meeting (see section 3.9). The committee concluded that the results of the company's original indirect treatment comparisons were highly uncertain but should be taken into account in its decision making.

The company did new indirect treatment comparisons using data from VISION and trials in wild-type NSCLC

- 3.9 At consultation, the company updated its original indirect treatment comparison with an additional dataset. This did not substantially alter the results. The company also provided new indirect treatment comparisons. Instead of comparing VISION data with real-world cohorts of people with METex14 skipping NSCLC, the new comparisons were between VISION

and data from trials in wild-type NSCLC, without any specific oncogenic biomarkers. The company selected the most relevant trial for each comparator treatment, in consultation with clinical experts. The committee agreed with the choice of trials but questioned the choice of the TAX320 study for docetaxel monotherapy ([Fossella et al. 2003](#)) because treatment of NSCLC has changed so much since this study was conducted. The company explained that it was selected because the other potential source of data for docetaxel was a trial that had a high proportion of treatment crossover with immunotherapy. This would therefore confound the results of any analyses. The TAX320 trial predates immunotherapy treatments for NSCLC, and so contained no such treatment crossover. The company used matching-adjusted indirect comparisons (MAICs) to compare VISION with the trials in wild-type NSCLC. Both the company and the ERG agreed that this approach has important limitations. The ERG explained that in a MAIC it is the intervention trial population that is matched to the comparator trial population, and that this introduces a risk of bias because the population being matched to is people with wild-type rather than METex14 NSCLC. Also, the matching process involved substantial reductions in the sample sizes of the VISION cohort. The ERG explained that the extent of the reductions suggested that substantial re-weighting of individuals was needed to balance the 2 populations in terms of the prognostic criteria identified. The committee understood that this reduction in the VISION sample sizes suggests a lack of generalisability of the indirect comparison results to the population in the decision problem, which is METex14 skipping NSCLC.

The company's new indirect treatment comparisons are also uncertain but are appropriate for decision making

- 3.10 The committee recalled that the company's new approach to the indirect treatment comparisons did allow comparison with the specific treatments that are relevant to NHS clinical practice, depending on treatment line and histology, whereas the original company approach only allowed for comparison of tepotinib with grouped treatment classes, and excluded chemo-immunotherapy because of a lack of real-world data for this key comparison. The company reiterated its view that the real-world cohort comparisons should be considered because they are

specific to METex14 skipping NSCLC. The ERG agreed with this, but stated that neither approach was clearly superior to the other and the choice was a trade-off between different types of uncertainty. Accepting the limitations of the MAIC approach, the company chose this new analysis for its base case. The committee agreed that the new MAICs were uncertain because of the risk of bias and reduced generalisability to the METex14 skipping NSCLC population caused by the re-weighting of VISION to the comparator wild-type populations. It concluded that the new MAICs for each comparison had limitations but were appropriate for decision making.

The company's economic model

The structure of the company's model is appropriate for decision making

- 3.11 The company used a partitioned-survival economic model that included 3 health states: progression-free, progressed and death. The ERG agreed with the choice of model, but explained that a state-transition model may have offered benefits. The committee concluded that the model was generally appropriate and consistent with the models used in other appraisals for NSCLC.

The company's original overall survival extrapolations for the comparators are implausible

- 3.12 In its original evidence submission, the company produced Kaplan–Meier curves from the VISION trial data for tepotinib and from the real-world cohort data for the comparators. The company then fitted different parametric survival models, piecewise models and spline models to the individual patient data. It considered statistical fit, visual assessment, and expert opinion on the clinical plausibility of the long-term survival profile to select the most plausible extrapolations. The clinical experts consulted by the company considered that the best models according to statistical fit either under- or overestimated survival for the comparators. For this reason, the company's clinical experts selected alternative survival models. The ERG explained that the company's clinical expert

elicitation was likely to have introduced some bias. It noted that the comparative efficacy of tepotinib was highly dependent on the choice of extrapolations, and that fitting them independently for each comparator added uncertainty. To explore the uncertainty, the ERG produced alternative (but not preferred) scenarios using extrapolations based only on statistical fit. The company did not consider any bias to have been introduced by seeking clinical expert opinion. It noted that such opinion was critical to establishing the clinical plausibility of the extrapolations. In response to technical engagement, the company referenced external sources to validate its choice of extrapolations, such as trials in wild-type NSCLC and published real-world studies in METex14 skipping NSCLC. The clinical experts at the committee meeting had concerns over the long-term overall survival estimates for the comparators. They agreed that they were higher than would be seen in NHS clinical practice, particularly for chemotherapy and chemo-immunotherapy. The committee concluded that the company's original overall survival extrapolations for the comparators were implausible.

The company's new overall survival extrapolations for the comparators are also uncertain but are acceptable for decision making

- 3.13 At consultation, the company provided new survival extrapolations based on its new MAICs comparing VISION to comparator data from trials in wild-type NSCLC (see [section 3.9](#)). Based on clinical expert opinion, fit of the curves and long-term plausibility, the company selected the log-logistic curve for overall survival and progression-free survival, for both the tepotinib and chemo-immunotherapy treatment arms for the untreated population. In the previously treated population comparison with docetaxel, the company selected the log-normal curve for overall survival and the log-logistic curve for progression-free survival in the comparator arm, and the exponential curve for overall survival and the log-normal curve for progression-free survival in the tepotinib arm. In the previously treated population comparison with docetaxel with or without nintedanib, the company selected the exponential curve for overall survival and the log-logistic curve for progression-free survival in the comparator arm, and the log-normal curve for overall survival and the log-normal curve for progression-free survival in the tepotinib arm. The

ERG would have preferred survival to have been estimated jointly for tepotinib and the comparators using the pseudo-patient level data, but acknowledged that this would be approximated because the log-logistic curve was selected for both treatments in the base case. It further explained that the selection of curves largely depended on the views of the clinical experts, and that the choice was highly uncertain. Most of the alternative options were also clinically plausible because of the immaturity of the data, in particular for tepotinib, and because of the closeness of the curves. Despite the inherent uncertainty, the ERG suggested that the company had selected one of the curves that estimated the greatest overall survival for chemo-immunotherapy in its base case comparison with tepotinib. However, the committee noted that this was based on a hypothesis that tepotinib is superior to chemo-immunotherapy, and that the evidence to support this is not without uncertainty. Most alternative choices estimated a greater relative treatment effect for tepotinib. The ERG stated that it would not have selected alternative curves based on the information available. The committee concluded that, despite the inherent uncertainty in the survival extrapolation, the company's preferred survival extrapolations were acceptable for decision making.

Subsequent treatment distributions based on prior treatment status in NHS practice are appropriate for decision making

- 3.14 Subsequent treatment costs were applied in the company model as a one-off average cost per patient after disease progression. For its base case, the company used subsequent treatment distributions from VISION for tepotinib and from the real-world cohort for the comparators. This matched efficacy and costs in the model. The company also provided a scenario analysis for subsequent treatments using UK distributions based on clinical expert input. The clinical experts stated that the UK distributions estimated by the company better reflected NHS clinical practice than those based on VISION and the real-world cohort. This was because in the latter, some people had crizotinib as a subsequent treatment, which is not used in this population in the UK. However, the clinical experts noted that separate distributions were needed for people having chemo-immunotherapy and based on prior treatment status. The committee understood that the cost-effectiveness results were highly

sensitive to the subsequent treatment assumptions. At the first meeting, the committee concluded that the subsequent treatment assumptions in the model were uncertain, and that they should reflect NHS clinical practice. At consultation, the company's new indirect treatment comparison (see [section 3.9](#)) allowed for analysis of tepotinib compared with specific comparators, in line with NICE guidance and NHS clinical practice. The company reiterated its opinion that the treatment distributions used in its original analysis were not too dissimilar to NHS clinical practice, with only a small minority of treatments used not available in the NHS, mainly crizotinib. For its new analysis, the company asked clinical experts about the subsequent treatments used in the NHS, by treatment line and histology. The company's new economic model assumed that 100% of people in the untreated population would have a subsequent treatment after tepotinib. Of these, in the base-case comparison with pembrolizumab plus pemetrexed and platinum, 90% were assumed to have nintedanib plus docetaxel, and 10% to have docetaxel monotherapy. In the previously treated subgroup, there were no subsequent treatments after either docetaxel monotherapy or docetaxel plus nintedanib. The committee recalled that nintedanib is recommended for NSCLC of adenocarcinoma histology only, and that 79% of METex14 skipping NSCLC is of adenocarcinoma histology. It also recalled that people with METex14 skipping NSCLC tend to be older, less fit, and have more comorbidities than the broader NSCLC population (see [section 3.1](#)). The Cancer Drugs Fund clinical lead suggested that these factors mean that people with this specific oncogenic driver are less likely to get docetaxel plus nintedanib than docetaxel monotherapy, because of the adverse events associated with nintedanib. For these reasons, fewer than 100% of people will have subsequent treatment, and the company's scenario analysis of 50% was likely to be closer to the true number seen in NHS clinical practice. The committee further agreed that of the 50% who do have subsequent treatment, less than 90% would receive docetaxel plus nintedanib. The committee considered that 50% receiving that combination and 50% receiving docetaxel monotherapy would likely better reflect clinical practice and that these proportions should be used in the company's base case. The committee concluded that these preferred assumptions for subsequent treatment distributions would be used in its decision making.

There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate

- 3.15 The company followed a similar process for extrapolating time on treatment as it did for extrapolating survival (see [section 3.12](#)). The company chose the generalised gamma curve for tepotinib despite the exponential and log-logistic models having the best statistical fit. The company explained that this was because the extended tail in the Kaplan–Meier plot was an artefact of patient censoring, and that clinical expert opinion suggested that almost nobody would be having tepotinib after 5 years. The ERG explained that other models were tried at technical engagement, but none were better fitting than the parametric models originally explored by the company. It suggested that the generalised gamma curve chosen may be the most appropriate model, but that the choice was associated with considerable uncertainty. The committee concluded that the generalised gamma model was likely to be appropriate, but that this was uncertain.

End of life

Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the previously treated subgroup only

- 3.16 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](#). At the first committee meeting, the company suggested that life expectancy for people having chemotherapy in the overall population was less than 2 years, but not for people having immunotherapy. The company considered that life expectancy was also less than 2 years for people having either chemotherapy or immunotherapy in the previously treated subgroup. The committee recalled that neither the indirect treatment comparison results or overall survival extrapolations in the company's original evidence submission could be considered robust. But, it noted that they both likely overestimated overall survival for the comparators. The clinical experts stated that life expectancy for people with METex14 skipping NSCLC is

likely to be less than 2 years, regardless of treatment. At the second meeting, the committee noted that the median life expectancies from the company's new indirect treatment comparisons and the mean life expectancies from the model were based on comparisons between tepotinib and wild-type NSCLC, and so could not be used to estimate life expectancy for the METex14 skipping NSCLC comparator populations. The company did not provide relevant end of life data for the untreated subgroup, because the company and ERG agreed that the end of life criteria would not be met in this subgroup. The committee concluded that the end of life criteria were not met for this group. It recalled that results from the company's real-world indirect treatment comparison suggested that life expectancy was less than 2 years in the previously treated setting, regardless of treatment. The committee further concluded that for people who have had treatment for METex14 skipping NSCLC, life expectancy is likely to be less than 2 years.

Tepotinib extends life by more than 3 months in the previously treated subgroup, so it meets the end of life criteria

- 3.17 The clinical experts felt that it was clinically plausible that tepotinib extends overall survival to some extent. However, the committee noted that the company's original indirect treatment comparisons did not show a statistically significant overall survival benefit for tepotinib in the overall population, and that the confidence intervals were wide. At the second meeting, the committee considered the company's new MAIC analyses and understood that these comparisons were with wild-type NSCLC. These were considered in addition to the company's original observational data from the METex14 skipping population. For the previously treated subgroup, tepotinib had a median overall survival benefit of substantially more than 3 months. The median overall survival benefit from the MAIC and the mean overall survival benefit from the model are academic in confidence and cannot be reported here. The committee concluded that tepotinib meets the end of life criteria in the previously treated subgroup.

Cost-effectiveness estimates

Tepotinib is recommended for advanced METex14 skipping NSCLC

3.18 At the first meeting, the committee agreed that there were problems with the company's original modelling approach in terms of the comparators used and modelling of comparator effectiveness. It noted the high level of uncertainty in the model, particularly around:

- the results of the indirect treatment comparisons (see [sections 3.7 to 3.10](#))
- the comparator overall survival extrapolations (see [section 3.12](#) and [section 3.13](#))
- the subsequent treatment distributions (see [section 3.14](#)).

Because of this, the committee did not consider the company's or the ERG's original base cases to be suitable for decision making. At the second committee meeting, the company presented new cost-effectiveness analyses using the MAIC comparisons between tepotinib and the specific comparators most commonly used in NHS clinical practice: pembrolizumab plus pemetrexed and platinum in the untreated subgroup (company base case), and docetaxel with or without nintedanib for the previously treated subgroup. The incremental cost-effectiveness ratios (ICERs) were calculated with confidential comparator patient access scheme discounts included, and so cannot be reported here. The ICERs were also calculated with the committee's preferred subsequent treatment assumptions incorporated (see [section 3.14](#)). The committee noted that the ICER for the untreated group was within the range that NICE considers to be a cost-effective use of NHS resources. In the previously treated subgroup, where the end of life criteria were met, the ICERs were within the range that could be considered a cost-effective use of NHS resources for a life-extending drug at the end of life. Tepotinib is therefore recommended for routine use for METex14 skipping NSCLC.

Other factors

There are no relevant equality issues

3.19 No relevant equalities issues were identified.

The cost-effectiveness calculations capture tepotinib's benefits

3.20 The committee noted that tepotinib is an oral drug, and it specifically targets METex14 skipping NSCLC. It understood from the clinical expert and patient expert feedback that tepotinib would be an improvement over the current treatments, and agreed that it would be beneficial. The committee considered that the model structure should have been able to capture the benefits and costs of tepotinib in terms of health-related quality of life and quality-adjusted life year (QALYs) gained. It had not been presented with evidence of any additional benefits that were not captured in the QALY calculations.

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 non-small-cell lung cancer with METex14 skipping alterations and the doctor responsible for their care thinks that tepotinib 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 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.

Luke Cowie

Technical lead

Charlie Hewitt

Technical adviser

Christian Griffiths

Technical adviser

Kate Moore

Project manager

ISBN: 978-1-4731-4589-4

Accreditation

