NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of tepotinib within its marketing authorisation for treating adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 (METex14) skipping mutations.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small-cell lung cancers[1]. NSCLC can be further classified into squamous cell carcinoma and non-squamous cell carcinoma. Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma[2]. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV).

In 2017, 39,205 people were diagnosed with NSCLC in England & Wales, and around 65% had stage IIIB or stage IV disease[3]. Around a third of people with lung cancer survive for more than 1 year after diagnosis[4], however this is reduced to a fifth of people diagnosed at stage IV[3]. Mesenchymal-epithelial transition (MET) exon 14 (METex14) skipping mutations occur in 3% to 4% of lung adenocarcinoma[5].

At advanced stage (III and IV) NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes chemotherapy, targeted drugs, radiotherapy and symptom control treatment. Treatment choices are influenced by the presence of biological markers (such as the checkpoint inhibitor programmed death-ligand 1 [PD-L1] and mutations in epidermal growth factor receptor-tyrosine kinase [EGFR-TK] or anaplastic-lymphoma-kinase [ALK], or), histology (squamous or non-squamous) and previous treatment experience. There are specific NICE treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations but not for METex14 skipping mutations.

For previously untreated, metastatic, non-squamous NSCLC if the tumours express PD-L1 with a tumour proportion score (TPS) between 0% and 49%, NICE guideline 122 recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine). NICE technology appraisal 557 recommends pembrolizumab with pemetrexed and platinum chemotherapy. NICE technology appraisal 584 recommends atezolizumab plus bevacizumab, carboplatin, and paclitaxel. Alternatively, people may receive pemetrexed in combination with cisplatin if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (NICE technology appraisal guidance 181).

People with metastatic, non-squamous NSCLC with PD-L1 <50% whose disease progress after initial treatment with platinum-based chemotherapy can receive chemotherapy with docetaxel and the multikinase inhibitor nintedanib (TA347), atezolizumab (TA520), nivolumab (TA484), or pembrolizumab (TA428). People whose disease progress after treatment with pembrolizumab combination (TA557)[a] or atezolizumab combination (TA584) can receive docetaxel with or without nintedanib (TA347).

For previously untreated, metastatic, non-squamous NSCLC if the tumours express PD-L1 TPS ≥50%, NICE guideline 122 recommends pembrolizumab monotherapy (TA531) or pembrolizumab with pemetrexed and platinum chemotherapy (TA557). If the disease progresses following pembrolizumab monotherapy (TA531), NICE guideline 122 recommends platinum doublet (TA181) or pemetrexed with carboplatin. If the disease progresses following pembrolizumab combination (TA557)[a], docetaxel with or without nintedanib (TA347) is recommended.

For previously untreated, metastatic, squamous NSCLC if the tumours express PD-L1 with TPS between 0% and 49%, NICE guideline 122 recommends platinum-based chemotherapy (that is, gemcitabine or vinorelbine with carboplatin or cisplatin) or pembrolizumab with carboplatin and paclitaxel (TA600)[a]. If the disease progresses, people can be offered docetaxel, atezolizumab (TA520), nivolumab (TA483), or pembrolizumab (TA428).

People with metastatic, squamous NSCLC with PD-L1 TPS ≥50%, NICE technology appraisal 531 recommends pembrolizumab monotherapy and technology appraisal 600[a] recommends pembrolizumab with carboplatin and paclitaxel. If disease progresses after pembrolizumab monotherapy, NICE guideline 122 recommends gemcitabine or vinorelbine with carboplatin or cisplatin. If disease progresses after pembrolizumab combination, NICE guideline 122 recommends docetaxel.

The technology

Tepotinib (brand name unknown, Merck) is an oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signalling caused by MET (gene) alterations. It selectively binds to MET tyrosine kinase and disrupts MET signal transduction pathways which are responsible for increasing numbers of tumour cells. It is administered orally.

Tepotinib does not have a marketing authorisation in the UK for treatment people with advanced NSCLC with METex14 skipping mutations. It is being studied in phase 2 single-arm trial assessing its effectiveness and safety in adults with advanced NSCLC with MET alterations.

[a] Recommended for use in the Cancer Drugs Fund. Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund

Intervention(s)	Tepotinib
Population(s)	Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations
Comparators	**Untreated disease:** For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Pembrolizumab combination with pemetrexed and platinum chemotherapy [subject to NICE appraisal] • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel **For previously treated disease:**

	People with non-squamous NSCLC PD-L1 ≥50%: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care People with non-squamous NSCLC PD-L1 <50%: • Atezolizumab monotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel (only after failed initial EGFR or ALK targeted treatment) • Pembrolizumab monotherapy • Nivolumab monotherapy • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care People with squamous NSCLC PD-L1 <50%: • Atezolizumab • Nivolumab • Pembrolizumab • Docetaxel • Best supportive care People with squamous NSCLC PD-L1 >50%: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The use of tepotinib in NSCLC is conditional on the presence of MET gene alterations. The economic modelling should include the costs associated with diagnostic testing for MET in people with advanced non-small-cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	If evidence allows, subgroup analysis by • previous therapy, • tumour histology (squamous or non-squamous), and • level of PD-L1 expression (strong positive or weak positive), will be considered. The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer' (2019) NICE Technology Appraisal 600. Review date to be confirmed. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (2019) NICE Technology Appraisal 584. Review date June 2022. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-squamous non-small-cell lung cancer (2019) NICE Technology Appraisal 557. Review date to be confirmed. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2018) NICE technology appraisals

	guidance 531. Review date July 2021. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (2018). NICE Technology Appraisal 520. Review date May 2021. Nivolumab for previously treated non-squamous non-small-cell lung cancer (2017) NICE technology appraisal guidance 484. Review date to be confirmed. Nivolumab for previously treated squamous non-small-cell lung cancer (2017) NICE technology appraisal guidance 483. Review date to be confirmed. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (2017) NICE technology appraisal guidance 428. Review date to be confirmed. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (2016) NICE Technology Appraisal 402. Review date to be confirmed. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (2015, reviewed 2019) NICE technology appraisal guidance 347. Review date to be confirmed. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010, updated 2017) NICE Technology Appraisal 190. Static guidance list. Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009) NICE Technology Appraisal 181. Static guidance list. Terminated appraisals Atezolizumab with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small-cell lung cancer (terminated appraisal) (2020) NICE Technology Appraisal 618. Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal) (2008) NICE technology appraisal guidance 148. Appraisals in development (including suspended appraisals) Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF Review TA600) NICE technology appraisal ID1683. Expected publication date August 2020 Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) NICE technology appraisal ID1584. Expected publication date December 2020 Atezolizumab with carboplatin or cisplatin and pemetrexed for

	untreated advanced non-squamous non-small-cell lung cancer NICE Technology Appraisal [ID1495]. Publication date to be confirmed. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer NICE technology guidance ID1566. Expected publication date June 2021 Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer. NICE technology appraisal guidance ID1277. Publication date to be confirmed. Avelumab for untreated PD-L1 positive non-small-cell lung cancer. NICE technology appraisal guidance ID1261. Publication date to be confirmed. Durvalumab with tremelimumab and standard chemotherapy for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations. NICE technology appraisal guidance ID1538. Suspended. Atezolizumab with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small-cell lung cancer. NICE technology appraisal guidance ID1513. Suspended. Durvalumab for untreated EGFR-negative, ALK-negative non-small-cell lung cancer NICE technology appraisal guidance ID1331. Suspended. Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score. NICE technology appraisal guidance ID1247. Suspended. Nivolumab with ipilimumab for untreated non-small-cell lung cancer that has a high tumour mutational burden NICE technology appraisal guidance ID1187. Suspended. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations. NICE technology appraisal guidance ID1143. Suspended. Nivolumab in combination with platinum-doublet chemotherapy for untreated non-small-cell lung cancer NICE technology appraisal guidance ID1135. Suspended. Nivolumab monotherapy for non-small-cell lung cancer. NICE technology appraisal guidance ID1088. Suspended. Lung cancer (non-small-cell, untreated) - paclitaxel formulated as albumin-bound nanoparticles (with carboplatin) NICE technology appraisal guidance ID553. Suspended. Lung cancer (non-small cell) - afatinib NICE technology appraisal guidance ID357. Suspended. Lung cancer (non-small-cell, advanced or metastatic maintenance treatment) - erlotinib (in combination with bevacizumab) NICE technology appraisal guidance ID44.

	Suspended. Lung cancer (non-small-cell) – cetuximab NICE technology appraisal guidance ID9. Suspended Related Guidelines: Lung cancer: diagnosis and management (2019) NICE guideline 122 Related Quality Standards: Lung cancer in adults (2012; updated 2019) NICE quality standard 17 Related NICE Pathways: Treating non-small-cell lung cancer (2020) NICE pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105: Specialist cancer services (adults) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 2, 4, 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for tepotinib been included in the scope?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate?

Are there any other subgroups of people in whom tepotinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider tepotinib will fit into the existing NICE pathway, Treating non-small-cell lung cancer?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tepotinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider tepotinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of tepotinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

[1] Lung cancer incidence by morphology. Cancer Research UK. Accessed September 2020

[2] Howlader, N et al. 2015 SEER Cancer Statistics Review, 1975-2012. National Cancer Institute. Accessed September 2020

[3] National Lung Cancer Audit: Annual report 2018 (for the audit period 2017) (2019). Royal College of Physicians. Accessed September 2020

[4] Falchook, G et al. 2016. Effect of the RET Inhibitor Vandetanib in a Patient With RET Fusion–Positive Metastatic Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 34:15

[5] Drilon, A et al. 2017. Targeting MET in Lung Cancer: Will Expectations Finally Be MET? Journal of Thoracic Oncology: 12:12-14