NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Capmatinib for treating locally advanced or metastatic non-small-cell lung cancer with METex14 skipping mutations

Draft scope

Draft remit/appraisal objective

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

Background

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 13% of all new cancer cases and 21% of all cancer deaths in 2017.[1] There are around 48,000 new lung cancer cases and 35,000 deaths from lung cancer in the UK every year. Around 85% of lung cancers are NSCLC.[2] Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma.[3]

The majority of 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), and usually cannot be surgically removed. In 2017, 88% (34,591) of people diagnosed with lung cancer had NSCLC in England, Wales, Jersey and Guernsey.[4] For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. Treatment choices are influenced by the presence of biological markers, such as MET exon 14 skipping or 15-17 MET amplification.

METex14 skipping mutations occur in approximately 3 to 4% of patients NSCLC, typically in the absence of other driver mutations and are associated with poor prognosis.[5]

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) 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), 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). 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 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.

NICE technology appraisal guidance 683 recommended pembrolizumab, with pemetrexed and platinum chemotherapy for people whose tumours have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations.

NICE technology guidance 600 recommended pembrolizumab with carboplatin and paclitaxel, as an option for use within the Cancer Drugs Fund for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults. This technology appraisal guidance is currently under review.

There is currently no NICE guidance specific to the population with METex14 skipping mutations.

The technology

Capmatinib (Tabrecta, Novartis) is an orally bioavailable inhibitor of the proto-oncogene cMet (hepatocyte growth factor receptor [HGFR]) with potential antineoplastic activity. Capmatinib is a small molecule kinase inhibitor targeted against c-Met, a receptor tyrosine kinase that, in healthy humans, activates signalling cascades involved in organ regeneration and tissue repair. Aberrant c-Met activation, via mutations, amplification, and/or overexpression, is known to occur in many types of cancer, and leads to overactivation of multiple downstream signalling pathways. It is administered orally.

Capmatinib does not currently have a marketing authorisation in the UK for treating people with locally advanced or metastatic NSCLC with a METex14 skipping mutations. It is being studied in a non-randomised Phase II trial of 368 adults with stage IIIB or stage IV NSCLC with MET alterations.

Intervention(s)	Capmatinib
Population(s)	Adults with locally advanced or metastatic NSCLC with METex14 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 • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) • Atezolizumab monotherapy • Tepotinib monotherapy (subject to ongoing appraisal ID3761) 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 • 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 • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) • Tepotinib monotherapy (subject to ongoing appraisal ID3761) 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 • Atezolizumab monotherapy • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) • Tepotinib monotherapy (subject to ongoing appraisal ID3761) 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 • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) • Tepotinib monotherapy (subject to ongoing appraisal ID3761) **For previously treated disease:** For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Tepotinib monotherapy (subject to ongoing appraisal ID3761) • Best supportive care For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 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 • Tepotinib monotherapy (subject to ongoing appraisal ID3761) • Best supportive care

	For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Atezolizumab monotherapy • Nivolumab monotherapy • Pembrolizumab monotherapy • Docetaxel • Tepotinib monotherapy (subject to ongoing appraisal ID3761) • Best supportive care For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Tepotinib monotherapy (subject to ongoing appraisal ID3761) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • time to treatment discontinuation • 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 capmatinib in NSCLC is conditional on the presence of METex14 skipping mutations. The economic modelling should include the costs associated with diagnostic testing for METex14 skipping mutations 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 • Squamous versus non-squamous status • Level of PD-L1 expression 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: Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (2021) NICE technology appraisals guidance 705. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (2021) NICE technology appraisals guidance 683. Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor (2021) NICE technology appraisals guidance 670.

	Durvalumab in combination for untreated extensive-stage small-cell lung cancer (2020) (terminated appraisal) NICE technology appraisals guidance 662. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy (2020) NICE technology appraisals guidance 655. Osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer (2020) NICE technology appraisals guidance 653. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer (2020) NICE technology appraisals guidance 654. Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer (2020) NICE technology appraisals guidance 643. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (2020) NICE technology appraisals guidance 638. Ramucirumab with erlotinib for untreated EGFR-positive metastatic non-small-cell lung cancer (2020) (terminated appraisal) NICE technology appraisals guidance 635. Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer (2020) NICE technology appraisals guidance 628. Atezolizumab with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small-cell lung cancer (2020) (terminated appraisal) NICE technology appraisals guidance 618. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer' (2019) NICE technology appraisals guidance 600. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (2019) NICE technology appraisal guidance 584 Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-squamous non-small-cell lung cancer (2019) NICE technology appraisals guidance 557. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2018) NICE technology appraisals guidance 531. Review date July 2021. Nivolumab for previously treated non-squamous non-small-cell lung cancer (2017) NICE technology appraisal guidance 484 Nivolumab for previously treated squamous non-small-cell lung cancer (2017) NICE technology appraisal guidance 483

	Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (2017) NICE technology appraisal guidance 428 Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (2016) NICE technology appraisal guidance 402 Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (2015) NICE technology appraisal guidance 347 Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010) NICE technology appraisal guidance 190 Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009) NICE technology appraisal 181. Static guidance list. Appraisals in development (including suspended appraisals): Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy NICE technology appraisal [ID3836]. Expected publication date October 2022. Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer NICE technology appraisal [ID3896]. Expected publication date April 2022. Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations NICE technology appraisal [ID3761]. Expected publication date March 2022. Cemiplimab for untreated PD-L1-postive advanced or metastatic non-small-cell lung cancer NICE technology appraisal [ID3839]. Expected publication date March 2022. Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer NICE technology appraisal [ID3780] Expected publication date March 2022. Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection NICE technology appraisal [ID3835]. Expected publication date September 2021. Nintedanib for treating progressive fibrosing interstitial lung disease NICE technology appraisal [ID1599]. Expected publication date September 2021. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) NICE technology appraisal [ID1572]. Expected publication date July 2021.

	Related Guidelines: Suspected cancer: recognition and referral (updated 2021) NICE guideline 12 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 capmatinib been included in the scope?

Where in the treatment pathway is capmatinib expected to be used?

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 capmatinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider capmatinib 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 capmatinib 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 capmatinib 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 capmatinib 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. Cancer Research UK. Accessed June 2021.

2. Types of lung cancer. Cancer Research UK. Accessed June 2021.

3. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. 2015 [Available from: https://seer.cancer.gov/csr/1975_2012/]

4. NLCA annual report 2018. Accessed June 2021.

5. Nguyen K, Kobayashi S and Costa D. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non–small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clinical Lung Cancer 2009;10(4):281-289 [Available from: https://pubmed.ncbi.nlm.nih.gov/19632948/]