NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of selpercatinib within its marketing authorisation for treating RET fusion-positive advanced non-small-cell lung cancer.

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]. Rearranged during transfection (RET) fusion-positive tumours occur in 1-2% of NSCLC and are more commonly found in people who are younger than 60 years, former light smokers or those who have never smoked[4].

Around a third of people with lung cancer survive for more than 1 year after diagnosis, however this is reduced to a fifth of people diagnosed at stage IV[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 mutations in epidermal growth factor receptor-tyrosine kinase [EGFR-TK], anaplastic-lymphoma-kinase [ALK] or PD-L1 status), 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 RET-fusions/mutations.

NICE guideline 122 recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with stage III or IV NSCLC if the tumours express PD-L1 with a tumour proportion score between 0% and 49%. 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).

For untreated, metastatic, non-squamous NSCLC people may have atezolizumab plus bevacizumab, carboplatin and paclitaxel (NICE technology appraisal guidance 584) if the tumours express PD-L1 with a tumour proportion score between 0% and 49%. People with untreated, metastatic NSCLC whose tumours express PD-L1 (with at least a 50% tumour proportion score) and have no epidermal growth factor receptor or anaplastic lymphoma kinase-positive mutations may receive pembrolizumab (NICE technology appraisal guidance 531).

NICE technology appraisal guidance 557 recommended pembrolizumab, with pemetrexed and platinum chemotherapy with a managed access agreement through the Cancer Drugs Fund for people whose tumours have no epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations. This technology appraisal guidance is currently under review.

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.

People with non-squamous NSCLC who progress after platinum-based therapy have treatment with platinum doublet (TA181) or pemetrexed with carboplatin. They can also receive chemotherapy with docetaxel and the multikinase inhibitor nintedanib (TA347). People with PD-L1 <50% could also have atezolizumab with bevacizumab, carboplatin and paclitaxel (TA584).

People with squamous NSCLC with PD-L1 <50% who progress after platinum-based therapy can have atezolizumab (TA520), nivolumab (TA483), pembrolizumab (TA428), or docetaxel. People with PD-L1 >50% can have gemcitabine with carboplatin or cisplatin, vinorelbine with carboplatin or cisplatin, or docetaxel.

The technology

Selpercatinib (brand name unknown, Eli Lilly) is a small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers, promoting cell proliferation and survival in tumour cell lines. Point mutations in RET can also result in constitutively activated RET proteins that can promote cell growth and survival in tumour cell lines. It is administered orally as a capsule.

Selpercatinib does not have a marketing authorisation in the UK for treating people with RET fusion positive advanced non-small-cell lung cancer. It is being studied in a single-arm trial designed to test the safety, tolerability, pharmacokinetics, and preliminary anti-tumour activity of selpercatinib in people with locally advanced or metastatic solid tumours who have progressed on or are intolerant to standard therapy or have declined standard therapy.

Intervention(s)	Selpercatinib
Population(s)	People with advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy
Comparators	**Untreated disease:** For people whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • 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 a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) **After previous chemotherapy treatments:** People with non-squamous NSCLC: • Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Atezolizumab with bevacizumab, carboplatin and paclitaxel (if PD-L1 <50%) • 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 • 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 selpercatinib in NSCLC is conditional on the presence of RET gene fusion. The economic modelling should include the costs associated with diagnostic testing for RET 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 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 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 Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (2015) NICE technology appraisal guidance 374 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) Lung cancer (non-small cell, advanced, inoperable) - liposomal vand (with chemotherapy) NICE technology appraisal guidance [ID657] Publication to be confirmed 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 June 2020 Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) NICE technology appraisal guidance [ID1572] Publication expected 6 May 2020 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 Atezolizumab with carboplatin or cisplatin and pemetrexed for untreated advanced non-squamous non-small-cell lung cancer NICE Technology Appraisal Guidance [ID1495] 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 for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations. NICE technology appraisal guidance [ID1143]. Suspended. Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer. NICE technology appraisal guidance [ID1187]. Suspended. Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small-cell lung cancer. NICE technology appraisal guidance [ID1135]. Suspended. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer NICE technology guidance [ID1566] Publication to be confirmed Nivolumab monotherapy for non-small-cell lung cancer. NICE technology appraisal guidance [ID1088]. 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. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer. NICE technology appraisal guidance [ID1277]. Publication date to be confirmed. 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. 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 selpercatinib been included in the scope?

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

Which treatments are considered to be established clinical practice in the NHS for RET fusion-positive advanced non-small-cell lung cancer in people who have progressed on or are intolerant to standard therapy, or have declined standard therapy?

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

Where do you consider selpercatinib 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 selpercatinib 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 selpercatinib 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 selpercatinib 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 April 2020

[2] 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/

[3] National Lung Cancer Audit: Annual report 2018 (for the audit period 2017) (2019). Royal College of Physicians. Accessed April 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] Royal College of Physicians (2017) National Lung Cancer Audit annual report 2016 (for the audit period 2015). Accessed April 2020.

