NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

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

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of selpercatinib within its marketing authorisation for treating untreated 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 2018, 39,754 people were diagnosed with NSCLC in England & Wales, and around 61% 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[3]. 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. Testing for RET fusion status is not routinely carried out as standard of care in the UK. People with unconfirmed RET fusion-positive advanced NSCLC would therefore follow the standard NSCLC treatment pathway.

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 683 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).

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For previously untreated, metastatic, non-squamous NSCLC if the tumours express PD-L1 TPS ≥50%, NICE guideline 122 recommends pembrolizumab monotherapy (TA531), atezolizumab monotherapy (TA705), or pembrolizumab with pemetrexed and platinum chemotherapy (TA683).

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 (TA770).

People with metastatic, squamous NSCLC with PD-L1 TPS ≥50%, NICE technology appraisal 531 recommends pembrolizumab monotherapy, technology appraisal 705 recommends atezolizumab monotherapy, and technology appraisal 770 recommends pembrolizumab with carboplatin and paclitaxel.

NICE technology appraisal 760 recommends selpercatinib for use within the Cancer Drugs Fund as an option for treating RET fusion-positive advanced NSCLC in adults who need systemic therapy after immunotherapy, platinum-based chemotherapy or both.

The technology

Selpercatinib (Retevmo, Eli Lilly) does not have a marketing authorisation in the UK for treating people with untreated RET fusion-positive advanced non-small-cell lung cancer. It is being studied in a randomised clinical trial comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab as initial treatment of advanced or metastatic RET fusion-positive NSCLC. The trial includes people with advanced RET fusion-positive non-squamous NSCLC who have not had prior systemic therapy for metastatic disease.

Intervention(s)	Selpercatinib
Population(s)	People with untreated advanced RET fusion-positive non-small cell lung cancer (NSCLC).
Subgroups	If the evidence allows the following subgroups will be considered: • tumour histology (squamous or non-squamous), and • level of PD-L1 expression (strong positive or weak positive).
Comparators	For people with advanced RET fusion positive NSCLC • Pralsetinib [subject to ongoing NICE appraisal ID3875] 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 • Atezolizumab

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	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 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 • Atezolizumab • 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
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.

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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 and cost of biosimilar and generic products should 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 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
Other considerations	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	Related Technology Appraisals: Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer. (2022) NICE technology appraisals guidance 770. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-squamous non-small-cell lung cancer. (2021) NICE technology appraisals guidance 683. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer. (2021) NICE technology appraisal 713. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer. (2021) NICE technology appraisal 724.

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	Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer. (2021) NICE technology appraisal 705. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. (2019) NICE technology appraisal guidance 584. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. (2018) NICE technology appraisals guidance 531. Pemetrexed for the maintenance treatment of non-small-cell lung cancer .(2017) NICE technology appraisal guidance 190 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 Pemetrexed for the first-line treatment of non-small-cell lung cancer. (2009) NICE technology appraisal 181. Appraisals in development (including suspended appraisals): Pralsetinib for RET fusion-positive advanced non-small-cell lung cancer. NICE Technology Appraisal Guidance [ID3875]. In progress. Atezolizumab with carboplatin or cisplatin and pemetrexed for untreated advanced non-squamous non-small-cell lung cancer. NICE Technology Appraisal Guidance [ID1495] Suspended. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations. NICE technology appraisal guidance [ID1143]. In progress. 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 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.

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	Durvalumab for untreated EGFR-negative, ALK-negative non-small-cell lung cancer. NICE technology appraisal guidance [ID1331]. Suspended. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer. NICE technology appraisal guidance [ID1277]. In progress. Avelumab for untreated PD-L1 positive non-small-cell lung cancer. NICE technology appraisal guidance [ID1261]. In progress. Durvalumab + Tremelimumab + standard chemotherapy for non-small cell lung cancer (NSCLC) lacking activating EGFR mutations and ALK fusions. NICE technology appraisals guidance [ID1538]. In progress. Durvalumab for untreated advanced non-small-cell lung cancer with no EGFR or ALK mutations and high PD-L1 expression. NICE technology appraisal guidance [ID3762]. In progress. 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 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)

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Questions for consultation

Which treatments are established clinical practice in the NHS for RET fusion-positive advanced non-small-cell lung cancer in people who have not received prior treatment?

Are the outcomes listed appropriate?

Are the subgroups suggested 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 care pathway for advanced NSCLC?

Would selpercatinib be a candidate for managed access?

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 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 committee to take account of these benefits.

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 is 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.

NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes

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is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).

NICE's health technology evaluations: the manual 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 March 2022

[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 2021 (for the audit period 2018) (2021). Royal College of Physicians. Accessed March 2022

[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

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