NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

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, 39,201 people were diagnosed with NSCLC in England & Wales, and around 57% 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.

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 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.

The technology

Selpercatinib (Retevmo, Eli Lilly) is a small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Chromosomal rearrangements involving fusions of RET with various partners can result in the growth of cancer cells. Point mutations in RET can also result in irregular RET proteins that can promote the growth of cancer cells. Administration of selpercatinib can target RET cancers and inhibit growth of tumour cells. 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 phase 1 and 2 basket trial (study designed to test the effect of a single drug across multiple cancer populations) in people with locally advanced or metastatic RET fusion-positive solid tumours. The trial included people with advanced NSCLC who require systemic 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 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 [subject to NICE appraisal] 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 [subject to NICE appraisal] 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 [subject to NICE appraisal] **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 • 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 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 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) 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 Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (CDF review TA484) NICE technology appraisal guidance [ID1572] Publication date to be confirmed 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] Expected publication date June 2021 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. 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

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.

