NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab with lenvatinib for untreated PD-L1 positive metastatic non-small-cell lung cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab with lenvatinib within its marketing authorisation for untreated PD-L1 positive metastatic 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 10-15% 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] Around a third of people with lung cancer survive for more than 1 year after diagnosis[4], however this is reduced to around a fifth of people diagnosed at stage IV.[3]

Cancer cells expressing an immunologic marker called programmed cell death 1 ligand (PD-L1) are believed to suppress certain immune responses and cause increased tumour aggressiveness. The proportion of NSCLC that express PD-L1 in England is unknown.

In metastatic stage 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)], anaplastic-lymphoma-kinase [ALK] or programmed death-ligand 1 [PD-L1] status), histology (squamous or non-squamous) and previous treatment experience.

NICE clinical 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).

NICE technology appraisal guidance 584 recommends atezolizumab with bevacizumab, carboplatin and paclitaxel as an option for untreated non-squamous NSCLC if the tumour expresses PD-L1 with less than 50% tumour proportion score and has no EGFR- or ALK-positive mutations. NICE technology appraisal guidance 531 recommends pembrolizumab monotherapy as an option for untreated PD-L1-positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR- or ALK-positive mutations. NICE technology appraisal guidance 557 recommends pembrolizumab combination therapy for use within the Cancer Drugs Fund, as an option for metastatic untreated non-squamous NSCLC if the tumour has no EGFR- or ALK-positive mutations. [a] NICE technology appraisal guidance 600 recommends pembrolizumab with carboplatin and paclitaxel for use within the Cancer Drugs Fund, as an option for metastatic untreated squamous NSCLC. [a]

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[a] 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/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf

The Technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, antiprogrammed cell death 1 (PD-1) antibody that acts by blocking immune suppression and the following reactivation of anergic T-cells. It is administered intravenously.

Lenvatinib (Kisplyx, Lenvima, Eisai) is a multiple receptor tyrosine kinase inhibitor (TKI) that selectively inhibits the kinase activities of all vascular endothelial growth factor (VEGF) receptors. It is administered orally.

Pembrolizumab with lenvatinib does not have a marketing authorisation in the UK for untreated PD-L1 positive metastatic non-small-cell lung cancer. Pembrolizumab with lenvatinib has been studied in a clinical trial compared with pembrolizumab with placebo in adults with untreated PD-L1 positive metastatic NSCLC with a PD-L1 tumour proportion score ≥1%.

Pembrolizumab has the following marketing authorisations in the UK for untreated non-small-cell lung cancer:

- as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations
- in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations
- in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

Pembrolizumab has the following marketing authorisation in the UK for previously treated non-small-cell lung cancer:

- as monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

Intervention(s)	Pembrolizumab with lenvatinib
Population(s)	Adults with untreated PD-L1 positive metastatic non-small-cell lung cancer
Comparators	For adults with non-squamous histology: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large-cell carcinoma only) ○ with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment

	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) ○ with or without pemetrexed maintenance treatment • Atezolizumab with bevacizumab, carboplatin and paclitaxel (for people whose tumours express PD-L1 with less than 50% tumour proportion score) • Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% tumour proportion score with no EGFR- or ALK- positive tumour mutations only) • Pembrolizumab in combination with pemetrexed and platinum chemotherapy (for people whose tumour has no EGFR- or ALK-positive mutations) (subject to ongoing NICE appraisal) For adults with squamous histology: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab (for people whose tumours express PD-L1 with at least a 50% tumour proportion score with no EGFR- or ALK- positive tumour mutations only)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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 patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If evidence allows, consideration will be given to subgroups based on biological markers (PD-L1). 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 in combination for treating metastatic non-squamous non-small-cell lung cancer' (2019) NICE Technology Appraisal 584. Review date June 2022. 'Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer' (2018) NICE Technology Appraisal 531. Review date July 2021. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (2016) NICE technology appraisal guidance 402. Review date 2019. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010) NICE technology appraisals guidance 190. Static guidance list. 'Pemetrexed for the first-line treatment of non-small cell lung cancer' (2009, updated 2014) NICE Technology Appraisal 181. Static list guidance. **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 appraisals guidance [ID1683]. Publication date to be confirmed. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) NICE technology appraisals guidance [ID1584]. Publication date to be confirmed. Durvalumab with chemotherapy for untreated advanced non-small-cell lung cancer with no EGFR or ALK mutations. NICE

	technology appraisals guidance [ID3751]. 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. 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. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer NICE Technology Appraisal [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. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer. NICE technology appraisal guidance [ID1678]. 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 [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. Atezolizumab with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small-cell lung cancer. NICE technology appraisal guidance [TA618]. Terminated. 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. NICE guideline 122. **Related Interventional Procedures:** Microwave ablation for treating primary lung cancer and metastases in the lung (2013). NICE interventional procedures guidance 469 **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: Domain 1, 2, 4, 5 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for pembrolizumab with lenvatinib been included in the scope?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate?

Where do you consider pembrolizumab with lenvatinib 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 pembrolizumab with lenvatinib 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 pembrolizumab with lenvatinib 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 pembrolizumab with lenvatinib 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 November 2020

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

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

[4] Lung cancer survival statistics (2010-11). Cancer Research UK. Accessed October 2020.