NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab within its marketing authorisation for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score.

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. NSCLC can be further classified into 3 histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma. 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 2015, around 33,000 people are estimated to be diagnosed with NSCLC in England.[1,2] Around 12% have stage IIIA, 9% had stage IIIB and 53% had stage IV disease[1]. The prognosis for people with non-small-cell lung cancer is generally poor. Between 2011 and 2015 around 39% of people with lung cancer survived for 1 year or longer and only 15% survived for 5 years or longer.[2]

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.

For the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. 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.

NICE clinical guideline 121 (CG121 'Lung cancer') recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with previously untreated stage III or IV NSCLC and good performance status. 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 people who are unable to tolerate a platinum combination, the clinical guideline recommends single-agent chemotherapy with docetaxel, gemcitabine, paclitaxel, or vinorelbine.

For non-squamous NSCLC that has not progressed immediately following initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option (NICE technology appraisal guidance 402).

Pembrolizumab is currently recommended within the Cancer Drugs Fund as a treatment option for untreated PD-L1-positve metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score (NICE technology appraisal guidance 447). The company for pembrolizumab was required to collect data from the KEYNOTE-024 trial in line with the managed access agreement. This guidance is currently under review.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, antiprogrammed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not have a marketing authorisation in the UK for untreated PD-L1 positive metastatic NSCLC for tumours that express PD-L1 with at least 1% tumour proportion score with no EGFR or ALK positive tumour mutations. It has been studied in a clinical trial, compared with platinum-based chemotherapy, in adults with PD-L1 positive advanced or metastatic NSCLC who have not had chemotherapy for advanced or metastatic disease.

Pembrolizumab has a marketing authorisation in the UK for:

- first line treatment of metastatic NSCLC for tumours that express PD-L1 with at least 50% tumour proportion score with no EGFR or ALK positive tumour mutations
- treating locally advanced or metastatic NSCLC for tumours that express PD-L1 with at least 1% tumour proportion score after at least one prior chemotherapy regimen.

Intervention(s)	Pembrolizumab
Population(s)	Adults with PD-L1-positive advanced or metastatic non-small-cell lung cancer (NSCLC) with at least 1% tumour proportion score that has not been treated with chemotherapy in the advanced or metastatic setting

Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)
	  ○ with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment
	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only)
	  ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only)
	• Single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate)

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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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. The use of pembrolizumab is conditional on the presence of programmed cell death 1 ligand (PD-L1). The economic modelling should include the costs associated with diagnostic testing for PD-L1 in people with NSCLC 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 tumour histology (squamous or non-squamous) and level of PD-L1 expression will be considered. 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 for untreated PD-L1-positive metastatic non-small-cell lung cancer' NICE technology appraisal 447. Review in progress [ID1349]. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer (2016) NICE technology appraisals guidance 402. Review expected August 2019. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010) NICE technology appraisals

	guidance 190. Static guidance list (review decision December 2014). Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009) NICE technology appraisals guidance 181. Static guidance list (review decision December 2014). **Related Guidelines:** Lung Cancer: The diagnosis and treatment of lung cancer (2011). NICE guideline 121. Review in progress. **Guidelines in development** 'Lung cancer: diagnosis and management (update)'. Publication expected January 2019. **Related Quality Standards:** Quality standard for lung cancer (2012). NICE quality standard 17 https://www.nice.org.uk/guidance/qs17 **Related NICE Pathways:** Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	Department of Health, Improving Outcomes: A strategy for cancer, fourth annual report, Dec 2014 https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report NHS England, Manual for prescribed specialised services, chapter 105: specialist cancer services (adults), May 2016. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2016-20167, April 2016. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Department of Health, Cancer commissioning guidance, Dec 2009. http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110115

Questions for consultation

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

Which treatments are considered to be established clinical practice in the NHS for untreated PD-L1-positive advanced or metastatic NSCLC?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab will fit into the existing NICE pathway, 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 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 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 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 technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 National lung cancer audit 2016 (2017). Royal college of Physicians. Accessed October 2017.

2 Cancer survival in England: adult, stage at diagnosis and childhood-patients followed up to 2016 (2017) Office for National Statistics. Accessed October 2017.

