# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447)

## Final scope

### Remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab 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 the remainder are small cell lung cancers[1,2]. 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 2013, approximately 26,800 people were diagnosed with NSCLC in England, of whom 13% had stage IIIA, 10% had stage IIIB and 46% had stage IV disease[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 is PD-L1 positive in England is unknown.

The median survival of people with lung cancer (all stages) is approximately 8 months[2]. Around a third of people with lung cancer, and a fifth of people with stage IV disease, survive for more than 1 year after diagnosis[3].

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) 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. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated. 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 190 and draft final NICE guidance from the review of technology appraisal 309 [CDF rapid reconsideration process]).

## The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed 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. It has been studied in clinical trials, compared with platinum-based chemotherapy, in adults with PD-L1 positive advanced or metastatic NSCLC who have not had chemotherapy for their metastatic disease.

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| **Intervention(s)** | Pembrolizumab |
| **Population(s)** | People with PD-L1 positive metastatic non-small-cell lung cancer (NSCLC) not treated with chemotherapy in the metastatic setting |
| **Comparators** | • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)<br>  ○ with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment<br>• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only)<br>  ○ with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only; subject to ongoing NICE guidance from the CDF rapid reconsideration process)<br>• Single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate) |

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| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• 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.<br>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.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>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 (strong positive or weak positive), will be considered.<br>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:**<br>Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (2014) NICE technology appraisals guidance 309. Review ongoing (CDF rapid reconsideration process ID1005). Publication expected August 2016. |

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| | Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010) NICE technology appraisals guidance 190. Static guidance list (review decision December 2014).<br><br>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).<br><br>**Appraisals in development:**<br><br>Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy NICE technology appraisals guidance [ID840]. Publication expected January 2017.<br><br>**Related Guidelines:**<br><br>The diagnosis and treatment of lung cancer (2011). NICE guideline 121. Review of guideline ongoing (review decision March 2016). Publication date to be confirmed.<br><br>**Related Quality Standards:**<br><br>Quality standard for lung cancer (2012). NICE quality standard 17<br><br>http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp<br><br>**Related NICE Pathways:**<br><br>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<br><br>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<br><br>Department of Health, NHS Outcomes Framework 2016-20167, April 2016. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 |

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| | 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 |

**References**

1 Cancer Research UK (2011 data) Lung cancer incidence statistics. Accessed May 2016.

2 Health and Social Care Information Centre (2014) National Lung Cancer Audit: 2013 patient cohort. Accessed May 2016.

3 Cancer Research UK (2010–12 data) Lung cancer survival statistics. Accessed May 2016.