NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of durvalumab with tremelimumab within its marketing authorisation for untreated non-small-cell lung cancer with no epidermal growth factor receptor (EGFR)- or anaplastic-lymphoma-kinase (ALK)-positive mutations.

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. The majority of 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 were 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]

For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. Treatment choices may be influenced by the presence of biological markers (such as the checkpoint inhibitor programmed death-ligand 1 [PD-L1] and mutations in epidermal growth factor receptor-tyrosine kinase [EGFR-TK] or anaplastic-lymphoma-kinase [ALK], or), 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 190 and 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). This guidance is currently under review.

The technology

Durvalumab (Imfinzi, AstraZeneca) is an human monoclonal antibody directed against programmed death ligand-1 (PD-L1). Durvalumab blocks PD-L1 interaction with both PD-1 and CD80 on T cells, countering the tumour's immune-evading tactics and activating the patient's immune system to attack the cancer.

Tremelimumab (brand name unknown, AstraZeneca) is an investigational, selective human antibody directed against cytotoxic T- lymphocyte-associated protein 4 (CTLA-4). By blocking the activity of CTLA-4, tremelimumab 'releases the brakes' on T cell activation and boosts the immune response against cancer cells.

Durvalumab with tremelimumab does not currently have a marketing authorisation for untreated locally advanced or metastatic NSCLC with no EGFR- or ALK-positive mutations. It has been studied in clinical trials compared with platinum-based chemotherapy in people, locally advanced or metastatic NSCLC with no EGFR- or ALK-positive mutations that has not been treated with chemotherapy.

Intervention(s)	Durvalumab with tremelimumab
Population	People with locally advanced or metastatic NSCLC with no EGFR- or ALK-positive mutations who have not had prior chemotherapy

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)
	• Pembrolizumab monotherapy (for people with at least 50% tumour proportion score with no EGFR or ALK positive tumour mutations only [subject to ongoing NICE appraisal, funded by the CDF in the interim])

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • 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, subgroup analysis by 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]. **Appraisals in development (including suspended appraisals)** 'Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score' NICE technology appraisal [ID1247]. Publication date to be confirmed. 'Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer' NICE technology appraisal [ID1173]. Publication date to be confirmed. 'Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer' NICE technology appraisal [ID1306]. Publication date to be confirmed. 'Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small-cell lung cancer' NICE technology appraisal [ID1135]. Publication date to be confirmed. 'Nivolumab monotherapy for non-small-cell lung cancer' NICE technology appraisal [ID1088]. Suspended. **Related Guidelines:** Lung Cancer: The diagnosis and treatment of lung cancer (2011). NICE guideline 121. Review ongoing. **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 No. 17

	http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways:** NICE Pathway: Lung cancer. Pathway created: March 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	NHS England, Manual for prescribed specialised services, service 105: specialist cancer services (adults), Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1, 2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) Improving outcomes: a strategy for cancer, 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2011) Cancer commissioning services

Questions for consultation

Have all relevant comparators for durvalumab with tremelimumab been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for untreated locally advanced or metastatic NSCLC with no EGFR- or ALK-positive mutations?

Are the outcomes listed appropriate?

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

- Is a subgroup based on PD-L1 expression appropriate?

Where do you consider durvalumab with tremelimumab 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 durvalumab with tremelimumab 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 durvalumab with tremelimumab 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 durvalumab with tremelimumab 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).

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

3 Thomas A, Büttner R, Wolf J et al. (2013) Genomics-based classification of human lung tumors. Science Translational Medicine 5(209): 209ra153.