

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab with ipilimumab for untreated non-small-cell lung cancer that has a high tumour mutational burden [ID1187]

Final scope

Draft remit

To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab, within its marketing authorisation, for untreated non-small-cell lung cancer in adults who have a high tumour mutational burden.

Background

Lung cancer falls into 2 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 main 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, approximately 31,900 people were diagnosed with NSCLC in England, of whom 60% had stage IIIB or stage IV disease².

Tumour mutational burden is a biomarker that reflects the total number of mutations carried by tumour cells. Tumour mutational burden is one type of biomarker that may help predict the likelihood that a person responds to immunotherapies. Cancer cells with more than 10 mutations per megabase are considered to have a high tumour mutational burden.

Around a third of people with lung cancer survive for more than 1 year after diagnosis², however this is reduced to a fifth of people diagnosed at stage IV³.

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 recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with 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 (NICE technology appraisal

National Institute for Health and Care Excellence

Final scope for the appraisal of nivolumab with ipilimumab for untreated non-small-cell lung cancer that has a high tumour mutational burden [ID1187]

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guidance 181). 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 402). NICE technology appraisal guidance 447 recommended pembrolizumab with a managed access agreement through the Cancer Drugs Fund for people whose tumours express PD-L1 with at least a 50% tumour proportion score and have no epidermal growth factor or anaplastic lymphoma kinase- positive mutations. A review of this guidance is in progress; the Final Appraisal Determination recommends pembrolizumab for routine commissioning [ID1349].

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a human IgG4 monoclonal antibody targeting the programmed cell death-1 receptor (PD-1). Blocking PD-1 may activate T-cell responses and promote an anti-tumour immune response. It is administered intravenously.

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human antibody that binds to and blocks the activity of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), thereby sustaining the immune attack on cancer cells. It is administered intravenously.

Nivolumab in combination with ipilimumab does not currently have a marketing authorisation in the UK for untreated non-small-cell lung cancer. Nivolumab is being studied in a clinical trial in adults with stage IV or recurrent untreated non-small-cell lung cancer. This trial studies nivolumab as a monotherapy, in combination with ipilimumab, and in combination with platinum-doublet chemotherapy, compared with platinum-doublet chemotherapy alone.

Nivolumab has a marketing authorisation in the UK for treating locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	Adults with untreated stage IV or recurrent non-small-cell lung cancer that has a high tumour mutational burden [with no known EGFR or ALK positive tumour mutations]

<p>Comparators</p>	<ul style="list-style-type: none"> • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) <ul style="list-style-type: none"> ○ 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) <ul style="list-style-type: none"> ○ with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • Pembrolizumab (for people whose tumours express PD-L1 with at least a 50% tumour proportion score); subject to ongoing appraisal (review of TA447).
<p>Outcomes</p>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life

<p>Economic analysis</p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes or commercial access agreements for the intervention or comparator technologies will be taken into account.</p> <p>The economic modelling should include the costs associated with diagnostic testing for TMB in people with untreated 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.</p>
<p>Other considerations</p>	<p>If evidence allows, subgroup analysis by tumour histology (squamous or non-squamous), tumour stage and PD-L1 expression level will be considered.</p> <p>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.</p>
<p>Related NICE recommendations and NICE Pathways</p>	<p>Related Technology Appraisals:</p> <p>Pemetrexed for the first-line treatment of non-small-cell lung cancer (2009). NICE technology appraisal 181. Static guidance list.</p> <p>Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010). NICE technology appraisal 190. Static guidance list.</p> <p>Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (2016). NICE technology appraisal 402. Review date April 2019.</p>

	<p>Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017). NICE technology appraisal 447. Review ongoing.</p> <p>Appraisals in development (including suspended appraisals):</p> <p>Nivolumab monotherapy for non-small-cell lung cancer. NICE technology appraisals guidance [ID1088]. Suspended.</p> <p>Nivolumab in combination with platinum doublet chemotherapy for untreated PD-L1 negative non-small-cell lung cancer. Proposed NICE technology appraisal [ID1135]. Publication date to be confirmed.</p> <p>Related Guidelines:</p> <p>Lung cancer: diagnosis and management (2011). NICE clinical guideline 121. Review date to be scheduled.</p> <p>Related Interventional Procedures:</p> <p>Microwave ablation for treating primary lung cancer and metastases in the lung (2013). NICE interventional procedures guidance 469.</p> <p>Related Quality Standards:</p> <p>Lung cancer in adults (2012). NICE quality standard 17.</p> <p>Related NICE Pathways:</p> <p>Lung cancer (2012) NICE pathway</p>
<p>Related National Policy</p>	<p>Department of Health (2014) Improving outcomes: a strategy for cancer. Fourth annual report</p> <p>NHS England (2016) Manual for prescribed specialised services. Chapter 105: Specialist cancer services (adults)</p> <p>Department of Health (2016) NHS Outcomes Framework 2016-2017. Domains 1, 2, 4 and 5.</p> <p>Department of Health (2011) Commissioning cancer services</p>

	NHS England (2016) Implementing the cancer taskforce recommendations: Commissioning person centred care for people affected by cancer
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References

1 Cancer Research UK (2017) [Lung cancer incidence statistics \(2011 data\)](#). Accessed February 2017.

2 Health and Social Care Information Centre (2017) [National Lung Cancer Audit annual report 2016 \(for the audit period 2015\)](#)

3 Cancer Research UK (2017) [Lung cancer survival statistics \(2014 data\)](#). Accessed February 2017.