

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer

Draft scope

Draft remit

To appraise the clinical and cost effectiveness of nivolumab in combination with ipilimumab within its marketing authorisation for untreated PD-L1-positive non-small-cell lung cancer.

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.

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.

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 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

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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). Pembrolizumab is recommended with a managed access agreement through the Cancer Drugs Fund (NICE technology appraisal guidance 447) 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. Best supportive care may be considered for some people for whom chemotherapy is unsuitable or may not be tolerated.

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.

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

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, as monotherapy, with ipilimumab, or with platinum-doublet chemotherapy compared with platinum-doublet chemotherapy alone.

Intervention(s)	Nivolumab in combination with ipilimumab
Population(s)	Adults with untreated PD-L1-positive stage IV or recurrent non-small-cell lung cancer

<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 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 (for people whose tumours express PD-L1 with at least a 50% tumour proportion score).
<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 for the intervention or comparator technologies will be taken into account.</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 date December 2017.</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>
Related National Policy	<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> <p>NHS England (2016) Implementing the cancer taskforce recommendations: Commissioning person centred care for people affected by cancer</p>

Questions for consultation

Would nivolumab in combination with ipilimumab be used to treat cancer, which in addition to being PD-L1 positive, has epidermal growth factor receptor or anaplastic lymphoma kinase-positive mutations?

Have all relevant comparators for nivolumab in combination with ipilimumab for PD-L1-positive non-small cell lung cancer been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for untreated stage IV or recurrent non-small cell lung cancer?
- Are there any groups of people for whom best supportive care would be an alternative treatment option for nivolumab in combination with ipilimumab? If so, how should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom nivolumab in combination with ipilimumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider nivolumab in combination with ipilimumab 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 nivolumab in combination with ipilimumab 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 nivolumab in combination with ipilimumab 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 nivolumab in combination with ipilimumab 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.

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 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.