

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with ipilimumab and standard chemotherapy (platinum-based combination chemotherapy) within its marketing authorisation for untreated metastatic non-small-cell lung cancer.

Background

Lung cancer falls into 2 main histological categories: 85-90% are non-small-cell lung cancers (NSCLC) and 10-15% are small-cell lung cancers¹. NSCLC can be further classified into squamous cell carcinoma and non-squamous cell carcinoma. Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma². 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 2016, approximately 32,500 people were diagnosed with NSCLC in England, and around 61% had stage IIIB or stage IV disease³.

Lung cancer caused over 35,620 deaths in England in 2016⁴. Thirty two percent of people with lung cancer survive for more than 1 year after diagnosis⁵.

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), anaplastic-lymphoma-kinase (ALK) or programmed death-ligand 1 (PD-L1) status), histology (squamous or non-squamous) and previous treatment experience.

NICE guideline 122 recommends platinum combination 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 (non-squamous) (NICE technology appraisal guidance 181). NICE technology appraisal guidance 584 recommends atezolizumab with bevacizumab, carboplatin and paclitaxel as an option for untreated NSLC if the tumour expresses PD-L1 with less than 50% tumour proportion score and has no EGFR- or ALK-

positive mutations. NICE technology appraisal guidance 531 recommends pembrolizumab monotherapy as an option for untreated PD-L1-positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR- or ALK-positive mutations. NICE technology appraisal guidance 557 recommends pembrolizumab combination therapy for use within the Cancer Drugs Fund, as an option for metastatic untreated NSCLC if the tumour has no EGFR- or ALK-positive mutations. NICE technology appraisal guidance 600 recommends pembrolizumab with carboplatin and paclitaxel with the Cancer Drugs Fund, as an option for metastatic untreated squamous NSCLC^a.

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 TA190 and 402).

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully humanised IgG4 monoclonal antibody which targets and blocks the PD-L1 receptor, to promote an anti-tumour immune response. It is administered intravenously.

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a recombinant human anti-CTLA-4 monoclonal antibody which blocks the effects of CTLA-4 to enhance T-cell mediated immune responses to tumour cells. It is administered intravenously.

Nivolumab with ipilimumab and standard chemotherapy for untreated metastatic NSCLC does not currently have a marketing authorisation in the UK. It has been studied in a clinical trial compared with chemotherapy (pemetrexed or paclitaxel, with platinum therapy) alone in adults with untreated metastatic NSCLC without EGFR or ALK mutations.

^a Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf>

Intervention	Nivolumab with ipilimumab and standard chemotherapy
Population	Adults with untreated metastatic NSCLC
Comparators	<p>For adults with non-squamous histology:</p> <ul style="list-style-type: none"> • 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 • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) <ul style="list-style-type: none"> ○ with or without pemetrexed maintenance treatment • Atezolizumab with bevacizumab, carboplatin and paclitaxel (for people whose tumours express PD-L1 with less than 50% tumour proportion score) • Pembrolizumab (for people whose tumours express PD-L1 with at least a 50% tumour proportion score) <p>For adults with squamous histology:</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 or without pemetrexed maintenance treatment • Pembrolizumab (for people whose tumours express PD-L1 with at least a 50% tumour proportion score)
Outcomes	<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>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.</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>If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (for example 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.</p>
<p>Other considerations</p>	<p>If evidence allows, subgroup analysis by level of PD-L1 expression 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>Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (2019) NICE technology appraisal 584. Review date June 2022.</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 appraisals guidance 190. Static guidance list.</p>

[Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin](#) (2016) NICE technology appraisal guidance 402. Review date April 2019.

[Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer](#) (2018) NICE technology appraisal guidance 531. Review data 2021.

[Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer](#) (2019) NICE technology appraisals guidance 557. CDF review expected June 2020.

[Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer](#) (2019) NICE technology appraisals guidance 600. CDF review expected August 2020.

Appraisals in development (including suspended appraisals):

[Avelumab for untreated PD-L1 positive non-small-cell lung cancer](#). NICE technology appraisal guidance [ID1261]. Publication date to be confirmed.

[Atezolizumab with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small-cell lung cancer](#). NICE technology appraisal guidance [TA618]. Terminated

[Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer](#). NICE technology appraisal guidance [ID1678]. Publication date to be confirmed

[Durvalumab for untreated EGFR-negative, ALK-negative non-small-cell lung cancer](#). NICE technology appraisal guidance [ID1331]. Publication date to be confirmed.

[Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK-positive mutations](#). NICE technology appraisal guidance [ID1143]. Publication date to be confirmed.

[Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer](#). NICE technology appraisal guidance [ID1187]. Suspended.

[Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small-cell lung cancer](#). NICE technology appraisal guidance [ID1135]. Suspended.

[Nivolumab monotherapy for non-small-cell lung cancer](#).

	<p>NICE technology appraisal guidance [ID1088]. Suspended.</p> <p>Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score. NICE technology appraisal guidance [ID1247]. Suspended.</p> <p>Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer. NICE technology appraisal guidance [ID1277]. Publication date to be confirmed.</p> <p>Related Guidelines:</p> <p>Lung cancer: diagnosis and management (2019). NICE guideline NG122.</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 (2019). NICE quality standard 17</p> <p>Related NICE Pathways:</p> <p>Lung cancer (2019) NICE pathway</p>
<p>Related National Policy</p>	<p>The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 105: Specialist cancer services (adults).</p> <p>Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1.</p>

Questions for consultation

Have all relevant comparators for nivolumab with ipilimumab and chemotherapy been included in the scope? Which treatments are considered to be established clinical practice in the NHS for metastatic, untreated, NSCLC?

Are the outcomes listed appropriate?

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

Where do you consider nivolumab with ipilimumab and chemotherapy will fit into the existing NICE pathway, [lung cancer](#)?

Draft scope for the appraisal of of nivolumab with ipilimumab and chemotherapy for untreated, metastatic non-small-cell lung cancer

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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 with ipilimumab and chemotherapy 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 with ipilimumab and chemotherapy 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 with ipilimumab and chemotherapy 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 technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

¹ [Lung cancer incidence by morphology](#). Cancer Research UK. Accessed March 2020

² Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. 2015 [Available from: https://seer.cancer.gov/csr/1975_2012/].

³ [National Lung Cancer Audit: Annual report 2017 \(for the audit period 2016\)](#) (2018). Royal College of Physicians. Accessed March 2020.

⁴ [Lung cancer mortality statistics \(2016\)](#). Cancer Research UK. Accessed March 2020.

⁵ [Lung cancer survival statistics \(2010-11\)](#). Cancer Research UK. Accessed March 2020.