

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab with ipilimumab within its marketing authorisation for untreated unresectable malignant pleural mesothelioma.

Background

Malignant pleural mesothelioma is a cancer affecting the membranes lining the outer surface of the lungs and the inside of the chest wall (the pleura). It is a highly aggressive tumour; the majority of people with this condition present and are diagnosed in the advanced stages of the disease and most have a poor prognosis.

In 2017 approximately 2,300 people were diagnosed with mesothelioma in England.¹ Mesothelioma is more common in men than women with 87% of diagnoses in England in 2017 in men.² Pleural mesothelioma accounts for approximately 90% of diagnoses and is linked to exposure to asbestos, with many cases of exposure to asbestos occurring in the workplace.³ People typically present with the condition 20 to 50 years after exposure, therefore the incidence rate is higher in older people, with around half of all diagnoses in the UK between 2013 and 2015 in people aged 75 and older.⁴

Mesothelioma can be divided into 3 histologic subtypes, epithelioid (about 60% of cases), sarcomatoid (10 to 20%) and a combination of epithelioid and sarcomatoid known as biphasic (about 30%).⁵ The survival of people with malignant pleural mesothelioma is typically around one year, with improved outcomes for people who have the epithelioid subtype or are surgically treated. People who have the sarcomatoid subtype have poorer outcomes overall with survival around 4 months, regardless of surgical status.⁶

The aim of treatment is to reduce tumour size and improve symptoms. Standard care includes chemotherapy and radiotherapy. NICE technology appraisal guidance 135 recommends [pemetrexed with cisplatin](#) as a treatment option for people with untreated malignant pleural mesothelioma for whom surgical resection is inappropriate. British Thoracic Society guidelines recommend carboplatin in combination with pemetrexed where cisplatin is contraindicated or has adverse risk. The guidelines also indicate that raltitrexed is an alternative to pemetrexed.⁴

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb) is a fully humanised IgG4 monoclonal antibody which targets and blocks the programmed cell death-1 receptor (PD-1), 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 in combination with ipilimumab does not currently have a marketing authorisation in the UK for the treatment of malignant pleural mesothelioma. It has been studied in a clinical trial compared with pemetrexed with cisplatin or carboplatin, in adults with untreated unresectable malignant pleural mesothelioma.

Intervention(s)	Nivolumab with ipilimumab
Population(s)	Adults with untreated unresectable malignant pleural mesothelioma
Comparators	<ul style="list-style-type: none"> • Pemetrexed with cisplatin • Raltitrexed with cisplatin (for people for whom treatment with pemetrexed is unsuitable) • Pemetrexed with carboplatin (for people for whom treatment with cisplatin is unsuitable) • Best supportive care
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	<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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.</p>

<p>Other considerations</p>	<p>If the evidence allows the following subgroups will be considered. These include:</p> <ul style="list-style-type: none"> • histologic subtype (epithelioid, sarcomatoid, biphasic) • level of programmed death-ligand 1 (PD-L1) expression <p>The availability and cost of biosimilar and generic products should be taken into account.</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 treatment of malignant pleural mesothelioma (2008). NICE Technology Appraisal Guidance 135. On static list, last reviewed: July 2017</p> <p>Terminated appraisals:</p> <p>Bevacizumab for untreated malignant pleural mesothelioma (terminated appraisal) (2017). NICE Technology Appraisal Guidance [ID1183]</p> <p>Appraisals in development (including suspended appraisals):</p> <p>Nintedanib for untreated malignant pleural mesothelioma. NICE technology appraisal guidance. Publication date to be confirmed</p> <p>Pegargiminase with pemetrexed and cisplatin for untreated advanced malignant pleural mesothelioma. NICE technology appraisal guidance. Publication date to be confirmed</p> <p>Related NICE Pathways:</p> <p>Respiratory conditions (2018) NICE Pathway</p>
<p>Related National Policy</p>	<p>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105: Specialist cancer services (adults).</p> <p>The NHS Long Term Plan, 2019. NHS Long Term Plan</p> <p>Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</p> <p>NHS England (2013) 2013/14 NHS Standard contract for cancer: malignant mesothelioma (adult) Ref: B10/S/a</p>

Questions for consultation

Have all relevant comparators for nivolumab with ipilimumab been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for malignant pleural mesothelioma?

- Is raltitrexed used in NHS clinical practice in people for whom pemetrexed is unsuitable?
- Is carboplatin used in the NHS in people for whom cisplatin is unsuitable?

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 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 with ipilimumab will fit into the existing NICE pathway, [Respiratory conditions](#) (2018)?

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 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 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 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. Office for National Statistics Cancer registration statistics, England (2017). Accessed July 2020. Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017>
2. Office for National Statistics (2019) Cancer registration statistics dataset, England (2017: Final) Accessed July 2020. Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland>
3. Cancer Research UK (2020) Mesothelioma incidence statistics. Accessed July 2020. Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/mesothelioma/incidence>
4. Woolhouse I, Bishop L, Darlison L et al. (2018) British Thoracic Society guideline for the investigation and management of malignant pleural mesothelioma. *Thorax* 73, Suppl. 1.
5. van Zandwijk N, Clarke C, Henderson D et al. (2013) Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. *Journal of Thoracic Disease* 5(6), E254–E307.
6. Meyerhoff RR, Yang CJ, Speicher PJ et al. (2015) Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. *Journal of Surgical Research* 196(1), 23–32.