NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma

Final scope

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.

Unlike other lung cancers, pleural mesothelioma is primarily occupation-related and is considered a preventable industrial injury. It accounts for approximately 89% of all mesothelioma diagnoses and is linked to exposure to asbestos, with many cases of exposure to asbestos occurring in the workplace.[1] Due to its association with heavy industry the incidence rates vary across England, with higher rates in areas of heavy industry including the North East and Southern England.[2] 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.[3] Because asbestos use was not banned completely in the UK until 1999,[4] the UK is currently experiencing its peak of expected incident cases of mesothelioma around 10 per 100,000 population.[1] Incidence rates of mesothelioma are projected to fall to 3 cases per 100,000 by 2035.[1] In 2017 approximately 2,300 people were diagnosed with mesothelioma in England.[5] Mesothelioma is more common in men than women with 87% of diagnoses in England in 2017 in men.[6]

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%).[7] 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.[8]

The primary aim of treatment is to prolong life expectancy. Treatment also aims 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.[3] The guidelines also indicate that raltitrexed is an alternative to pemetrexed. For people who are not fit enough to receive chemotherapy, best supportive care is used to control disease symptoms.

There is no current standard for best supportive care in pleural mesothelioma. Symptoms management is based on current guidelines for cancer in general.[3]

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	• 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 (Raltitrexed does not have a marketing authorisation in the UK for this indication)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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 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.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • histologic subtype (epithelioid, sarcomatoid, biphasic) • level of programmed death-ligand 1 (PD-L1) expression The availability and cost of biosimilar and generic products should be taken into account. 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: Pemetrexed for the treatment of malignant pleural mesothelioma (2008). NICE Technology Appraisal Guidance 135. On static list, last reviewed: July 2017 Terminated appraisals: Bevacizumab for untreated malignant pleural mesothelioma (terminated appraisal) (2017). NICE Technology Appraisal Guidance [ID1183] Appraisals in development (including suspended appraisals): Nintedanib for untreated malignant pleural mesothelioma. NICE technology appraisal guidance. Publication date to be confirmed Pegargiminase with pemetrexed and cisplatin for untreated advanced malignant pleural mesothelioma. NICE technology appraisal guidance. Publication date to be confirmed

	Related NICE Pathways: Respiratory conditions (2018) NICE Pathway
Related National Policy	NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 105: Specialist cancer services (adults). The NHS Long Term Plan, 2019. NHS Long Term Plan 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 NHS England (2013) 2013/14 NHS Standard contract for cancer: malignant mesothelioma (adult) Ref: B10/S/a

References

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3. 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.

4. Mesothelioma UK (Publication year not reported) About Mesothelioma. Accessed September 2020. Available at: https://www.mesothelioma.uk.com/information/about-mesothelioma/

5. 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

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7. 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.

8. 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.