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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Nivolumab in combination with ipilimumab for malignant pleural mesothelioma – first line

NIHRIO ID	13149	**NICE ID**	9585
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	643142

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Nivolumab in combination with ipilimumab is in development as first-line treatment in adult patients with unresectable malignant pleural mesothelioma (MPM). MPM is rare a type of cancer that affects the outer linings of the lungs and the internal chest wall. Mesothelioma is often diagnosed at an advanced stage and surgery is not always possible. Treatment is usually given to keep symptoms under control (palliative care) for as long as possible, although patients tend to respond poorly to current chemotherapy and radiation therapy.

Nivolumab works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab works in a different way but also to increase the activity of T-cells. It is thought that when used in combination, both drugs may be more effective than each drug on its own. Both drugs given by injection are already used in combination to treat advanced cancers in the kidney and skin. If licenced, nivolumab in combination with ipilimumab has the potential to improve long-term outcomes in MPM patients who currently have limited first-line treatment options.

PROPOSED INDICATION

Malignant pleural mesothelioma (unresectable) – first line[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo; BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Ipilimumab (Yervoy; BMS-734016) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoral T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is in development as first-line treatment in patients with unresectable malignant pleural mesothelioma (MPM). In the phase III trial (NCT02899299; CheckMate 743), subjects receive nivolumab at a concentration of 10 mg/mL solution for injection/infusion and ipilimumab at a concentration of 5 mg/mL solution for intravenous (IV) infusion at a specified dose on specified days. Duration of treatment was not reported on the trial registry.[4]

INNOVATION AND/OR ADVANTAGES

There is no recommended therapy for MPM that has evolved beyond first-line pemetrexed and platinum-based chemotherapy. Furthermore, no targeted immunotherapies or dual immunotherapies have been approved for MPM indications. [5, 6]

Phase I and II data suggest that targeting immune checkpoint pathways (e.g., programmed death [PD]-1/PD-ligand 1 [PD-L1] and/or cytotoxic T-lymphocyte antigen-4 [CTLA-4]) may provide benefit with acceptable safety in MPM.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with ipilimumab is licensed in the EU/UK for the treatment of advanced (unresectable or metastatic) melanoma in adults and for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma. The most common adverse reactions (≥ 1/10) associated with treatment with nivolumab in combination with ipilimumab are: hypothyroidism, decreased appetite, headache, dyspnoea, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue and pyrexia. [3]

Nivolumab in combination with ipilimumab is currently in development for the treatment of various types of cancers including NSCLC, breast, ovarian, and gastric.[8]

PATIENT GROUP

DISEASE BACKGROUND

Mesothelioma (malignant mesothelioma) is a form of cancer that affects the mesothelium (the lining that covers the outer surface of some of the body's organs). Mesothelioma that affects the pleura (outer lining of the lungs and internal chest wall) is called pleural mesothelioma. Pleural mesothelioma is the most common form of mesothelioma.[9,10,11] Mesothelioma is also grouped according to how the cells look under a microscope. These are epithelioid, biphasic, sacromatoid, and desmoplastic.[12]

Mesothelioma is almost always caused by exposure to asbestos.[10] Current evidence suggests that around 85% of all mesotheliomas that occur in males are attributable to asbestos exposures that occurred in occupational settings. The long latency period (i.e. the time between initial exposure to asbestos and the manifestation of the disease) is typically at least 30 years, which means that most mesothelioma deaths occurring today are a result of past exposures that occurred because of the widespread industrial use of asbestos during 1950-1980.[13]

Pleural mesothelioma causes the pleura to thicken. This thickening of the pleura may begin to press onto the lungs or attach to the inside of the chest wall. In either case the expansion of the lung becomes progressively restricted by the tumour. Fluid, sometimes several litres, can collect between the two layers of the pleura; this affects the lungs ability to expand and causes the person to feel breathless. This is known as a pleural effusion.[9] Symptoms of pleural mesothelioma include chest pain, shortness of breath, fatigue, fever and sweating, persistent cough, loss of appetite and unexplained weight loss, and swollen fingertips.[9,10]

Mesothelioma is often diagnosed at an advanced stage.[10] Different systems have been established for staging mesothelioma. The staging system most commonly used in the UK for pleural mesothelioma is called the International Mesothelioma Interest Group (IMIG) system. Stage 1 is the earliest stage and stage 4 is the most advanced stage where the cancer cannot be removed by surgery because it has spread to distant organs or tissues or invaded deeply into tissues close to the pleura.[9,12]

CLINICAL NEED AND BURDEN OF DISEASE

Due to the short average survival time following a diagnosis of mesothelioma, incidence and mortality data are more reliable than prevalence data in depicting trends. In 2012, an estimated 5,400 people were living with mesothelioma in the UK.[14] The worldwide incidence of the disease continues to increase; in Western Europe, more than 5,000 new cases per year are estimated to occur, with more than a quarter of a million deaths expected to occur over the next 40 years.[15]

There were 2,595 mesothelioma deaths (2,197 males; 398 females) in Great Britain in 2016, broadly similar to the previous four years. The latest projections suggest that there will continue to be around 2,500 deaths per year for the rest of this current decade before annual numbers begin to decline. The continuing increase in annual mesothelioma deaths in recent years has been driven mainly by deaths among those aged 70 years and above.[13]

With the 20–50 year lag between exposure to asbestos and the development of MPM, estimates of the likely burden of disease suggest that numbers of cases in the UK are likely to peak between 2020

and 2025.[16] In England in 2017 there were 9,418 finished consultant episodes (FCEs) of mesothelioma (ICD-10 code C45) resulting in 19,140 FCE bed days.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no standard treatment pathway for MPM in England and Wales. The clinical management is multimodal and a patient may receive a combination of treatments. A multidisciplinary team will discuss the best treatment options. The main treatment of advanced MPM is chemotherapy to help shrink the cancer. Radiotherapy may be used to shrink the cancer, slow down its growth, or control symptoms.[10, 18] MPMs are most often surgically unresectable, and they respond poorly to current chemotherapy and radiation therapy.[19]

MPM is often found when it is advanced. Nearly all treatment aims to control MPM for as long as possible and keep symptoms under control (palliative care). The patient may also have treatment for their individual symptoms to help them feel as comfortable as possible. For example, regularly draining fluid from the chest may help the patient's breathing and strong painkillers may help relieve the pain. Sometimes, a procedure is carried out to stop the fluid coming back again by making the outside of the lungs stick to the inside of the chest (pleurodesis), or a tube is put in the chest to drain the fluid regularly at home. [10]

Given the symptom burden associated with a mesothelioma diagnosis, timely referral to specialist palliative care or pain management is advisable (regional access may vary). Referral to centres offering access to cordotomy for pain management should correspondingly be considered.[16]

CURRENT TREATMENT OPTIONS

Pemetrexed is licensed in the UK for the treatment of unresectable MPM which has not previously been treated with chemotherapy (in combination with cisplatin).[20]

NICE recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate. Patients currently receiving pemetrexed who do not fall into the patient population as defined above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.[6]

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab will offer an additional first line treatment option for MPM patients who currently have few well-tolerated effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 743, NCT02899299, EudraCT 2016-001859-43; nivolumab combined with ipilimumab vs pemetrexed and cisplatin or carboplatin; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing

Source of Information	Abstract[7], Trial registry[1,4]
Location	EU (incl UK), USA, and other countries
Design	Randomised, active-controlled, parallel assignment, open label
Participants	n=600 (planned); males and females ≥18 years of age; histologically confirmed pleural malignant mesothelioma not eligible for curative surgery; ECOG Performance status of 0 or 1; available tumour sample for testing; acceptable blood work
Schedule	**Experimental: nivolumab + ipilimumab** • Subjects receive nivolumab at a concentration of 10 mg/mL solution for injection/infusion and ipilimumab at a concentration of 5 mg/mL solution for infusion (IV) at a specified dose on specified days. **Active comparator: pemetrexed and cisplatin or carboplatin** • Subjects receive pemetrexed and cisplatin (or carboplatin) intravenously (IV) at a concentration of 1 mg/mL at a specified dose on specified days Duration of treatment was not reported on the trial registry.
Follow-up	Not reported.
Primary Outcomes	• Overall Survival (OS) [Time Frame: 3.5 years] • Progression Free Survival (PFS) [Time Frame: 3.5 years]
Secondary Outcomes	• Objective Response Rate (ORR) [Time Frame: 3 years] • Disease Control Rate (DCR) [Time Frame: 3 years] • Composite correlation of PD-L1 expression level and efficacy [Time Frame: 3 years] ○ Efficacy determined by the ORR, PFS, and OS
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date Oct 2020. Estimated study completion date Sep 2021.

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg/10mL concentrate for solution for infusion vial costs £1,097, a 240mg/24mL concentrate for solution for infusion vial costs £2,633, and a 40mg/4ml concentrate for solution for infusion vial costs £439.[21]

Ipilimumab (Yervoy) is already marketed in the UK; a 200mg/40mL concentrate for solution for infusion vial costs £15,000 and a 50mg/10mL concentrate for solution for infusion vial costs £3,750.[22]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nintedanib for untreated malignant pleural mesothelioma (ID1424). Expected date of issue to be confirmed.
- NICE technology appraisal. Pemetrexed for the treatment of malignant pleural mesothelioma (TA135). January 2008.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Malignant Mesothelioma (Adult). B10/S/a.

OTHER GUIDANCE

- Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2015[23]
- Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma, 2010[24]

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