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EVIDENCE BRIEFING
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Nivolumab in combination with ipilimumab in addition to chemotherapy for treating non-small cell lung cancer – first line

NIHRIO ID	18297	**NICE ID**	9779
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	646305

Licencing and market availability plans	Nivolumab in combination with ipilimumab in addition to chemotherapy is in phase III clinical trials for the first line treatment of non-small cell lung cancer

SUMMARY

Nivolumab in combination with ipilimumab in addition to standard of care chemotherapy is in clinical development for the treatment of metastatic (stage 4) non-small cell lung cancer (NSCLC). NSCLC accounts for the majority of lung cancer cases. The main symptoms of NSCLC include persistent cough, shortness of breath and coughing up blood. Factors increasing the risk of developing lung cancer include smoking tobacco, radiation and chemical exposure, previous lung disease, family history of lung cancer and certain genetic mutations.

Nivolumab works by binding to a receptor called programmed death-1 (PD-1) receptor, which blocks the proteins PD-L1 and PD-L2 from interacting with it. This stimulates immune cells to attack tumours, slowing their growth. Ipilimumab works in the same way but by blocking the effect of a different protein, CTLA-4. It is thought these drugs in combination may result in an improved or greater anti-tumour effect. If licenced, Nivolumab in combination with ipilimumab in addition to standard of care chemotherapy would provide an additional first-line treatment option for patients with metastatic NSCLC.

PROPOSED INDICATION

Stage 4 non-small cell lung cancer – first line[1]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo) 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) 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]

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.[2]

Nivolumab and ipilimumab in combination with chemotherapy is currently in development for the treatment of stage 4 non-small cell lung cancer (NSCLC) as a first line therapy. In the phase III clinical trial (CheckMate9LA, NCT03215706), participants received nivolumab and ipilimumab in addition to standard of care chemotherapy, including carboplatin, paclitaxel, pemetrexed and cisplatin.[1]

INNOVATION AND/OR ADVANTAGES

Previous results from the CheckMate 227 trial showed that the combination of nivolumab and ipilimumab improved progression free survival compared to chemotherapy as a first-line treatment for patients with advanced NSCLC and a high tumour mutational burden.[4] Therefore the combination of nivolumab plus ipilimumab and chemotherapy may also be effective in improving survival (although there are no results available from the trial, Checkmate 9LA, as of yet) and may provide an additional first line treatment option for those with NSCLC.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with ipilimumab is currently licenced for the treatment of advanced (unresectable or metastatic) melanoma in adults.[2]

The most common adverse reactions (affecting more than one in ten people) 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.[2]

Nivolumab in combination with ipilimumab is currently in development for the treatment of various types of cancers including breast, ovarian and gastric cancers.[5]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main histologic types: small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC).[6] NSCLC comprises approximately 87% of lung cancers in the UK. There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[7] NSCLC can be graded to give an idea of how quickly the cancer may grow and whether it is likely to spread. NSCLC is graded from stages 1 to 4,[8] with stage 4 indicating cancer which has spread to other areas and organs.[9]

Certain factors can increase the risk of developing lung cancer, including; smoking tobacco, exposure to radiation (by exposure to radon gas and previous radiotherapy treatment), exposure to certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes), previous lung disease (e.g. tuberculosis and COPD), family history of lung cancer and certain genetic mutations and lowered immunity (e.g. due to certain conditions e.g. HIV/AIDS, rheumatoid arthritis and systemic lupus erythematosus, or immunosuppressive medications).[10]

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2015. Age standardised incidence rates of lung cancer in England in 2015 was 76 per 100,000.[12] In 2012 there were 85,000 people living in the UK with a lung cancer diagnosis including people living with the condition, those in remission and those who have been cured.[13] According to the National Cancer Registration and Analysis Service (NCRAS), there were 7299 diagnosed cases of stage 4 lung cancer in 2016. [14] NSCLC comprises of 87% lung cancer cases in the UK[7], so if this figure is applied to the number of stage 4 lung cancer cases, it can be estimated there are approximately 6350 people with diagnosed stage 4 NSCLC in 2016.

Survival rates for lung cancer depend on at which stage of disease the cancer is identified. Survival statistics from an area of England in 2002-2006 reported one year survival statistics as 20% and five year survival as unknown for stage 4 lung cancer.[15]

In England and Wales in 2017 there were 30,131 deaths with malignant neoplasm of trachea, bronchus and lung (ICD-10 codes C33-34) recorded as the underlying cause.[16]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. The main treatment options for stage 1, 2 and 3 NSCLC are surgery, chemotherapy and radiotherapy. Stage 4 NSCLC treatment generally includes chemotherapy, immunotherapy, radiotherapy and symptom control management.[17]

CURRENT TREATMENT OPTIONS

Metastatic NSCLC[18, 19, 20]

- First line:
  - Chemotherapy in combination with a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin).
  - A single third generation drug alone can be offered to those who cannot tolerate platinum therapies.
  - Afatinib – for EGFR-TK mutation positive advanced NSCLC who have not received a EGFR-TK inhibitor
  - Alectinib - for untreated ALK positive NSCLC (according to commercial arrangement)
  - Ceritinib – for untreated ALK positive advanced NSCLC (with discount agreed in the patient access scheme)
  - Crizotinib – for ROS-1 positive NSCLC (use within Cancer Drugs Fund)
  - Erlotinib – for EGFR-TK mutation positive NSCLC
  - Gefitinib – for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation positive NSCLC (under fixed price agreement)
  - Pemetrexed in combination with cisplatin – for NSCLC with a confirmed histology of adenocarcinoma or large cell carcinoma
  - Pembrolizumab monotherapy - for people whose tumours express PD-L1 with at least a 50% tumour proportion score and without EGFR mutation or ALK translocation

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab in addition to standard of care chemotherapy will offer an additional first line treatment option for patients with stage 4 NSCLC.

CLINICAL TRIAL INFORMATION	
Trial	**CheckMate 9LA, NCT03215706, 2017-001195-35; nivolumab and ipilimumab in combination with chemotherapy vs chemotherapy only; phase III**
Sponsor	Bristol-Myers Squibb Pharmaceuticals Ltd
Status	Ongoing
Source of Information	Trial registry[1, 21]
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, open label, parallel assignment
Participants	n=700 (planned); aged 18 years and older; NSCLC; stage 4 or recurrent; no prior systemic anticancer therapy
Schedule	Participants were randomised to one of two treatment arms: 1. Experimental arm: participants were given nivolumab in combination with ipilimumab in addition to standard of care chemotherapy including carboplatin, paclitaxel, pemetrexed and cisplatin 2. Active comparator arm: participants were given standard of care chemotherapy including carboplatin, paclitaxel, pemetrexed and cisplatin
Follow-up	Follow up for up to 25 months
Primary Outcomes	• Overall survival (OS) [time frame: up to 25 months] – experimental vs active comparator arm
Secondary Outcomes	• Progression free survival (PFS) [time frame: up to 25 months] – experimental vs active comparator arm • Overall response rate (ORR) [time frame: up to 25 months] – experimental vs active comparator arm • ORR [time frame: up to 25 months] - in participants with different PD-L1 levels • PFS [time frame: up to 25 months] - in participants with different PD-L1 levels • OS [time frame: up to 25 months] - in participants with different PD-L1 levels • ORR [time frame: up to 25 months] - in association with tumor cell total somatic mutation numbers • PFS [time frame: up to 25 months] - in association with tumor cell total somatic mutation numbers • OS [time frame: up to 25 months] - in association with tumor cell total somatic mutation numbers
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as May 2020

ESTIMATED COST

Nivolumab is already marketed in the UK; a 100mg/10ml concentrate for solution for infusion vials (10mg/ml) costs £1,097.[22]

Ipilimumab is already marketed in the UK for the treatment of advanced melanoma; a 200mg/40ml concentrate for solution for infusion vials (5mg/ml) costs £15,000.[23]

ADDITIONAL INFORMATION

Bristol-Myers Squibb Pharmaceuticals Ltd

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer (ID1277). Expected publication date TBC.
- NICE technology appraisal guidance in development. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (ID1306). Expected publication date 4 July 2019.
- NICE technology appraisal guidance in development. Nivolumab with ipilimumab for untreated non-small-cell lung cancer that has a high tumour mutational burden (ID1187). Expected publication date 02 May 2019.
- NICE technology appraisal guidance in development. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (ID1173). Expected publication date 13 March 2019.
- NICE technology appraisal guidance. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal guidance. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal guidance. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal guidance. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

- NHS England. Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. NHS England: 16024/P. July 2016.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). NHSCB/B01/P/a. April 2013.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[24]
- European Society for Medical Oncology. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. 2016.[25]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[26]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[27]

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