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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Nivolumab in combination with ipilimumab for early stage non-small cell lung cancer - neoadjuvant

NIHRIO ID	24006	**NICE ID**	10296
Developer/Company	Bristol-Meyers Squibb Pharmaceuticals Ltd	**UKPS ID**	Not Available

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

SUMMARY

Nivolumab in combination with ipilimumab is in clinical development as a neoadjuvant treatment for early stage (stage IB-IIIA), resectable non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Early stage lung cancer is typically treated with surgery consisting of removing either part of the affected lung or the whole lung, followed by chemotherapy and/or radiotherapy. However, the long-term outlook for patients undergoing this treatment pathway is still poor. Neoadjuvant therapy, which is administered prior to surgery to reduce the tumour size, may provide better long-term survival prospects for patients with early-stage operable NSCLC.

Nivolumab is a medicinal product called an immune checkpoint inhibitor. It works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab has a different mode of action but also increases the activity of T-cells against the cancer cells. If licensed, nivolumab in combination with ipilimumab may offer an additional treatment option for patients with early-stage, operable NSCLC.

PROPOSED INDICATION

Neoadjuvant treatment of early stage (IB-IIIA), operable non-small cell lung cancer (NSCLC).[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 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 the ligands 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. 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. CTLA-4 is a key regulator of T-cell activity 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 currently in development for the treatment of early stage, resectable NSCLC. In the phase III clinical trial (CheckMate 816, NCT02998528), participants received nivolumab and ipilimumab, the regimen was not specified.[1]

INNOVATION AND/OR ADVANTAGES

The addition of adjuvant chemotherapy to surgery only provides a 5% absolute overall survival (OS) benefit at 5 years. Neoadjuvant treatment with immunotherapy may extend OS in early stage NSCLC by enhancing systemic immunity and eradicating micrometastatic disease. In contrast to the adjuvant setting, the neoadjuvant setting is associated with a higher tumour burden, the presence of abundant tumour antigens, and the consequent potential for tumour-associated neoantigen presentation to the immune system.[4]
Also nivolumab in combination with ipilimumab has been seen to be effective in the first line treatment of advanced NSCLC, showing a better response rate than nivolumab monotherapy and longer overall survival than chemotherapy alone.[5]
If licensed, nivolumab in combination with ipilimumab will offer a neoadjuvant treatment option for those with early-stage NSCLC who currently have few well tolerated and effective therapies available.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab as a monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy.[2] Nivolumab in combination with ipilimumab is currently licenced for the treatment of advanced (unresectable or metastatic) melanoma and advanced renal cell carcinoma in adults.[2] Neither are indicated (in combination nor as monotherapy) as neoadjuvant treatment for any indication.

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 clinical development for the treatment of various types of cancers including renal, breast, ovarian and gastric cancers.[6]

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). 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). NSCLC is graded from stages I to IV:[7]
Stage I: the cancer is small and is contained inside the lung. It has not spread to lymph nodes.
Stage IIA: the cancer is between 4cm and 5cm in size but has not spread to any lymph nodes.
Stage IIB:

- the cancer is up to 5cm in size and has spread into nearby lymph nodes or
- the cancer is between 5cm and 7cm but has not spread into any lymph nodes or
- there is more than one area of cancer in one lobe of the lung or
- the cancer has spread into structures close to the lung

Stage III: the cancer is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest.
Stage IV: the cancer has spread to the other lung or to a distant part of your body such as the liver or bones.

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).[8]

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.[9]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer was the third most common cancer in the UK in 2016, accounting for 13% of all new cancer cases, with an incidence rate in the UK of 72.2 per 100,000. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2014-2016). Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[10]

In 2017, there were 38,888 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[11] According to the National Cancer Registration and Analysis Service (NCRAS), 18,175 of these cases were stage I-III lung cancer, representing 46.7% of all

diagnosed cases for that year.[12] In the UK it is estimated that up to 87% of lung cancer cases are NSCLC, applying this figure to the number of stage I-III lung cancer cases diagnosed in 2017,[11] it can be estimated that approximately 15,812 cases were NSCLC.[13]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[14]

Survival rates for lung cancer depend on factors including at which stage of disease the cancer is identified.[15] In England between 2013 to 2017 the age-standardised net lung cancer survival rate at 1-year for stage I, II and III were 87.7%, 73.0% and 48.7% respectively. The age-standardised net cancer survival rate at 5-years for stage I, II and III were 56.6%, 34.1% and 12.6% respectively.[16]

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.[17] In 2018 there were 29,602 registrations of death from malignant neoplasms of bronchus and lung in adults in England and Wales (ICD-10 code C34).[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for NSCLC differs by stage. For stage I and II NSCLC, the main treatment option is surgery, consisting of either a lobectomy (removal of part of your lung) or a pneumonectomy (removal of all of the lung), potentially followed by adjuvant chemotherapy. For patients that are not well enough to undergo surgery, treatment consists of either radiotherapy or radiofrequency ablation. For stage III NSCLC, surgery is carried out if the surgeon deems the tumour to be excisable, potentially followed by chemotherapy and/or radiotherapy. If surgery is not possible, patients may undergo treatments including chemotherapy or radiotherapy.[19]

CURRENT TREATMENT OPTIONS

NICE currently recommends that people with stage I–II NSCLC that are suitable for surgery are not offered neoadjuvant treatment outside a clinical trial.[20]
NICE recommends:

- NSCLC patients who are well enough and for whom treatment with curative intent is suitable, lobectomy is offered.
- Stage I–IIA NSCLC patients who decline or cannot have surgery are offered radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection. If SABR is not appropriate for the patient they may receive either conventional or hyperfractionated radiotherapy.
- Patients with stage IIIA NSCLC who cannot tolerate or who decline chemoradiotherapy (with or without surgery), may receive radical radiotherapy (either conventional or hyperfractionated).[20]

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with ipilimumab will offer a neoadjuvant treatment option for patients with early stage operable NSCLC who currently have few well tolerated and effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 816, NCT02998528, EudraCT2016-003536-21;** Randomized, Open Label, Phase 3 Trial of Nivolumab Plus Ipilimumab or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Early Stage NSCLC **Phase III** **Location:** EU (not including UK), USA, Canada and other countries.
Trial design	Randomised, open label, parallel assignment
Population	N=350 (planned); aged ⩾18 years; NSCLC; Early stage IB-IIIA.
Intervention(s)	10 mg/ml doses of nivolumab plus 5mg/ml of ipilimumab.
Comparator(s)	Platinum doublet chemotherapy alone and 10mg/ml doses of nivolumab plus platinum doublet chemotherapy.
Outcome(s)	Primary outcome: • Event-Free Survival [Time frame: up to 69 months] • Pathological Complete Response [Time frame: at the time of surgery] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[21]

- Opdivo 100mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £1097.00 (Hospital only)
- Opdivo 240mg/24ml concentrate for solution for infusion (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £2633.00 (Hospital only)
- Opdivo 40mg/4ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £439.00 (Hospital only).

Ipilimumab (Yervoy) is already marketed in the UK. The NHS indicative price for ipilimumab solution for infusion is as follows:[22]

- Yervoy 200mg/40ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £15000.00 (Hospital only)
- Yervoy 50mg/10ml concentrate for solution for infusion vials (1 vial) (Bristol-Myers Squibb Pharmaceuticals Ltd) costs £3750.00 (Hospital only)

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. Nivolumab in combination with platinum-doublet chemotherapy for untreated non-small-cell lung cancer (ID1135). Expected publication date TBC.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019. NICE quality standard. Lung cancer in adults (QS17). March 2012 (Last updated December 2019).

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

- European Society for Medical Oncology. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[23]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[24]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[25]

ADDITIONAL INFORMATION

Bristol Meyers Squib did not create a UK PharmaScan for this record however it is linked to ID 653921 which describes the other arm of the pivotal trial, nivolumab plus platinum doublet chemotherapy.

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