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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

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

NIHRIO ID	28077	**NICE ID**	10307
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	653921

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

SUMMARY

Nivolumab in combination with chemotherapy is in clinical development as a neoadjuvant treatment for early-stage (stage IB-IIIA) operable 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 or the whole of the lung, followed by chemotherapy and/or radiotherapy (adjuvant). However, the long-term outlook for patients undergoing this treatment pathway is still poor. Treatment with medicines prior to surgery (neoadjuvant) 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 is administered by intravenous infusion (injection into the vein) and works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Nivolumab as a monotherapy is already licensed for a range of advanced cancers where it has shown treatment benefits. If licensed in combination with chemotherapy, it may offer an additional neoadjuvant treatment option for patients with early-stage, operable NSCLC who currently have few well tolerated and effective therapies available.

PROPOSED INDICATION

The 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 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[2]

Nivolumab in combination with chemotherapy is being developed as a neoadjuvant treatment for early-stage, operable NSCLC.[1] In the phase III clinical trial (NCT02998528; CheckMate 816), patients in the experimental arm are given nivolumab in combination with platinum doublet chemotherapy every 3 weeks for a maximum period of 6 weeks until resection surgery.[1]

INNOVATION AND/OR ADVANTAGES

At initial diagnosis, 20% of patients with NSCLC present with early-stage disease. The 5-year overall survival (OS) rate after surgery for stage IB–IIIA NSCLC is 25%–60%. Addition of adjuvant chemotherapy to surgery only provides a 5% absolute OS benefit at 5 years. Neoadjuvant treatment with immune checkpoint inhibitors may extend OS in early-stage NSCLC by enhancing systemic immunity and eradicating micrometastatic disease.[3] Removal of micrometastatic disease is thought to reduce the chance of disease recurrence.[4] In contrast to the adjuvant setting, the neoadjuvant setting is also 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.[3]

In an ongoing feasibility trial in patients with stage IB–IIIA NSCLC, nivolumab given alone as neoadjuvant treatment induced a major pathological response (MPR; < 10% residual viable tumour cells) rate of 39% (7/18), did not delay or interfere with surgery, and was not associated with new safety signals.[3] Although conventional chemotherapy directly targets tumour cell replication strategies, preclinical evidence demonstrates that chemotherapeutic agents are less effective in immunodeficient hosts, suggesting the antitumour effects of cytotoxic chemotherapy also occur through modulation of the immune system. The immunogenic properties of conventional chemotherapy and rapid emergence of chemotherapy resistance provide a good rationale for combining platinum doublet chemotherapy with immunotherapy, particularly immune checkpoint inhibitors.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab as monotherapy is licenced in the UK for the treatment of a range of advanced cancers including melanoma, renal carcinoma, NSCLC, etc.[2]

The most common side effects with nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[6]

Nivolumab plus chemotherapy is in phase II and phase III clinical development for a range of conditions including gastric cancer, stomach cancer, urothelial cancer, colorectal cancer, pancreatic cancer and various advanced solid tumours.[7]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC is the most common type of lung cancer in the UK, accounting for 87 out of 100 (87%) of lung cancers.[8] The stages of lung cancer are as follows:[9]

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.

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of lung cancers. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and is reaching a plateau for women. An increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries. These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified.[10]

Several other factors have been described as lung cancer risk factors including; exposure to radiation certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g. tuberculosis and chronic obstructive pulmonary disease). Other factors include family history of lung cancer and certain genetic mutations.[11]

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 phlegm with blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[12]

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[10] Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2016. There are around 47,200 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (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.[13]

In England in 2017, there were 38,888 newly diagnosed cases of malignant neoplasm of the bronchus and lung (ICD-10 code C34).[14] 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 cases for that year.[15] 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, it can be estimated that approximately 15,812 cases were NSCLC.[8]

Survival rates for lung cancer depend on factors including at which stage of disease the cancer is identified.[16] In England between 2013 to 2017 the age-standardised net 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.[17]

There are around 35,300 lung cancer deaths in the UK every year. Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035 to 58 deaths per 100,000 people by 2035.[18] 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.[19]

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 the 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 immunotherapy, chemotherapy or radiotherapy.[9]

For people with stage I–II NSCLC that are suitable for surgery, neoadjuvant treatment is not currently recommended by NICE outside a clinical trial.[20] As neoadjuvant chemotherapy has shown equivalent outcomes in terms of overall survival (OS) to adjuvant chemotherapy, consistent results and broad evidence base support adjuvant chemotherapy as the timing of choice.[21]

CURRENT TREATMENT OPTIONS

There are currently no recommended neoadjuvant treatments for early-stage (IB-IIIA) NSCLC.

PLACE OF TECHNOLOGY

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

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 816; NCT02998528; 2016-003536-21; adults aged 18 years and older; nivolumab plus chemotherapy vs chemotherapy alone; phase III.**
Sponsor	Bristol-Myers Squibb.
Status	Ongoing.
Source of Information	Trial registry[1,22], abstract[3].
Location	EU (not incl. UK), USA, Canada and other countries.
Design	Randomised, open label.
Participants	N=350 (planned); aged ≥18; early-stage IB-IIIA operable NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; lung function capacity capable of tolerating the proposed lung surgery.
Schedule	Participants were randomised to:[a] • Nivolumab plus platinum doublet chemotherapy (PDC) every 3 weeks for a maximum of 6 weeks (≤3 doses). • Investigators choice PDC, every 3 weeks for a maximum of 6 weeks (≤3 doses). Following surgery, patients received adjuvant chemotherapy with or without radiation at investigator discretion.
Follow-up	Active treatment until surgery, follow-up up to approximately 193 months.
Primary Outcomes	• Event-Free Survival (EFS) [Time frame: up to 69 months] • Pathological Complete Response (pCR) [Time frame: at the time of surgery]
Secondary Outcomes	• Overall survival (OS) [Time frame: up to approximately 193 months] • Major pathological response (MPR) [Time frame: at time of surgery] • Time to Death or Distant Metastases (TTDM) [Time frame: up to 69 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date for primary outcome measures: May 2023.[a]

[a] Information provided by Bristol-Myers Squibb

ESTIMATED COST

Nivolumab is already marketed in the UK. The NHS indicative price for nivolumab solution for infusion is as follows:[23]

- 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).

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 (TA10233). Expected publication date TBC.
- NICE technology appraisal guidance. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal guidance. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
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- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
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- NICE quality standard. Lung cancer in adults (QS17). March 2012.

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. Clinical Commissioning Policy: Robotic-assisted lung resection for primary lung cancer. 16024/P. July 2016.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). 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.[21]

ADDITIONAL INFORMATION

This briefing is linked to ID 10296 which describes the other arm of the pivotal trial, nivolumab plus ipilimumab.

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