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HEALTH TECHNOLOGY BRIEFING
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Atezolizumab in combination with chemotherapy for non-small-cell lung cancer-neoadjuvant and adjuvant

NIHRIO ID	24042	**NICE ID**	10175
Developer/Company	Roche Products Ltd	**UKPS ID**	656130

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

SUMMARY

Atezolizumab in combination with chemotherapy is in clinical development as a neoadjuvant and adjuvant treatment for stage II, IIIA, or select IIIB 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) and adjuvant (treatment after primary treatment) may provide better long-term survival prospects and reduce the risk of disease recurrence for patients with resectable NSCLC.

Atezolizumab is a type of protein called an antibody, which can bind to a protein called programmed death-ligand 1 (PD-L1) to prevent it from interacting with its target (PD-1). Thus, helping immune cells kill cancer cells and is used to treat many different types of cancer that express PD-L1. If licensed, atezolizumab would offer a neoadjuvant and adjuvant treatment option for patients with stage II, IIIA, or select IIIB NSCLC.

PROPOSED INDICATION

Neoadjuvant and adjuvant therapy for stage II, IIIA, or select IIIB non-small-cell lung cancer (NSCLC).[a]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is a monoclonal antibody and immune checkpoint inhibitor. Atezolizumab binds to programmed death-ligand 1 (PD-L1) to help immune cells kill cancer cells and is used to treat many different types of cancer that express PD-L1.[1] Programmed death 1 (PD-1) and its ligands PD-L1 and PD-L2 are key co-inhibitory molecules in the modulation of T-cell mediated immune responses. PD-1 is a type I membrane protein that is expressed on the surface of activated T cells in peripheral tissues. PD-L1 and PD-L2 are commonly expressed on dendritic cells and macrophages. Ligation of PD-1 with its two ligands initiates co-inhibitory signalling through the cytoplasmic domain of PD-1, leading to activation of SHP phosphatases that downregulate T-cell receptor signalling by dephosphorylating effector molecules involved in the signalling. As a result, PD-1 signalling prevents excessive or harmful inflammation and maintains immune tolerance to self-antigens under normal conditions.[2]

Atezolizumab in combination with chemotherapy is in clinical development for the treatment of patients with resectable stage II, IIIA, or select IIIB NSCLC. In the phase III clinical trial, (IMpower030; NCT03456063), patients will be administered neoadjuvant treatment of 4 cycles; atezolizumab (1200 mg) and platinum-based chemotherapy. Post-operative adjuvant treatment will consist of 16-cycles of atezolizumab (1200 mg) every 3 weeks.[3]

INNOVATION AND/OR ADVANTAGES

Both neoadjuvant and adjuvant chemotherapy has been shown to improve survival of patients with early-stage surgically resectable NSCLC, with no significant differences in terms of either disease-free or overall survival between the two strategies. However, in routine clinical practice, adjuvant chemotherapy is often preferred to the neoadjuvant approach, mainly because of the fear that, if treatment-related complications arise during neoadjuvant chemotherapy, surgery may be delayed to a point that is no longer feasible because of rapid tumour progression. However, there are a few issues favour the use of neoadjuvant therapy include early cure of micrometastatic disease, better chemotherapy drug delivery and tolerability, ability to assess sensitivity to treatment, and acquisition of prognostic information based on whether a major pathologic response ($\leqslant$10% of residual viable tumour at pathologic examination) has occurred.[4]

The preliminary results of phase 2 clinical trial (LCMC3; NCT02927301) seemed to confirm the activity of a short course of atezolizumab in the neoadjuvant setting shows that preoperative treatment is feasible and well-tolerated in resectable NSCLCs. It also highlights the fact that surgical resection can be accomplished safely with no major delays.[4,5]

[a] Information provided by Roche Products Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is currently licensed in the UK for the following indications:[6,7]

- As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:
  - after prior platinum-containing chemotherapy, or
  - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ⩾ 5%
- As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab.
- In combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.
- In combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.
- In combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression ⩾ 1% and who have not received prior chemotherapy for metastatic disease.

The most common adverse reactions are: fatigue, decreased appetite, nausea, cough, dyspnoea, pyrexia, diarrhoea, rash, musculoskeletal pain, back pain, vomiting, asthenia, arthralgia, pruritus and urinary tract infection. The safety of atezolizumab given in combination with other medicinal products, has been evaluated in 3,878 patients across multiple tumour types. The most common adverse reactions were anaemia, neutropenia, nausea, fatigue, alopecia, thrombocytopenia, diarrhoea, rash, constipation, peripheral neuropathy, and decreased appetite.[8]

Atezolizumab is currently in phase II and III development in combination, and as a monotherapy for several lines of treatment and cancers including NSCLC, bladder cancer, melanoma and cervical cancer.[9]

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:[10]

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.

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).[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 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-melanoma skin cancer, and in 2012 deaths from lung cancer exceeded those from any other malignancy worldwide.[13] Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2015-2017). 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.[14]

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 and 79,628 day cases.[15]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,175 diagnosed cases of stage I-III lung cancer in 2017 in England.[16] In the UK, it is estimated that up to 85% 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 15,448 cases diagnosed with stage I-III in 2017 were NSCLC.[17]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage I was 87.7% at one year and 56.6% at five years; for stage II, 73.0% at one year and 34.1% at five years; for stage III, 48.7% at one year and 12.6% at five years.[18] There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[14] In England and Wales in 2019 there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for NSCLC differs by stage. For stage 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 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.[20]

CURRENT TREATMENT OPTIONS

There are currently no recommended neoadjuvant treatments for stage II, IIIA, or select IIIB patients with NSCLC. NICE currently recommends that people with stage I–II NSCLC that are suitable for surgery are not offered neoadjuvant treatment outside a clinical trial.[21] Adjuvant chemotherapy should be offered with resected stage II and III. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board.[22]

PLACE OF TECHNOLOGY

If licensed, atezolizumab in combination with chemotherapy will provide a neoadjuvant and adjuvant treatment option for patients with resectable stage II, IIIA, or select IIIB NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**IMpower030;NCT03456063;** A Phase III, Double-Blinded, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment With Atezolizumab or Placebo in Combination With Platinum-Based Chemotherapy in Patients With Resectable Stage II, IIIA, or Select IIIB Non-Small Cell Lung Cancer **Phase III-**Recruiting **Location(s):** EU (not incl UK), US, Canada and other countries **Primary completion date:** November 2024
Trial design	Randomised, parallel assignment, double-blinded
Population	N= 450 (planned); aged 18 and older; resectable stage II, IIIA, or select IIIB (T3N2 only) NSCLC
Intervention(s)	Atezolizumab + platinum-based chemotherapy • Neoadjuvant treatment will consist of 4 cycles; atezolizumab + platinum-based chemotherapy • Post-operative adjuvant treatment will consist of 16-cycles of atezolizumab
Comparator(s)	Placebo + platinum-based chemotherapy • Neoadjuvant treatment will consist of 4 cycles; placebo + platinum-based chemotherapy • Participants will receive best supportive care and monitoring after surgery

Outcome(s)	• Major pathological response (MPR) (Time frame: at time of surgery) • Independent Review Facility (IRF)-Assessed Event Free Survival (EFS) (Time frame: approximately 73 months) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Atezolizumab 1200mg/20mL concentrate for solution for infusion vials costs £3807.69 per vial; 840mg/14mL concentrate for solution for infusion vials costs £2665.38 per vial.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Pemetrexed for the first-line treatment of non-small cell lung cancer (TA181). September 2009.
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- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.

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. 2016

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.[22]
- 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

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