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Atezolizumab in addition to chemotherapy for stage IV squamous non-small cell lung cancer – first line

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LAY SUMMARY

Squamous non-small cell lung cancer (NSCLC) is a type of lung cancer that develops in the cells that line the airways. This lung cancer is relatively fast growing and is usually caused by smoking. Squamous NSCLC starts in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs and tend to be found in the central area of the lung, e.g. near the main airway (bronchus). Symptoms include a persistent cough, hoarseness, shortness of breath, weight-loss or lack of appetite, feeling weak or tired, coughing up blood and pneumonia/or infections that keep coming back. Stage IV squamous NSCLC is the most advanced form of the disease where the cancer has spread beyond the lungs into other areas of the body. The aim of treatment at this stage is to prolong survival, improve quality of life, and control disease-related symptoms.

Atezolizumab is a monoclonal antibody designed to recognise and attach to a protein called 'programmed death-ligand 1' (PD-L1), which is present on the surface of many cancer cells. PD-L1 switches off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effect, atezolizumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease. Atezolizumab is administered by intravenous infusion. If licensed, atezolizumab in addition to chemotherapy will offer an additional first line treatment option for patients with untreated, advanced, squamous non-small cell lung cancer.

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TARGET GROUP

Non-small cell lung cancer (NSCLC) (squamous, stage IV) – first line; in combination with chemotherapy (carboplatin, paclitaxel, nab-paclitaxel)

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors. It releases PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.[1]

In the phase III clinical trial (IMpower131, NCT02367794), the three treatment arms being studied are atezolizumab with paclitaxel and carboplatin (Arm A), versus atezolizumab with nab-paclitaxel and carboplatin (Arm B), versus nab-paclitaxel and carboplatin (Arm C) for chemotherapy in naïve Stage IV squamous NSCLC. Within the study (1) atezolizumab is administered by intravenous (IV) infusion at 1200 milligrams (mg) on day 1 of each 21-day cycle, for four or six cycles in combination with; (2) carboplatin at 6 mg per millilitre (ml) per minute on day 1 of each 21-day cycle for 4 or 6 cycles; (3) paclitaxel at 200 mg/m^2 on day 1 of each 21-day cycle for four or six cycles and; (4) nab-paclitaxel at 100 mg/m^2 on day 1,8, and 15 of each 21-day cycle for four or six cycles.[2]

Atezolizumab is already licensed in the EU as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible. It is also licensed as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab. [1,3] The most common side effects with atezolimumab (which may affect more than 1 in 10 people) are tiredness, reduced appetite, nausea and vomiting, difficulty breathing, diarrhoea, rash, fever, joint pain, weakness and itching.[3]

Atezolizumab is in phase II and phase III clinical development, as monotherapy or in combination with other drugs, for the treatment of a range of different types of cancers such as breast cancer, hepatocellular carcinoma, ovarian cancer or solid tumours.[4]

INNOVATION and/or ADVANTAGES

Stage IV squamous NSCLC is difficult to treat and there have been limited new treatment options over the last few decades. The addition of atezolizumab to frontline carboplatin and nab-paclitaxel delayed progression or death compared with carboplatin and nab-paclitaxel alone, according to top line findings from the phase III IMpower131 trial.[5]

If licensed, atezolizumab in combination with carboplatin and nab-paclitaxel will offer an additional first line treatment option for patients with squamous NSCLC not previously treated.

DEVELOPER

Roche Products Ltd

PATIENT GROUP

BACKGROUND

Lung cancer is classified as one of two main histologic types: small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC).[6] NSCLC comprises approximately 87% of lung cancers.[7] NSCLC can be further divided into different subtypes, including non-squamous and squamous NSCLC.[8] Squamous cell (epidermoid) carcinoma starts in young versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway (bronchus).[6] As a consequence of this, the tumour is more likely to invade larger blood vessels and other vital resulting in bronchial obstruction. Squamous NSCLC has a worse prognosis than other histologic subtypes of NSCLC.

Squamous cell carcinoma is usually faster growing than adenocarcinomas and is more commonly found in men. In recent years, there has been a gradual decline in the incidence of this form of lung cancer.[8] NSCLC is often asymptomatic until it has become well advanced. Upon initial NSCLC diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have distant metastasis.[9] Often, the first sites of metastases are the regional lymph nodes and other nearby tissues, such as the pericardium, diaphragm, or mediastinal pleura. Metastasis to another lobe of the same lung usually occurs before metastasis to the opposite lung, which generally occurs in the later stages of progression. Finally, distant metastases to the kidney, adrenal gland, bones, or brain mark the advanced stages of disease progression.[10]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 46,403 new cases of lung cancer and 35,895 deaths in the UK.[11] NSCLC is the more common type of lung cancer, found in approximately 85% to 90% of patients with lung cancer with an estimated 450,000 cases worldwide in 2012.[6] There are three common types: adenocarcinoma, squamous cell cancer and large cell carcinoma. They are grouped together because they behave and respond to treatment in a similar way.[8]

Stage IV squamous patients have a 5 year survival rate of 1.6%.[12] In England in 2016-17, there were 112,905 finished consultant episodes for malignant neoplasm of bronchus and lung (ICD 10 C34), resulting in 91,902 hospital admissions and 267,931 FCE bed days.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (ID1306). Expected publication date TBC.
- NICE technology appraisal in development. Nivolumab in combination with ipilimumab for untreated PD-L1-positive non-small-cell lung cancer (ID1187). Expected publication date TBC.
- NICE technology appraisal in development. Nivolumab in combination with platinum-doublet chemotherapy for untreated PD-L1-negative non-small –cell lung cancer (ID1135). Expected publication date TBC.
- NICE technology appraisal in development. Avelumab for untreated PD-L1 positive non-small cell lung cancer (ID1261). Expected publication date TBC.
- NICE technology appraisal in development. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) (ID1349). Expected publication date July 2018.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA447). June 2017.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011. Update expected March 2019.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE quality standards. Suspected cancer (QS124). June 2016. Updated December 2017.
- NICE quality standards. Lung cancer in adults (QS17). March 2012.

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

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[14]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (137). 2014.[15]

- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[16]

CURRENT TREATMENT OPTIONS

For locally advanced or metastatic NSCLC, the aim of treatment is to prolong survival, improve quality of life, and control disease-related symptoms.[10] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.[17] The current NICE Pathway reflects these recommendations.[18]

Patients with stage IV squamous NSCLC are recommended to have third generation drug (gemcitabine, vinorelbine, paclitaxel or docetaxel) in combination with platinum agent (cisplatin or carboplatin when cisplatin is contraindicated).[19]

In England, NICE clinical guideline 121 (CG121) is currently being updated in the effectiveness of chemotherapy and radiotherapy for treatment of NSCLC and the first line treatment of limited-stage and extensive-stage SCLC. The newly updated guideline is expected to be published in January 2019. A technology appraisal is in development recommending pembrolizumab with carboplatin and paclitaxel for untreated squamous NSCLC.[20]

EFFICACY and SAFETY

Trial	**IMpower131,** NCT02367794**; atezolizumab with paclitaxel and carboplatin vs. atezolilumab with nab-paclitaxel and carboplatin vs. nab-paclitaxel and carboplatin; phase III**
Sponsor	Hoffmann-La Roche
Status	Active, not recruiting
Source of Information	Trial Registry[2]
Location	13 EU countries (excl UK), USA, Canada, and other countries
Design	Randomised, active-controlled, parallel assignment, open label
Participants	n=1021; aged 18 years and older; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; Histologically or cytologically confirmed, treatment-naïve Stage IV squamous NSCLC; Previously obtained archival tumour tissue or tissue obtained from biopsy at screening; Measurable disease as defined by RECIST v1.1; Adequate hematologic and end organ function
Schedule	**Experimental Arm A: Atezolizumab + Paclitaxel + Carboplatin** The induction phase of the study will consist of four or six cycles; atezolizumab (1200 mg IV), paclitaxel (200 mg/m^2 IV), and carboplatin (6 mg/mL/min) will be administered on Day 1 of each 21-day cycle. The Day 1 order of drug administration is as follows: atezolizumab, then paclitaxel, then carboplatin. Participants who experience no further clinical benefit at any time during the induction phase will discontinue all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, participants will begin maintenance therapy with atezolizumab. Atezolizumab will be continued as long as there is a clinical benefit to the participant.

	Experimental Arm B: Atezolizumab + Nab-paclitaxel + Carboplatin The induction phase of the study will consist of four or six cycles; atezolizumab (1200 mg IV) and carboplatin (6 mg/mL/min) will be administered on Day 1 of each 21-day cycle. Nab-Paclitaxel (100 mg/m^2) will be administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration is as follows: atezolizumab, then nab-paclitaxel, then carboplatin. Participants who experience no further clinical benefit at any time during the induction phase will discontinue all study treatments. In the absence of the above criteria, after the 4- or 6-cycle induction phase, participants will begin maintenance therapy with atezolizumab. Atezolizumab will be continued as long as there is a clinical benefit to the participant. **Active comparator Arm C: Nab-paclitaxel + Carboplatin** The induction phase of the study will consist of four or six cycles; carboplatin (6 mg/mL/min) will be administered on Day 1 of each 21-day cycle, nab-paclitaxel (100 mg/m^2) will be administered on Days 1, 8, and 15 of each 21-day cycle. The Day 1 order of drug administration is as follows: nab-paclitaxel, then carboplatin. Participants who experience disease progression at any time during the induction phase will discontinue all study treatment. In the maintenance phase, participants will receive best supportive care.
Follow-up	Not reported
Primary Outcomes	• Progression Free Survival (PFS) as determined by the investigator using response evaluation criteria in solid tumours version 1.1 (RECIST v1.1) in the intent-to-treat (ITT) population [Time Frame: Up to approximately 30 months after first participant enrolled] • Overall Survival (OS) in the ITT population [Time Frame: Up to approximately 39 months after first participant enrolled]
Secondary Outcomes	• OS in the tumour gene expression (tGE) population [Time Frame: Up to approximately 39 months after first participant enrolled] • PFS as determined by the investigator using RECIST v1.1 in the tGE population [Time Frame: Up to approximately 30 months after first participant enrolled] • PFS as determined by the investigator using RECIST v1.1 in the tumour cell (TC) 2/3 or tumour-infiltrating immune cell (IC) 2/3 population [Time Frame: Up to approximately 30 months after first participant enrolled] • PFS as determined by the investigator using RECIST v1.1 in the TC1/2/3 or IC1/2/3 population [Time Frame: Up to approximately 30 months after first participant enrolled] • OS in the TC2/3 or IC2/3 population [Time Frame: Up to approximately 39 months after first participant enrolled] • OS in the TC1/2/3 or IC1/2/3 population [Time Frame: Up to approximately 39 months after first participant enrolled]

	• Percentage of participants with objective response as determined by the investigator using RECIST v1.1 in the ITT population [Time Frame: Up to approximately 30 months after first participant enrolled] • Duration of response as determined by the investigator using RECIST v1.1 in the ITT population [Time Frame: Up to approximately 30 months after first participant enrolled] • OS at 1 and 2 Years in the ITT population [Time Frame: 1 and 2 years], defined as the proportion of participants alive at 1 and 2 years after randomization estimated using Kaplan-Meier (KM) methodology • Time to deterioration (TTD) in patient-reported lung cancer symptoms using EORTC QLQ-C30 symptom subscales in the ITT population [Time Frame: Up to approximately 30 months after first participant enrolled] • TTD in patient-reported lung cancer symptoms using EORTC QLQ-LC13 symptom subscales in the ITT population [Time Frame: Up to approximately 30 months after the first participant enrolled] • Change from baseline in patient-reported lung cancer symptoms score using the SILC scale symptom severity score in the ITT population [Time Frame: baseline up to approximately 30 months after first participant enrolled] • PFS as determined by the investigator using RECIST v1.1 in the ITT population (Arm A vs. Arm B) [Time Frame: Up to approximately 30 months after first participant enrolled] • OS in the ITT population (Arm A vs. Arm B) [Time Frame: Up to approximately 39 months after first participant enrolled] • Percentage of participants with adverse events [Time Frame: Up to approximately 39 months after first participant enrolled] • Percentage of participants with anti-therapeutic antibody (ATA) response to atezolizumab [Time Frame: Predose on day 1 of cycles 1-4, 8, 16, every 8 cycle thereafter (up to 39 months), at treatment discontinuation (up to 39 months), and at 120 days after the last dose of atezolizumab (up to approximately 39 months, each cycle is 21 days)] • Maximum Observed serum atezolizumab concentration (Cmax) [Time Frame: Predose on day 1 of cycles 1-4, 8, 16, every 8 cycle up to 39 months; 30 minutes postdose on day 1 of cycles 1 and 3; at treatment discontinuation (up to 39 months), and at 120 days after last dose of atezolizumab (up to 39 months, each cycle is 21 days)] • Minimum observed serum atezolizumab concentration (Cmin) [Time Frame: Predose on day 1 of cycles 1-4, 8, 16, every 8 cycle thereafter (up to 39 months), at treatment discontinuation (up to 39 months), and at 120 days

	after the last dose of atezolizumab (up to approximately 39 months, each cycle is 21 days)] • Plasma concentrations for paclitaxel [Time Frame: Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 180 minutes) on day 1 of cycles 1 and 3 (each cycle is 21 days)] • Plasma concentrations for nab-paclitaxel [Time Frame: Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 30 minutes) on day 1 of cycles 1 and 3 (each cycle is 21 days)] • Plasma concentrations for carboplatin [Time Frame: Prior to infusion (within same day of treatment administration), 5-10 minutes before the end of infusion, and 1 hour after the end of infusion (infusion duration 15 to 30 minutes) on day 1 of cycles 1 and 3 (each cycle is 21 days)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date August 2018. Estimated study completion date February 2023.

ESTIMATED COST and IMPACT

COST

The cost of atezolizumab 60mg/1ml concentrate for solution for infusion vials is £3807.69.[21]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs ☐ Reduced drug treatment costs

☐ Other increase in costs ☐ Other reduction in costs

☐ Other ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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