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EVIDENCE BRIEFING
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Atezolizumab in addition to chemotherapy for small cell lung cancer – first line

NIHRIO ID	12880	**NICE ID**	9748
Developer/Company	Roche Products Ltd	**UKPS ID**	645028

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

SUMMARY

Atezolizumab is being investigated in addition to other chemotherapy (carboplatin and etoposide) as an initial (first-line) treatment for patients with extensive stage small cell lung cancer (ES-SCLC). SCLC is one of the two main types of lung cancer and the ES-SCLC means that the cancer has spread beyond a single area that can be treated with radiotherapy. The most common symptoms of lung cancer include cough, coughing up blood or rust-coloured sputum, chest pain, and shortness of breath, hoarseness, and weight loss.

Atezolizumab, given by intravenous infusion, acts by binding to a protein called anti-programmed death-ligand 1 (PD-L1) that is found on the cancer cells or immune cells trying to attack cancer cells. Binding to this protein can lead to the activation of the body's immune system to fight tumour cells. Some studies have reported that the addition of atezolizumab to chemotherapy (carboplatin and etoposide) has the potential to increase survival and in patients with ES-SCLC who have not previously received any treatment, when compared to chemotherapy alone.

PROPOSED INDICATION

Small cell lung cancer (Extensive stage) – first line, in combination with chemotherapy (carboplatin and etoposide).

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) anti-programmed death-ligand 1 (PD-L1) monoclonal antibody. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour 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. Atezolizumab directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour 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.[1]

Atezolizumab in addition to chemotherapy is being investigated for the treatment of previously untreated extensive-stage (ES) small cell lung cancer (SCLC). [2] In the phase III clinical trial (NCT02763579; IMpower133), participants in the experimental arm will receive intravenous infusions (IV) of atezolizumab 1200 mg in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 mg/mL/min followed by etoposide 100 mg/m^2 on day 1 of every 21-day cycle during the induction phase (cycles 1-4). On days 2 and 3 of every 21-day cycle during the induction phase (cycles 1-4), etoposide 100 mg/m^2 will be administered alone. Thereafter, participants will receive maintenance (cycle 5 onward) atezolizumab 1200 mg on day 1 of every 21-day cycle until persistent radiographic PD, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the sponsor.[2]

INNOVATION AND/OR ADVANTAGES

It is reported that the phase III study (NCT02763579; IMpower133) demonstrated that first-line treatment with the combination of atezolizumab plus chemotherapy (carboplatin and etoposide) helped people with ES-SCLC live significantly longer compared to chemotherapy alone and reduced the risk of disease worsening or death (PFS) compared to chemotherapy alone. The company also indicated that these are the first positive phase III survival results for any immunotherapy-based combination in the initial treatment of ES-SCLC.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab is licensed in the UK as a monotherapy for the following indications:[1]

- adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%.
- adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.

Some very common (≥ 10%) and common (≥ 1% to < 10%) adverse events associated with atezolizumab are thrombocytopenia, hypersensitivity, hypothyroidism, hyperthyroidism, decreased appetite, hypokalaemia, etc.1

Atezolizumab is a designated orphan drug in the USA for the treatment of SCLC in October 2016.[4]

Atezolizumab is in phase III stage of development for the treatment of various types of cancers such as:[5]

- Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract
- High-Risk Muscle-Invasive Urothelial Carcinoma
- Renal Cell Carcinoma (RCC) at High Risk of Developing Metastasis Following Nephrectomy
- Previously Untreated Locally Advanced or Metastatic Triple Negative Breast Cancer
- High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Atezolizumab is in phase II stage of development for the treatment of different types of cancers such as:[6]

- Locally Advanced or Metastatic Urothelial Bladder Cancer
- Locally Advanced or Metastatic Non-Small Cell Lung Cancer
- Locally Advanced or Metastatic Breast Cancer
- Advanced Renal Cell Carcinoma
- Non-Muscle-Invasive Bladder Cancer
- Relapsed or Refractory Follicular Lymphoma
- Relapsed or Refractory Diffuse Large B-Cell Lymphoma

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer starts when cells of the lung become abnormal and begin to grow out of control. The two main types of lung cancer are SCLC and NSCLC.[7] In SCLC, the cancer cells appear very small (compared to NSCLC) when observed under a microscope.[8]

Extensive stage SCLC (ES-SCLC) means that the cancer has spread beyond a single area that can be treated with radiotherapy within the chest – to the other lung or to lymph nodes further away from the cancer, or to other parts of your body.[9]

The most common symptoms of SCLC include cough that does not go away or gets worse, haemoptysis (blood in sputum), chest pain, hoarseness, weight loss and loss of appetite, shortness of breath, feeling tired or weak, infections that do not go away or keep coming back and new onset of wheezing.[10]

When the lung cancer spreads to other parts of the body, it may cause:[10]

- Bone pain (like pain in the back or hips)
- Nervous system changes (such as headache, weakness or numbness of an arm or leg, dizziness, balance problems, or seizures), from cancer spread to the brain
- Yellowing of the skin and eyes (jaundice), from cancer spread to the liver
- Lumps near the surface of the body, due to cancer spreading to the skin or to lymph nodes (collection of immune system cells) such as those in the neck or above the collarbone

Risks and causes of lung cancer include smoking tobacco, exposure to radon gas, chemicals and workplace risks (such as exposure to asbestos, silica, and diesel exhaust), air pollution, previous lung disease (such as tuberculosis, and chronic obstructive pulmonary disease), family history of lung cancer, previous radiotherapy treatment, lowered immunity (such as having HIV and AIDS, taking immunosuppressant medicines, having an autoimmune condition such as rheumatoid arthritis or systemic lupus erythematosus).[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 (2015). 53% of lung cancer cases in the UK are in males, and 47% are in females. There were 46,388 new cases of lung cancer in the UK in 2015 of which 37,637 were in England.

SCLCs constitute about 10-15% of lung cancer cases[12] which equates to approximately 4,639 to 6,958 SCLC cases in the UK in 2015 of which 3,764 to 5,645 cases were in England.

In 2014, there were 37,453 cases of lung cancer registered in England.[13] Stage 4 lung cancer and ES-SCLC have the same TNM staging (Any T, Any N, M1a, M1b, or M1c).[9,14] Stage 4 lung cancer constituted 48% of lung cancer cases in England in 2014[12] which is equivalent to 17,977 cases of which approximately 1,798 to 2,696 cases were SCLC.

Lung cancer incidence rates in the UK are projected to fall from 94.41 per 100,000 in 2014 to 87.99 per 100,000 in 2035.[15]

Data for 2014 in England shows that one-year net survival for lung cancer is the lowest for patients diagnosed at stage 4 (17% of diagnosed patients). Five-year survival of people diagnosed with stage 4 lung cancer during 2003-2006 could not be calculated at five years due to the small number of people surviving more than two years.[16]

In the UK in 2016, there were 35,620 deaths from lung cancer of which 28,566 were in England. This constitutes 21% of cancer deaths. Lung cancer mortality is strongly related to age, with the highest mortality rates being in older people. In the UK in 2014-2016, on average each year almost half (48%) of deaths were in people aged 75 and over.[17]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Treatment of ES-SCLC aims to control the cancer for as long as possible and help with symptoms. If the patient is well enough he/she usually has chemotherapy. If the chemotherapy works well, the patient might have radiotherapy to the lungs afterwards. After treatment the patient might also have radiotherapy to the head if the cancer has stopped growing and the patient is well enough. Radiotherapy to the head is called prophylactic cranial radiotherapy (PCR). It aims to kill any cancer cells that might have spread to the brain but are too small to see on scans.[18]

To control symptoms, the patient might also have other treatments such as radiotherapy, internal radiotherapy (brachytherapy), laser treatment, freezing the tumour (cryotherapy), a rigid tube called a stent to keep the airway open, light therapy (photodynamic therapy - PDT).[18]

CURRENT TREATMENT OPTIONS

For ES-SCLC (broadly corresponding to T1–4, N0–3, M1a/b – including cerebral metastases), NICE recommends platinum-based combination chemotherapy if patients are fit enough. The patient's condition needs to be assessed before each cycle of chemotherapy for ES-SCLC. NICE recommends to offer up to a maximum of six cycles, depending on response and toxicity. Thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax.[19]

Thopaz+ should be considered for people who need chest drainage after pulmonary resection or because of a pneumothorax. The system can increase patient mobility because it is portable.[19]

PLACE OF TECHNOLOGY

If licensed, atezolizumab in addition to chemotherapy (carboplatin and etoposide) will offer an additional first-line treatment option for patients with ES-SCLC.

CLINICAL TRIAL INFORMATION

Trial	**IMpower133, NCT02763579; adults aged 18 years and older; atezolizumab vs placebo, both in combination with carboplatin and etoposide; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry,[2] Press release[3]
Location	EU (incl UK), USA, and other countries.
Design	Randomised, double-blind, placebo-controlled, parallel assignment
Participants	n=500 (planned); aged 18 years and older; ES-SCLC; no prior systemic treatment for ES-SCLC.
Schedule	Randomised to IV of atezolizumab 1200 mg in combination with carboplatin to achieve an initial target area under the concentration-time curve (AUC) of 5 mg/mL/min followed by etoposide 100 mg/m^2 on day 1 of every 21-day cycle during the induction phase (cycles 1-4). On days 2 and 3 of every 21-day cycle during the induction phase (cycles 1-4), etoposide 100 mg/m^2 will be administered alone. Thereafter, participants will receive maintenance (cycle 5 onward) atezolizumab 1200 mg on day 1 of every 21-day cycle until persistent radiographic pd, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the sponsor. Or IV placebo in combination with carboplatin to achieve an initial target AUC of 5 mg/mL/min followed by etoposide 100 mg/m^2 on day 1 of every 21-day cycle during the induction phase (cycles 1-4). On days 2 and 3 of every 21-day cycle during the induction phase (cycles 1-4), etoposide 100 mg/m^2 will be administered alone. Thereafter, participants will receive maintenance (cycle 5 onward) placebo on day 1 of every 21-day cycle until persistent radiographic pd,

	symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the sponsor.
Follow-up	List active treatment period: 4 cycles (each cycle is 21 days) and maintenance phase (cycle 5) until persistent radiographic pd, symptomatic deterioration, intolerable toxicity, withdrawal of consent, death, or study termination by the sponsor. Overall follow-up period: 37 months
Primary Outcomes	- Duration of Progression-Free Survival (PFS) [Time Frame: Baseline until PD or death, whichever occurs first (up to approximately 37 months)] - Duration of Overall Survival (OS) [Time Frame: Baseline until death from any cause (up to approximately 37 months)]
Secondary Outcomes	- Percentage of Participants With Objective Response (OR) [Time Frame: Baseline until partial response (PR) or complete response (CR), whichever occurs first (up to approximately 37 months)] - Duration of Response (DOR) [Time Frame: First occurrence of PR or CR until PD or death, whichever occurs first (up to approximately 37 months)] - Time in Response (TIR) [Time Frame: Baseline until PD or death, whichever occurs first (up to approximately 37 months)] - Time to Response (TTR) [Time Frame: Baseline until PR or CR, whichever occurs first (up to approximately 37 months)] - Percentage of Participants Alive and Without PD[Time Frame: 6 months, 1 year] - Percentage of Participants Alive at 1 Year and 2 Years [Time Frame: 1 year, 2 years] - Time to Deterioration (TTD) per European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) Score [Time Frame: Baseline until deterioration per symptom subscale (up to approximately 37 months)] - TTD per EORTC QLQ Lung Cancer Module (LC13) Score [Time Frame: Baseline until deterioration per symptom subscale (up to approximately 37 months)] - Percentage of Participants with Adverse Events [Time Frame: Baseline until up to 90 days after end of treatment (up to approximately 37 months)] - Percentage of Participants With Anti-Therapeutic Antibodies (ATAs) [Time Frame: Predose (0 hours [H]) on Day (D) 1 of Cycles (C) 1, 2, 3, 4, 8, 16, and every 8 cycles (Q8C) thereafter (cycle = 21 days) until treatment discontinuation (up to 37 months) and 120 days after last dose (up to approximately 37 months overall)] - Maximum Observed Serum Concentration (Cmax) of Atezolizumab [Time Frame: Predose (0 H) and postdose (0.5 H) on D1 of C1; predose (0 H) on D1 of C2, 3, 4, 8, 16, and Q8C thereafter (cycle = 21 days) until treatment discontinuation (up to 37 months) and 120 days after last dose (up to approximately 37 months overall)] - Minimum Observed Serum Concentration (Cmin) of Atezolizumab [Time Frame: Predose (0 H) on D1 of C1, 2, 3, 4, 8, 16, and Q8C thereafter (cycle = 21 days) until treatment discontinuation (up to 37 months) and 120 days after last dose (up to approximately 37 months overall)] - Plasma Concentration of Carboplatin [Time Frame: Predose (0 H) and 5-10 minutes before end/1 H after end of carboplatin infusion (infusion duration = 1 H) on D1 of C1 and C3 (cycle = 21 days)] - Plasma Concentration of Etoposide [Time Frame: Predose (0 H) and 5-10 minutes before end/1 H and 4H after end of etoposide infusion (infusion duration = 1 H) on D1 of C1 and C3 (cycle = 21 days)]

Key Results	First interim analysis demonstrated that initial (first-line) treatment with the combination of atezolizumab plus chemotherapy (carboplatin and etoposide) helped people with ES-SCLC live significantly longer compared to chemotherapy alone. The atezolizumab-based combination also reduced the risk of disease worsening or death (PFS) compared to chemotherapy alone. Safety for the atezolizumab and chemotherapy combination appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination.
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date reported as August 2019.

ESTIMATED COST

Atezolizumab is already marketed in the UK. Tecentriq 1200mg/20ml (Atezolizumab 60 mg per 1 ml) concentrate for solution for infusion vials (1 vial) (Roche Products Ltd) costs £3807.69.[20] There is also a Patient Access Scheme in operation for atezolizumab.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Lefitolimod maintenance treatment for small-cell lung cancer (1122). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Rovalpituzumab tesirine for treating small-cell lung cancer after 2 therapies (ID1288). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Nivolumab with ipilimumab for maintenance treatment of extensive stage small-cell lung cancer after chemotherapy (ID1264). Expected date of issue to be confirmed.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- American Society of Clinical Oncology. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. 2015.[21]

- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer: a national clinical guideline (137). February 2014.[22]
- London Cancer Alliance West and South. LCA Lung Cancer Clinical Guidelines. December 2013.[23]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer (SCLC). Clinical practice guidelines for diagnosis, treatment and follow-up. 2013.[24]

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