Health Technology Briefing
December 2023

Lurbinectedin with atezolizumab maintenance therapy for extensive-stage small-cell lung cancer

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33959	NICE ID: Not available	UKPS ID: 665729

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Lurbinectedin in combination with atezolizumab is in clinical development for patients with extensive stage small-cell lung cancer (ES-SCLC) after first-line induction therapy. Small-cell lung cancer (SCLC) is a type of lung cancer that usually develops in the central part of the lungs, and in which the cancer cells are small compared with other types of lung cancer. In extensive-stage, cancer has spread beyond the lung or the area between the lungs or the lymph nodes above the collarbone to other places in the body. Symptoms of ES-SCLC include chest pain, a cough that does not go away or gets worse, coughing up blood, and breathlessness. Smoking is the biggest risk factor for SCLC. Chemotherapy is often effective in the first instance, but relapse rates are high, and the outcome remains very poor. Therefore, new treatments are needed to improve the outcome of ES-SCLC.

Lurbinectedin, administered intravenously (IV) is expected to work by breaking down an enzyme (protein) called RNA polymerase II, which plays a key role in the production of proteins that are needed for the cancer cells to grow and multiply. By breaking down RNA polymerase II, lurbinectedin reduces production of these growth-related proteins and so reduces the growth of the cancer. Atezolizumab, administered IV, works by blocking a protein that stops the immune system from working properly and attacking cancer cells, thereby slowing down progression of the disease. Licensing the combination of lurbinectedin and atezolizumab will provide an additional treatment option for ES-SCLC, where there is currently an unmet clinical need.

Proposed Indication

Maintenance therapy for patients with extensive-stage small-cell lung cancer (ES-SCLC) following first-line induction therapy with carboplatin, etoposide and atezolizumab.[1]

Technology

Description

Lurbinectedin (Zepzelca) is a synthetic alkaloid that covalently binds DNA, generating double-strand breaks, and disrupts DNA-protein interactions and RNA transcription. Lurbinectedin may also modulate the tumour microenvironment by inducing apoptosis of peripheral blood monocytes and tumour associated macrophages, decreasing expression of the inflammatory chemokine (C-C motif) ligand 2 (CCL2) and reducing tumour angiogenesis.[2]

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, releasing 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.[3]

Lurbinectedin with atezolizumab is currently in clinical development as maintenance therapy for patients with ES-SCLC following first-line induction therapy with carboplatin, etoposide and atezolizumab. In the phase III clinical trial (IMforte; NCT05091567), 1200 mg of atezolizumab will be administered intravenously (IV) on day 1 of each 21-day cycle in combination with carboplatin on day 1 and etoposide on days 1, 2, and 3 of each 21-day cycle for 4 cycles in the induction phase. In the maintenance phase, 1200 mg of atezolizumab (IV) will be administered in combination with 3.2 mg/m² of lurbinectedin (IV) on day 1 of each 21-day cycle.[1]

Key Innovation

Despite the effectiveness of PD-L1 inhibitors in combination with platinum-based chemotherapy as first-line treatment for ES-SCLC, most patients still have disease progression and prognosis remains poor.[4] In the phase III clinical trial (Impower133; NCT02763579), the addition of atezolizumab to chemotherapy improved median overall survival to 12.3 months compared with 10.3 months in the chemotherapy plus placebo arm.[4,5]

Lurbinectedin, as a single agent, has shown promising activity in many tumour types, including as second-line (2L) treatment for SCLC with an objective response rate (ORR) of 35%.[4] In the phase I study (2SMALL; NCT04253145), the combination of lurbinectedin and atezolizumab showed promising preliminary anti-tumour activity (overall response rate (ORR, 57.7%) as a second line treatment for ES-SCLC.[4,6]

SCLC represents an unmet medical need in the UK and worldwide, therefore if licensed, lurbinectedin in combination with atezolizumab will offer an additional treatment option for patients with ES-SCLC.

Regulatory & Development Status

Lurbinectedin does not currently have Marketing Authorisation in the EU/UK for any indication.

Lurbinectedin has the following regulatory designations/awards: [7,8]

- Innovation Passport by the MHRA in August 2022
- an Orphan drug in the EU in 2019 for the treatment of SCLC

Lurbinectedin is in phase III/II clinical development as a monotherapy for: [9]

- Advanced malignant pleural mesothelioma
- Urothelial cancer
- Desmoplastic small round cell tumour
- FET-fused solid tumors
- Relapsed SCLC
- Solid tumours
- Ewing sarcoma
- Pancreatic cancer
- Ovarian cancer

Patient Group

Disease Area and Clinical Need

Small cell lung cancer (SCLC) is a malignant epithelial tumour arising from cells lining the lower respiratory tract. [10] About 15% to 20% of all lung cancers are SCLC.[11] SCLC is an aggressive cancer and approximately two-thirds of patients have evidence of distant metastasis at presentation. In ES-SCLC, cancer has spread beyond the lung or the area between the lungs or the lymph nodes above the collarbone to other places in the body.[12] Smoking cigarettes, pipes, or cigars is the most important risk factor for lung cancer. Other risk factors include family history of lung cancer, and being exposed to irritants, such as second-hand smoke, asbestos, arsenic, chromium, beryllium, nickel, soot or tar in the workplace, radiation, and air pollution. Most common presenting symptoms are cough, chest pain, haemoptysis (coughing up blood), dyspnoea, and weight loss.[10,12]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016-2018). In females in the UK, lung cancer is the 2nd most common cancer, with around 23,300 new cases every year (2016-2018). In males in the UK, lung cancer is the 2nd most common cancer, with around 25,300 new cases every year (2016-2018). Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2016-2018).[13] ES-SCLC accounts for 1 in 8 lung cancer cases in the UK.[14] In England, 2022-23, there were 122,866 finished consultant episodes (FCE) and 104,232 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34) which resulted in 217,569 FCE bed days and 80,131 day cases. [15]

Recommended Treatment Options

Currently, the National Institute for Health and Care Excellence (NICE) recommends the following treatment options for patients with ES-SCLC: [14,16]

- Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (ES-SCLC)
- Platinum-based combination chemotherapy

Clinical Trial Information

Trial	**IMforte:** NCT05091567; A Phase III, Randomized, Open-Label, Multicentre Study of Lurbinectedin in Combination With Atezolizumab Compared With Atezolizumab as Maintenance Therapy in Participants With Extensive-Stage Small-Cell Lung Cancer (ES-SCLC) Following First-Line Induction Therapy With Carboplatin, Etoposide and Atezolizumab **Phase III –** Recruiting **Location(s):** 7 EU countries, UK, USA, and other countries **Primary completion date –** April 2025
Trial Design	Randomised, parallel assignment, open label
Population	N = 690 (estimated); aged 18 Years and older; participants with histologically or cytologically confirmed ES-SCLC, who have had no prior systemic therapy for ES-SCLC and have been treatment-free for at least 6 months since last chemo/radiotherapy, among those treated (with curative intent) with prior chemo/radiotherapy for limited-stage SCLC
Intervention(s)	• Induction phase: atezolizumab (IV) at a fixed dose of 1200 mg on day 1 of each 21-day cycle + carboplatin on day 1 + etoposide on days 1, 2, and 3 of each 21-day cycle for 4 cycles • Maintenance phase: atezolizumab (IV) at a fixed dose of 1200 mg on day 1 of each 21-day cycle + lurbinectedin 3.2 mg/m² (IV) on day 1 of each 21-day cycle
Comparator(s)	• Induction phase: atezolizumab (IV) at a fixed dose of 1200 mg on day 1 of each 21-day cycle + carboplatin on day 1 + etoposide on days 1, 2, and 3 of each 21-day cycle for 4 cycles • Maintenance phase: atezolizumab (IV) at a fixed dose of 1200 mg on day 1 of each 21-day cycle
Outcome(s)	• IRF-Assessed Progression-Free Survival (PFS) [Time Frame: Randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) (up to approximately 52 months)] • Overall Survival (OS) [Time Frame: Randomization to death from any cause (up to approximately 52 months)]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of lurbinectedin is not yet known.

Atezolizumab is already marketed in the UK; a 60 mg vial (1200mg/20ml) costs £3,807.69. [17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Serplulimab with chemotherapy for untreated extensive-stage small-cell lung cancer (TA11405). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Tislelizumab with platinum-based chemotherapy and etoposide for untreated extensive-stage small-cell lung cancer (TA11094). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab–vibostolimab with etoposide and platinum-based chemotherapy for untreated extensive-stage small-cell lung cancer (TA11401). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (TA638). July 2020.
- NICE guideline. Lung cancer: diagnosis and management (NG122). July 2023.
- NICE quality standard. Lung cancer in adults (QS17). December 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.

Other Guidance

- National Comprehensive Cancer Network (NCCN). Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. December 2021.[18]
- NHS Northern Cancer Alliance. Lung Cancer Clinical Guidelines. May 2019.[19]
- London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. March 2016. [20]
- Scottish Intercollegiate Guidelines Network. SIGN 137 – Management of lung cancer. February 2014. [21]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.