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Newcastle University

Health Technology Briefing
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Durvalumab with tremelimumab for limited stage small-cell lung cancer

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26783	NICE ID: 10342	UKPS ID: 663174

Licensing and Market Availability Plans

Currently in phase III trials

Summary

Durvalumab in combination with tremelimumab is in clinical development for patients with limited stage small cell lung cancer (LS-SCLC). SCLC is a fast-growing cancer that forms in the tissues of the lung and may have spread to the area between the lungs or to the lymph nodes above the collarbone. SCLC is described as limited if the cancer is contained in one lung, tissues between the lungs and in nearby lymph nodes. Although most patients with LS-SCLC will respond to initial treatment, the majority experience disease relapse.

Durvalumab and tremelimumab, both administered through intravenous (IV) infusion, are antibodies (proteins) which act through different pathways to interact with immune molecules located on the tumour cells and white blood cells. They are believed to boost the body's immune system by allowing immune cells to be more active and fight the cancer, thereby slow down disease progression. The combined effect of the two products may produce a stronger, more targeted immune response against the cancer cells when compared to current treatments. If licensed durvalumab in combination with tremelimumab could provide an additional treatment option for LS-SCLC.

Proposed Indication

Treatment of limited Stage Small-Cell Lung Cancer (LS-SCLC).[1]

Technology

Description

Durvalumab (Imfinzi, MEDI-4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with programmed cell death-1 (PD-1) and CD80 . Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances anti-tumour immune responses and increases T-cell activation. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.[2]

Tremelimumab (CP-675,206) is a human immunoglobulin IgG2 monoclonal antibody specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a cell surface receptor that is expressed primarily on activated T cells. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion. Inhibition of CTLA-4 can shift the balance of signalling in the immune system in favour of greater T-cell activation, engendering a greater immune response and potentially resulting in the rejection of tumour by the host's immune system.[3]

Durvalumab in combination with tremelimumab is in clinical development for the treatment of patients with LS-SCLC. In the phase III clinical trial (ADRIATIC; NCT03703297), subjects in the combination therapy arm receive durvalumab (1500 mg IV) every four weeks (Q4W) and tremelimumab (75mg IV) Q4W for up to four doses or cycles each, followed by durvalumab monotherapy (1500 mgQ4W). The first durvalumab monotherapy 1500 mg dose Q4W will be four weeks after the final dose of durvalumab in combination with tremelimumab.[1] Treatment will continue until disease progression in accordance with the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1), intolerable toxicity, or a maximum of 24 months.[4]

Key Innovation

Although most patients with LS-SCLC will respond to initial concurrent chemoradiotherapy, the majority experience disease relapse.[4] There is therefore a need for further treatment options.

Combined durvalumab and tremelimumab had a numerically higher objective response rate (ORR) as compared to durvalumab monotherapy in advanced gastric and gastroesophaegeal junction adenocarcinoma and preclinical data of tremelimumab indicate that PDL1/PD-1 and CTLA-4 pathways are non-redundant, suggesting that targeting both pathways could have additive or synergistic effects.[5,6]

Recently, durvalumab has also shown antitumour activity as monotherapy and combined with tremelimumab in pre-treated patients with extensive-stage SCLC.[4] If licensed, durvalumab combined with tremelimumab will offer an additional treatment option for patients with LS-SCLC.

Regulatory & Development Status

Durvalumab in combination with tremelimumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Durvalumab has a Marketing Authorisation in the UK for the monotherapy treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy and in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[2]

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

Durvalumab in combination with tremelimumab is currently in phase III clinical trials for several cancers including hepatocellular carcinoma, SCLC extensive disease, non-small-cell lung cancer, advanced urothelial cancer and others. Durvalumab in combination with tremelimumab is also in a large number of phase II trials for numerous cancer types.[7]

Patient Group

Disease Area and Clinical Need

SCLC is the most aggressive form of lung cancer that forms in tissues of the lung and can spread to other parts of the body; it only accounts for around 15% lung cancer cases.[4,8] Limited stage means that the cancer is only on one side of the chest. This generally includes cancers that are only in one lung (unless tumours are widespread throughout the lung), and that might also have reached the lymph nodes on the same side of the chest.[9] SCLC are also classed as neuroendocrine tumours. Neuroendocrine tumours (NETs) are rare tumours that develop in cells of the neuroendocrine system. In SCLC, the tumour starts in the neuroendocrine cells of the lung.[10] Signs and symptoms of small cell lung cancer include coughing, shortness of breath, and chest pain. Other symptoms may include fatigue, loss of appetite, unexplained weight loss, blood in the sputum, swelling of the neck (veins in the neck) and face, trouble swallowing, wheezing and hoarseness.[11,12] Smoking is the main cause of lung cancer. Around 9 out of 10 people who get lung cancer (90%) are smokers or ex-smokers. Lung cancer is also more common in older people with more than 4 in 10 people (44%) who are diagnosed being aged 75 and over.[13] Other causes and risk factors include exposure to chemicals, air pollution, genetic predisposition and lowered immunity.[13,14]

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.[15] 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.[16] In the UK it is estimated that up to 15% of lung cancer cases are SCLC, which would mean around 7,200 of the annual new lung cancer cases are SCLC.[17] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[18] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV (metastatic) was 19.3% at one year and 2.9% at five years, and for stage III it was 48.7% at one year and 12.6% at five years.[19] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[20] In England and Wales in 2020 there were 28,730 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[21]

Recommended Treatment Options
For people with LS-SCLC, the National Institute for Health and Care Excellence (NICE) recommends:[22] • Cisplatin-based combination chemotherapy -consider substituting carboplatin in people with impaired renal function, poor World Health Organisation (WHO) performance status (2 or more) or significant comorbidity. • Twice-daily radiotherapy with concurrent chemotherapy for people with WHO performance status of 0 or 1, if they present with disease that can be encompassed in a radical thoracic radiotherapy volume. Start the radiotherapy during the first or second cycle of chemotherapy. • Once-daily radiotherapy for people who refuse twice daily radiotherapy • Sequential radical thoracic radiotherapy for people with who are not well enough for concurrent chemoradiotherapy but who respond to chemotherapy. • Prophylactic cranial irradiation for people with WHO performance status 0 to 2, if their disease has not progressed on first-line treatment.

Clinical Trial Information

Trial	**ADRIATIC,** NCT03703297; A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients With Limited Stage Small Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy **Phase III** – Active, not recruiting **Location(s):** 6 EU countries, UK, USA, Canada and other countries **Primary completion date:** May 2024
Trial Design	Randomised, parallel assignment, triple-blinded
Population	N=728; adult patients with limited-stage SCLC (stage I-III) who have received four cycles of chemotherapy concurrent with radiotherapy; aged 18-130 years
Intervention(s)	Durvalumab via IV infusion in combination with placebo saline solution OR Durvalumab (IV) in combination with tremelimumab (IV)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Progression-free survival (PFS) [Time frame: approximately 4 years] • Overall Survival (OS) [Time frame: approximately 6 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Durvalumab is already indicated in the UK for the treatment of NSCLC and extensive-stage small cell lung cancer; a 120mg/2.4ml vial costs £592 and 500mg/10ml vial costs £2,466.[23]

The cost of tremelimumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- 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

- American Society for Radiation Oncology. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. 2020.[24]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). February 2014.[25]
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Additional Information

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