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Health Technology Briefing
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Durvalumab with platinum-based chemotherapy for the neoadjuvant/adjuvant treatment of resectable non-small-cell lung cancer

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27053	NICE TSID: 10304	UKPS ID: 665476

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Durvalumab in combination with platinum-based chemotherapy is in clinical development for the neoadjuvant/adjuvant treatment of resectable non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Early-stage lung cancer is typically treated with surgery to remove the tumour, followed by chemotherapy and/or radiotherapy. However, survival rates are still poor. Symptoms include a persistent cough, shortness of breath, coughing up blood, among others. Treatment with medicines prior to surgery (neoadjuvant) may provide better long-term survival prospects and reduce the risk of disease recurrence for patients with resectable NSCLC.

Durvalumab is a type of protein 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 acts to switch off immune cells that would otherwise attack the cancer cells. Durvalumab is administered intravenously (IV). Interim results from a phase III trial demonstrate that durvalumab in combination with platinum-based chemotherapy is efficacious. If licensed, neoadjuvant/adjuvant durvalumab in combination with neoadjuvant chemotherapy will offer an additional treatment option for patients with NSCLC who currently have few well-tolerated effective therapies available.

Proposed Indication

Neoadjuvant/adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small cell lung cancer (NSCLC).[1]

Technology

Description

Durvalumab (Imfinzi, MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with death ligand 1 (PD-1) and CD80 (B7.1). Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection by the immune system. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.[2]

Durvalumab in combination with platinum-based chemotherapy is currently in clinical development for resectable NSCLC. In the phase III trial, durvalumab was administered via intravenous infusion (IV) at an unspecified dose.[3]

Key Innovation

For patients diagnosed with early stage (Stages I-IIIA) NSCLC, surgery is the primary curative treatment in patients where resection is possible. However, 5-year survival rates for patients with early-stage NSCLC remain poor, with survival rates in resected patients of 61.7% (Stage IA) to 43.0% (Stage IIB) being reported. Postoperative recurrence remains a key concern, and additional treatment options are required. The advantages of a neoadjuvant treatment approach include the timely treatment of subclinical micrometastatic disease, reduction in tumour bulk prior to surgery, increased tumour T-cell infiltration, improved R0 resection rate, increased knowledge of drug sensitivity, along with higher treatment compliance and drug delivery rates compared with adjuvant therapy.[4]

Durvalumab attaches to PD- L1, which acts to switch off immune cells that would otherwise attack the cancer cells, and thus by blocking its effects, durvalumab increases the ability of the immune system to attack the cancer cells and thereby slow down the progression of the disease.[5] Positive high-level results from a planned interim analysis of the AEGEAN (NCT03800134) phase III trial showed treatment with durvalumab in combination with neoadjuvant chemotherapy before surgery a statistically significant and meaningful improvement in pathologic complete response (pCR) compared to neoadjuvant chemotherapy alone for patients with resectable NSCLC. A statistically significant improvement in major pathologic response (MPR) was also observed.[6] If licensed, neoadjuvant/adjuvant durvalumab in combination with platinum-based chemotherapy will offer an additional treatment option for patients with NSCLC who currently have few well-tolerated effective therapies available.

Regulatory & Development Status

Durvalumab as monotherapy is licensed for the 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. It is also approved in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).[2]
Durvalumab is in phase III/II clinical development for several indications, some of which include:[7]

- SCLC
- Bladder cancer
- Ovarian cancer

- Urothelial cancer
- Mesothelioma

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main histologic types: SCLC or NSCLC. NSCLC comprises about 80-85% of lung cancers in the UK.[8] A stage IIA cancer describes a tumour larger than 4 cm but 5 cm or less in size that has not spread to the nearby lymph nodes. Stage IIB lung cancer describes a tumour that is 5 cm or less in size that has spread to the lymph nodes within the lung, called the N1 lymph nodes. A stage IIB cancer can also be a tumour more than 5 cm wide that has not spread to the lymph nodes. Stage III lung cancers are classified as either stage IIIA, IIIB, or IIIC. The stage is based on the size of the tumour and which lymph nodes the cancer has spread to. Stage III cancers have not spread to other distant parts of the body.[9] 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).[10] 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.[11]

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.[12] 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 and 62,688 day cases.[13] 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.[14] 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.[8] 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.[15] There are around 34,800 lung cancer deaths in the UK every year (based on data from 2017-2019). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035, to 58 deaths per 100,000 people by 2035.[12]

Recommended 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.[16] 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.[17]

Clinical Trial Information

Trial	**AEGEAN**; NCT03800134; EudraCT 2018-002997-29; A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN) **Phase III –** Active, not recruiting **Location(s):** 11 EU countries, USA, Canada and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, double-blinded
Population	N=816 (actual); adult patients who are newly diagnosed and previously untreated with histologically or cytologically documented NSCLC with resectable (Stage IIA to select [ie, N2] Stage IIIB) disease
Intervention(s)	• IV durvalumab • All patients will receive one of the following platinum-based standard of care chemotherapy options, based on tumour histology and Investigator discretion: ○ carboplatin/paclitaxel ○ cisplatin/gemcitabine ○ pemetrexed/cisplatin ○ pemetrexed/carboplatin
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures • Pathological Complete Response (pCR) in modified intent-to-treat (mITT) [time frame: from screening pathology to an average of 15 weeks after first dose.] • Event-Free Survival (EFS) [Time Frame: Up to 5.5 years after first patient randomized]. See trial record for a full list of other outcomes
Results (efficacy)	Interim results show statistically significant and meaningful improvement in pathologic complete response and in major pathologic response were observed in the experimental arm (durvalumab and neoadjuvant chemotherapy).[18]
Results (safety)	-

Estimated Cost

Durvalumab is already marketed in the UK for various indications; a 120mg/2.4ml concentrate for solution for infusion vial costs £592.00 and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Pemetrexed for the first-line treatment of non-small cell lung cancer (TA181). September 2009.

- NICE technology appraisal guidance. Pemetrexed for the treatment of non-small cell lung cancer (TA124). August 2007.
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019. Last updated: August 2022.
- NICE quality standard. Lung cancer in adults (QS17). March 2012. Last updated: 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.
- 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.[17]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[20]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). 2014.[21]

Additional Information

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