Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Durvalumab with or without tremelimumab in addition to platinum based chemotherapy for extensive-stage disease small-cell lung cancer

NIHRIO ID	26898	**NICE ID**	10162
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Durvalumab with or without tremelimumab in addition to platinum based chemotherapy, is in clinical development for people with extensive-stage disease small-cell lung cancer (SCLC). SCLC is an aggressive type of lung cancer that is associated with smoking. The condition is often diagnosed at a late stage, when the cancer has spread to other parts of the body (extensive-stage). If patients are fit enough, they may be given chemotherapy as first-line treatment, although the cancer will usually return quickly (within 6 months). The average length of survival from diagnosis is under 10 months.

There are few treatment options available for this condition, and the standard treatment of chemotherapy has not changed for several decades. Durvalumab and tremelimumab are a new kind of treatment for this cancer called immunotherapy that helps the body's immune system to fight the cancer. These medicinal products are given by intravenous infusion together with chemotherapy. Durvalumab is already licensed in the UK for the treatment of a different type of lung cancer. The combination treatment may be more effective than either treatment alone, and could provide an additional treatment for patients who currently have few effective therapies.

PROPOSED INDICATION

Small-cell lung cancer (SCLC), extensive-stage disease, suitable to receive platinum-based chemotherapy (PBC) as first-line treatment[1]

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) with PD-1 and CD80 (B7.1). 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. 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., interferon (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 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.[2]

Tremelimumab is a selective human immunoglobulin G2 (IgG2) monoclonal antibody inhibitor of cytotoxic T-lymphocyte associated protein 4 (CTLA-4). It promotes T-cell activity through CTLA-4 inhibition but does not seem to deplete regulatory T-cells directly.[3]

In the phase III clinical trial (CASPIAN; NCT03043872), durvalumab is administered by intravenous (IV) infusion at 50mg/ml every 3 weeks for 12 weeks and every 4 weeks thereafter, with or without tremelimumab IV infusion at 20mg/ml every 3 weeks for 12 weeks and an additional dose at week 16, in addition to 10mg/ml carboplatin IV infusion or 1mg/ml cisplatin IV infusion + 20mg/ml etoposide IV infusion every 3 weeks for up to 4 cycles. Treatment with durvalumab is continued until treatment progression or other discontinuation criteria are reached.[1,4]

INNOVATION AND/OR ADVANTAGES

The standard options for therapy for SCLC have not changed over the last three decades, and the effectiveness of the few available treatment options is limited. However, the high mutational burden of SCLC, resulting in a large number of potential tumour-specific antigens, provides opportunities for therapeutic intervention.[5]

Drugs that block the PD-L1/PD-1 pathway act in the tumour microenvironment and prevent inhibition of T-cell function, whereas drugs that block CTLA-4 pathway act in the lymphoid compartment to expand the number and repertoire of tumour-reactive T-cells. Preclinical data indicate that these pathways are non-redundant, suggesting that targeting both pathways could have additive or synergistic effects.[3,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Durvalumab has Marketing Authorisation in the EU/UK as a monotherapy for the treatment of locally advanced, unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[2]

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

Durvalumab in combination with tremelimumab is in phase II/III clinical development for:[7]

- Bladder cancer
- Non-small-cell lung cancer
- Squamous cell carcinoma of the head and neck
- Hepatocellular carcinoma
- Breast cancer

PATIENT GROUP

DISEASE BACKGROUND

SCLC is an aggressive high-grade neuroendocrine tumour associated with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor prognosis of patients with the disease. Among the major lung cancer subtypes, SCLC has the strongest association with smoking, with only 2% of cases occurring in never-smokers. Consequently, SCLCs have a high load of somatic mutations induced by tobacco carcinogens.[5] Quitting smoking has been related not only to a reduction in the incidence of SCLC, but also to a significant reduction in the risk of mortality. The association with smoking means that the treatment of patients with SCLC can be complicated, as they usually present with multiple important comorbidities secondary to tobacco use such as chronic obstructive pulmonary disease, ischaemic cardiopathy and hypertension, thus deteriorating their functional status.[8]

The most common presenting symptoms of SCLC are cough, chest pain, haemoptysis (coughing up blood), dyspnoea (breathlessness) and weight loss.[9] SCLC is usually classified as limited-stage or extensive-stage disease. Limited-stage SCLC is defined as disease confined to a single radiation port, with or without mediastinal lymph-node involvement, whilst in extensive-stage SCLC the disease has spread beyond a single radiation port, generally synonymous with distant metastasis.[5] European guidelines equate the term “extensive-stage” with metastatic tumours, classifying this as stage 4 cancer.[10]

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 in 2015.[11] In England in 2016 there were 38,363 registrations of newly diagnosed cases of malignant neoplasm of bronchus and lung (ICD-10 code C34).[12] Across the UK, incidence rates are expected to decrease from 94.41 per 100,000 in 2014 (46,400 cases) to 87.99 per 100,000 in 2035 (62,832 cases) (European age-standardised rates).[13]

In England in 2016, there were 3,754 cases of SCLC, equating to 10% of newly diagnosed lung cancer cases.[14] Extensive-stage disease accounts for around two-thirds of all SCLC diagnoses.[5,15,16]

Survival for lung cancer is strongly related to stage of disease at diagnosis.[17] Patients with extensive-stage disease SCLC are not curable and, in the UK, have a two-year survival rate of less than 5%.[18] Despite response rates close to 70%, outcomes remain poor, with a median progression-free survival of 5.5 months and a median overall survival of <10 months.[10,19,20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

SCLC is a particularly aggressive cancer, which is nearly always advanced at the time of diagnosis, so surgery is often not appropriate. However, these tumours are very sensitive to chemotherapy and radiotherapy, and this can improve survival and quality of life. Patients may deteriorate quickly in the time between presentation and treatment, so it is important that the pathway is expeditious. As the vast majority of patients with SCLC present with extensive-stage disease, timely use of palliative chemotherapy is often the most appropriate measure.[21]

In England and Wales in 2016, 68% of patients with SCLC received chemotherapy (slightly below the audit target of 70% set by the Royal College of Physicians in the National Lung Cancer Audit). Of these patients, 34% received their chemotherapy within 14 days of pathological diagnosis.[21]

If chemotherapy works well, patients may then receive radiotherapy to the lungs or head. For patients in England diagnosed with Stage 4 SCLC in 2013-15, 33% received chemotherapy only, and 31% received chemotherapy and radiotherapy.[22]

The objective response rate associated with platinum-based chemotherapy ((either cisplatin or carboplatin) and etoposide) approach 70%, but most patients suffer rapid disease relapse within 6 months.[5]

CURRENT TREATMENT OPTIONS

As first-line treatment for extensive-stage SCLC, NICE recommends:[23]

- Offer platinum-based combination chemotherapy to patients if they are fit enough
- Assess the patient's condition before each cycle of chemotherapy and 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

PLACE OF TECHNOLOGY

If licensed, durvalumab with or without tremelimumab in addition to platinum-based chemotherapy will offer an additional first-line treatment option for patients with extensive-stage SCLC, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CASPIAN, NCT03043872, EudraCT-2016-001203-23; durvalumab + tremelimumab + platinum-based chemotherapy (PBC) vs durvalumab + PBC vs PBC; phase III**
Sponsor	AstraZeneca UK Ltd
Status	Ongoing
Source of Information	Trial registry[1,4]
Location	EU (not UK), USA and other countries
Design	Randomised, active-controlled

Participants	n=988; aged 18yrs and older; small-cell lung cancer; extensive disease; suitable to receive first-line PBC
Schedule	Randomised to: Arm 1: 50mg/ml durvalumab IV infusion every 3 wks for 12 wks (4 cycles) and every 4 wks thereafter until disease progression or other discontinuation criteria, in combination with 20mg/ml tremelimumab IV infusion every 3 wks for 12 wks (4 cycles) and an additional dose at wk 16, in addition to 10mg/ml carboplatin IV infusion or 1mg/ml cisplatin IV infusion + 20mg/ml etoposide IV infusion every 3 wks for up to 4 cycles Arm 2: 50mg/ml durvalumab IV infusion every 3 wks for 12 wks (4 cycles) and every 4 wks thereafter until disease progression or other discontinuation criteria, in addition to 10mg/ml carboplatin IV infusion or 1mg/ml cisplatin IV infusion + 20mg/ml etoposide IV infusion every 3 wks for up to 4 cycles Arm 3: carboplatin or 1mg/ml cisplatin IV infusion + 20mg/ml etoposide IV infusion every 3 wks for up to 6 cycles
Follow-up	Active treatment until disease progression or other discontinuation criteria, follow-up to 3 yrs
Primary Outcomes	• Overall survival [Time frame: up to 3 yrs] • Progression-free survival using Blinded Independent Central Review (BICR) assessments according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 [Time frame: up to 2 yrs]
Secondary Outcomes	• Proportion of pts alive and progression-free at 6 mths from randomisation using BICR assessments according to RECIST 1.1 [Time frame: up to 6 mths] • Proportion of pts alive and progression-free at 12 mths from randomisation using BICR assessments according to RECIST 1.1 [Time frame: up to 12 mths] • Proportion of pts alive at 18 mths [Time frame: up to 18 mths] Time frame: up to 2 yrs: • Objective response rate using BICR assessments according to RECIST 1.1 • Disease-related symptoms measured by European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • Health-related quality of life measured by EORTC QLQ-C30 • Disease-related symptoms measured by European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) • Immunogenicity of durvalumab and tremelimumab as assessed by frequency of pts with positive anti-drug antibody (ADA) titers • Pharmokinetics (PK) of durvalumab and tremelimumab as determined by peak concentration • PK of durvalumab and tremelimumab as determined by trough concentration • Changes in World Health Organisation / Eastern Cooperative Oncology Group (WHO/ECOG) performance status • Safety and tolerability profile of durvalumab +/- tremelimumab in combination with PBC treatment compared with PBC as determined by vital signs, laboratory data, electrocardiograms and physical examination
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as September 2019

ESTIMATED COST

Durvalumab is already marketed in the UK for the treatment of non-small-cell lung cancer; a 120mg/2.4ml concentrate for solution for infusion vial costs £592, and a 500mg/10ml concentrate for solution for infusion vial costs £2,466.[24]

The cost of tremelimumab is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab with chemotherapy for untreated extensive-stage small-cell lung cancer (ID1509) (GID-TA10413). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer (ID1504) (GID-TA10400). Expected October 2019.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.
- NICE interventional procedures guidance. Microwave ablation for treating primary lung cancer and metastases in the lung (IPG469). November 2013.
- NICE interventional procedures guidance. Percutaneous radiofrequency ablation for primary or secondary lung cancer (IPG372). December 2010.

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

- Royal College of Physicians. National Lung Cancer Audit Annual Report 2017 (for the audit period 2016). Jan 2018.[21]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). February 2014.[18]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer: ESMO Clinical Practice Guidelines. June 2013.[10]

REFERENCES

1 ClinicalTrials.gov. *Durvalumab ± Tremelimumab in Combination With Platinum Based Chemotherapy in Untreated Extensive-Stage Small Cell Lung Cancer (CASPIAN). Trial ID: NCT03043872*. Status: Active, not recruiting. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03043872 [Accessed 18 February 2019].

2 Electronic Medicines Compendium. *IMFINZI 50 mg/mL concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/9495 [Accessed 18 February 2019].

3 Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. *The Lancet Oncology*. 2016 Mar;17(3):299-308. Available from: https://doi.org/10.1016/S1470-2045(15)00544-6.

4 EU Clinical Trials Register. *A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN). Trial ID: EudraCT2016-001203-23*. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-001203-23/NL [Accessed 18 February 2019].

5 Sabari JK, Lok BH, Laird JH, Poirier JT, Rudin CM. Unravelling the biology of SCLC: implications for therapy. *Nature Reviews Clinical Oncology*. 2017 May 23;14:549. Available from: https://doi.org/10.1038/nrclinonc.2017.71.

6 Stewart R, Mullins S, Watkins A, Morrow M, Sainson R, Robbins P, et al. Preclinical modelling of immune checkpoint blockade (P2012). *The Journal of Immunology*. 2013;190(1 Supplement):214.7-.7. Available from: http://www.jimmunol.org/content/190/1_Supplement/214.7.

7 AstraZeneca. *Clinical trials appendix - Q4 2018 results update.* Available from: https://www.astrazeneca.com/content/dam/az/PDF/2018/full-year/Full-Year_2018_Results_clinical_trials_appendix.pdf [Accessed 18 February 2019].

8 Alvarado-Luna G, Morales-Espinosa D. Treatment for small cell lung cancer, where are we now?-a review. *Transl Lung Cancer Res*. 2016 Feb;5(1):26-38. Available from: 10.3978/j.issn.2218-6751.2016.01.13.

9 British Medical Journal Best Practice. *Small cell lung cancer.* Available from: https://bestpractice.bmj.com/topics/en-gb/1081 [Accessed 25 February 2019].

10 Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2013;24(suppl_6):vi99-vi105. Available from: https://dx.doi.org/10.1093/annonc/mdt178.

11 Cancer Research UK. *Lung cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 19 February 2019].

12 Office for National Statistics (ONS). *Cancer Registration Statistics, England, 2016*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 24 August 2018].

13 Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Downloaded 9 March 2018].

14 Royal College of Physicians. *National Lung Cancer Audit Annual Report 2017 (for the audit period 2016). 2017 information sheet.* 2018. Available from:

https://www.rcplondon.ac.uk/file/8703/download?token=2UCmNec9 [Accessed 19 February 2019].

15 Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006 Oct 1;24(28):4539-44. Available from: 10.1200/jco.2005.04.4859.

16 Gaspar LE, McNamara EJ, Gay EG, Putnam JB, Crawford J, Herbst RS, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. *Clin Lung Cancer*. 2012 Mar;13(2):115-22. Available from: 10.1016/j.cllc.2011.05.008.

17 Cancer Research UK. *Lung cancer survival by stage at diagnosis.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Three [Accessed 19 February 2019].

18 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137)*. 2014. Available from: https://www.sign.ac.uk/assets/sign137.pdf.

19 Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011 Sep 1;81(1):77-84. Available from: 10.1016/j.ijrobp.2010.05.013.

20 Foster NR, Qi Y, Shi Q, Krook JE, Kugler JW, Jett JR, et al. Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer: findings on the basis of North Central Cancer Treatment Group trials. *Cancer*. 2011 Mar 15;117(6):1262-71. Available from: 10.1002/cncr.25526.

21 Royal College of Physicians. *National Lung Cancer Audit Annual Report 2017 (for the audit period 2016)*. 2018. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2017.

22 Public Health England. *Chemotherapy, Radiotherapy and Surgical Tumour Resections in England. 2013-15 diagnoses. Workbook 1*. 2018. Available from: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/topic_specific_work/main_cancer_treatments

23 National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management (CG121)*. April 2011. Available from: https://www.nice.org.uk/guidance/cg121/resources/lung-cancer-diagnosis-and-management-pdf-35109444863941.

24 British National Formulary. *Durvalumab.* Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 18 February 2019].

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