NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Durvalumab for advanced, EGFR/ALK wild-type, high PD-L1 expression, non-small cell lung cancer- first line

NIHRIO ID	28236	**NICE ID**	10308
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	653761

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Durvalumab is in development for patients with advanced/metastatic non-small cell lung cancer (NSCLC) who are EGFR/ALK wild-type and whose tumours have a high PD-L1 expression. NSCLC makes up the majority of lung cancers in the UK. Advanced/metastatic (Stage IV) NSCLC is when the cancer has spread beyond the lung which was initially affected, most often to the liver, the adrenal glands, the bones and the brain. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. Currently, chemotherapy remains the first line treatment option but this is often not well tolerated by many patients.

Durvalumab is given by intravenous infusion into the vein. Durvalumab works by blocking an immune protein called programmed cell death ligand-1 (PD-L1). Normally, the immune system recognises and kills cancer cells. However, cancer cells can develop PD-L1 on their surface, allowing the cancer cells to avoid recognition by the immune system. By blocking PD-L1, durvalumab allows the immune system to recognise and target the cancer cells. If licenced, durvalumab may offer an additional treatment

option for patients with NSCLC who are EGFR/ALK wild-type and whose tumours have a high PD-L1 expression.

PROPOSED INDICATION

First line treatment of patients with advanced/metastatic non-small cell lung cancer (NSCLC) who are epithelial growth factor (EGFR) and anaplastic (ALK) wild-type and whose tumours have a high PD-L1 expression.[1, a]

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 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 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 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.[2]

Durvalumab is in clinical development for previously untreated metastatic NSCLC with wild type EGFR/ALK. In the clinical trial PEARL (NCT03003962) patients are given durvalumab every 4 weeks through intravenous administration.[1]

INNOVATION AND/OR ADVANTAGES

Personalized medicine in lung cancer is heavily dependent on histological subtypes and other molecular features of the tumours. EGFR positive mutation was found to be a strong predictive marker for tumour response and progression free survival following tyrosine kinase inhibitor (TKI) therapy. Subsequently, EGFR wild type tumours were deemed not suitable for TKI therapy. Therefore, patients with wild type EGFR were deprived of such treatments options leaving them to classic chemotherapy which is more toxic and has limited benefits.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

[a] Information provided by AstraZeneca UK Ltd

Very common (≥10%) adverse events associated with durvalumab include: upper respiratory tract infections, pneumonia, hypothyroidism, cough/productive cough, pneumonitis, diarrhoea, abdominal pain, rash, pruritus and pyrexia.[4]

Durvalumab is currently in phase II/III development for several oncology indications such as solid tumours, bladder cancer, hepatocellular carcinoma, etc.[5]

PATIENT GROUP

DISEASE BACKGROUND

There are two major types of lung cancer, NSCLC and small cell lung cancer. NSCLC is the most common type of lung cancer, accounting for about 87% of lung cancers. NSCLC can be further classified into adenocarcinoma (which starts in the mucus making glands in the lining of the airways), squamous cell cancer (which develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).[6] Metastatic cancer is a cancer that has spread from the part of the body where it started to other parts of the body usually the liver bones or brain.[7] [8] Cancers occur when genetic mutations build up in critical genes, specifically those that control cell growth and division (proliferation) or the repair of damaged DNA. These changes allow cells to grow and divide uncontrollably to form a tumour. In nearly all cases of lung cancer, these genetic changes are acquired during a person's lifetime and are present only in certain cells in the lung. These changes, which are called somatic mutations, are not inherited. Somatic mutations in many different genes have been found in lung cancer cells.[9]

EGFR is a protein on the surface of cells which normally helps the cells grow and divide. Some NSCLC cells have too much EGFR, making them grow faster.[10] The ALK gene provides instructions for making a protein called ALK receptor tyrosine kinase, which is part of a family of proteins called receptor tyrosine kinases (RTKs).[11] A mutation in the ALK gene results in an abnormal ALK fusion protein. This abnormal protein causes this type of lung cancer (ALK positive NSCLC) to grow and spread to other parts of the body.[12] For NSCLC cancers that have spread widely throughout the body (metastatic), the tumour will be tested for common gene mutations such as EGFR or ALK.[13] EGFR/ALK wild-type tumours do not harbour such mutations.

PD-L1 is a type 1 transmembrane protein that belongs to the B7 ligands family and may be expressed both on hematopoietic cells and non-hematopoietic cells. Expression of PD-L1 on tumour cells promotes down-regulation and self-tolerance of the immune system from rejecting the tumour by supressing T-cell inflammatory activity through binding the regulatory T-cell receptor, PD-1. In advanced NSCLC high tumour proportion score is defined as tumour proportion score (TPS) ≥ 50%.[14]

A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors. The greatest risk factor is long-term tobacco smoking, which increases a person's risk of developing lung cancer 25-fold. Other risk factors include exposure to air pollution, radon, asbestos, certain metals and chemicals, or second hand smoke; long-term use of hormone replacement therapy for menopause; and a history of lung disease such as tuberculosis, emphysema, or chronic bronchitis. A history of lung cancer in closely related family members is also an important risk factor; however, because relatives with lung cancer are frequently smokers, it is unclear whether the increased risk is the result of genetic factors or exposure to second hand smoke.[9] Key symptoms of lung cancer include a cough,

breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.[15]

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 2016 incidence rates were 77.4 per 100,000 men and 67.2 per 100,000 women.[16] Lung cancer in England is more common in people living in the most deprived areas. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2014-2016). Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035.[17]

In 2017, there were 18,655 diagnosed cases of stage IV lung cancer. Based on the estimate that 87% of these would be NSCLC this would equate to around 16,230 cases of stage 4 NSCLC.[18,19] In 2018/19 there were 107,010 hospital admissions with a primary diagnosis of malignant neoplasm of bronchus and lung (ICD-10 code C34). This resulted in 128,985 finished consultant episodes (FCE) and 249,196 FCE bed days.[20]

Survival for lung cancer depends on the stage at diagnosis.[21] In England, 2013-2017 followed up to 2018, the 1 year survival rate for people with stage IV lung cancer was 19.3% and the 5 year survival rate was 2.9%.[22] In 2017, there were 30,131 registrations of death from cancer in England for malignant neoplasms of trachea, bronchus and lung in England (ICD-10 code C33-34).[23]

In England and Wales 16.6% of patients with NSCLC are thought to harbour EGFR-TK mutations and 5% patients with stage III or IV NSCLC have ALK fusion genes mutation.[24,25] Therefore, the majority of NSCLC patients have wild-type EGFR and NSCLC. Approximately a third of patients with NSCLC have high PD-L1 expression levels.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of cancer, the specific gene mutation and the general health of the patient.[26,27] The main treatment option for the locally advanced or metastatic disease includes surgery, systemic anti-cancer therapy (SACT) and radiotherapy.[13]

At stage 4, NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally includes chemotherapy, targeted drugs, radiotherapy and symptom control treatment to help patients breathe more easily.[28]

CURRENT TREATMENT OPTIONS

In England, for patients with advanced stage NSCLC who do not have a gene mutation and whose tumours are PD-L1 positive (50% or over), NICE recommends the following first line treatments:[29]

- Pembrolizumab, with pemetrexed and platinum chemotherapy (non-squamous)
- Pembrolizumab (squamous and non-squamous)
- Pembrolizumab with carboplatin and paclitaxel (squamous)

PLACE OF TECHNOLOGY

If licenced, durvalumab will offer an additional treatment option for people with advanced NSCLC who are EGFR/ALK wild-type and whose tumours have a high expression of PD-L1.

CLINICAL TRIAL INFORMATION

Trial	**PEARL, NCT03003962, EudraCT-2018-001375-21, D419AC00002;** adults aged 18 to 130 years; durvalumab vs platinum based standard of care chemotherapy; phase III
Sponsor	AstraZeneca UK Ltd
Status	Ongoing
Source of Information	Trial Registry[1,30]
Location	EU (not incl UK), USA and other countries
Design	Randomized, parallel assignment (open-label)
Participants	n=669, adults aged 18 to 130 yrs; documented evidence of stage IV NSCLC; high PD-L1 expression; no sensitizing EGFR mutation and ALK rearrangement; PD-L1 high expression; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
Schedule	Arm 1: Durvalumab Arm 2: Standard of care platinum based chemotherapy: • Carboplatin + paclitaxel • Carboplatin/cisplatin + gemcitabine (squamous NSCLC only) • Carboplatin/cisplatin + pemetrexed followed by pemetrexed maintenance (non-squamous NSCLC only)
Follow-up	4 yrs
Primary Outcomes	The efficacy of durvalumab therapy compared to standard of care in terms of overall survival in patients with NSCLC [time frame: 4 yrs]
Secondary Outcomes	• The efficacy of durvalumab compared to standard of care in terms of objective response [time frame: 4 yrs] • The efficacy of durvalumab compared to standard of care in terms of duration of response [time frame: 4 yrs] • The efficacy of Durvalumab compared to SoC in terms of a proportion of patients alive and progression free at 12 months from randomization (APF12) [time frame: 12 mths] • The efficacy of durvalumab compared to standard of care in terms of progression-free survival after subsequent anticancer therapy [time frame: 4 yrs] • Disease related symptoms and health-related quality of life in subjects treated with durvalumab compared to standard of care using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [time frame: 4 yrs]

	• The immunogenicity of durvalumab by measuring the presence of Anti-drug Antibodies [time frame: 4 yrs] • The efficacy of durvalumab therapy compared to standard of care in terms of progression-free survival in patients with NSCLC [time frame: 4 yrs] • The efficacy of durvalumab therapy compared to standard of care in terms of overall survival in PD-L1 high patients with NSCLC [time frame: 4 yrs] • Proportion of patients alive at 18 months from randomization [time frame: 18 mths] • Proportion of patients alive at 24 months from randomization [time frame: 24 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	The estimated primary (and study) completion date is reported as January 2021.

ESTIMATED COST

Durvalumab is already marketed in the UK for the treatment of non-small-cell lung cancer patients whose PD-L1 expression; 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.[31]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019
- NICE technology appraisal. Pembrolizumab for untreated PD-L1 positive metastatic non-small cell lung cancer (TA531). July 2018
- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019
- NICE quality standard. Lung cancer in adults (QS17). March 2012
- NICE interventional procedure guidance. Microwave ablation for treating primary lung cancer and metastases in the lung (IPG469). November 2013
- NICE interventional procedure guidance. Irreversible electroporation for treating primary cancer and metastases in the lung (IPG441). February 2012
- NICE interventional procedure guidance. Percutaneous radiofrequency ablation for primary or secondary lung cancers (IPG372). December 2010.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.[32]
- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[33]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[34]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *Study of Durvalumab Alone or Chemotherapy for Patients With Advanced Non Small-Cell Lung Cancer (PEARL). Trial ID: NCT03003962*. 2018. Status: Active, not recruiting. Available from: https://ClinicalTrials.gov/show/NCT03003962 [Accessed 26 November 2019].

2 Electronic Medicines compendium (EMC). *Imfinzi 50mg/mL concentrate for solution for infusion.* 2018. Available from: https://www.medicines.org.uk/emc/product/9495/smpc [Accessed 07 January 2020].

3 Jazieh A-R, Al Sudairy R, Abu-Shraie N, Al Suwairi W, Ferwana M, Murad M. Erlotinib in wild type epidermal growth factor receptor non-small cell lung cancer: A systematic review. *Annals of Thoracic Medicine*. 2013 October 1, 2013;8(4):204-8. Available from: https://doi.org/10.4103/1817-1737.118503 10.4103/1817-1737.118503.

4 Electronic Medicines Compendium (EMC). *Imfinzi 50mg/ml concentrate for solution for infusion.* 2019. Available from: https://www.medicines.org.uk/emc/product/9495#PHARMACOLOGICAL_PROPS [Accessed 23 January 2020].

5 AstraZeneca. *Clinical trials appendix Q3 2019 results update.* 2019. Available from: https://www.astrazeneca.com/content/dam/az/PDF/2019/q3/Year-to-date_and_Q3_2019_Results_clinical_trials_appendix.pdf [Accessed 07 January 2020].

6 Lungcancer.org. *Types and Staging of Lung Cancer.* 2020. Available from: https://www.lungcancer.org/find_information/publications/163-lung_cancer_101/268-types_and_staging [Accessed 07 January 2020].

7 Cancer Treatment Centers of America. *Lung cancer stages.* 2020. Available from: https://www.cancercenter.com/cancer-types/lung-cancer/stages [Accessed 07 January 2020].

8 American Cancer Society. *Understanding Advanced cancer, Metastatic cancer and Bone Metastasis.* 2016. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 07 January 2020].

9 Genetics Home Reference. *Lung cancer.* 2017. Available from: https://ghr.nlm.nih.gov/condition/lung-cancer#genes [Accessed 07 January 2020].

10 National Cancer Institute. *NCI Dictionary of Cancer Terms; epidermal growth factor receptor inhibitor.* 2020. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/epidermal-growth-factor-receptor-inhibitor [Accessed 07 January 2020].

11 Reference GH. *ALK gene.* 2011. Available from: https://ghr.nlm.nih.gov/gene/ALK# [Accessed 07 January 2020].

12 Genentech. *What is ALK+ mNSCLC?* 2020. Available from: https://www.alecensa.com/patient/what-is-alk-positive-mnsclc/what-is-alk-positive-mnsclc.html [Accessed 07 January 2020].
13 American Cancer Society. *Treatment choices for Non-Small Cell Lung Cancer, by stage.* 2020. Available from: https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/by-stage.html [Accessed 07 January 2020].
14 Teixidó C, Vilariño N, Reyes R, Reguart N. PD-L1 expression testing in non-small cell lung cancer. *Therapeutic advances in medical oncology*. 2018;10:1758835918763493-. Available from: https://doi.org/10.1177/1758835918763493 10.1177/1758835918763493.
15 Cancer Research UK. *Lung cancer symptoms.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 07 January 2020].
16 Cancer Research UK. *Lung Cancer Incidence Statitstics* 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero [Accessed 23 January 2020].
17 Cancer Research UK. *Lung cancer statistics.* 2020. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 07 January 2020].
18 National Cancer Registration and Analysis Service (NCRAS). *Cancer by Stage Breakdown Clinical Comissioning Group 2016*. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Downloaded 21 September 2018].
19 Cancer Research UK. *Lung Cancer Types.* 2017. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 31 July 2017].
20 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis.* . Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 04 November 2019].
21 Cancer Research UK. *Lung Cancer Survival.* 2017. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/survival [Accessed 07 January 2020].
22 Office for National Statistics. *Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Downloaded 12 August 2019].
23 Office for National Statistics. *Death registrations summary tables - England and Wales.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 14 November 2019].
24 National Institute for Health and Care excellence (NICE). *EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG9)*. Last Update Date: August 2013. Available from: https://www.nice.org.uk/guidance/dg9/chapter/3-Clinical-need-and-practice [Accessed 06 January 2020].
25 National Institute for Health and Care Excellence (NICE). *LDK378 for previously treated anaplastic lymphoma kinase-positive non-small cell lung cancer (TA395)*. Last Update Date: March 2014. Available from: https://www.nice.org.uk/guidance/ta395/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-positive-previously-treated-ceritinib-draft-scope-for-consultation-prereferral-march-2014-2 [Accessed 06 January 2020].
26 Cabanero M, Sangha R, Sheffield BS, Sukhai M, Pakkal M, Kamel-Reid S, et al. Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. *Current oncology (Toronto, Ont)*. 2017;24(2):111-9. Available from: https://doi.org/10.3747/co.24.3524 10.3747/co.24.3524.
27 Cancer Research UK. *Lung Cancer Treatment.* 2019 Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment [Accessed 06 January 2020].
28 National Cancer Institute. *Non-Small Cell Lung Cancer Treatment (PDQ®)– Patient Version.* 2019. Available from: https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq [Accessed 07 January 2020].

29 National Institute for Health and Care Excellence (NICE). *NICE Pathways: Treating non-small-cell lung cancer*. 2020. Available from: https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/treating-non-small-cell-lung-cancer.xml&content=view-index [Accessed 24 January 2020].
30 EU Clinical Trials Register. *A Phase III Randomized, Open-Label, Multi-Center Study of Durvalumab (MEDI4736) Versus Standard of Care (SoC) Platinum-Based Chemotherapy as First Line Treatment in Patients with PD-L1-High Expression Advanced Non Small-Cell Lung Cancer (NSCLC). Trial ID: 2018-001375-21*. 2018. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001375-21/NL/ [Accessed 26 November 2019].
31 National Institute for Health and Care Excellence (NICE). *Durvalumab*. 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/durvalumab.html [Accessed 07 January 2020].
32 European Society For Medical Oncology (ESMO). *Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. 2019. Available from: https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer [Accessed 18 September 2019].
33 Journal Of The National Comprehensive Cancer Network (JNCCN). *Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology*. 2017. Available from: https://jnccn.org/view/journals/jnccn/15/4/article-p504.xml [Accessed 20 November 2019].
34 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer (SIGN 137)*. Last Update Date: February 2014. Available from: https://www.sign.ac.uk/sign-137-management-of-lung-cancer.html [Accessed 20 November 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.