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HEALTH TECHNOLOGY BRIEFING DECEMBER 2019

Durvalumab in addition to chemotherapy for metastatic non-small-cell lung cancer - first line

NIHRIO ID	27625	**NICE ID**	10284
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	653762

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Durvalumab in addition to chemotherapy is in clinical development for stage 4 non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK. Stage 4 (advanced/metastatic) 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 through intravenous infusion. It is a form of immunotherapy that works by increasing T-cell activity in order to stimulate the body's immune system to fight cancerous cells. Durvalumab is already licensed in the UK for the treatment of a different form of NSCLC. Durvalumab may be more effective than chemotherapy alone which is the current standard of care and may offer an additional treatment option for patients with NSCLC.

PROPOSED INDICATION

Advanced (metastatic, stage IV) non-small cell lung cancer (NSCLC) without activating epithelial growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions-first line.[a,1]

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi, MEDI4736) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of 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 programmed cell death ligand-1 (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 in combination with chemotherapy is in clinical development for previously untreated metastatic NSCLC tumours without activating EGFR mutations and ALK fusions. In the phase III study of durvalumab in combination with standard of care chemotherapy versus standard of care chemotherapy participants receive IV infusions of durvalumab every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progresses. [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 treatment with tyrosine kinase inhibitors (TKI). Subsequently EGFR wild type tumours, those without a mutation in the EGFR gene, were deemed not suitable for TKI therapy.[3]

Durvalumab in combination with chemotherapy if licensed as first line immunotherapy could provide an alternative treatment option for patients with advanced NSCLC who have EGFR and ALK wild type genes. The clinical trial POSEIDON met a primary endpoint by showing a statistically significant and clinically meaningful improvement in progression free survival in patients treated with a combination of durvalumab and a broad choice of five standard-of care platinum-based chemotherapy options vs chemotherapy alone.[4]

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-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. The most common side effects with durvalumab (which may affect more than 1 in 5 people) are nose and throat infections, cough and rash. [2]

[a] Information provided by AstraZeneca UK Ltd in UK PharmaScan

Durvalumab in combination with chemotherapy is also in phase II/III clinical development for:[5]

- small-cell lung cancer, bladder cancer and biliary tract cancer

Durvalumab monotherapy is in phase II/III development for:[5]

- solid tumours
- breast cancer
- cervical cancer
- bladder cancer
- hepatocellular carcinoma

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 85% 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] The cancer is named and treated based on the part of the body where the cancer started.[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). RTKs transmit signals from the cell surface into the cell through a process called signal transduction. Although the specific function of ALK receptor tyrosine kinase is unknown, it is thought to act early in development to help regulate the proliferation of nerve cells.[11] A mutation in the ALK gene result 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 and if one of these genes is mutated the first treatment will be a targeted therapy drug.[13] The majority of NSCLC patients do not have such mutations and have ALK and EGFR wild-type NSCLC.[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.[15] Key symptoms of lung cancer include a cough, breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.[16]

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 and an incidence rate in the UK of 72.2 per 100,000 in 2016. 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, to 88 cases per 100,000 people by 2035.[17]

In 2017, there were 38,888 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[18] In 2018/19 there were 107,010hospital 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.[19]

Survival for lung cancer depends on the stage at diagnosis.[20] In England 2013-2017 followed up to 2018, the 1 year survival rate for people with stage 4 lung cancer was 19.3% and the 5 year survival rate was 2.9%.[21] 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).[22]

The estimated proportion of EGFR mutations in NSCLC in England and Wales is 16.6%.[23] ALK gene mutations occur in approximately 3-5% of patients with NSCLC.[24] Therefore, the majority of NSCLC patients have wild-type EGFR and NSCLC.

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.[25] The main treatment option for the locally advanced or metastatic disease includes surgery, systemic anti-cancer therapy (SACT) and radiotherapy.[26]

At stage IV, 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.[27]

CURRENT TREATMENT OPTIONS

In England, for patients with advanced stage NSCLC who do not have a gene mutation NICE recommends: [28-31]

- Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 (with at least a 50% tumour proportion

score) and have no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations
- Pembrolizumab, with pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund, as an option for untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR) - or anaplastic lymphoma kinase (ALK)-positive mutations.
- Atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended as an option for metastatic non-squamous non-small-cell lung cancer (NSCLC) in adults whose PDL-1 tumours proportion score is between 0% and 49%
- Pembrolizumab, with carboplatin and paclitaxel is recommended within the Cancer Drugs Fund, as an option for untreated, metastatic, squamous non-small-cell lung cancer (NSCLC)

PLACE OF TECHNOLOGY

If licensed, durvalumab will offer a first line treatment option for patients with advanced/metastatic EGFR/ALK wild type NSCLC.

CLINICAL TRIAL INFORMATION

Trial	**POSEIDON**, NCT03164616, **D419MC00004**; adults aged 18 to 130 years old; durvalumab or durvalumab + tremelimumab both in combination with standard of care chemotherapy vs standard of care chemotherapy alone; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[1] Publication[4]
Location	4 EU countries (incl UK), USA and other countries.
Design	Randomized, open-label, multi-centre study
Participants	Adults aged 18 years and older; histologically or cytological documented stage IV NSCLC, confirmed tumour PD-L1 status prior to randomization; tumours lacking EGFR mutations and ALK fusions, no prior chemotherapy or any other systemic therapy for metastatic NSCLC; World Health Organisation/Eastern Cooperative Oncology Group performance status of 0 or 1; no prior exposure to immune-mediated therapy; excluding therapeutic anticancer vaccines
Schedule	Experimental Arm 1: • IV infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progression of durvalumab + tremelimumab in combination with standard of care chemotherapy Experimental Arm 2: • IV infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progression of durvalumab in combination with standard of care chemotherapy Experimental Arm 3:

	• Standard of care chemotherapy alone [b] - abraxane + carboplatin - cisplatin or carboplatin + gemcitabine (squamous patients only) - cisplatin or carboplatin + pemetrexed (non-squamous patients only)
Follow-up	Up to four years after first patient randomized to treatment arm
Primary Outcomes	• Progression-free survival using Blinded Independent Central Review (BICR) assessments according to RECIST 1.1. comparing Arm 2 vs Arm 3 [Time Frame: Up to 3 years after first patient randomized] [c] • Overall survival comparing Arm 2 vs Arm 3 [Time Frame: Up to 4 years after first patient randomisation] [c]
Secondary Outcomes	[Time Frame: Up to 3 years after first patient randomized] • Progression-free survival using BICR assessments according to RECIST 1.1 in Arm 1 vs Arm 3 [c] • Overall survival using BICR assessments according to RECIST 1.1 in Arm 1 vs Arm 3 [c] • Objective response rate using BICR assessments according to RECIST 1.1 • Duration of response using BICR assessments according to RECIST 1.1 • Time from randomization to second progression • Proportion of patients alive and progression free at 12 months from randomization using BICR assessments according to RECIST 1.1 • Best objective response using BICR assessments according to RECIST 1.1 • The pharmacokinetics of durvalumab and tremelimumab as determined by concentration • The immunogenicity of durvalumab and tremelimumab as assessed by presence of anti-drug antibodies • Health-related quality of life measured by EORTC QLQ-C30 v3 • Disease-related symptoms measured by EORTC QLQ-LC13 • Changes in WHO/ECOG performance status
Key Results	• This trial met a primary endpoint by showing a statistically significant and clinically meaningful improvement in the final PFS analysis in patients treated with the combination of durvalumab and a broad choice of five standard-of-care platinum based chemotherapy options vs chemotherapy alone. • The safety and tolerability of durvalumab was consistent with its known safety profile.
Adverse effects (AEs)	-
Expected reporting date	The reported primary completion date is April 2021

[b] Information provided by AstraZeneca UK Ltd
[c] Information provided by AstraZeneca UK Ltd

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.[32]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab for untreated PD-L1 positive non-small-cell lung cancer (ID1261). Expected publication date to be confirmed.
- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019. [CDF Review ID1683. Expected publication date 12 August 2020]
- NICE technology appraisal. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019
- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019. [CDF Review ID1584. Expected publication date to be confirmed].NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). 18 July 2018.
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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