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Durvalumab (Imfinzi) monotherapy for advanced or metastatic non-small cell lung cancer (EGFR and ALK wild type) – first line

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LAY SUMMARY

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. It is more common in older people and is primarily linked to smoking. There are several different types of NSCLC. While chemotherapy is still the main treatment option for most people with NSCLC, some targeted treatments have been developed for people with a particular gene mutation (e.g. EGFR and ALK mutations).

Durvalumab is a new drug which is delivered directly into the bloodstream. It is being trialled in people who have NSCLC which has advanced locally (in the lungs) or has spread to other parts of the body. One clinical trial focuses on patients who do not have either an EGFR or an ALK gene mutation and therefore cannot receive treatments targeted for patients with those gene mutations. If licensed, durvalumab could provide a new treatment alternative to chemotherapy.

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TARGET GROUP

Non-small cell lung cancer (NSCLC), advanced or metastatic, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild type (i.e. no mutation) – first line; monotherapy

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi; MEDI4736) is a fully human monoclonal IgG1 κ antibody directed against programmed cell death-1 ligand 1 (PD-L1; B7 homolog 1). The fragment crystallisable (Fc) domain of the antibody molecule contains a triple mutation in the constant domain of the IgG1 heavy chain, reducing binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC). It has previously been shown that the structural modification of the Fc domain is responsible for the absence of ADCC potential, and therefore, durvalumab has no ADCC activity. Durvalumab binds with high affinity and specificity to the PD-L1 receptor expressed on tumour cells. It blocks the interaction between PD-L1 and its ligands (PD-1 and CD-80 expressed on immune cells), which inhibit primary T-cell activation, and therefore restores the cytotoxic function of T-cells.[1]

Durvalumab is administered as an intravenous infusion. In the ongoing phase III trial (NCT02453282) in the first line setting for locally advanced or metastatic NSCLC (EGFR or ALK wild type), patients randomised to the durvalumab monotherapy arm receive 20 mg/kg of durvalumab intravenously every 4 weeks for up to 12 months.[2]

Durvalumab is also studied in multiple other monotherapy and combination trials (with tremelimumab and other potential new medicines) in immuno-oncology. Durvalumab is being assessed in phase III trials as a monotherapy in various stages of NSCLC, in small-cell lung cancer (SCLC), in locally advanced or metastatic urothelial carcinoma (mUC) and in head and neck squamous cell carcinoma (HNSCC). The combination of durvalumab and tremelimumab is being assessed in phase III trials in mUC, NSCLC, SCLC and HNSCC and in phase I/II trials in hepatocellular carcinoma (HCC) and haematological malignancies.[3]

Durvalumab is not approved for any indication in the UK/EU. AstraZeneca received accelerated approval from the FDA in the USA for durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma, who have disease progression during or following platinum-containing chemotherapy, or whose disease has progressed within 12 months of receiving platinum-containing chemotherapy before (neoadjuvant) or after (adjuvant) surgery. Durvalumab is approved for this mUC indication under the FDA's accelerated approval pathway, based on tumour response rate and duration of response, and continued approval is contingent upon verification and description of clinical benefit in confirmatory trials.[4]

INNOVATION and/or ADVANTAGES

Patients with NSCLC who do not have a positive EGFR or ALK mutation cannot make use of novel treatment options targeted towards these gene mutations. Novel, less toxic alternatives to chemotherapy are however also required for this patient population.[5] Durvalumab monotherapy, if licensed as first line immunotherapy, could provide an alternative treatment for patients with advanced NSCLC. However, some commentary indicates that patient selection may remain a challenge

in the coming years, as PD-L1 expression and other potential predictive biomarkers are in development.[1]

DEVELOPER

AstraZeneca (MedImmune LLC)

AVAILABILITY, LAUNCH or MARKETING

Durvalumab monotherapy is currently in phase III clinical trials for this indication.

In an earlier disease setting, durvalumab has received breakthrough status for locally advanced, unresectable NSCLC in patients whose disease has not progressed following platinum-based chemoradiation therapy.[4]

PATIENT GROUP

BACKGROUND

Lung cancer is classified into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[6] NSCLC is the more common type, accounting for approximately 90% of all lung cancers, while small cell lung cancer (SCLC) makes up the remaining tenth of all lung cancers. There are three main types of NSCLC: adenocarcinoma, which develops from mucus-producing cells that line the airways; squamous cell carcinoma, which is usually caused by smoking and also develops in the cells that line the airways; and large cell carcinoma that spreads more quickly than other types and is usually found in outer parts of the lungs – which means usual symptoms of lung cancer may not be present until much later on in the progression of the disease.

Common symptoms of lung cancer include having a cough for a long period of time (often painful, bringing up mucus or phlegm), being short of breath, coughing up blood, an ache or pain in the chest or shoulder, loss of appetite, losing weight and feeling very tired. Smoking can be linked to 86% of lung cancer cases. Other causes or risk factors include exposure to radon gas or certain chemicals in the workplace, history of other lung diseases such as tuberculosis, family history of lung cancer, previous cancer treatment, or a lowered immune system.[7]

As understanding of the pathobiology of NSCLC has improved, small molecules that target genetic mutations known to play a critical role in its progression have been developed. Epidermal growth factor receptor (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. The estimated proportion of EGFR mutations in NSCLC in England and Wales is 16.6%.[8] About 5% of NSCLCs have a rearrangement in a gene called anaplastic lymphoma kinase (ALK). This rearrangement produces an abnormal ALK protein that causes the cells to grow and spread. Mutations in EGFR and ALK are mutually exclusive in patients with NSCLC. Their presence influences patient responses to targeted therapy. The majority of people with NSCLC do not have these mutations, and have EGFR or ALK wild type NSCLC.[9, 10]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, about 87 out of 100 lung cancers are of the non-small cell type. In 2014, there were 46,403 new cases of lung cancer in the UK.[11] The prognosis for patients diagnosed with NSCLC depends on

the stage of the disease at diagnosis. Patients who are diagnosed in the earliest stages can have a five-year survival rate between 53 to 78%, however, for those diagnosed at the latest stage the five-year survival rate drops to two to 13%.[8]

The incidence of NSCLC increases with age; 60% occur in patients aged 60 years and older, and 30% to 40% occurs in patients aged 70 years and older.[12] In the UK, there were 35,419 deaths (6.2%) due to lung cancer (sub-type not specified) in 2012.[13]

In the latest Hospital Episode Statistics for England (2015/2016) there were 110,013 finished consultant episodes, 89,945 admissions to hospital and 266,522 bed days for malignant neoplasms of bronchus and lung (ICD-10 code C34).[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lung cancer (non-small-cell, untreated) - paclitaxel formulated as albumin-bound nanoparticles (with carboplatin) (ID553). Expected TBC.
- NICE technology appraisal in development. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (ID1173). Expected TBC.
- NICE technology appraisal in development. Nivolumab monotherapy for non-small-cell lung cancer (ID1088). Expected TBC.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated EGFR-positive, ALK-negative non-small-cell lung cancer (ID1143). Expected January 2019.
- NICE technology appraisal in development. Durvalumab for treating unresectable non-small-cell lung cancer after platinum-based chemoradiation (ID1175). Expected January 2019.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA447). June 2017.
- NICE technology appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). January 2017.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 2016.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). June 2010.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE clinical guidance. Lung cancer: diagnosis and management (CG121). April 2011. (Update expected in January 2019.)

- NICE diagnostic guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG9). August 2013.

NHS ENGLAND and POLICY 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. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[15]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (137). 2014.[16]
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[17]

CURRENT TREATMENT OPTIONS

NICE recommends that chemotherapy is offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. Pembrolizumab is recommended for use in some patients with untreated PD-L1-positive metastatic NSCLC.[18]

EFFICACY and SAFETY

Trial	MYSTIC, NCT02453282, D419AC00001; durvalumab monotherapy vs durvalumab plus tremelimumab vs standard of care chemotherapy; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry,[19] published trial protocol,[2] company press releases[3] [20]
Location	EU (not UK), USA, Canada and other countries (167 centres across 17 countries)
Design	Randomised, active-controlled, open-label trial

Participants	n=675; aged ≥18 years; stage IV NSCLC; no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement; no prior treatment for recurrent or metastatic NSCLC
Schedule	Patients randomised to durvalumab monotherapy receive 20 mg/kg of durvalumab intravenously every 4 weeks for up to 12 months.
Follow-up	Three years
Primary Outcomes	Efficacy of durvalumab monotherapy vs. standard of care (SoC) chemotherapy in terms of overall survival (OS); Efficacy of durvalumab + tremelimumab combination therapy compared to SoC in terms of Progression-Free Survival (PFS) and Overall Survival (OS) in patients with NSCLC. Primary endpoints of the trial only evaluate patients with PD-L1>=25%.
Secondary Outcomes	Efficacy of durvalumab monotherapy compared to SoC in terms of Objective Response Rate (ORR) or Progression-Free Survival (PFS); safety and tolerability profile of durvalumab monotherapy compared to SoC (determined using vital signs, laboratory data, electrocardiograms (ECGs), and physical examination)
Key Results	The **combination** of durvalumab and tremelimumab did not meet the primary endpoint of improving PFS compared to SoC in patients whose tumours express PD-L1 on 25% or more of their cancer cells (as determined by the VENTANA PD-L1 (SP263) assay). Although not formally tested, **durvalumab monotherapy** would not have met a pre-specified threshold of PFS benefit over SoC in this disease setting. The trial will continue to assess two additional primary endpoints of overall survival (OS) for monotherapy and OS for the combination.
Adverse effects (AEs)	-
Expected reporting date	Some results published in press release in July 2017. Final OS data expected in the first half of 2018.

ESTIMATED COST and IMPACT

COST

No information on the potential cost of durvalumab for NSCLC was available at this stage.

Following the FDA approval for urothelial carcinoma, AstraZeneca said that the average wholesale acquisition cost of durvalumab in the USA would be around USD $15,000 a month (before discounts/rebates).[21]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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