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Durvalumab in combination with tremelimumab and standard of care chemotherapy for EGFR negative, ALK negative metastatic NSCLC– 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. Certain genetic mutations (EGFR and ALK) are now known to play a critical role in the progression of NSCLC. People with the NSCLC that have the EGFR and ALK gene mutation are likely to have their disease progress faster. The majority of people with NSCLC do not have these mutations. Many treatment options are now being developed for populations with or without these gene mutations as their presence or absence influences patient responses to targeted therapy.

Durvalumab in combination with tremelimumab is being developed to be added to current standard of care chemotherapy for the treatment of patients with NSCLC who do not have the EGFR and ALK gene mutation. Both drugs are administered by intravenous infusions and act in different unique ways to stimulate the body's natural defences that fight the cancer cells. The combined effect of this potentially produces a stronger and more targeted immune response against the cancer cells when compared to current treatment. If licensed, durvalumab in combination with tremelimumab added to standard chemotherapy could provide a new first line treatment alternative to chemotherapy alone.

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TARGET GROUP

Non-Small Cell Lung Cancer (PD-L1 expressing tumours with no sensitizing EGFR mutation or ALK rearrangement, metastatic/Stage IV) – first line

TECHNOLOGY

DESCRIPTION

Durvalumab (Imfinzi) is an Fc optimized monoclonal antibody directed against programmed cell death-1 ligand 1 (PD-L1), with potential immune checkpoint inhibitory and antineoplastic activities. Upon intravenous administration, durvalumab binds to PD-L1, thereby blocking its binding to and activation of its receptor programmed death 1 (PD-1) expressed on activated T cells. This may reverse T-cell inactivation and activate the immune system to exert a cytotoxic T-lymphocyte (CTL) response against PD-L1-expressing tumour cells. PD-L1, a member of the B7 protein superfamily, is overexpressed on certain tumour cell types and on various tumour-infiltrating immune cells. PD-L1 binding to PD-1 on T cells suppresses the immune system and results in increased immune evasion. The Fc region of durvalumab is modified in such a way that it does not induce either antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[1]

Tremelimumab is a human immunoglobulin (Ig) G2 monoclonal antibody directed against the human T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4), with potential immune checkpoint inhibitory and antineoplastic activities. Tremelimumab binds to CTLA4 on activated T-lymphocytes and blocks the binding of the antigen-presenting cell ligands B7-1 (CD80) and B7-2 (CD86) to CTLA4, resulting in inhibition of CTLA4-mediated downregulation of T-cell activation. This promotes the interaction of B7-1 and B7-2 with another T-cell surface receptor protein CD28, and results in a B7-CD28-mediated T-cell activation that is unopposed by CTLA4-mediated inhibition. This leads to a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells. CTLA4, an inhibitory receptor and member of the immunoglobulin superfamily, plays a key role in the downregulation of the immune system.[2]

Durvalumab in combination with tremelimumab is under development as first line treatment in patients with metastatic non-small-cell lung cancer (NSCLC) with tumours that lack activating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions. In the phase III trial (POSEIDON; NCT03164616) durvalumab was administered by intravenous (IV) infusion every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progression or discontinuation in combination with tremelimumab administered by intravenous (IV) infusion every 3 weeks for 12 weeks (4 cycles) with an additional dose administered at week 16 with standard of care chemotherapy.[3]

Durvalumab in combination with tremelimumab does not currently have Marketing Authorisation in the EU for any indication.[1, 2]

Durvalumab in combination with tremelimumab is currently in phase III clinical trials for:[4]

- 3rd-line non-small cell lung cancer
- 1st-line bladder cancer
- 2nd-line head and neck squamous cell carcinoma
- 1st-line hepatocellular carcinoma

- 1st-line head and neck squamous cell carcinoma
- 1st-line non-small cell lung cancer
- 1st-line small cell lung cancer[a]

Durvalumab in combination with tremelimumab is currently in phase II clinical trials for:[4]

- gastric cancer
- biliary tract, oesophageal cancer

INNOVATION and/or ADVANTAGES

Patients with NSCLC who do not have a positive EGFR or ALK mutations cannot make use of novel treatment options targeted towards these gene mutations. There is a recognised need of better efficacy and safer alternatives for this patient population.[5]

The combination of durvalumab and tremelimumab allows for simultaneous inhibition of two independent pathways that act to suppress T cell responses to tumours. Targeting both checkpoint pathways provides the potential for additive or synergistic effects as the mechanisms of activation for PD-1 and CTLA-4 are non-redundant.[6]

If licensed, the combination of durvalumab and tremelimumab in addition to SoC chemotherapy, as first line treatment regime, could provide an alternative treatment for patients with metastatic NSCLC.

DEVELOPER

MedImmune (part of the AstraZeneca Pharmaceuticals Ltd group)

PATIENT GROUP

BACKGROUND

Lung cancer is classified into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[7] NSCLC is the more common type, accounting for 87% of all lung cancers in the UK. There are three main types of NSCLC: adenocarcinoma (accounting for approximately 40% of all lung cancers), which develops from mucus-producing cells that line the airways; squamous cell carcinoma (accounting for approximately 25-30% of all lung cancers), which is usually caused by smoking and also develops in the cells that line the airways; and large cell carcinoma (accounting for approximately 10-15% of all lung cancers), 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.[7, 8]

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 epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations in NSCLC in England and Wales

[a] Information provided by company

is 16.6%.[9] 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.[10, 11]

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.[12]

CLINICAL NEED and BURDEN OF DISEASE

In 2015, there were 46,388 new cases of lung cancer in the UK.[13] The prognosis for patients diagnosed with NSCLC depends on the stage of the disease at diagnosis. Patients who are diagnosed in the earliest stages (stage I and stage II) can have a one-year survival rate between 81% in males and 85% in females and 66% in males and 68% in females respectively to 78%, however, for those diagnosed at the latest stage (stage IV) the one-year survival rate drops to two to 15% for males and 19% for females.[14]

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.[15] In the UK, there were 35,419 deaths (6.2%) due to lung cancer (sub-type not specified) in 2012.[16]

In the latest Hospital Episode Statistics for England (2016/2017) there were 112,905 finished consultant episodes, 91,902 admissions to hospital and 267,931 bed days for malignant neoplasms of bronchus and lung (ICD-10 code C34).[17]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Nivolumab monotherapy for non-small-cell lung cancer (ID1088). Expected publication date TBC.
- NICE technology appraisal guidance in development. Lung cancer (non-small-cell) – afatinib (ID357). Expected publication date TBC.
- NICE technology appraisal guidance in development. Lung cancer (non-small-cell) – cetuximab (ID9). Expected publication date TBC.
- NICE technology appraisal guidance in development. Durvalumab for untreated EFRG-negative, ALK-negative non-small cell lung cancer (ID1331). Expected publication date TBC.
- NICE technology appraisal guidance in development. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (ID1306). Expected publication date TBC.
- NICE technology appraisal guidance in development. Avelumab for untreated PD-L1 positive non-small-cell lung cancer (ID1261). Expected publication date TBC.

- NICE technology appraisal guidance in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer (ID1277). Expected publication date TBC.
- NICE technology appraisal guidance in development. Atezolizumab for untreated non-squamous non-small-cell lung cancer (ID1210). Expected publication date TBC.
- NICE technology appraisal guidance in development. Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score (ID1247). Expected publication date TBC.
- NICE technology appraisal guidance in development. Lung cancer (non-small cell, advanced, inoperable) – liposomal cisplatin (with chemotherapy) (ID657). Expected publication date TBC.
- NICE technology appraisal guidance in development. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (ID1173). Expected March 2019.
- NICE technology appraisal guidance in development. Durvalumab with tremelimumab for untreated non-small-cell lung cancer with no EGFR- or ALK- positive mutations (ID1143). Expected January 2019.
- NICE technology appraisal guidance in development. Pembrolizumab for untreated PD-L1 positive metastatic non-small-cell lung cancer (CDF Review of TA447) (ID1349). Expected July 2018.
- NICE technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA447). June 2017.
- NICE technology appraisal guidance. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal guidance. Gefitinib fir the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
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- 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 (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. Photodynamic therapy for advanced bronchial carcinoma (IPG87). August 2004.

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

- National Comprehensive Cancer Network. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[18]

- European Society for Medical Oncology – ESMO. Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. 2017.[19]
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CURRENT TREATMENT OPTIONS

The main treatments available for NSCLC include surgery, chemotherapy, radiotherapy, chemoradiotherapy and symptoms control treatment. The treatment given depends on the cancer stage and how well the treatment works.[25]

The aim of treatment for stage 4 (metastatic) NSCLC is to control the cancer for as long as possible and to treat symptoms. Treatment for stage 4 NSCLC includes:[25, 26]

- Chemotherapy: should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Patients who are unable to tolerate a platinum drug can be offered a single agent chemotherapy with a third generation drug. For example, NICE recommends first line treatment with pembrolizumab for PD-L1+ NSCLC with no epidermal growth factor receptor- or anaplastic lymphoma kinase-positive mutations.
- Radiotherapy
- Symptom control treatment

EFFICACY and SAFETY

Trial	POSEIDON, NCT03164616, EudraCT-2017-000920-81, NCI-2017-02015; durvalumab + tremelimumab combination therapy + Standard of Care (SoC) chemotherapy vs durvalumab monotherapy + SoC chemotherapy vs SoC chemotherapy alone; phase III
Sponsor	AstraZeneca
Status	ongoing - recruiting
Source of Information	trial registry[3]
Location	6 EU countries (incl the UK), USA, 7 countries in Asia, 2 countries in South America, Mexico, Russian Federation and South Africa
Design	Randomised, active-controlled
Participants	n=1000 (estimated); aged 18 years and above; non-small-cell lung cancer; confirmed tumour PD-L1 status; tumours lacking activating EGFR mutations or ALK fusions; stage IV.
Schedule	Participants were randomised to one of three treatment arms:

	1. Durvalumab + tremelimumab combination therapy + SoC chemotherapy: Durvalumab IV infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progression or other discontinuation criteria. Tremelimumab IV infusions every 3 weeks for 12 weeks (4 cycles). An additional dose of tremelimumab will be administered in the week 16. Standard of care chemotherapy is given according to NSCLC subtype.* 2. Durvalumab monotherapy + SoC chemotherapy: durvalumab IV infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until disease progression or other discontinuation criteria. Standard of care chemotherapy is given according to NSCLC subtype.* 3. SoC chemotherapy alone.* *SOC chemotherapy for squamous and non-squamous NSCLC patients was abraxane + carboplatin. SOC chemotherapy for squamous NSCLC only was gemcitabine + cisplatin or gemcitabine + carboplatin. SOC chemotherapy for non-squamous NSCLC only was pemetrexed + carboplatin or pemetrexed + cisplatin.
Follow-up	Active treatment continued for up to 16 weeks and follow up was up to 3 years after the first patient was randomised.
Primary Outcomes	Progression-free survival (PFS) using Blinded Independent Central Review (BICR) assessments according to RECIST 1.1 [Time Frame: Up to 3 years after first patient randomized]
Secondary Outcomes	1. Progression-free survival using BICR assessments according to RECIST 1.1 [time frame: up to 3 years after first patient randomized] 2. Overall survival (OS) [time frame: up to 4 years after first patient randomized] 3. Objective response rate (ORR) using BICR assessments according to RECIST 1.1 [time frame: up to 3 years after first patient randomized] 4. Duration of response (DoR) using BICR assessments according to RECIST 1.1 [time frame: Up to 3 years after first patient randomized] 5. Time from randomization to second progression (PFS2) [time frame: Up to 3 years after first patient randomized] 6. Proportion of patients alive and progression free at 12 months from randomization (APF12) using BICR assessments according to RECIST 1.1 [time frame: up to 12 months] 7. Best objective response (BoR) using BICR assessments according to RECIST 1.1 [time frame: up to 3 years after first patient randomized] 8. The pharmacokinetics (PK) of durvalumab and tremelimumab as determined by concentration [time frame: up to 3 years after first patient randomized] 9. The immunogenicity of durvalumab and tremelimumab as assessed by presence of anti-drug antibodies (ADAs) [time frame: up to 3 years after first patient randomized]

	10. Health-related QoL measured by EORTC QLQ-C30 v3 [time frame: up to 3 years after first patient randomized] 11. Disease-related symptoms measured by EORTC QLQ-LC13 [time frame: up to 3 years after first patient randomized] 12. Changes in WHO/ECOG performance status [time frame: up to 3 years after first patient randomized]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date recorded as 31 July 2019 Estimated study completion date recorded as 12 July 2021

ESTIMATED COST and IMPACT

COST

The cost of durvalumab and Tremelimumab is not yet known.

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: *additional costs for IV administration in clinic*

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *results from phase III trial not yet available*

☐ None identified

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