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HEALTH TECHNOLOGY BRIEFING
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Pembrolizumab in combination with lenvatinib, platinum chemotherapy, and pemetrexed for non-small cell lung cancer

NIHRIO ID	27178	**NICE ID**	10281
Developer/Company	Merck Sharp & Dohme Ltd Eisai Co Ltd	**UKPS ID**	653313 655586

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

SUMMARY

The combination of pembrolizumab, lenvatinib, platinum chemotherapy, and pemetrexed is in clinical development for the treatment of metastatic non-squamous non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK and at the metastatic stage (stage IV), the disease has already spread from the lungs to other sites. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable.

Pembrolizumab is an immunotherapy, administered intravenously, that stimulates the body's immune system by triggering T-cells (a type of white blood cells) to find and kill cancer cells. Lenvatinib is a targeted therapy drug, administered orally, that inhibits cancer growth by preventing the formation of new blood vessels. These drugs modulate different aspects of tumour biology and combining them may result in improved efficacy and help overcome resistance to immunotherapy. If licenced, the combination of pembrolizumab, lenvatinib, platinum chemotherapy, and pemetrexed could provide an additional first line treatment for metastatic non-squamous non-small cell lung cancer (NSCLC).

PROPOSED INDICATION

First-line treatment in adults with metastatic non-squamous NSCLC.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-347) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2]

Lenvatinib (Lenvima) is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.[3]

In the phase III trial (NCT03829319) patients received carboplatin area under curve (AUC) 5mg/mL/min or cisplatin 75mg mg/m^2 via IV infusion on day 1 of a 3-week cycle, for 4 cycles plus pemetrexed 500mg/m^2 via IV infusion once every 3 weeks plus pembrolizumab IV infusion once every 3 weeks for up to 35 cycles plus lenvatinib via oral capsule once daily.[1]

INNOVATION AND/OR ADVANTAGES

Pembrolizumab in combination with pemetrexed and platinum chemotherapy is licensed for first-line metastatic, non-squamous NSCLC but pembrolizumab is not licensed for this indication in combination with pemetrexed, platinum chemotherapy and lenvatinib.[2,4] It is thought that co-inhibition of VEGF and PD-1 signalling, such as the combination of pembrolizumab and lenvatinib, could be an efficacious anti-tumour strategy.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations as well as metastatic squamous NSCLC in adults. Pembrolizumab is also currently licenced as a monotherapy for a range of cancers including NSCLC.[2]

Very common adverse events (frequency ≥ 1/10) of pembrolizumab in combination with chemotherapy include: anaemia, neutropenia, thrombocytopenia, hypokalaemia, decreased appetite, dizziness, headache, neuropathy peripheral, dysgeusia, dyspnoea, cough, diarrhoea, nausea, vomiting, constipation, abdominal pain, rash, alopecia, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, pyrexia, oedema and blood creatinine increased.[2]

Lenvatinib is currently licensed as a monotherapy for the following indications:[3]

- Progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine

- Advanced or unresectable hepatocellular carcinoma (HCC) in patients who have received no prior systemic therapy

It is also currently licenced in combination with:[6]

- Everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy

Very common adverse events (frequency ≥ 1/10) of lenvatinib as monotherapy include: urinary tract infection, thrombocytopenia, leukopenia, neutropenia, hypothyroidism, hypocalcaemia, hypokalaemia, decreased weight and appetite, insomnia, dizziness, headache, dysgeusia, haemorrhage, hypertension, hypotension, dysphonia, diarrhoea, gastrointestinal and abdominal pains, vomiting, nausea, oral inflammation and pain, constipation, dyspepsia, dry mouth, increased blood bilirubin, hypalbuminaemia, increased alanine aminotransferase, increased aspartate aminotransferase, palmar-plantar erythrodysaesthesia syndrome, rash, alopecia, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, proteinuria, fatigue, asthenia and peripheral oedema.[3]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is one of the most common and serious types of cancer. There are usually no signs or symptoms in the early stages of lung cancer, but many people with the condition eventually develop symptoms such as a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, and/or an ache or pain when breathing or coughing.[7]

Smoking cigarettes is the single biggest risk factor for lung cancer and is responsible for more than 70% of cases. Other risk factors include passive smoking, radon (a radioactive gas), and exposure to chemicals such as arsenic, asbestos, beryllium, cadmium, coal/coke, silica and nickel.[8]

NSCLC is the most common type of lung cancer. Non-squamous NSCLC is a non-small cell lung carcinoma without evidence of squamous differentiation (squamous cells are the flat cells that cover the surface of the airways).[9,10]

In addition to being diagnosed by type of lung cancer, patients will also have the cancer graded. Grading is based on how cells look under a microscope, and gives an estimate of how quickly or slowly the cancer is growing, and whether it is likely to spread.[11] Advanced lung cancer means that the cancer has spread from where it started in the lung. It is also called metastatic cancer. Advanced cancer cannot usually be cured, but treatment can control it, help symptoms and improve quality of life.[12]

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 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2015-2017). 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.[13]

In 2019/20 there were 111,188 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 132,969 finished consultant episodes

(FCEs), resulting in 243,883 FCE bed days.[14] According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,213 diagnosed cases of stage IV lung cancer in 2017, this represents 47% of the overall number of lung cancer cases diagnosed for that year.[15] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,481 cases diagnosed with stage IV in 2017 were NSCLC.[9]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.[16] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer, histology, and the general health of the patient. The main treatment options for stage I, II and III NSCLC are surgery, chemotherapy and radiotherapy. At advanced stage III disease, where patients are not candidates for surgical resection or definitive chemoradiation and stage IV metastatic disease, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.[18]

CURRENT TREATMENT OPTIONS

Current treatment options for advanced NSCLC include:[19]

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 under 50% are:

- Atezolizumab combination
- Pembrolizumab with pemetrexed and platinum chemotherapy
- Pemetrexed with cisplatin

Current first-line treatment for adults with advanced non-squamous NSCLC with PD-L1 over 50% are:

- Atezolizumab monotherapy
- Pembrolizumab
- Pembrolizumab with pemetrexed and platinum chemotherapy

PLACE OF TECHNOLOGY

If licenced, the combination of pembrolizumab, lenvatinib, platinum chemotherapy, and pemetrexed would provide an additional first line treatment for metastatic non-squamous non-small cell lung cancer (NSCLC).

CLINICAL TRIAL INFORMATION

Trial	**MK-7902-006/E7080-G000-315/LEAP-006;** NCT03829319, 2018-003824-35; A Phase 3 Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) With or Without Lenvatinib (E7080/MK-7902) as

	First-line Intervention in Participants With Metastatic Nonsquamous Non-small Cell Lung Cancer **Phase III** - Active, not recruiting **Location(s):** 4 EU countries, UK, Canada, USA and other countries. **Primary completion date:** August 2023
Trial design	Randomized, parallel assignment, quadruple-blinded
Population	N=726, histologically or cytologically confirmed diagnosis of Stage IV, nonsquamous NSCLC, aged 18 years and older
Intervention(s)	Participants receive carboplatin Area Under Curve 5 mg/mL/min (AUC5) or cisplatin 75 mg/m^2via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for 4 cycles PLUS pemetrexed 500 mg/m^2 via IV infusion Q3W PLUS pembrolizumab 200mg via IV infusion Q3W for up to 35 cycles (up to 2 years) PLUS lenvatinib 8mg via oral capsule once daily.
Comparator(s)	As above with matched lenvatinib placebo
Outcome(s)	Primary Outcomes: • Part 1: Number of Participants with a Dose-limiting Toxicity [Time Frame: Cycle 1; each cycle is 21 days (up to 21 days)] • Part 1: Number of Participants with One or More Adverse Events [Time Frame: Through 90 days post last dose of study treatment (Up to approximately 27 months)] • Part 2: Progression-free Survival (PFS) as Assessed by BICR according to RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ [Time Frame: Up to approximately 24 months] • Part 2: Overall Survival (OS) [Time Frame: Up to approximately 60 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Lenvatinib is already marketed in the UK. The NHS indicative price for 4 mg and 10 mg capsules (30 units) is £1,437.[20]

Pembrolizumab is already marketed in the UK. The NHS indicative price is:[21]
A 100 mg/4 ml concentrate for solution for infusion vial costs £2,630.

Pemetrexed is already marketed in the UK. The NHS indicative price is:[22]
- £160 for 100mg powder for concentrate for solution for infusion vials
- £800 for 500mg powder for concentrate for solution for infusion vials.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer [GID-TA10472]. Expected publication date: To Be Confirmed.
- NICE technology appraisal in development. Veliparib with carboplatin and paclitaxel for untreated non-squamous non-small-cell lung cancer [GID-TA10248]. Expected publication date: To Be Confirmed.
- NICE technology appraisal. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [TA705]. June 2021
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

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