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HEALTH TECHNOLOGY BRIEFING
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Cemiplimab as a monotherapy for advanced or metastatic non-small-cell lung cancer whose tumours express PD-L1 – first line

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Developer/Company	Sanofi	**UKPS ID**	650466

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Cemiplimab is in clinical development for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Advanced/metastatic cancer is when the cancer has spread outside of the original tumour site, into other areas of the body, and is not usually curable. A proportion of these patients are positive for a protein called PD-L1, which controls the activity of immune cells called T-cells, and therefore the ability of the immune system to attack cancer cells. Advanced NSCLC is not usually curable; there is therefore the need for additional treatment options.

Cemiplimab is a type of protein called an antibody, which can bind to PD-1 and prevent it interacting with PD-L1. Therefore, it allows the T-cells to attack the cancer cells. Cemiplimab is administered by intravenous infusion. The results from clinical trials have suggested that intravenous administration of cemiplimab increases overall survival in individuals with advanced/metastatic NSCLC who are positive for PD-L1. Therefore, if licensed, cemiplimab would offer an additional treatment option for patients with advanced/metastatic PD-L1 positive NSCLC.

PROPOSED INDICATION

First-line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 in ≥50% of tumour cells.[1]

TECHNOLOGY

DESCRIPTION

Cemiplimab (Libtayo, REGN2810) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[2]

In a phase III study, EMPOWER Lung-1 (NCT03088540), cemiplimab will be administered as a monotherapy to patients with advanced or metastatic NSCLC whose tumours express PD-L1 in ≥50% of tumour cells, and compared to standard of care chemotherapy.[1]

INNOVATION AND/OR ADVANTAGES

Approximately 85-90% of all lung cancers are NSCLC, with an estimated 20-30% of cases expected to test positive for PD-L1 in more than 50% of tumour cells.[3] The evidence that PD-L1 is commonly up-regulated in NSCLC and that PD-1 is expressed on the majority of tumour infiltrating lymphocytes, represented the rationale for the development of monoclonal antibodies against PD-L1 or PD-1. Studies so far suggest that PD-L1 positivity may correlate with response to treatment with PD-1 pathway inhibitors.[4] While immunotherapies have transformed advanced NSCLC treatment in recent years, there remains an unmet need to optimize the identification and treatment of patients with high PD-L1 expression.[3]

A protocol-specified interim analysis of the phase III study, NCT03088540, conducted by the Independent Data Monitoring Committee demonstrated that patients treated with cemiplimab monotherapy had a significant increase in overall survival. Cemiplimab decreased the risk of death by 32.4% compared to platinum doublet chemotherapy.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK/EU, cemiplimab is licensed as monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.[2]

Common or very common side effects associated with cemiplimab include: arthralgia; arthritis; asthenia; colitis; diarrhoea; hepatic disorders; hyperthyroidism; hypothyroidism; infusion related reaction; myalgia; pain; pneumonitis; skin reactions; stomatitis.[5]

Cemiplimab is also been tested in phase II/III clinical trials for:[6]

- High risk cutaneous squamous cell carcinoma (after surgery and radiation)
- Lung cancer (in combination with platinum therapy)
- Cervical cancer
- Advanced basal cell carcinoma (in patients who experienced progression of disease on hedgehog pathway inhibitor therapy, or were intolerant of prior hedgehog pathway inhibitor therapy)

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 accounts for around 85-90% of lung cancers in the UK.[9] There are three main types of NSCLC:[10]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

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. Unfortunately 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

Primary lung cancer remains the most common malignancy after non-melanoma skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.[13]

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.[14]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[15]
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 the 47% of the overall number of lung cancer cases diagnosed for that year.[16] In the UK 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.[10]

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.[17] There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[14] In England and Wales in 2018

there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer 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.[19]

CURRENT TREATMENT OPTIONS

Patients with a PD-L1 mutation in ≥ 50% tumours, and no gene mutation or fusion protein, NICE recommends a first-line treatment of immunotherapy, pembrolizumab alone or in combination with pemetrexed and platinum chemotherapy. [20]

PLACE OF TECHNOLOGY

If licensed, cemiplimab would offer an additional treatment option for patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 in ≥50% of tumour cells.[1]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT03088540; EudraCT 2016-004407-31 A Global, Randomised, Phase 3, Open-label Study of REGN2810 (ANTI-PD 1 Antibody) Versus Platinum Based Chemotherapy in First Line Treatment of Patients With Advanced or Metastatic PD L1+Non-small Cell Lung Cancer **Phase III – active, not recruiting** **Locations:** Europe (excluding the UK) and other countries **Estimated primary completion date:** November 2022
Trial design	Randomised, crossover assignment, open label study
Population	N = 712; aged 18 years and older; with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or stage IIIC disease who are not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease who received no prior systemic treatment for recurrent or metastatic NSCLC; archival or newly obtained formalin-fixed tumour tissue from a metastatic/recurrent site, which has not previously been irradiated; tumour cells expressing PD L1 above a specific percentage of tumour cells by IHC performed by the central laboratory
Intervention(s)	Cemiplimab as a monotherapy as per study protocol
Comparator(s)	Standard of care chemotherapy: - Paclitaxel + cisplatin OR - Paclitaxel + carboplatin OR

	- Gemcitabine + cisplatin OR - Gemcitabine + carboplatin OR - Pemetrexed + cisplatin with/without subsequent pemetrexed maintenance OR - Pemetrexed + carboplatin with/without subsequent pemetrexed maintenance
Outcome(s)	Primary outcomes; - Overall survival (OS) [time frame: from date of randomisation until the date of death, assessed up to 68 months] - Progression-free survival (PFS) as assessed by a blinded independent review committee using RECIST 1.1. [time frame: from date of randomisation until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 68 months] For full list of outcomes, see trial record
Results (efficacy)	A protocol-specified interim analysis of the phase III study, NCT03088540, conducted by the Independent Data Monitoring Committee demonstrated that patients treated with cemiplimab monotherapy had a significant increase in overall survival. Cemiplimab decreased the risk of death by 32.4% compared to platinum doublet chemotherapy.[3]
Results (safety)	No new cemiplimab safety signal was identified.[3]

ESTIMATED COST

Cemiplimab costs £4,650 per 350-mg vial, excluding VAT.[21]

RELEVANT GUIDANCE

NICE GUIDANCE

- 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 date of issue to be confirmed.
- NICE technology appraisal guidance. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019.
- NICE technology appraisal guidance. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019
- NICE technology appraisal guidance. Pembrolizumab with pemetrexed and platinum based chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557). January 2019.
- NICE technology appraisal guidance. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal guidance. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal guidance. Pemetrexed for the first-line treatment of non-small cell lung cancer (TA181). September 2009.

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.

NHS ENGLAND (POLICY/COMMISSIONING) 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.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[22]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[23]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.[24]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[25]

ADDITIONAL INFORMATION

This technology is co-developed and co-marketed with Regeneron Pharmaceuticals Inc.

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