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HEALTH TECHNOLOGY BRIEFING
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Canakinumab in addition to pembrolizumab and platinum-based chemotherapy for locally advanced or metastatic non-small-cell lung cancer (NSCLC)

NIHRIO ID	26910	**NICE ID**	10386
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	648450

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

SUMMARY

Canakinumab in addition to pembrolizumab and platinum-based chemotherapy is in clinical development for non-small-cell lung cancer (NSCLC). In the UK, 85% of lung cancers are NSCLC. Advanced cancers can be locally advanced or metastatic. Locally advanced (stage III) is cancer that has grown outside the body part it started in but has not yet spread to other parts of the body. Metastatic cancers (stage IV) have spread from where they started to other parts of the body.

Canakinumab will be given as a solution for injection in pre-filled syringe. Canakinumab works by stopping inflammation by blocking interleukin-1 beta (IL1β). This reduced the incidence and mortality due to lung cancer among patients with atherosclerosis in the CANTOS trial, where lung cancer incidence and mortality were secondary endpoints. Pembrolizumab is a type of immunotherapy delivered intravenously that stimulates the body's immune system to fight cancer cells. Canakinumab in combination with

pembrolizumab and platinum-based chemotherapy may offer a first-line treatment option for NSCLC patients.

PROPOSED INDICATION

Canakinumab, in addition to pembrolizumab and platinum-based chemotherapy, is indicated for the first-line treatment of previously untreated locally advanced or metastatic NSCLC in patients.[1]

TECHNOLOGY

DESCRIPTION

Canakinumab (Ilaris, ACZ885) is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a messenger molecule or 'cytokine' in the body called interleukin-1 beta (IL1β). This messenger is involved in causing inflammation and is found in high levels in patients with periodic fever syndromes, Still's disease and gouty arthritis. By attaching to IL1β, canakinumab blocks its activity, helping to reduce inflammation thereby relieving the symptoms of the diseases.[2] Canakinumab will be given as a solution for injection in pre-filled syringe.[3]

The phase III clinical trial (CANOPY-1, NCT03631199) is a two-part study. In part 1 (time frame of 18 months), participants received canakinumab 200 mg subcutaneously (s.c) every 3 weeks (Q3W) + pembrolizumab (PEM) 200 mg intravenously (i.v) (Q3W) + platinum-based Chemotherapy (Ctx) [Cohort A (non-squamous) received carboplatin (CBCDA) + pemetrexed (PTX); Cohort B (non-squamous) received cisplatin + PTX; Cohort C (squamous or non-squamous) received CBCDA + paclitaxel]. In part 2 (time frame of 38 months), participants will be randomised to receive canakinumab/placebo (Pb) + PEM + platinum-based Ctx (patients with non-squamous NSCLC received CBCDA or cisplatin + PTX; patients with squamous NSCLC received CBCDA + paclitaxel or nab-paclitaxel).[1,4]

INNOVATION AND/OR ADVANTAGES

The investigation of IL-1β inhibition with canakinumab as a therapeutic target in NSCLC was prompted by the results of the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial. In this Phase III study, canakinumab was evaluated in the secondary prevention of cardiovascular events in post-myocardial infarction patients with CRP ≥2 mg/l. During this trial, it was observed that compared with placebo, lung cancer occurrence was lower in the canakinumab arms.[5]

Immune checkpoint inhibitors, specifically PD-1 directed agents such as pembrolizumab, have changed the treatment paradigm of NSCLC. Initial studies have demonstrated a survival advantage with these agents in patients with recurrent NSCLC and recent data suggests that the addition of these agents to chemotherapy may improve survival compared with chemotherapy alone.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Canakinumab is currently indicated, through subcutaneous injection, in the UK for the following:[7]

- Periodic fever syndromes
    - Cryoprin-associated periodic syndromes
    - Tumour necrosis factor receptor-associated periodic syndrome
    - Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency
    - Familial Mediterranean fever
- Gouty arthritis
- Still's disease

The most frequent (≥10%) adverse drug reactions were infections predominantly of the upper respiratory tract, this includes pneumonia, bronchitis, influenza, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis and upper respiratory tract infection. Other very common adverse reactions include ear infection, cellulitis, gastroenteritis, and urinary tract infections.[7]

Canakinumab is currently in clinical development for the following indications:

- In phase II for myelodysplastic syndrome, multiple leukaemia conditions (e.g. chronic myelomonocytic leukaemia), lung carcinoma, knee osteoarthritis, mild cognitive impairment, Alzheimer disease, NSCLC, Duchenne muscular dystrophy, HIV, cardiovascular disease, alcoholic hepatitis, and melanoma.[8]
- In phase III for Adult-Onset Still's Disease, NSCLC, COVID-19, and type 2 diabetes.[9]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is the uncontrolled growth of abnormal cells in one or both lungs.[10] 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).[11] Anaplastic lymphoma kinase (ALK) rearrangements occur in approximately 5% of patients with NSCLC. While initially identified as echinoderm microtubule-associated protein-like 4- (EML4-) ALK, fusions with a variety of other genes have been reported, all leading to dysregulated over-expression of ALK. Patients with ALK positive tumours tend to be younger and more likely to be never or light smokers with ALK rearrangements occurring in 12% of never-smokers compared to only 2% of former or current smokers. ALK rearrangements almost never co-occur with activating mutations in epidermal growth factor receptor (EGFR) or KRAS. As compared to patients with EGFR mutant NSCLC, patients with ALK-positive tumours are more likely to be men and radiographically, are associated with larger volume, multifocal thoracic lymphadenopathy.[12]

Advanced cancers can be locally advanced or metastatic. Locally advanced is cancer that has grown outside the body part it started in but has not yet spread to other parts of the body. Metastatic cancers have spread from where they started to other parts of the body. Cancers that have spread are often thought of as advanced when they can't be cured or controlled with treatment. Not all metastatic cancers are advanced cancers.[13]

A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors. 79% of lung cancer cases are preventable caused by things such as smoking, workplace exposures, air pollution and ionising radiation.[14] There are usually no signs or symptoms in the early stages. Symptoms of lung cancer develop as the condition progresses. The main symptoms of lung cancer include a cough that doesn't go away after 2 or 3 weeks, a long-standing cough that gets worse, chest infections that keep coming back, coughing up blood, an ache or pain when breathing or coughing, persistent breathlessness, persistent tiredness or lack of energy, loss of appetite or unexplained weight loss.[15]

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. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (2015-2017).[16] 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.[17]

In 2019/20 there were 111,188 hospital admissions with a primary diagnosis of malignant neoplasm of bronchus and lung (ICD-10 code C34) resulting in 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.[18]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 7,564 diagnosed cases of stage III lung cancer and 18,213 diagnosed cases of stage IV lung cancer in 2017; this represents 66% of the overall number of lung cancer cases diagnosed for that year.[19] In the UK it is estimated that 85% of lung cancers are NSCLC, applying this figure to the number of stage III and IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 6,429 were stage III NSCLC and 15,481 were stage IV NSCLC.[11,19]

Survival from lung cancer depends on many different factors, including the type and stage of cancer, the patients' level of fitness, and previous treatment.[20] In England (2013-2017, followed up to 2018), the 1-year survival rate for people with stage III lung cancer was 48.7% and the 5-year survival rate was 12.6%. For people with stage IV cancer, the 1-year survival rate 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 the trachea, bronchus and lung in England (ICD-10 code C33-34).[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment options for NSCLC are based mainly on the stage (extent) of cancer, but other factors, such as a person's overall health and lung function, as well as certain traits of the cancer itself, are also important. The main treatment options for the locally advanced or metastatic disease include surgery, chemotherapy, systemic anti-cancer therapy (SACT) and radiotherapy.[23]

At stage III and 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.[24]

CURRENT TREATMENT OPTIONS

NICE guidelines currently recommend the following first-line treatment options for patients with NCSCLC and a known PD-L1 determination:

- Non-squamous with PD-L1 under 50% (no gene mutation, fusion protein or biomarker):[25]
  - Atezolizumab combination
  - Pembrolizumab with pemetrexed and platinum chemotherapy
  - Pemetrexed with cisplatin
- Non-squamous with PD-L1 50% or over:[26]
  - Atezolizumab monotherapy
  - Pembrolizumab with pemetrexed and platinum chemotherapy
  - Pembrolizumab
- Squamous with PD-L1 under 50%:[27]
  - Pembrolizumab with carboplatin and paclitaxel
- Squamous with PD-L1 50% or over:[28]
  - Atezolizumab monotherapy
  - Pembrolizumab
  - Pembrolizumab with carboplatin and paclitaxel

PLACE OF TECHNOLOGY

If licenced, canakinumab in addition to pembrolizumab and platinum-based chemotherapy will offer a first-line treatment of locally advanced or metastatic NSCLC in patients.[1]

CLINICAL TRIAL INFORMATION

Trial	**CANOPY-1; NCT03631199, EudraCT-2018-001547-32;** A Randomized, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Pembrolizumab Plus Platinum-based Doublet Chemotherapy With or Without Canakinumab as First-Line Therapy for Locally

	Advanced or Metastatic Non-squamous and Squamous Non-small Cell Lung Cancer Subjects (CANOPY-1) **Phase III:** Active, not recruiting **Location(s):** 16 EU countries, UK, USA, Canada, and other countries. **Primary Completion Date:** July 2021
Trial design	Double-blind, randomised, parallel assignment, open-label.
Population	N=673; adults aged 18 years and older; histologically confirmed locally advanced stage IIIB or stage IV NSCLC for treatment in the first-line setting; known PD-L1 status.

Intervention(s)	• In part 1 (time frame of 18 months):[1,4]
	  ○ Participants received canakinumab 200 mg s.c (Q3W) + PEM 200 mg i.v (Q3W) + platinum-based Chemotherapy (Ctx)
	• In part 2 (time frame of 38 months):[1,4]
	  ○ Participants will be randomised to receive canakinumab/Pb + PEM + platinum-based Ctx

Comparator(s)	• In part 1 (time frame of 18 months): [1,4]
	  ○ Cohort A (non-squamous): carboplatin (CBCDA) + pemetrexed (PTX)
	  ○ Cohort B (non-squamous): cisplatin + PTX
	  ○ Cohort C (squamous or non-squamous): CBCDA + paclitaxel
	• In part 2 (time frame of 38 months): [1,4]
	  ○ Non-squamous: CBCDA or cisplatin + PTX
	  ○ Squamous: CBCDA + paclitaxel or nab-paclitaxel

Outcome(s)	Primary outcome(s): • Safety run-in (6 months): Incidence of dose-limiting toxicities (DLT) [Time Frame: 6 months from start of safety run-in] • Progression-free survival (PFS) per investigator assessment using RECIST v1.1 [Time Frame: 18 months from randomisation] • Overall survival (OS) per investigator assessment using RECIST v1.1 [Time Frame: 38 months from randomisation] See trial record for the full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indictive price for canakinumab is £9,927.80 for a 150mg/1ml solution for injection vials (150mg/ml).[29]

The NHS indictive price for pembrolizumab is £2,630 for a 100mg/4ml concentrate for solution for infusion vial (25mg/ml) costs.[30]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA683). March 2021.
- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA600). September 2019.
- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 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. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). December 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

- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[31]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[32]

ADDITIONAL INFORMATION

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