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Newcastle University

Health Technology Briefing
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Tusamitamab Ravtansine for previously treated advanced Non-Small-Cell Lung Cancer

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28873	NICE ID: 10735	UKPS ID: 662689

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Tusamitamab ravtansine is being developed for previously treated, CEACAM5 positive metastatic non-squamous non-small-cell lung cancer (NSCLC). This form of lung cancer develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung. Metastatic NSCLC is when the cancer has spread beyond the lung that was initially affected, most often to the liver, adrenal glands, bones, and the brain. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. There is therefore the need for additional treatment options.

Tusamitamab ravtansine targets CEACAM5 molecules on tumour cells. When tusamitamab ravtansine binds, a cytotoxic agent is released which results in tumour cell death. As CEACAM5 is overexpressed on the surface of tumour cells in some patients with NSCLC, but is not found in normal lung tissue, this treatment mechanism may be able to destroy cancer cells without having a large effect on normal lung cells. Tusamitamab ravtansine is administered intravenously (IV). If licensed, Tusamitamab ravtansine will be an additional treatment option for individuals with advanced, non-squamous CEACAM5 positive NSCLC.

Proposed Indication

Tusamitamab ravtansine is being developed for previously treated, CEACAM5 positive metastatic non-squamous NSCLC.[1]

Technology

Description

Tusamitamab ravtansine (SAR408701) is an immunoconjugate consisting of anti-CEACAM5 conjugated to a cytotoxic agent, with potential antineoplastic activity. Tusamitamab ravtansine targets CEACAM5 on tumour cells. CEACAM5, a member of the CEA family of proteins plays a key role in cell migration, cell invasion, and cell adhesion, and is overexpressed by a variety of cancer cell types including in NSCLC. Upon antibody/antigen binding, the immunoconjugate releases the cytotoxic agent, which results in tumour cell death.[2,3]

Tusamitamab ravtansine is being developed for previously treated, CEACAM5 positive non-squamous NSCLC. In the phase III trial (CARMEN-LC03; NCT04154956) tusamitamab ravtansine is administered via IV once every 2 weeks for approximately 6.5 months, but may vary based on progression date.[1]

Key Innovation

In patients with metastatic NSCLC lacking targetable mutations who progress on immunotherapy and platinum-based chemotherapy, treatment options are generally limited to docetaxel ± a VEGF inhibitor such as ramucirumab.[4]

CEACAM5 is overexpressed on the surface of multiple solid tumours, including in about 20% of patients with NSCLC adenocarcinoma, but is not found in normal lung tissue. This makes CEACAM5 a potentially attractive therapeutic target. Currently, tusamitamab ravtansine, an antibody-drug conjugate (ADC), is the most advanced novel agent in clinical testing targeting CEACAM5 specifically in patients with NSCLC.[2]

Regulatory & Development Status

Tusamitamab ravtansine does not currently have Marketing Authorisation in the EU/UK for any indication.

Tusamitamab Ravtansine is also in phase II trials for breast cancer, pancreatic carcinoma, gastric cancer and other solid tumours.[5]

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main types: small-cell lung cancer and NSCLC. NSCLC comprises approximately 80 to 85% of lung cancers in the UK and can be classified into three different types (adenocarcinoma, squamous cell, and large cell carcinoma) according to how the cancer behaves. Approximately 30% of NSCLC cases are classified as squamous cell, where the cancer develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung.[6,7] Metastatic (stage IV) lung cancer is the most advanced form of lung cancer where the cancer has spread from the site of origin in the lung to other parts of the body.[8] Tobacco smoking is the primary cause of lung cancer and

the biggest risk factor. Other risk factors include passive smoking, increasing age, exposure to high levels of radon gas, exposure to chemicals e.g. asbestos, previous cancer treatment, lowered immunity and family history of lung cancer.[9] Symptoms of advanced (metastatic) lung cancer include: a persistent cough; a change in cough that has been present for a long time; breathlessness; unexplained weight loss; ongoing chest infections; coughing up blood; a hoarse voice; difficulty swallowing; finger clubbing; swelling of the face; and loss of appetite.[10,11]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017.[12] In England (2017), the European-age standardised incidence rates of lung cancer was 86.9 per 100,000 amongst males and 67.0 per 100,000 amongst females.[13] Lung cancer incidence rises with increasing age; 44% of all new lung cancer cases in the UK were diagnosed in those aged 75 and over, and the highest incidence rate occurs amongst those aged 85-89 (2015-2017). Incidence rates for lung cancer in the UK are predicted to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[12] 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, and 70% of these are classified as non-squamous cell NSCLC. Applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,480 lung cancer cases diagnosed at stage IV are non-squamous cell NSCLC.[16,17] It is not possible to estimate how many of these will be CEACAM5 positive, based on information in published sources.

Recommended Treatment Options

There is no specific guidance for the treatment of CEACAM5 positive advanced non-squamous NSCLC. For previously treated advanced non-squamous cell NSCLC with PD L1 > 50%, the National Institute for Health and Care Excellence (NICE) recommends:[18]

- Nintedanib in combination with docetaxel or docetaxel monotherapy if there has been treatment progression after first-line chemotherapy with pembrolizumab combination
- On progression after pembrolizumab monotherapy, pemetrexed with carboplatin or other platinum doublet chemotherapy
- Pemetrexed when patient's disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their ECOG performance status is 0 or 1 at the start of maintenance treatment

For previously treated advanced non-squamous cell NSCLC with PD L1 < 50%, the National Institute for Health and Care Excellence (NICE) recommends:[18]

- Nintedanib in combination with docetaxel or docetaxel monotherapy if there has been treatment progression after first-line chemotherapy with pembrolizumab combination or atezolizumab combination
- Pemetrexed when patient's disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their ECOG performance status is 0 or 1 at the start of maintenance treatment
- Atezolizumab for PD L1 negative tumours in adults who have had chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour) if atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses

- Nivolumab for PD-L1 positive tumours after chemotherapy if it is stopped at 2 years of uninterrupted treatment, or earlier if their disease progresses, and the patient has not had a PD-1 or PD-L1 inhibitor before.

Clinical Trial Information

Trial	**CARMEN-LC03,** NCT04154956; 2019-001273-81; Randomized, Open Label Phase 3 Study of SAR408701 Versus Docetaxel in Previously Treated Metastatic Non- Squamous Non-Small Cell Lung Cancer Patients With CEACAM5 Positive Tumours **Phase III -** Recruiting **Location(s):** 11 EU countries, Canada, United States and other countries **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, open label
Population	N = 544; adults aged 18 years and older with histologically or cytologically proven diagnosis of non-squamous NSCLC with CEACAM 5 expression with metastatic disease at study entry, that had disease progression after platinum-based chemotherapy and immune checkpoint inhibitor.
Intervention(s)	Tusamitamab ravtansine via IV infusion
Comparator(s)	Docetaxel via IV infusion
Outcome(s)	Primary Outcome Measures: • Progression free survival (PFS) [Time frame: baseline to up to approximately 15 months from randomisation] • Overall Survival (OS) [Time frame: baseline up to approximately 2 years]. OS will be defined as the time of randomization to the date of death due to any cause. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tusamitamab ravtansine is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy. (TA713). July 2021.

- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- 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 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

- NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021[19]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[20]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[21]

Additional Information

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