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Newcastle University

Health Technology Briefing
January 2023

Telisotuzumab vedotin for previously treated c-MET overexpressing EGFR wild-type non-squamous non-small cell lung cancer

Company/Developer	AbbVie

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 25466	NICE TSID: 10684	UKPS ID: 654241

Licensing and Market Availability Plans

Currently in phase 2/3 clinical trials.

Summary

Telisotuzumab vedotin is in development for the treatment of c-Met+ non-small cell lung cancer. Non-small cell lung cancer is the most common form of lung cancer. A c-Met is a protein in humans that is encoded by the MET gene that leads to growth in cells. Smoking is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace carcinogens, radiation exposure, environmental pollution, and family history of lung cancer. Current standard of care treatment can help to control the cancer for some time and reduce symptoms, however, sometimes non-small cell lung cancer can continue to grow despite chemotherapy and immunotherapy.

Telisotuzumab vedotin is administered intravenously and targets the c-Met proteins expressed by the tumour cells. Upon binding, a cytotoxic agent, a substance that causes damage to cells, is released into the cancer cell leading to cell death and shrinkage of the tumour. If licensed telisotuzumab vedotin will offer a new treatment for c-Met+ non-small cell lung cancer.

Proposed Indication

Previously Treated c-Met+ Non-Small Cell Lung Cancer.[1]

Technology

Description

Telisotuzumab vedotin (ABBV-399), is a first-in-class antibody–drug conjugate (ADC) composed of the anti–c-Met humanized monoclonal antibody ABT-700 coupled to the cytotoxic monomethyl auristatin E (MMAE) through a valine–citrulline linker (ABT-700–vcMMAE).[2] Telisotuzumab vedotin targets c-Met–expressing tumour cells with specific and high-affinity binding, and it mediates the delivery of MMAE directly to tumour cells.[3] Engagement of c-Met by telisotuzumab vedotin results in the internalisation of the ADC and intracellular release of MMAE after proteolysis of the linker. MMAE then binds to tubulin, thereby inhibiting mitosis and causing tumour cell death.[2,4] Preclinical studies have indicated that telisotuzumab vedotin has antitumour activity in c-Met expressing cells with and without MET gene amplification.[2,3,5]

In the phase II trial (LUMINOSITY, NCT03539536), telisotuzumab vedotin is being developed in a second or third line setting for NSCLC in populations that overexpress c-Met. Telisotuzumab vedotin will be administered via intravenous infusion (IV) every 14 days.[1] A phase III trial (NCT04928846), to study the disease activity and adverse events of IV telisotuzumab vedotin in patients with previously treated NSq NSCLC, is also currently recruiting.[6]

Key Innovation

C-Met is known to be overexpressed, mutated and gene amplified, specifically in NSCLC, and has also been implicated in the development of resistance against other small-molecule inhibitors.[5,7] Currently there are no approved pharmacological treatment options specifically for c-Met overexpressing NSCLC.[8] Telisotuzumab vedotin is a first-in-class ADC targeting c-Met which has shown a tolerable safety profile and antitumour activity in c-Met overexpressing NSCLC.[9] If licenced, telisotuzumab vedotin will offer the first treatment option specific to patients with c-Met overexpressing NSCLC.

Regulatory & Development Status

Telisotuzumab vedotin does not currently have marketing authorisation in the EU/UK for any indication.

Telisotuzumab vedotin is also in phase II development for adults with advanced/metastatic non-squamous NSCLC.[10]

Telisotuzumab vedotin has been designated as a breakthrough therapy by the US Food and Drug administration (FDA) for the treatment of patients with advanced/metastatic EGFR Wild-type, non-squamous cell NSCLC with high levels of C-Met over expression whose disease has progressed on or after platinum-based therapy in December 2021.[11]

Patient Group

Disease Area and Clinical Need

NSCLC is the most common form of lung cancer. Around 80 to 85% of lung cancer cases in the UK are NSCLC. The three main types are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[12] C-mesenchymal-epithelial is known to be overexpressed, mutated and gene amplified, specifically in NSCLC, and has also been implicated in the development of resistance against other small-molecule inhibitors (e.g. EGFR).[7] Stage 3 NSCLC is considered a locally advanced cancer, meaning the tumour has not spread to distant regions of the body but it is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest.[13-15] Metastatic NSCLC is a stage of NSCLC where the cancer has spread from the primary site (in the lung) to a secondary site in other parts of the body.[15] NSCLC would usually be considered metastatic at stage 4.[15] The most common symptoms of lung cancer are a persistent cough, easily becoming out of breath, coughing up phlegm with blood in it, having an ache or pain in the chest or shoulder, persistent chest infections, loss of appetite, chronic fatigue and unintentional weight loss.[16] The risk factors for NSCLC include; smoking, being exposed to second hand smoke, being exposed to asbestos, arsenic, chromium, beryllium, nickel, soot or tar in the workplace, being exposed to radiation, living where there is air pollution, having a family history of lung cancer, being infected with human immunodeficiency virus (HIV) and being older age. When smoking is combined with any of the other risk factors, the risk of lung cancer is increased.[17]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016-2018).[18] The age standardised incidence rate of lung cancer in England (2016-2018) is 88.4 and 67.4 per 100,000 amongst males and females respectively.[18] In England (2021-22), there were 119,396 finished consultant episodes (FCEs) and 99,551 hospital admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 75,969 day cases and 206,640 FCE bed days.[19] In England (2017), there were 38,888 patients diagnosed with malignant neoplasm of bronchus and lung and 28,170 deaths where malignant neoplasm of bronchus and lung was the underlying cause. In England, there were 7,564 newly diagnosed cases of stage 3 lung cancer and 18,213 newly diagnosed cases of stage 4 lung cancer.[20] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage III lung cancer were 48.7% and 12.6% respectively. The 1-year and 5-year survival rates for stage IV lung cancer were 19.3% and 2.9% respectively.[21]

Recommended Treatment Options

Treatment for lung cancer includes surgery, chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. People may be offered one or more different treatments depending on the stage, histology, and type of lung cancer as well as their general health. Systemic anti-cancer treatments are increasingly used to treat advanced NSCLC.[22]

There are currently no approved pharmacological treatment options for previously treated c-MET overexpressing NSCLC.

Clinical Trial Information

Trial	**LUMINOSITY;** NCT03539536; EudraCT2018-001772-38; Phase 2, Open-Label Safety and Efficacy Study of Telisotuzumab Vedotin (ABBV-399) in Subjects With Previously Treated c-Met+ Non-Small Cell Lung Cancer. **Phase II:** Recruiting **Location(s):** 15 European Countries, UK, Canada, USA, and other countries

	Primary completion date: September 2025
Trial Design	Open label, single group assignment
Population	N=270 (estimated); histologically confirmed NSq NSCLC with known EGFR status, has locally advanced or metastatic NSCLC, has c-Met+ NSCLC, have received no more than 2 lines of prior systemic therapy in the locally advanced or metastatic setting.
Intervention(s)	Telisotuzumab vedotin
Comparator(s)	No comparators used
Outcome(s)	Primary outcome measures: • Overall Response Rate (ORR) (Stage 1 and Stage 2) [Time Frame: Up to approximately 3 years] ORR is defined as the percentage of participants with a confirmed complete response (CR) or confirmed partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. • Number of Participants with Adverse Events (Alternate dose cohort) [Time frame: Up to approximately 3 years] See trial record for full outcome lists.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT04928846; EudraCT2021-001811-94; A Phase 3 Open-Label, Randomized, Controlled, Global Study of Telisotuzumab Vedotin (ABBV-399) Versus Docetaxel in Subjects With Previously Treated c-Met Overexpressing, EGFR Wildtype, Locally Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer **Phase III**: Recruiting **Location(s)**: 19 EU countries, UK, USA, Australia and Canada **Primary completion date:** June 2025
Trial Design	Randomised, parallel assignment, no masking
Population	N=698 (estimated), participants must have c-Met overexpressing NSCLC, a histologically documented non-squamous cell NSCLC that is locally advanced or metastatic, a known EGFR activating mutation status, have received no more than one line of prior systemic cytotoxic chemotherapy.
Intervention(s)	Telisotuzumab vedotin (IV infusion)
Comparator(s)	Docetaxel (IV infusion)
Outcome(s)	The primary outcome measures: • Progression free survival (PFS) per independent central review (ICR) [Time frame: up to approximately 39 months]

	• Overall survival (OS) [Time frame: up to approximately 39 months] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of Telisotuzumab Vedotin is not yet known.

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance. Nintedanib for previously treated locally advanced, metastatic or locally recurrent non-small cell lung cancer (TA347). July 2015.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). December 2012.
- NICE interventional procedures guidance. Microwave ablation for primary or metastatic cancer in the lung (IPG716). February 2022.
  NICE interventional procedures guidance. Percutaneous radiofrequency ablation for primary or secondary lung cancers (IPG372). December 2010.

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.[23]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2019.[24]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[25]

Additional Information

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