Health Technology Briefing
October 2023

Tiragolumab with atezolizumab and pemetrexed and carboplatin or cisplatin for previously untreated advanced non-small-cell lung cancer

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30858	NICE TSID: N/A	UKPS ID: 665697

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Tiragolumab in combination with atezolizumab, pemetrexed and carboplatin or cisplatin is currently in development for patients with previously untreated locally advanced unresectable or metastatic programmed death-ligand 1 (PD-L1) selected non-small cell lung cancer (NSCLC). NSCLC makes up most lung cancers in the UK. 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. Symptoms of lung cancer include cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. However, patients may not always be symptomatic in the early stages. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable.

Tiragolumab is administered intravenously (IV) and is a monoclonal antibody targeting the TIGIT protein which expresses immune responses to cancer. Tiragolumab helps the mechanism of action of the combination treatments which inhibit PD-L1/PD-1 proteins, that aid tumour growth. A phase II clinical trial has shown that atezolizumab in combination with tiragolumab, results in improved patient outcomes compared to atezolizumab alone. Therefore, if licensed, tiragolumab will offer an additional treatment option for patients with previously untreated locally advanced unresectable or metastatic PD-L1-selected NSCLC.

Proposed Indication

Patients with previously untreated locally advanced unresectable or metastatic programmed death-ligand 1 (PD-L1) selected non-small cell lung cancer (NSCLC).[1]

Technology

Description

Tiragolumab (Tecentriq) is a fully human monoclonal antibody IgG1/kappa with an intact Fc region targeting TIGIT (T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif) which is expressed on natural killer cells and T cells. It inhibits immune-cell activity by binding to the receptor/poliovirus receptor (PVR) ligand on tumour and antigen-presenting cells, and its expression strongly correlates with that of PD-1.[2,3]

Tiragolumab in combination with atezolizumab, pemetrexed and carboplatin or cisplatin is currently in clinical development for patients with previously untreated locally advanced unresectable or metastatic PD-L1-selected NSCLC. In the phase III clinical trial SKYSCRAPER-06 (NCT04619797), tiragolumab at a fixed dose of 600 milligrams (mg), atezolizumab at a fixed dose of 1200 mg, pemetrexed 500 milligrams per square meter (mg/m^2) will be administered by intravenous (IV) infusion, every 3 weeks (Q3W) on day 1 of each 21-day cycle. Carboplatin at dose of area under the concentration-time curve of 5 or cisplatin 75 mg/m^2, administered by IV infusion, every 3 weeks on day 1 of each 21-day cycle for 4 cycles.[1]

Key Innovation

It has been theorised that anti-TIGIT antibodies, such as tiragolumab, which prevent TIGIT from binding to its ligand, could restore the antitumour response and could complement the activity of anti–PD-L1/PD-1 antibodies.[2] Tiragolumab is the first anti-TIGIT molecule to be granted Breakthrough Therapy Designation (BTD) from the US Food and Drug Administration (FDA), and the designation is based on randomised data from the phase II CITYSCAPE (NCT03563716) trial.[4,5]

Tiragolumab in combination with atezolizumab, has shown a clinically meaningful improvement in objective response rate and progression-free survival compared with placebo plus atezolizumab, in patients with chemotherapy-naive, PD-L1-positive, metastatic NSCLC. Tiragolumab in combination with atezolizumab was well tolerated, with a safety profile like that of atezolizumab alone. Therefore, tiragolumab in combination with atezolizumab is a promising immunotherapy combination for the treatment of previously untreated, locally advanced unresectable or metastatic NSCLC.[6]

The SKYSCRAPER-06 trial (NCT04619797) is part of a broad development program that builds on the benefit observed with atezolizumab while expanding into earlier stages of disease and new areas of unmet need.[1,7] By exploring a novel combination of tiragolumab with atezolizumab, pemetrexed and carboplatin or cisplatin, may further enhance anti-tumour activity by potentially amplifying the immune response.[7] Therefore, if licensed, tiragolumab with atezolizumab and pemetrexed and carboplatin or cisplatin would offer an additional treatment option for patients previously untreated locally advanced unresectable or metastatic PD-L1-selected NSCLC.

Regulatory & Development Status

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

Tiragolumab is in phase II/III clinical development for the following indications: [8]

- Bladder cancer
- Cell carcinoma
- Cervical cancer
- Endometrial cancer
- Gastric cancer
- Head and neck cancer
- Liver cancer
- Lymphoma
- Melanoma
- Non-small cell lung cancer
- Oesophageal cancer
- Pancreatic cancer
- Rectal cancer
- Urothelial carcinoma

Tiragolumab has the following regulatory designation:

- BTD by the US FDA, in combination with atezolizumab for the first-line treatment of people with metastatic NSCLC whose tumours have high PD-L1 expression with no EGFR or ALK genomic tumour aberrations in January 2021.[9]

Patient Group

Disease Area and Clinical Need

There are different types of primary lung cancer, and they are divided into 2 main groups: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 80 to 85% of lung cancers in the UK. There are three common types of NSCLC: adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways); squamous cell cancer (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).[10] Stage 4 non-small cell lung cancer is also called metastatic (advanced) lung cancer and means the cancer has spread to beyond the lung.[11] If the cancer is also unresectable, it means the cancer or tumour cannot be removed completely through surgery.[12] The following factors may raise the risk of developing NSCLC: smoking tobacco, exposure to asbestos air pollution and exposure to radon gas.[13] Other factors include: family history of lung cancer, lowered immunity and previous cancer treatment.[14] The main symptoms of lung cancer include: a persistent cough, recurrent chest infections, coughing up blood, painful breathing, persistent breathlessness, persistent tiredness, unexplained weight loss and loss of appetite.[15]

Lung cancer is one of the most common and serious cancers in the UK. More than 43,000 new lung cancer cases in the UK yearly.[16] In the UK it is estimated that up to 85% of 100 lung cancer cases are NSCLC, which would mean around 40,800 of the annual new lung cancer cases are NSCLC.[10] In England, 2022-23, there were 122,866 finished consultant episodes (FCE) of malignant neoplasm of bronchus and lung (ICD-10 code C34), resulting in 80,131 day cases and 217,569 FCE bed days.[17] 1 in 10 (9.5%) people diagnosed with lung cancer in England survive their disease for ten years or more, it is predicted (2013-2017) but lung cancer survival has not shown much improvement in the last 50 years in the UK.[18] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV (metastatic) was 19.3% at one year and 2.9% at five years, and for stage III it was 48.7% at one year and 12.6% at five years.[19]

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.[20] Recommendations by the National Institute for Health and Care Excellence (NICE) include the following systemic anti-cancer treatments for people with:[21] Non-squamous NSCLC with no targetable mutations and PD-L1 <50% • Pemetrexed and cisplatin • Pemetrexed and carboplatin • Atezolizumab and bevacizumab, carboplatin and paclitaxel • Pembrolizumab and pemetrexed and platinum chemotherapy Non-squamous NSCLC with no targetable mutations and PD-L1 ≥ 50% • Pembrolizumab and pemetrexed and platinum chemotherapy • Pembrolizumab • Atezolizumab The following treatment options are licensed in the UK for the first line treatment of advanced NSCLC:[22,23] • Vinorelbine • Gemcitabine

Clinical Trial Information	
Trial	**SKYSCRAPER-06; NCT04619797 EudraCT; 2020-002851-39;** A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study of Tiragolumab in Combination With Atezolizumab Plus Pemetrexed and Carboplatin/Cisplatin Versus Pembrolizumab Plus Pemetrexed and Carboplatin/Cisplatin in Patients With Previously Untreated Advanced Non-Squamous Non-Small-Cell Lung Cancer. **Phase II/III** – Recruiting **Location(s):** 8 EU countries, UK, USA, Canada, and other countries **Primary completion date:** May 2027
Trial Design	Randomised, parallel assignment, quadruple blinding
Population	N = 540 (planned); aged 18 years and older; participant must have histologically or cytologically documented locally advanced unresectable or metastatic non-squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy.
Intervention(s)	• Tiragolumab at a fixed dose of 600 mg, administered by IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle. • Atezolizumab at a fixed dose of 1200 mg, administered by IV infusion, Q3W on Day 1 of each 21-day cycle.

	• Pemetrexed 500 mg/m^2, administered by IV infusion, Q3W on Day 1 of each 21-day cycle. And: • Carboplatin at dose of area under the concentration-time curve (AUC) of 5, administered by IV infusion, Q3W on Day 1 of each 21-day cycle for 4 cycles. Or: • Cisplatin 75 mg/m^2, administered by IV infusion, Q3W on Day 1 of each 21-day cycle for 4 cycles.
Comparator(s)	• Tiragolumab matching placebo, administered by IV infusion, Q3W on Day 1 of each 21-day cycle. • Pembrolizumab at a fixed dose of 200 mg, administered by IV infusion, Q3W, on Day 1 of each 21-day cycle. • Pemetrexed 500 mg/m^2, administered by IV infusion, Q3W on Day 1 of each 21-day cycle. And: • Carboplatin at dose of AUC of 5, administered by IV infusion, Q3W on Day 1 of each 21-day cycle for 4 cycles. Or: • Cisplatin 75 mg/m^2, administered by IV infusion, Q3W on Day 1 of each 21-day cycle for 4 cycles.
Outcome(s)	Primary outcomes: • Investigator-Assessed Confirmed Objective Response Rate (ORR) (Phase 2) [Time Frame: Up to approximately 5 years] • Investigator-Assessed Progression-Free Survival (PFS) (Phase 2 and Phase 3) [Time Frame: From randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 5 years [Phase 2], up to approximately 7 years [Phase 3])] • Overall Survival (Phase 3) [Time Frame: From randomization to death from any cause (up to approximately 7 years)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tiragolumab is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Avelumab for untreated PD-L1 positive recurrent or metastatic non-small-cell lung cancer (TA10250). Expected publication date: TBC.

- NICE technology appraisal in development. Avelumab for untreated PD-L1 positive recurrent or metastatic non-small-cell lung cancer (TA10250). Expected publication date: TBC.
- NICE technology appraisal. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA770). February 2022.
- NICE technology appraisal. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (TA705). June 2021.
- 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 for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE Guideline. Lung cancer: diagnosis and management (NG122). March 2019. Last updated: July 2023.

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) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[24]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2019.[25]

Additional Information

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