NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2022

Tiragolumab with atezolizumab for previously untreated non-small cell lung cancer

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26622	NICE ID: 10759	UKPS ID: 658369

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Tiragolumab with atezolizumab 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 the majority of lung cancers in the UK. Metastatic (or advanced) 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.

Atezolizumab, administered via intravenous (IV) injection, is already an established therapy for NSCLC. Tiragolumab is an antibody targeting TIGIT protein which is expressed on natural killer cells and T cells. Its action complements the mechanism of action of PD-L1/PD-1 inhibitors. It is also administered via IV infusion. A phase II clinical trial has shown that atezolizumab with tiragolumab results in improved patient outcomes compared to atezolizumab alone. Therefore, if licensed, tiragolumab with atezolizumab 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

Atezolizumab (Tecentriq) is already an established therapy for NSCLC. Tiragolumab (RG-6058, MTIG7192A) 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]

Tiragolumab with atezolizumab 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-01 (NCT04294810), 1200 milligrams (mg) of atezolizumab and 600 mg of tiragolumab will be administered by intravenous (IV) infusion every 3 weeks on day 1 of each 21-day cycle.[1]

Key Innovation

It is hypothesised that anti-TIGIT antibodies, 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] The phase II trial CITYSCAPE (NCT03563716) results show that the combination of tiragolumab and atezolizumab have potential in improving NSCLC patient outcomes. The results demonstrated that the medicinal products reduced the risk of disease worsening or death by 38% and improved overall response rates (ORR) (38.8% vs. 20.6%) compared with atezolizumab alone. Data suggest that the combination was generally well-tolerated, showing similar rates of grade 3-4 treatment-related adverse events (AEs) when adding tiragolumab to atezolizumab compared with atezolizumab alone (22.4% vs. 25%).[3] Therefore, if licensed, tiragolumab with atezolizumab will offer an additional treatment option for patients with 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 trials for the following indications:[4]

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

- Cervical cancer

In January 2021, tiragolumab with atezolizumab were granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) 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.[3]

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main types: 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).[5] Metastatic (or advanced) cancer has spread, either to both lungs, the chest or beyond.[6] Unresectable cancer means that a cancer or tumour that cannot be removed completely through surgery.[7] Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades.[8] Several other factors have been described as lung cancer risk factors including: exposure to radiation, certain chemicals (e.g., asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g., tuberculosis and chronic obstructive pulmonary disease). Other factors include family history of lung cancer and certain genetic mutations.[9] Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, chest infections that keep coming back, loss of appetite, weight loss and fatigue.[10]

Primary lung cancer remains the most common malignancy, and deaths from lung cancer exceed those from any other malignancy worldwide.[8] 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.[11] In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, which would mean around 40,800 of the annual new lung cancer cases are NSCLC.[5] In 2020/21 there were 86,043 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 103,856 finished consultant episodes (FCEs), resulting in 170,030 FCE bed days.[12] Survival rates for lung cancer depend on at which stage of disease the cancer is identified.[11] 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.[13] There are around 35,100 lung cancer deaths in the UK every year (based on data from 2016-2018). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[11] In England and Wales in 2020 there were 28,730 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[14] However, the population likely to be eligible to receive tiragolumab with atezolizumab could not be estimated from available published sources.

Recommended Treatment Options

Currently, NICE recommends the following options for advanced squamous NSCLC (PD-L1≥50%):[15]

- Atezolizumab
- Pembrolizumab
- Pembrolizumab plus platinum-based chemotherapy

Clinical Trial Information	
Trial	**SKYSCRAPER-01** NCT04294810; EudraCT- 2019-002925-31; A Phase III, Randomized, Double-Blinded, Placebo-Controlled Study of Tiragolumab, an Anti-Tigit Antibody, in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer **Phase III** – Recruiting **Location(s):** 11 EU countries, USA and other countries **Primary completion date:** August 2022
Trial Design	Randomised, parallel assignment, triple-blinded
Population	N=635 (estimated enrolment); subjects with histologically or cytologically documented locally advanced or recurrent NSCLC and high tumour tissue PD-L1 expression not eligible for curative surgery and/or definitive radiotherapy with or without chemoradiotherapy, or metastatic stage IV non-squamous or squamous NSCLC; aged 18 years and older
Intervention(s)	IV atezolizumab (1200mg) and IV tiragolumab (600mg)
Comparator(s)	IV atezolizumab (1200mg) and matching placebo
Outcome(s)	• Investigator-assessed progression-free survival (PFS) in the primary analysis set [time frame: from randomisation to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 59 months)] • Overall survival (OS) in the primary analysis set [time frame: from randomisation to death from any cause (up to approximately 59 months)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT03563716; A Phase II, Randomized, Blinded, Placebo-Controlled Study of Tiragolumab, An Anti-TIGIT Antibody, In Combination With Atezolizumab In Chemotherapy-Naïve Patients With Locally Advanced Or Metastatic Non-Small Cell Lung Cancer **Phase II** – Active, not recruiting **Location(s):** 3 EU countries, USA, Republic of Korea and Taiwan **Primary completion date:** June 2019
Trial Design	Randomised, parallel assignment, double-blinded
Population	N=135; subjects with histologically or cytologically documented locally advanced unresectable NSCLC, recurrent, or metastatic NSCLC of either squamous or non-squamous histology; aged 18 years and older

Intervention(s)	IV atezolizumab (1200mg) and IV tiragolumab (600mg)
Comparator(s)	IV atezolizumab (1200mg) and matching placebo
Outcome(s)	• Objective Response Rate (ORR) [time frame: from baseline until a total of 80 progression free survival (PFS) events have occurred (up to approximately 11 months)] • Progression free survival (PFS) [time frame: from baseline until a total of 80 PFS events have occurred (up to approximately 11 months)] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of tiragolumab is not yet known.

NHS indicative price of 1200mg/20ml concentrate of atezolizumab (60 mg per 1 ml) is £3807.69, and £2665.38 of 840mg/14m atezolizumab concentrate.[16]

Relevant Guidance

NICE Guidance

- 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 for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE Guideline. Lung cancer: diagnosis and management (NG122). 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.[17]
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[18]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[19]

Additional Information

References

1 ClinicalTrials.gov. *A Study of Tiragolumab in Combination With Atezolizumab Compared With Placebo in Combination With Atezolizumab in Patients With Previously Untreated Locally Advanced Unresectable or Metastatic PD-L1-Selected Non-Small Cell Lung Cancer (SKYSCRAPER-01).* 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04294810 [Accessed 18 February 2022].

2 Tiragolumab Impresses in Multiple Trials. *Cancer Discovery*. 2020;10(8):1086-7. Available from: https://doi.org/10.1158/2159-8290.Cd-nb2020-063.

3 Roche. *New data from the phase II CITYSCAPE trial show encouraging results with Roche's novel anti-TIGIT tiragolumab plus Tecentriq.* 2021. Available from: https://www.roche.com/investors/updates/inv-update-2021-12-10.htm [Accessed 18 February 2022].

4 ClinicalTrials.gov. *Tiragolumab | Phase 2, 3.* Available from: https://clinicaltrials.gov/ct2/results?term=Tiragolumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 18 February 2022].

5 Cancer Research UK. *Types of lung cancer.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types [Accessed 18 February 2022].

6 Cancer Research UK. *Stage 4.* 2020. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-4 [Accessed 18 February 2022].

7 Verywellhealth. *Unresectable Cancer Reasons and Exceptions.* 2020. Available from: https://www.verywellhealth.com/unresectable-tumors-reasons-treatment-2249210 [Accessed 18 February 2022].

8 Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2018 2018/10/01/;29:iv192-iv237. Available from: https://doi.org/10.1093/annonc/mdy275.

9 Cancer Research UK. *Risks and causes.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed 18 February 2022].

10 National Health Service (NHS). *Symptoms Lung cancer.* 2019. Available from: https://www.nhs.uk/conditions/lung-cancer/symptoms/ [Accessed 18 February 2022].

11 Cancer Research UK. *Lung cancer statistics.* 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 18 February 2022].

12 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 18 Februaru 2022].

13 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 18 February 2022].

14 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality.* 2021. Available from:

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 18 February 2022].

15 National Institute for Health and Care Excellence (NICE). *Lung cancer: diagnosis and management.* 2019. Available from: https://www.nice.org.uk/guidance/ng122 [Accessed 18 February 2022].

16 NICE. *Atezolizumab.* Available from: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html [Accessed 18 February 2022].

17 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2017 01 Apr. 2017;15(4):504-35. Available from: https://doi.org/10.6004/jnccn.2017.0050.

18 Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020. Available from: https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer.

19 Scottish Intercollegiate Guidelines Network. *Management of lung cancer (SIGN 137).* Available from: https://www.sign.ac.uk/media/1075/sign137.pdf [Accessed 18 February 2022].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.