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Newcastle University

Health Technology Briefing
January 2023

Tiragolumab with atezolizumab for treating stage III non-small cell lung cancer after platinum-based chemoradiotherapy

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30377	NICE ID: 11841	UKPS ID: 658370

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Tiragolumab with atezolizumab is currently in development for locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) in patients who have received at least two cycles of chemoradiotherapy. Stage III NSCLC describes a locally advanced disease state where the cancer has spread beyond the lung that was initially affected, such as surrounding lymph nodes, the heart, spinal bones and windpipe. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. Therefore chemotherapy/radiotherapy along with systemic anti-cancer treatments are given to patients to improve long-term survival outcomes.

Tiragolumab is administered intravenously (IV) and is a monoclonal antibody targeting the TIGIT protein which suppresses immune responses to cancer. Atezolizumab is also a monoclonal antibody administered via intravenous injection and is already an established therapy for NSCLC. It attaches to a protein called PD-L1, which is present on many cancer cells. PD-L1 switches off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effects, atezolizumab increases the immune system's ability to attack cancer cells and thereby slow down disease progression. Tiragolumab has a mechanism of action which complements the mechanism of action of atezolizumab to enhance anti-tumour effects.

Proposed Indication

For the treatment of locally advanced, unresectable stage III, non-small cell lung cancer (NSCLC) in patients who have received at least two cycles of concurrent platinum-based chemoradiotherapy (CRT) and have not had radiographic disease progression.[1]

Technology

Description

Tiragolumab (MTIG7192A, RG6058)[2] is a monoclonal antibody 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.[3,4] Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death ligand (PD-L)-1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/Programmed cell death protein 1 (PD-1) mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.[5]

In phase III clinical trial (SKYSCRAPER-03, NCT04513925) participants received 1680mg atezolizumab administered via intravenous (IV) infusion every 4 weeks (Q4W) on day 1 of each 28-day cycle and 840mg tiragolumab administered via IV infusion on day 1 of each 28-day cycle (Q4W) for a maximum of 13 cycles.[1]

Key Innovation

It has been theorised 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.[3] Preclinical studies suggest that targeting both TIGIT and PD-L1 (such as the combination of atezolizumab and tiragolumab) may synergistically enhance immune-mediated tumour rejection, and prolong survival.[2,3]

If licensed, tiragolumab in combination with atezolizumab will provide an additional treatment option for stage III NSCLC in patients who have received chemoradiotherapy.

Regulatory & Development Status

Tiragolumab in combination with atezolizumab is not currently licensed in the EU or UK. Tiragolumab does not currently have Marketing Authorisation in the EU or UK for any indication.

Tiragolumab in combination with atezolizumab is in phase II/III clinical development for solid tumours, melanoma and rectal cancer, amongst other indications.[6]

Atezolizumab is currently licensed in the EU and UK. Atezolizumab currently has Marketing Authorisation in the UK for:[5]

- As a monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin-ineligible and whose tumours have a PD-L1 expression >5%
- As adjuvant treatment following complete resection for adult patients with Stage II to IIIA NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells and whose disease has not progressed following platinum-based adjuvant chemotherapy

- In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC and in patients with EGFR mutant or ALK-positive NSCLC
- In combination with nab-paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC
- As a monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC
- As monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab
- In combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer
- In combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease
- In combination with bevacizumab, for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy

Patient Group

Disease Area and Clinical Need

NSCLC is one of two types of lung cancer, and makes up approximately 80-85% of lung cancers in the UK.[7] Stage III NSCLC describes a locally advanced disease state where the cancer has spread beyond the lung that was initially affected, such as surrounding lymph nodes, the heart, spinal bones and trachea.[8] Lung cancer symptoms include persistent cough, a chest infection that does not improve or repeated chest infections, unexplained breathlessness and wheezing, coughing up blood, chest or shoulder pain, and a hoarse voice. Other symptoms include loss of appetite, unexplained weight loss, tiredness and swollen fingers which is more common in NSCLC.[9,10] There are a number of risk factors for developing lung cancer, including ageing, family history of lung cancer, air pollution and exposure to certain chemicals, however smoking is the most common cause of lung cancers.[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 (2019) there were 7,390 patients diagnosed with stage III lung cancer, accounting for 21.1% of lung cancers diagnosed with a known stage at diagnosis.[13] Based on NCSLC accounting for approximately 80-85% of UK lung cancers, it can be estimated that up to 6,281 patients were diagnosed with stage III NSCLC in 2019.[7,13] In England, 2021-22, there were 119,396 finished consultant episodes (FCE) of malignant neoplasm of bronchus and lung (ICD-10 code C34), resulting in 75,969 day cases and 206,640 FCE bed days.[14] In England between 2013 and 2017, the age-standardised net lung cancer survival for stage III was 48.7% at one year and 12.6% at five years.[15] There are around 34,800 lung cancer deaths in the UK every year (based on data from 2017 - 2019). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035, to 58 deaths per 100,000 people by 2035.[16]

Recommended Treatment Options

Treatment for unresectable lung cancer includes chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. Patients may be offered one or more different treatments depending on stage, histology, and types of lung cancer as well as their general health. Systemic anti-cancer treatments are increasingly used to treat advanced NSCLC.[17]

Recommendations by the National Institute for Health and Care Excellence (NICE) include the following systemic anti-cancer treatments for people with:[18]

- Squamous NSCLC with no targetable mutations and PD-L1 <50%
  - Platinum doublet chemotherapy
  - Pembrolizumab
  - Atezolizumab,
  - Nivolumab
  - Docetaxel

- Squamous NSCLC with no targetable mutations and PD-L1 ≥50%
  - Pembrolizumab in combination with platinum doublet chemotherapy
  - Docetaxel
  - Atezolizumab
  - Pembrolizumab

- Non-squamous NSCLC with no targetable mutations and PD-L1 <50%
  - Pembrolizumab and pemetrexed and platinum-based chemotherapy
  - Atezolizumab and bevacizumab and platinum-based chemotherapy
  - Docetaxel
  - Platinum doublet chemotherapy
  - Pemetrexed maintenance

- Non-squamous NSCLC with no targetable mutations and PD-L1 ≥50%
  - Pembrolizumab and pemetrexed and platinum-based chemotherapy
  - Platinum doublet chemotherapy
  - Pemetrexed maintenance
  - Atezolizumab Pembrolizumab

NICE also recommends the following treatment options for locally advanced or metastatic NSCLC:[19]
- Nivolumab
- Atezolizumab
- Durvalumab

Clinical Trial Information

Trial	**SKYSCRAPER-03;** NCT04513925, **EudraCT**2019-004773-29 A Phase III, Open-Label, Randomized Study of Atezolizumab and Tiragolumab Compared With Durvalumab in Patients With Locally Advanced, Unresectable Stage III Non-Small Cell Lung Cancer Who Have Not Progressed After Concurrent Platinum-Based Chemoradiation **Phase III** – Recruiting **Locations:** 12 EU countries, UK, USA, Canada, and other countries **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, open label

Population	N=800 (estimated); adult patients with newly diagnosed, histologically or cytologically documented NSCLC with locally advanced, unresectable Stage III NSCLC with no progression during or following concurrent platinum-based CRT
Intervention(s)	IV tiragolumab + IV atezolizumab
Comparator(s)	IV durvalumab
Outcome(s)	**Primary outcome measure:** Independent Review Facility (IRF) Assessed Progression Free Survival (PFS) [Time Frame: From randomisation to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 90 months)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tiragolumab is not yet known.

Atezolizumab is already licensed for several indications in the EU and UK. A 1200mg/20ml concentrate for solution for infusion (1 vial) has an NHS indicative price of £3,807.69 and a 840mg/14ml concentrate for solution for infusion vial costs £2665.38.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy (TA713). July 2021.
- NICE technology appraisal guidance. Nivolumab for advanced squamous non-small-cell lung cancer after chemotherapy (TA655). October 2020.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal guidance. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). September 2017.
- NICE quality standard. Lung cancer in adults (QS17). December 2019.
- NICE guideline. Lung cancer: diagnosis and management (NG122). September 2022.

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 of Medical Oncology (ESMO). Early and locally advanced non-small cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[21]
- National Comprehensive Cancer Network (NNCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[22]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). 2014.[23]

Additional Information

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