NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2022

Tislelizumab with chemotherapy for previously untreated advanced oesophageal squamous cell carcinoma

Company/Developer	Novartis Pharmaceuticals UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27131	NICE ID: 10685	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Tislelizumab with chemotherapy is in clinical development to treat patients with advanced oesophageal squamous cell carcinoma (ESCC). ESCC is a type of cancer that begins in the thin, flat cells lining the food pipe (oesophagus) and may spread to other parts of the body. Symptoms include difficulty swallowing, persistent indigestion or heartburn, weight loss, pain in the throat, and chronic cough. In the UK it is more common in older people (≥75 years old) and males. There is a need for new treatment options, including immunotherapies, as ESCC progresses rapidly and is associated with a high mortality.

Tislelizumab is a drug, administered intravenously, that has been designed to recognise and block a target called PD-1 found on certain cells of the immune system. Some cancers make a protein that attaches to PD-1 and switches off the immune cells' ability to attack the cancer. By blocking PD-1, tislelizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licenced, tislelizumab with chemotherapy will provide an additional first-line treatment option for adult patients with localised ESCC.

Proposed Indication

First line treatment in participants with advanced oesophageal squamous cell carcinoma (ESCC).[1]

Technology

Description

Tislelizumab (BGB-A317) is a humanised IgG4 anti–PD-1 (programmed cell death protein-1) monoclonal antibody specifically designed to minimise binding to FcγR on macrophages. Binding to FcγR on macrophages compromises the anti-tumour activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. PD-1 is a cell surface receptor that plays an important role in allowing tumour cells to evade the immune system. Many types of cancer cells have hijacked the PD-L1 (programmed death ligand 1) expression system that normally exists in healthy cells. By expressing PD-L1, cancer cells can interact with PD-1 expressing cytotoxic T-lymphocytes (CTLs) and protect themselves from being killed by these CTLs. Tislelizumab can potentially restore the ability of CTLs to kill cancer cells by binding to PD-1, without activating the receptor, thereby preventing PD-L1 from engaging PD-1.[2]

Tislelizumab with chemotherapy is currently in phase III clinical development for the treatment of adult patients with advanced ESCC (NCT03783442). In this trial, 200 mg of tislelizumab is administered intravenously (IV) once in every 3-week cycle in combination with oral and intravenously administered chemotherapy.[1]

Key Innovation

Tislelizumab, as an antagonist to PD-L1/PD-L2 mediated cell signalling, leads to increased cytokine production and restoration of T-cell activation, resulting in immune-mediated tumour cell death. Tislelizumab has a higher affinity to PD-1 than other anti-PD-1 antibodies, potentially due to its differential PD-1 binding orientation. In early clinical research, tislelizumab has demonstrated promising efficacy results, a manageable safety profile and longer duration of response.[3] Tislelizumab is an innovative immunotherapy for the treatment of ESCC.[4]

Regulatory & Development Status

Tislelizumab with chemotherapy does not currently have Marketing Authorisation in the EU/UK for any indication.

Tislelizumab, alone and in combination, is in phase II and III clinical development for the treatment of various types of cancers, some of which include:[5]

- Hepatocellular carcinoma
- Muscle-invasive bladder cancer
- Non-small cell lung cancer
- Classical Hodgkin lymphoma
- Gastric/Gastroesophageal junction
- Nasopharyngeal cancer
- MSI-H/dMMR solid tumors

Tislelizumab was granted orphan drug designation by the European Medicines Agency in November 2020 for the treatment of oesophageal cancer (EU/3/20/2357).[6]

Patient Group

Disease Area and Clinical Need

Oesophageal cancer is a type of cancer affecting the food pipe (oesophagus), the long tube that carries food from the mouth to the stomach.[7,8] Most oesophageal cancers can be categorised into two main histologic subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the most common oesophageal cancer subtype diagnosed worldwide.[9] Advanced cancer is difficult to cure or control with treatment. The cancer can spread from where it first started to surrounding tissues, lymph nodes, or distant parts of the body.[10] Advanced cancers can be locally advanced or metastatic.[11] The most common symptoms of oesophageal cancer include: difficulty swallowing (dysphagia), persistent indigestion or heartburn, weight loss, pain in the throat or behind the breastbone, and persistent cough.[7]

Oesophageal cancer is more common in men than women. It is also more common in older people. In the UK, on average each year around 40% of new cases are in people aged 75 years and over, whereas the condition is very rare in people aged younger than 40 years.[7] There were approximately 9,300 new cases of oesophageal cancer in the UK every year in 2016-2018.[12] Oesophageal cancer was the 7th most common cause of cancer death in the UK in 2018. The crude mortality rate in England was 11.7 per 100,000 in 2018 which accounted for 5% of cancer related deaths.[13] In the 2020 death registrations in England and Wales, there were 6,952 deaths due to malignant neoplasm of the oesophagus (C15).[14] In England, in 2020-21, there were 37,125 finished consultant episodes (FCE) for malignant neoplasm of the oesophagus (ICD 10: C15), resulting in 29,505 hospital admissions and 64,565 FCE bed days.[15]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends patients with ESCC definitive chemoradiotherapy.[4] Current guidelines for the first-line treatment of advanced or metastatic ESCC recommend platinum-based chemotherapy in combination with fluoropyrimidine.[9] NICE also recommends pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy as a treatment option for patients with advanced or metastatic ESCC whose tumour has a combined positive score of 10 or more.[16]

Clinical Trial Information

Trial	NCT03783442; 2018-000587-28; A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination With Chemotherapy as First-Line Treatment in Patients With Unresectable, Locally Advanced Recurrent or Metastatic Esophageal Squamous Cell Carcinoma **Phase III –** Active, Not recruiting **Location(s):** Seven EU countries, UK, USA, Canada, Russia and countries in SE Asia. **Primary completion date:** June 2022
Trial Design	Randomised, double blind, parallel assignment
Population	N=649 (actual); subjects aged 18 and older with unresectable, locally advanced recurrent or metastatic ESCC who have stage IV unresectable ESCC at first diagnosis (i.e., stage IV disease at the original diagnosis of ESCC) or who have unresectable, locally advanced recurrent or metastatic disease with at least a 6-month treatment-free interval, if prior definitive therapy (chemotherapy, chemo-radiation therapy or surgery) was given.

Intervention(s)	Tislelizumab 200mg (IV) every 3 weeks with chemotherapy doublet (any of the two available chemotherapy drug combinations) for up to 24 months
Comparator(s)	Placebo administered with chemotherapy doublet (any of the two available chemotherapy drug combinations) for up to 24 months
Outcome(s)	Primary outcomes: • Progression-free survival (PFS) - defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the blinded independent review committee (BIRC) per RECIST v1.1 or death, whichever occurs first [time frame: approximately 31 months from date of the first participant randomization] • Overall survival (OS) - defined as the time from the date of randomization until the date of death due to any cause [time frame: approximately 31 months from date of the first participant randomization] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tislelizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021.
- NICE clinical guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Proposition: 18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer (all ages). Publishing date to be confirmed.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and Gastric (Adult). B11/S/a.
- 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

- Jaffer A. A., Thomas A. D., David J. B. et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. 2019.[17]

- European Society of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[18]
- Allum W.H., Blazeby J.M., Griffin S.M. et al. Guidelines for the management of oesophageal and gastric cancer. 2011.[19]

Additional Information

References

1 ClinicalTrials.gov. *A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination With Chemotherapy as First-Line Treatment in Patients With Unresectable, Locally Advanced Recurrent or Metastatic Esophageal Squamous Cell Carcinoma*. *Trial ID: NCT03783442*. 2018. Status: Active. Available from: https://clinicaltrials.gov/ct2/show/NCT03783442 [Accessed 10 February 2022].

2 BeiGene. *Tislelizumab*. Available from: https://www.beigene.com/science-and-product-portfolio/pipeline/tislelizumab [Accessed 10 February 2022].

3 Liu S-Y, Wu Y-L. Tislelizumab: an investigational anti-PD-1 antibody for the treatment of advanced non-small cell lung cancer (NSCLC). *Expert Opinion on Investigational Drugs*. 2020;29(12):1355-64. https://www.tandfonline.com/doi/full/10.1080/13543784.2020.1833857.

4 National Institute for Health and Care Execellence (NICE) Guidance. *Oesophago-gastric cancer: assessment and management in adults*. 2018. Available from: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations#radical-treatment-2 [Accessed 10 February 2022].

5 ClinicalTrials.gov. *Tislelizumab | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=tislelizumab&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&recrs=m&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 14 February 2022].

6 European Medicines Agency. *EU/3/20/2357: Orphan designation for the treatment of oesophageal cancer* 2021. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202357#key-facts-section [Accessed 14 February 2022].

7 Cancer Research UK. *What is oesophageal cancer?* Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/about [Accessed 14 February 2022].

8 National Health Service (NHS). *What is oesophageal cancer?* Available from: https://www.nhs.uk/conditions/oesophageal-cancer/ [Accessed 14 February 2022].

9 Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal

cancer. *Future Oncology*. 2019;15(10):1057-66. https://www.futuremedicine.com/doi/epub/10.2217/fon-2018-0609.

10 National Cancer Institute (NCI). *Advanced cancer*. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/advanced-cancer [Accessed 14 February 2022].

11 American Cancer Society. *ADVANCED AND METASTATIC CANCER*. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html#:~:text=For%20others%2C%20the%20cancer%20may,other%20parts%20of%20the%20body. [Accessed 14 February 2022].

12 Cancer Research UK. *Oesophageal cancer incidence*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer#heading-Zero [Accessed 14 February 2022].

13 Cancer Research UK. *Oesophageal cancer mortality by sex and UK country*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/mortality#heading-Zero [Accessed 14 February 2022].

14 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality*. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset?__cf_chl_captcha_tk__=Ph0B60CdiF10PbjaK2HBXSveQc4Qb5ARf2hzYwV7334-1638883387-0-gaNycGzNCCU [Accessed 14 February 2022].

15 NHS Digital. *Hospital Admitted Patient Care Activity*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity [Accessed 14 February 2022].

16 National Institute for Health and Care Execellence (NICE) Guidance. *Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer*. 2021. Available from: https://www.nice.org.uk/guidance/ta737/chapter/1-Recommendations [Accessed 7 March 2022].

17 Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*. 2019;17(7):855-83. https://jnccn.org/view/journals/jnccn/17/7/article-p855.xml?ArticleBodyColorStyles=full%20html.

18 Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016;27:v50-v7. https://www.annalsofoncology.org/article/S0923-7534(19)31647-3/fulltext.

19 Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2011;60(11):1449-72. https://www.bsg.org.uk/wp-content/uploads/2019/12/BSG-guidelines-for-the-management-of-oesophageal-and-gastric-cancer.pdf.

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.