Health Technology Briefing
June 2022

Tislelizumab with chemotherapy for previously untreated unresectable or metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma

Company/Developer	Novartis Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27137	NICE ID: 10686	UKPS ID: 665345

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Tislelizumab in combination with chemotherapy is being developed for the first-line treatment of locally advanced, unresectable or metastatic gastric cancer (GC) or gastroesophageal junction (GEJ) adenocarcinoma. GC is a cancer that starts in the stomach. GEJ adenocarcinoma is cancer that starts at the gastro-oesophageal junction, where the food pipe (oesophagus) joins the stomach. Risk factors of GC and GEJ adenocarcinoma include smoking, alcohol consumption, obesity, older age, gastro-oesophageal reflux disease and long-term helicobacter pylori infection. Symptoms can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen.

Tislelizumab, administered intravenously, is an antibody (a type of protein) that has been designed to recognise and block a target called PD-1 found on certain cells of the immune system. Some cancers interact with PD-1 by making a protein which attaches to it and prevents immune cells from killing the cancer cells. By blocking this target, tislelizumab prevents the cancer cells from interacting with PD-1 and therefore increases the immune system's ability to kill cancer cells. If licenced, tislelizumab in combination with chemotherapy will provide an additional first-line treatment option for patients with locally advanced unresectable or metastatic GC or GEJ adenocarcinoma.

Proposed Indication

First-line treatment of locally advanced, unresectable or metastatic GC or GEJ adenocarcinoma.[1]

Technology

Description

Tislelizumab is a humanised monoclonal antibody (mAb) with high affinity and specificity for programmed cell death protein 1 (PD-1) that was engineered to minimise binding to Fcγ receptor (FcγR) on macrophages to greatly reduce antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti–PD-1 therapy.[2] Binding to FcγR on macrophages has been shown to compromise 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 programmed cell death ligand 1 (PD-L1) 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.[3]

Tislelizumab in combination with chemotherapy is currently in phase III clinical development for the first-line treatment of patients with locally advanced, unresectable or metastatic GC or GEJ adenocarcinoma (NCT03777657). In this trial, 200mg of tislelizumab in combination with 80mg/m^2 of cisplatin and 130mg/m^2 of oxaliplatin is administered intravenously (IV) on day 1 during each 21-day cycle. This is also in combination with 1000mg/m^2 of capecitabine orally twice daily on days 1 through 14 of each cycle and 800mg/m^2 5-FU daily IV on days 1 through 5 of each cycle.[1]

Key Innovation

Tislelizumab is differentiated from other PD-1 inhibition therapies because it was engineered to minimise binding to FcγR. Preclinical studies have shown that FcγR1 binding may compromise the activity of PD-1 antibodies.[4] Growing evidence from cancer immunology research shows that immune checkpoint proteins, especially PD-1 and PD-L1, play a crucial role in antitumour immunotherapy. PD-L1/PD-1 inhibitors can induce durable antitumour responses across multiple types of cancer, including advanced GC.[5] In certain solid tumours, immune checkpoint inhibitors have been shown to provide benefit when combined with standard chemotherapy regimens.[3] Data has shown that tislelizumab combined with chemotherapy can contribute to long-lasting antitumour activity and indicate that this therapeutic regimen can help patients with advanced GC to extend their progression-free survival and overall survival.[5]

If licensed, tislelizumab in combination with chemotherapy will offer and additional treatment option for patients with locally advanced unresectable or metastatic GC or GEJ adenocarcinoma.

Regulatory & Development Status

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

Tislelizumab has been awarded an orphan drug designation by the FDA in May 2020 for the treatment of gastric cancer, including cancer of the gastroesophageal junction.[6]

Tislelizumab in combination with chemotherapy is also in phase II/III clinical development for the treatment of various types of cancer, some of which include:[7]

- Nasopharyngeal carcinoma
- Oesophageal squamous cell carcinoma
- Non-small cell lung cancer
- Urothelial carcinoma

Patient Group

Disease Area and Clinical Need

GC, also called stomach cancer, is cancer that starts anywhere inside the stomach or the stomach wall. Most stomach cancers start in the gland cells in the inner stomach lining. These are called adenocarcinomas.[8] GEJ cancer starts at the gastro-oesophageal junction, where the food pipe (oesophagus) joins the stomach.[9] Locally advanced cancer is cancer that has spread into the tissues around the stomach or gastro-oesophageal junction. Metastatic cancer occurs when the cancer has spread to another part of the body.[10,11] Older age is the main risk factor for cancer and 54% of GC cases in the UK are preventable, with lifestyle factors such as smoking, alcohol and obesity contributing to the risk.[12] Incidence is highest in men and most often seen in those aged 85-90 (2016-18).[13] GC or GEJ adenocarcinoma can also be linked to certain medical conditions such as gastro-oesophageal reflux disease, long-term helicobacter pylori infection, Barrett's oesophagus, or gastritis, with genetic factors also influencing development risk.[14,15] Exposure to various occupational chemicals can increase the risk of developing GC, such as those found in rubber production plants.[16] Symptoms of gastro-oesophageal cancers can include difficulty and pain when swallowing, nausea or vomiting, heartburn, indigestion, loss of appetite, fatigue, unexplained weight loss, or a lump in the upper abdomen.[17,18]

Stomach cancer is the 17th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-18).[13] The age standardised incidence rate of stomach cancer in England is 14.6 and 6.4 per 100,000 amongst males and females respectively (2016-18).[19] In England (2020-21), there were 6,328 finished consultant episodes (FCEs) and 4,754 admissions for malignant neoplasm of the stomach (ICD-10 code: C16.9), which resulted in 3,319 day cases and 12,839 FCE bed days. For malignant neoplasms of the lower third of the oesophagus (ICD-10 code: C15.5) in England (2020-21), there were 19,522 FCE, with 15,925 hospital admissions that resulted in 31,158 bed days and 11,925 day cases.[20] In England (2017), there were 5,143 patients diagnosed with malignant neoplasm of the stomach (ICD-10 code: C16) and 3,476 deaths registered where malignant neoplasm of the stomach was the underlying cause.[21] There were 930 newly diagnosed cases of stage III stomach cancer and 2,001 newly diagnosed cases of stage IV stomach cancer in England in 2017.[22] For patients diagnosed in England between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage III stomach cancer were 63.2% and 23.5% respectively.[23]

Recommended Treatment Options

NICE guidelines recommend the following first-line palliative chemotherapy treatment options for locally advanced or metastatic oesophago-gastric cancer:[24]

- Doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
- Triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended by NICE as an option for untreated locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative GEJC in adults whose tumours express PD-L1.[25]

Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer.[26]

Clinical Trial Information

Trial	**RATIONALE 305,** NCT03777657, 2018-000312-24; A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study Comparing the Efficacy and Safety of Tislelizumab (BGB-A317) Plus Platinum and Fluoropyrimidine Versus Placebo Plus Platinum and Fluoropyrimidine as First-Line Treatment in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma **Phase III** – Active, not recruiting **Locations:** 4 EU countries, UK, USA and other countries. **Primary completion date:** August 2022
Trial Design	Randomized, parallel assignment, triple-blind
Population	N=997; Subjects with locally advanced unresectable or metastatic GC or GEJ carcinoma and have histologically confirmed adenocarcinoma; No previous systemic therapy for locally advanced unresectable or metastatic gastric/GEJ cancer; aged 18 years and older
Intervention(s)	Tislelizumab (IV) + cisplatin (IV) + oxaliplatin (IV) + capecitabine (oral twice daily) + 5-FU (IV)
Comparator(s)	Placebo for tislelizumab (IV) + cisplatin (IV) + oxaliplatin (IV) + capecitabine (oral twice daily) + 5-FU (IV)
Outcome(s)	**Primary outcome:** Overall survival (OS) [Time frame: up to 48 months] See trial record for full list of other outcomes
Results (efficacy)	At the interim analysis, tislelizumab in combination with chemotherapy met the primary endpoint of overall survival (OS) in patients with PD-L1 expression, with additional follow-up needed to assess OS benefits in the intention-to-treat (ITT) population.[27]
Results (safety)	The safety profile of tislelizumab was consistent with that observed in previous trials, with no new safety signals identified with the addition of chemotherapy.[27]

Estimated Cost

The cost of tislelizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (GID-TA10352). Expected date of issue to be confirmed.
- NICE technology appraisal. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE quality standard. Oesophago-gastric cancer (QS176). December 2018.
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.

NHS England (Policy/Commissioning) Guidance

- 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.

Other Guidance

- National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. July 2019.[28]
- European Society of Medical Oncology (ESMO). Oesophageal cancer: ESMO clinical practice guidelines. 2016.[29]
- European Society of Medical Oncology (ESMO). Gastric cancer: ESMO clinical practice guidelines. 2016.[30]
- London Cancer Alliance. LCA oesophageal and gastric cancer clinical guidelines. 2014.[31]
- British Society of Gastroenterology. Guidelines for the management of oesophageal and gastric cancer. 2011.[32]

Additional Information

References

1 Clinicaltrials.gov. *Tislelizumab in Combination With Chemotherapy as First-Line Treatment in Adults With Inoperable, Locally Advanced or Metastatic Gastric, or Gastroesophageal Junction Carcinoma*. *Trial ID: NCT03777657*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03777657 [Accessed 14 April 2022].

2 Xu J, Bai Y, Xu N, Li E, Wang B, Wang J, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma. *Clinical Cancer Research*. 2020;26(17):4542-50. Available from: https://doi.org/10.1158/1078-0432.Ccr-19-3561.

3 BeiGene. *Tislelizumab.* 2021. Available from: https://www.beigene.com/our-science-and-medicines/tislelizumab/ [Accessed 9 March 2022].

4 Qin S, Finn RS, Kudo M, Meyer T, Vogel A, Ducreux M, et al. RATIONALE 301 study: tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular

carcinoma. *Future Oncology*. 2019;15(16):1811-22. Available from: https://doi.org/10.2217/fon-2019-0097.

5 Qiu H-B. Safety and efficacy of tislelizumab plus chemotherapy for first-line treatment of advanced esophageal squamous cell carcinoma and gastric/gastroesophageal junction adenocarcinoma. *Thoracic cancer*. 2020;11(12):3419-21. Available from: https://doi.org/10.1111/1759-7714.13690.

6 US Food and Drug Administration. *Search Orphan Drug Designations and Approvals.* 2020. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=738120 [Accessed 29 April 2022].

7 Clinicaltrials.gov. *Search of: Tislelizumab + chemotherapy.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?cond=&term=tislelizumab+%2B+chemotherapy&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 22 June 2022].

8 Cancer Research UK. *What is stomach cancer?* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/about-stomach-cancer [Accessed 26 April 2022].

9 Cancer Research UK. *What is gastro oesophageal junction cancer?* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/gastro-oesophageal-junction-cancer/about [Accessed 26 April 2022].

10 Cancer Research UK. *About advanced oesophageal cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/advanced-cancer/about-advanced-cancer [Accessed 9 May 2022].

11 Cancer Research UK. *What is advanced stomach cancer?* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/advanced-cancer/about-advanced-cancer [Accessed 9 May 2022].

12 Cancer Research UK. *Stomach cancer risk.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/risk-factors [Accessed 26 April 2022].

13 Cancer Research UK. *Stomach cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer [Accessed 26 April 2022].

14 National Health Service. *Stomach cancer: causes.* 2019. Available from: https://www.nhs.uk/conditions/stomach-cancer/causes/ [Accessed 26 April 2022].

15 National Health Service. *Oesophageal cancer: causes.* 2020. Available from: https://www.nhs.uk/conditions/oesophageal-cancer/causes/ [Accessed 26 April 2022].

16 Cancer Research UK. *Risks and causes of stomach cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/causes-risks [Accessed 26 April 2022].

17 National Health Service. *Stomach cancer: symptoms.* 2019. Available from: https://www.nhs.uk/conditions/stomach-cancer/ [Accessed 26 April 2022].

18 National Health Service. *Oesophageal cancer: symptoms.* 2020. Available from: https://www.nhs.uk/conditions/oesophageal-cancer/symptoms/ [Accessed 26 April 2022].

19 Cancer Research UK. *Stomach cancer incidence statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/incidence [Accessed 26 April 2022].

20 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 7 June 2022].

21 Office for National Statistics. *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 7 June 2022].

22 National Cancer Registration and Analysis Service. *Survival by stage.* Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 26 April 2022].

23 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 9 June 2022].

24 National Institute for Health and Care Excellence. *Oesophago-gastric cancer: assessment and management in adults* (*NG83)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng83/resources/oesophagogastric-cancer-assessment-and-management-in-adults-pdf-1837693014469 [Accessed 26 April 2022].

25 National Institute for Health and Care Excellence. *Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer* (*TA737)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta737 [Accessed 26 April 2022].

26 National Institute for Health and Care Excellence. *Capecitabine for the treatment of advanced gastric cancer* (*TA191)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ta191/resources/capecitabine-for-the-treatment-of-advanced-gastric-cancer-pdf-82598551569349 [Accessed 21 June 2022].

27 BeiGene. *BeiGene Announces Positive Findings from Phase 3 Trial of Tislelizumab in Combination with Chemotherapy in First-Line Gastric or Gastroesophageal Junction Cancer.* 2022. Available from: https://ir.beigene.com/news-details/?id=b8b9f75d-c374-4593-95c0-ed8bd3e649cb [Accessed 19 May 2022].

28 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 J Natl Compr Canc Netw*. 2019;17(7):855-83. Available from: https://doi.org/10.6004/jnccn.2019.0033.

29 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. Available from: https://doi.org/10.1093/annonc/mdw329.

30 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016;27:v38-v49. Available from: https://doi.org/10.1093/annonc/mdw350.

31 London Cancer Alliance. *LCA Oesophageal and Gastric Cancer Clinical Guidelines.* 2014. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2017/03/LCA-OG-Cancer-Clinical-Guidelines-April-2014.pdf [Accessed 26 April 2022].

32 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. Available from: https://doi.org/10.1136/gut.2010.228254.

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.