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HEALTH TECHNOLOGY BRIEFING
OCTOBER 2021

Tislelizumab for oesophageal cancer – second line

NIHRIO ID	28859	**NICE ID**	10689
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	663010

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Tislelizumab is being developed for patients with recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy. Advanced or metastatic ESCC begins in the food pipe and spreads to other parts of the body. Symptoms include difficulty swallowing, persistent indigestion or heartburn, weight loss, pain in the throat, and chronic cough. Advanced or metastatic cancer cannot usually be cured and current treatment with chemotherapy aims to control the disease, relieve symptoms, and give patients a better quality of life. There is a need for new treatment options, including immunotherapies, as ESCC progresses rapidly and has high mortality.

Tislelizumab is a protein that has been designed to recognise and block a target called PD-1 found on certain cells of the immune system. It is administered intravenously. 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 will provide a second-line treatment for patients with recurrent locally advanced or metastatic ESCC.

PROPOSED INDICATION

Second line treatment in patients with advanced unresectable/metastatic ESCC.[1]

TECHNOLOGY

DESCRIPTION

Tislelizumab (BGB-A317) is a humanised IgG4 anti–PD-1 monoclonal antibody specifically designed to minimise binding to FcγR on macrophages. Tislelizumab is designed to bind to PD-1, 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 expression system that normally exists in healthy cells. By expressing PD-L1, cancer cells can interact with PD-1 expressing cytotoxic T-lymphocytes, or 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]

In the phase III trial (NCT03430843), tislelizumab 200mg is administered intravenously every 21 days.[1]

INNOVATION AND/OR ADVANTAGES

The standard of care for oesophageal cancer is chemotherapy, tislelizumab is an immunotherapy option. While nivolumab is another immunotherapy that was recently approved for second line treatment of oesophageal cancer, tislelizumab has higher affinity to PD-1 than nivolumab, potentially due to its differential PD-1 binding orientation.[3]

In the RATIONALE 302 trial of 512 advanced unresectable or metastatic ESCC patients who previously received a systemic treatment, tislelizumab met its primary endpoint of clinically and significantly improving overall survival, compared with chemotherapy. The safety profile of tislelizumab was also more favourable than the investigator-chosen standard chemotherapy.[4]

Tislelizumab could be a new treatment option in oesophageal cancer, an area with "significant unmet medical need with rapid progression and high mortality".[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

The EMA granted orphan designation to tislelizumab for the treatment of oesophageal cancer in November 2020.[6]

Tislelizumab monotherapy is in phase III clinical development for Non-Small Cell Lung Cancer (NSCLC) and hepatocellular carcinoma.[7]

Tislelizumab monotherapy is in phase II clinical development for:[7]

- relapsed or refractory mature T- and NK- neoplasms,
- microsatellite instability-high or a mismatch repair deficient solid tumours,

- locally advanced or metastatic urothelial bladder cancer and
- relapsed or refractory classical hodgkin lymphoma.

Tislelizumab in combination with chemotherapy or chemoradiotherapy is in phase III clinical development for:[7]

- the treatment of advanced esophageal cancer
- locally advanced, unresectable NSCLC
- inoperable, locally advanced or metastatic gastric, or gastroesophageal junction carcinoma
- untreated extensive-stage small cell lung cancer
- urothelial carcinoma and
- recurrent or metastatic nasopharyngeal cancer.

Tislelizumab in combination with chemotherapy or chemoradiotherapy is in phase II clinical trials for muscle-invasive bladder carcinoma, head and neck cancer and HER2-negative breast cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

Oesophageal cancer is a type of cancer affecting the food pipe (oesophagus), the long tube that carries food from the mouth to the stomach.[8,9] 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.[10] Cancer can develop in any part of the oesophagus: upper and middle part, lower part, and gastro oesophageal junction.[9]

The exact cause of oesophageal cancer is unknown, but the risk of developing oesophageal cancer depends on many things including: age, lifestyle (smoking, drinking too much alcohol over many years), being overweight or obese, having an unhealthy diet that is low in fruit and vegetables, and other medical conditions.[11] 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.[9]

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.[12]

Unfortunately, advanced cancer cannot usually be cured. Treatments can control the disease, relieve symptoms, and give patients a better quality of life for a period of time. Sometimes cancer is advanced when it is first diagnosed or the cancer has come back and spread after treatment(s) for the original cancer. Cancers that have spread to another part of the body are called secondary cancer, metastases or metastatic cancer. Locally advanced cancer means that the cancer has spread into the tissues around the oesophagus but has not spread to other organs.[13]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, oesophageal cancer was the 14th most common cancer in the UK. There were approximately 9,200 new cases of oesophageal cancer in the UK every year in 2015-2017.[14]

The age-standardised incidence rate in England for oesophageal cancer, in 2016, was 22.2 per 100,000 in males and 8.1 per 100,000 in females.[15]

Oesophageal cancer patients with a known stage are diagnosed at a late stage (70-80% are diagnosed at stage III or IV), than an early stage (21-30% are diagnosed at stage I or II). Between 37% and 42% of patients have metastases at diagnosis (stage IV).[16] According to 2013-2017 data, the 1-year and 5-year age-standardised survival for cancer of the oesophagus is 46.5 and 17.0, respectively.[17]

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.[18]

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.[19] Oesophageal cancer mortality is strongly related to age, with the highest mortality rates being in older people.[20] In the 2020 death registration in England and Wales, there were 6,952 deaths due to malignant neoplasm of the oesophagus (C15).[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of oesophageal cancer depends on several factors. These include the type of oesophageal cancer, how big it is and whether it has spread (the stage), and what the cancer cells look like under the microscope (grade). It also depends on patient general health. A team of health professionals should discuss the best treatment and care for each individual patient.[22]

The main treatments for oesophageal cancer are surgery, radiotherapy, chemotherapy and the immunotherapy drug nivolumab.[23] The patient may have one of these treatments or a combination. Chemotherapy combined with radiotherapy is called chemoradiotherapy. Patients might have it on its own as the main treatment, or before surgery.[22]

CURRENT TREATMENT OPTIONS

Unresectable advanced, recurrent or metastatic ESCC is usually first treated with fluoropyrimidine and platinum-based therapy. Then if the cancer progresses, it is treated with a taxane (docetaxel or paclitaxel).[23]

NICE recommends nivolumab for treating unresectable advanced, recurrent or metastatic ESCC in adults after fluoropyrimidine and platinum-based therapy.[23]

PLACE OF TECHNOLOGY

If licenced, tislelizumab will provide an additional second-line treatment for patients with recurrent locally advanced or metastatic ESCC.

CLINICAL TRIAL INFORMATION

Trial	**BGB-A317-302;** NCT03430843, 2017-003699-30; A Randomised, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of

	the Anti-PD-1 Antibody Tislelizumab (BGB-A317) Versus Chemotherapy as Second Line Treatment in Patients With Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma **Phase III** - Active, not recruiting **Location(s):** 5 EU countries, UK, USA and other countries. **Study completion date:** September 2021
Trial design	Randomised, controlled, parallel assignment, open label.
Population	N=513; Subjects with advanced unresectable / metastatic esophageal squamous cell carcinoma that has progressed after first-line treatment; aged 18 years and older
Intervention(s)	Tislelizumab 200 mg IV, every 21 days
Comparator(s)	Investigator-chosen chemotherapy (Paclitaxel, docetaxel or irinotecan), every 21 days
Outcome(s)	Primary outcome measure: - Overall survival (OS) in the Intention-to-Treat (ITT) Analysis Set [Time Frame: approximately 2 years from date of first randomization] See trial record for full list of other outcomes.
Results (efficacy)	- The study met its primary endpoint: tislelizumab clinically and significantly improved OS vs Investigator-chosen chemotherapy (ICC) in the ITT population (median OS: 8.6 vs 6.3 months (m); HR 0.70, 95% CI 0.57-0.85, p=0.0001). - Tislelizumab also demonstrated significant improvement in OS vs ICC in the PD-L1+ population (median OS: 10.3 vs 6.8 m; HR 0.54, 95% CI: 0.36-0.79, p=0.0006). - Survival benefit was consistently observed across pre-defined subgroups, including baseline PD-L1 status and region. - Treatment with tislelizumab was also associated with a higher ORR (20.3% vs 9.8%) and more durable response (median DoR: 7.1 vs 4.0 m; HR 0.42, 95% CI 0.23-0.75) than ICC in the ITT population.[4]
Results (safety)	- Fewer patients had ≥Grade 3 (46% vs 68%) treatment-emergent adverse events (TRAE) with tislelizumab vs ICC. Of these, fewer ≥Grade 3 AEs were treatment-related with tislelizumab vs ICC (19% vs 56%). - Fewer patients discontinued tislelizumab vs ICC (7% vs 14%) due to a TRAE.[4]

ESTIMATED COST

The cost of tislelizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer (TA707). June 2021.
- NICE clinical guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.

- NICE quality standard. Oesophago-gastric cancer (QS176). December 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). Published 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

- European Society of Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.[24]

ADDITIONAL INFORMATION

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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.