Health Technology Briefing
April 2022

Tislelizumab for treating unresectable, previously untreated hepatocellular carcinoma

Company/Developer	Novartis Pharmaceuticals Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23980	NICE ID: 10683	UKPS ID: 663297

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Tislelizumab is being developed for the first-line treatment of unresectable hepatocellular carcinoma (HCC). HCC is the most common type of liver cancer and the leading cause of cancer related death worldwide. This type of cancer develops from the main liver cells, called hepatocytes. Liver cancer is more common in people who have long- term damage to the liver (cirrhosis) due to hepatitis infection or excessive alcohol intake and metabolic causes such as obesity. HCC is also more likely to develop in men than in women and it becomes more common as people get older. Patients with unresectable HCC, where the tumour cannot be removed through surgery, have a poor prognosis and there are currently few first-line treatment options available.

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 will provide an additional first-line treatment option for patients with unresectable HCC.

Proposed Indication

Treatment of adults in the first line setting with unresectable hepatocellular carcinoma (HCC).[1]

Technology

Description

Tislelizumab (BGB-A317) is a humanised immunoglobulin G4 (IgG4) monoclonal antibody which has a high affinity and binding specificity for programmed death ligand 1 (PD-1).[2] It is 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 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] The PD-1/PD-L1 axis plays a central role in supressing anti-tumour immunity and cancer cells can take advantage of this suppression by interfering with interactions between PD-L1 and PD-1 through numerous pathways. Immunotherapeutic approaches that target this axis have demonstrated anti-tumour activity across multiple malignancies.[2]

Tislelizumab as a monotherapy is currently in phase III clinical development for the first-line treatment of adult patients with unresectable HCC (NCT03412773). In this trial, 200mg of tislelizumab is administered intravenously (IV) once every 3 weeks.[1]

Key Innovation

Tislelizumab is differentiated from other PD-1 inhibition therapies because it was engineered to minimise binding to Fcγ receptors (FcγR). Preclinical studies have shown that FcγR1 binding may compromise the activity of PD-1 antibodies.[2] As an antagonist to PD-L1/PD-L2 mediated cell signalling, tislelizumab 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.[4] In clinical research, tislelizumab has demonstrated promising efficacy results, a manageable safety profile and longer duration of response, as well as anti-tumour activity in HCC.[2,4]

Patients with unresectable HCC have a poor prognosis and there are currently few first-line treatment options available for patients.[2] If licenced, tislelizumab will offer an additional first-line treatment option for patients with unresectable HCC.

Regulatory & Development Status

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

Tislelizumab has been awarded the following regulatory designations:[5,6]

- An orphan drug designation by the EMA in April 2020 for the treatment of HCC
- An orphan drug designation by the FDA in November 2019 for the treatment of HCC

Tislelizumab is currently in phase III/II development for the treatment of various cancer indications, some of which include:[7]

- Non-small cell lung cancer
- Esophageal carcinoma

- Classical Hodgkin lymphoma
- Solid tumours
- Urothelial carcinoma

Patient Group

Disease Area and Clinical Need

HCC is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide.[8] This type of liver cancer develops from the main liver cells called hepatocytes.[9] Liver cancer is most common in people who already have liver disease, especially if they have cirrhosis (scarring of the liver due to previous damage), but it can also develop in people with no history of liver disease.[9,10] The leading risk factors for HCC include: viral hepatitis infection, excessive alcohol intake, liver cirrhosis, smoking, high body weight or obesity, non-alcoholic fatty liver disease and it is more common is older people.[8,11] HCC often has no symptoms until it is at a late stage and, therefore, people with cirrhosis are offered regular screening for signs of HCC.[10] The main symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, itching, loss of appetite, feeling sick and feeling full after eating a small amount of food.[12]

Liver cancer is the 18th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-18).[13] The age standardised incidence rate of liver cancer in England is 14.3 and 6.2 per 100,000 amongst males and females respectively.[14] HCC made up 55.3% of male and 28.2% of female primary liver cancer diagnoses in England for the period of 1998-2007.[15] In England (2020/21), there were 4,955 hospital admissions with primary diagnosis of liver cell carcinoma (ICD-10 code: C22.0), and 7,736 finished consultant episodes (FCEs), resulting in 18,483 FCE bed days and 1,530 day cases.[16] In England (2017), there were 2,714 patients diagnosed with liver cell carcinoma.[17] There are approximately 5,600 liver cancer deaths in the UK every year and in England between 2013 and 2017, the age-standardised liver cancer survival (all stages) was 38.1% at 1 year and 12.7% at 5 years.[13,18]

Recommended Treatment Options

For the treatment of untreated, unresectable HCC, The National Institute for Health and Care Excellence (NICE) currently recommends:[19-21]

- Sorafenib
- Lenvatinib
- Atezolizumab with bevacizumab

Clinical Trial Information

Trial	**RATIONALE-301, NCT03412773, 2017-002423-19;** A Randomized, Open-label, Multicenter Phase 3 Study to Compare the Efficacy and Safety of BGB-A317 Versus Sorafenib as First-Line Treatment in Patients With Unresectable Hepatocellular Carcinoma **Phase III** – Active, not recruiting **Locations:** 6 EU countries, UK, USA and other countries **Primary completion date:** May 2022
Trial Design	Randomised, parallel assignment, open-label, active controlled
Population	N=674; confirmed diagnosis of HCC; no prior systemic therapy for HCC (with the exception of HCC participants enrolled in the safety run-in sub-study [Japan only])

Intervention(s)	Tislelizumab, IV administration (200mg once every 3 weeks)
Comparator(s)	Sorafenib, oral administration (400mg twice daily)
Outcome(s)	Primary outcomes: Overall Survival (OS) [Time frame: from date of randomization up to 4 years, approximately] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of tislelizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Cabozantinib with atezolizumab for untreated advanced hepatocellular carcinoma (GID-TA10830). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Lenvatinib with pembrolizumab for untreated advanced or unresectable hepatocellular carcinoma (GID-TA10811). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab with tremelimumab for untreated unresectable hepatocellular carcinoma (GID-TA10571). Expected August 2021.
- NICE technology appraisal. Selective internal radiation therapies for treating hepatocellular carcinoma (TA688). March 2021.
- NICE technology appraisal. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma (TA666). December 2020.
- NICE technology appraisal. Lenvatinib for untreated advanced hepatocellular carcinoma (TA551). December 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.
- NICE interventional procedures guidance. Radiofrequency ablation of hepatocellular carcinoma (IPG2). July 2003.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. 16022/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and Pancreas (Adult). A02/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 Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018.[22]
- European Society for Medical Oncology (ESMO). Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.[23]

- British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. 2003.[24]

Additional Information

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