NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
March 2023

Toripalimab in combination with paclitaxel and cisplatin for treating advanced or metastatic oesophageal squamous cell cancer without previous systemic chemotherapy

Company/Developer	Junshi Biosciences

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 36077	NICE ID: 11862	UKPS ID: Not available

Licensing and Market Availability Plans

The company's regulatory procedure with the MHRA is currently unknown. The company submitted a Marketing Authorisation Application (MAA) to the MHRA and EMA in November 2022.[1]

Summary

Toripalimab in combination with paclitaxel and cisplatin is in clinical development for the treatment of previously untreated, advanced or metastatic oesophageal squamous cell cancer (ESCC). ESCC is when cancer cells form in the tissues of the oesophagus (food pipe), particularly forming in the thin, flat cells lining the inside of the oesophagus. Metastatic cancer is when the cancer spread to other parts of the body, and advanced cancer is cancer that has also spread or come back, and usually cannot be cured. Symptoms include painful swallowing, weight loss, pain behind breastbone, hoarseness, cough, indigestion, heartburn and/or a lump under the skin. Risk factors include smoking, heavy alcohol use and older age. There is an urgent unmet need for new drugs and treatments to increase the survival of patients with ESCC.

Toripalimab is a drug that binds to a protein called programmed cell dead 1 (PD-1) on the surface of cells, which prevents binding of it to PD ligand 1 and 2, thus promoting the immune system's ability to attack and kill tumour cells. Toripalimab will be administered as an injection. If approved, toripalimab will provide an alternative treatment option for patients with untreated, advanced or metastatic ESCC.

Proposed Indication

First-line treatment of advanced or metastatic oesophageal squamous cell cancer (ESCC) without previous systemic chemotherapy.[1,2]

Technology

Description

Toripalimab (JS001, TAB-001) is a humanised immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed cell death 1 (programmed death-1; PD-1), with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, toripalimab binds to PD-1 and inhibits the binding of PD-1 to its ligands, programmed cell death-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2). This prevents the activation of PD-1 and its downstream signalling pathways. This may restore immune function through the activation of both T cells and T-cell-mediated immune responses against tumour cells. PD-1, a transmembrane protein in the Ig superfamily that is expressed on activated T-cells, negatively regulates T-cell activation and effector function when activated by its ligands; it plays an important role in tumour evasion from host immunity.[3]

Toripalimab in combination with paclitaxel and cisplatin is in clinical development for the first-line treatment of advanced or metastatic ESCC without previous systemic chemotherapy. In the phase III clinical trial (JUPITER06, NCT03829969), toripalimab will be administered as an injection, combined with paclitaxel and cisplatin, every 3 weeks for up to 6 cycles.[2,4]

Key Innovation

For patients with advanced ESCC, recently updated ESMO guidelines recommend a platinum-fluoropyrimidine doublet with a PD-1 blocking antibody for treatment of locally advanced or metastatic ESCC. Of note, the indications for those PD-1 inhibitors approved in Europe are restricted to a subset of patients with ESCC.[1,5] Therefore, there is an urgent unmet need for new drugs and treatments to extend the survival of patients with ESCC, particularly those with low PD-1 tumour expression.[1] In the phase III (NCT03829969) clinical trial, toripalimab in combination with paclitaxel and cisplatin significantly improves progression-free survival (PFS) and overall survival (OS) in patients with treatment-naïve, advanced ESCC, with a manageable safety profile.[4] If licensed, toripalimab in combination with paclitaxel and cisplatin will offer an additional treatment option for first-line treatment of advanced or metastatic ESCC.

Regulatory & Development Status

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

Toripalimab in combination with other therapies is also currently in phase II and III clinical trials for the development of several cancer indications, some of which include:[6]

- Nasopharyngeal carcinomas
- Hepatocellular carcinoma
- Biliary tract cancers
- Urinary bladder cancers

Toripalimab was granted an orphan drug designation in the USA in 2021 for the treatment of oesophageal cancer.[7]

Patient Group

Disease Area and Clinical Need

The oesophagus is the hollow, muscular tube that moves food and liquid from the throat to the stomach. Oesophageal cancer is a disease in which malignant (cancer) cells form in the tissues of the oesophagus. Squamous cell carcinoma (SCC) is cancer that forms in the thin, flat cells lining the inside of the oesophagus. This cancer is most often found in the upper and middle part of the oesophagus, but can occur anywhere along the oesophagus. This is also called epidermoid carcinoma. Oesophageal cancer starts on the inside lining of the oesophagus and spreads outward through the other layers as it grows. When cancer spreads to another part of the body, it is called metastasis.[8] Advanced cancer is cancer that has spread or come back. It is usually used to describe cancer that cannot be cured.[9] Symptoms of oesophageal cancer include painful or difficult swallowing, weight loss, pain behind breast bone, hoarseness and cough, indigestion and heartburn and/or a lump under the skin. Risk factors include tobacco use, heavy alcohol use, having Barrett's oesophagus and older age.[8]

There are around 9,300 new oesophageal cancer cases in the UK every year, that's 25 every day (2016-2018). Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018). There are around 8,000 oesophageal cancer deaths in the UK every year (2017-2019). Oesophageal cancer is the 7th most common cause of cancer death in the UK, accounting for 5% of all cancer deaths (2017-2019). Almost 1 in 2 (46.5%) of people diagnosed with oesophageal cancer in England survive their disease for one year or more (2013-2017), and more than 3 in 20 (17%) of people survive their disease for five years or more (2013-2017).[10] In 2020, over 7,800 people in England were diagnosed with oesophageal cancer. The most affected age group was among those aged 70 to 74 years with 971 diagnoses in men of this age and 373 cases for women.[11]

Recommended Treatment Options

NICE recommend the following for first-line treatment options of advanced or metastatic oesophageal cancer:[12,13]

- Nivolumab with fluoropyrimidine- and platinum-based chemotherapy.
- Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy.

Clinical Trial Information

Trial	**JUPITER-06, NCT03829969;** A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Compare Toripalimab Injection (JS001) Combined With Standard Chemotherapy Versus Placebo Combined With Standard Chemotherapy in Treatment of Advanced or Metastatic Oesophageal Squamous Cell Cancer (ESCC) Without Previous Systemic Chemotherapy **Phase III –** Active, not recruiting **Location(s) –** China **Primary completion date –** March 2021
Trial Design	Randomised, sequential assignment, quadruple-masked
Population	N = 514 (actual); histologically or cytologically diagnosed locally advanced/recurrent or metastatic ESCC without radical treatment; no prior systemic anti-tumour therapy for recurrent or metastatic tumour; 18 years to 75 years.

Intervention(s)	Toripalimab injection, in combination with paclitaxel and cisplatin
Comparator(s)	Placebo, in combination with paclitaxel and cisplatin
Outcome(s)	• PFS [Time frame: PFS, defined as the time from randomisation to the first progression of disease, or the time from randomisation to death for any reason, whichever comes first, will be determined by blind independent centre review (BICR) in accordance with RECIST 1.1] • OS [Time frame: OS is defined as the time from randomisation to death for any cause.] See trial record for full list of other outcomes.
Results (efficacy)	At a follow up of 7.4 months in the experimental arm and 7.3 months in the control arm, OS was found to be significantly improved with toripalimab. In the experimental arm, the OS was 17 months versus 11 months in the control (HR,0.58; 95% CI, 0.43-0.78; P =.00037). Additionally, the one-year OS rate in the control arm was 43.7% versus 66% in the experimental arm. PFS was also found to be significantly improved in the experimental arm over the control arm (HR, 0.58; 95% CI, 0.46-0.74; P <.00001).[14]
Results (safety)	Grade 3 or higher adverse events (AEs) occurred in the 73.2% of patients in the experimental arm and 70% of patients in the control arm. AEs led to discontinuation in 11.7% of patients in the experimental arm and 6.2% of patients in the control arm. Immune-related AEs occurred in37% of patients in the control arm and 26.5% of patients in the experimental arm.[14]

Estimated Cost

The cost of toripalimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable metastatic oesophageal squamous cell carcinoma (GID-TA10841). Expected date of publication to be confirmed.
- NICE technology appraisal in development. Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma (GID-TA10572). Expected date of publication February 2023.
- NICE technology appraisal. Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (TA865). February 2023.
- NICE technology appraisal. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737). October 2021.
- NICE guideline in development. Oesophago-gastric cancer: assessment and management in adults (GID-NG10363). Expected date of publication June 2023.
- NICE 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 for Medical Oncology. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. October 2022.[5]
- West Midlands Cancer Alliance. Clinical Guidelines for Oesophagogastric Cancer. October 2020.[15]
- National Cancer Comprehensive Network (NCCN). Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. July 2019.[16]
- Spanish Society for Medical Oncology. SEOM Clinical Guideline for the diagnosis and treatment of esophageal cancer (2016). 2016.[17]

Additional Information

Junshi Biosciences did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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