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Newcastle University

Health Technology Briefing
March 2022

Pembrolizumab with lenvatinib for previously treated metastatic colorectal cancer

Company/Developer	Merck Sharp & Dohme Ltd, Eisai Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31397	NICE ID: 10758	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in combination with lenvatinib is being developed for patients with previously treated metastatic colorectal cancer (mCRC). Colorectal (or bowel) cancer starts in the large bowel (colon) and the back passage (rectum). The cause of colorectal cancer is unknown but various factors increase the risk of contracting it, including having a diet high in red or processed meats and low in fibre, smoking, and being overweight or obese. Colorectal cancer is the fourth most common cancer in the UK. Metastatic cancer is cancer that has spread around the body from the place it had originally started from. There is a need for additional treatment therapies as colorectal cancer in the fourth most common cancer in the UK.

Pembrolizumab is a type of protein (monoclonal antibody) that is administered intravenously and has been designed to increase the immune system's ability to kill cancer cells. Pembrolizumab is mainly used in adults for cancers that are advanced, have spread to other parts of the body (metastatic) or are not responding to other treatments. Lenvatinib administered orally, is multi-targeted tyrosine kinase inhibitor, which blocks the activity of enzymes in cancer cells. Through the blocking of these enzymes, lenvatinib can inhibit the formation of new blood vessels and hence cut off the blood supply that allows cancer cells to grow. Pembrolizumab in combination with Lenvatinib has shown good safety profile for patients with colorectal cancer. If licensed, pembrolizumab in combination with lenvatinib will offer an additional treatment option for adults with mCRC.

Proposed Indication

Treatment of metastatic colorectal cancer.[1]

Technology

Description

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2,3]

Lenvatinib (Lenvima) is a multi-targeted tyrosine kinase inhibitor(TKI) that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors FLT1, KDR, and FLT4, in addition to other proangiogenic and oncogenic pathway-related kinases including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.[4]

Pembrolizumab in combination with lenvatinib is currently in phase III clinical development for adult patients with previously treated mCRC. In the phase III clinical trial (NCT04776148), 400 mg of pembrolizumab is administered intravenously once every 6 weeks for up to 18 cycles in addition to 20 mg lenvatinib administered orally until disease progression.[1]

Key Innovation

Current therapy for colorectal cancer includes chemotherapy and immunotherapy.[5] Although there are therapies available for colorectal cancer, pembrolizumab in combination with lenvatinib may offer a further treatment for patients with previously treated non-microsatellite instability-high (MSI-H) or mismatch repair proficient (pMMR) mCRC.[6] In addition, this treatment regimen has demonstrated modest antitumour activity and a good safety profile in colorectal cancer.[7]

If approved, pembrolizumab in combination with lenvatinib would provide an additional therapy option for adults with previously treated mCRC.

Regulatory & Development Status

Pembrolizumab as a monotherapy or in combination with various medicinal products is currently licensed in the UK for the following indications:[3,8]

- Melanoma
- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma (RCC)
- Oesophageal carcinoma
- Colorectal cancer
- Triple negative breast cancer
- Endometrial carcinoma (EC)

Lenvatinib (Lenvima) is currently licensed in the UK as a monotherapy in advanced or unresectable hepatocellular carcinoma who have received no prior systemic therapy.

Lenvatinib (Lenvima) is currently licensed in the UK as a combination therapy with pembrolizumab for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.[3,9-11]

Lenvatinib (Kisplyx) is also licensed in the UK in combination with pembrolizumab as a first line treatment in adults with advanced RCC and in combination with everolimus for adults with advanced RCC following one prior VEGF-targeted therapy.

Pembrolizumab in combination lenvatinib is currently in phase II and III clinical development for the treatment of various types of cancer, some of which include:[12]

- HCC
- Advanced adenoid cystic carcinoma and other salivary gland cancers
- Endometrial carcinoma
- Advanced melanoma

Patient Group

Disease Area and Clinical Need

Colorectal cancer, also known as bowel cancer, is cancer that starts in the large bowel (colon cancer) or the back passage (rectal cancer).[13] Colorectal cancer is one of the most common types of cancers diagnosed in the UK. Although, the exact cause of colorectal cancer is not known there are risk factors that can contribute to the development. These factors can include smoking, alcohol consumption, family history of the disease, being overweight or obese and being inactive.[14] The symptoms of colorectal cancer can include a change in bowel habits or bleeding from the back passage, blood in the faeces, weight loss, and anaemia. If the cancer causes a bowel obstruction it may cause cramping pains in the abdomen, bloating, constipation and being unable to pass wind, or being sick.[15] Metastatic cancer is cancer that has spread from the place or origin to other parts of the body.[16]

Colorectal cancer is the fourth most common cancer in the UK, accounting for 11% of all new cancer cases. This equates to around 42,900 new colorectal cancer cases in the UK annually (2016-2018). Colorectal cancer is more common in the Caucasian population than in other ethnicities.[17] In 2016 to 2018, there were approximately 16,600 deaths annually attributable to colorectal cancer in the UK.[18] In England in 2020 to 2021 there were 89,253 finished consultant episodes (FCE) for malignant neoplasm of the colon (ICD 10; C18) and 42,170 FCE for malignant neoplasm of the rectum (ICD 10; C20). This resulted in 79,464 hospital admissions and 171,955 FCE bed days for malignant neoplasm of the colon. For malignant neoplasm of the rectum there were 39,137 hospital admissions and 72,552 FCE bed days.[19]

Recommended Treatment Options

For previously treated mCRC NICE recommends the following therapeutic options:[5]

- Trifluridine–tipiracil in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable

- Nivolumab plus ipilimumab as an option for treating mCRC with high MSI or MMR deficiency after fluoropyrimidine-based combination chemotherapy
- Encorafenib plus cetuximab as an option for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment

Clinical Trial Information

Trial	NCT04776148; 2020-004289-20; A Phase 3 Randomized Study of Lenvatinib in Combination With Pembrolizumab Versus Standard of Care in Participants With Metastatic Colorectal Cancer Who Have Received and Progressed On or After or Became Intolerant to Prior Treatment **Phase III –** Active, not recruiting **Location(s):** 3 EU countries, UK, USA, Canada and other countries **Primary completion date:** January 2024
Trial Design	Randomised, open-label, parallel assignment
Population	N= 434; aged 18 and older unresectable and metastatic colorectal adenocarcinoma; tumour must be determined to be NOT microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) by local testing; subjects who have been previously treated for their disease and has shown disease progression on or after or could not tolerate standard treatment
Intervention(s)	Pembrolizumab 400 mg IV on day 1 of each 6-week (Q6W) cycle for up to 18 cycles (up to approximately 2 years) + lenvatinib 20 mg oral once daily until disease progression
Comparator(s)	Regorafenib 160 mg oral once daily on days 1 through 21 of each 4-week cycle OR TAS-102 (trifluridine and tipiracil hydrochloride) 35 mg/m^2 oral twice a day on days 1 through 5 and days 8-12 of each 4-week cycle until progressive disease
Outcome(s)	Primary outcome: Overall Survival (OS) [Time Frame: up to approximately 40 months] See trial record for the full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml vial costs £2630.00[20] Lenvatinib is also marketed in the UK; a 4mg capsule costs £1437.00 and a 10mg capsule costs £1437.00.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Regorafenib for previously treated metastatic colorectal cancer (GID-TA10924). Expected publication date February 2023.
- NICE technology appraisal . Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716). July 2021.
- NICE technology appraisal. Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer (TA668). January 2021.
- NICE technology appraisal . Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016.
- NICE technology appraisal . Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (TA307). March 2014.
- NICE technology appraisal. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (TA242). January 2012.
- NICE guidance. Colorectal cancer (NG151). December 2021.
- NICE quality standard. Colorectal cancer (QS20). February 2022.

NHS England (Policy/Commissioning) Guidance

- 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. Management and treatment adapted recommendations in the covid-19 era: colorectal cancer (CRC). 2020.[22]
- Scottish Intercollegiate Guidelines Network. Diagnosis and management of colorectal cancer (SIGN 126). 2016.[23]
- European Society for Medical Oncology. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2014.[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.