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Newcastle University

Health Technology Briefing
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Favezelimab-pembrolizumab for treating metastatic PD-L1 positive colorectal cancer

Company/Developer	Merck Sharp & Dohme Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34007	NICE ID: 11859	UKPS ID: 668002

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Favezelimab-pembrolizumab is in development for adult patients with previously treated programme death ligand-1 positive (PD-L1+) metastatic colorectal cancer. Colorectal cancer, which is also called bowel cancer, is a type of cancer that starts from the large bowel (colon) and the back passage (rectum). Metastatic cancer is when the cancer has spread from where it started, elsewhere in the body. PD-L1+ means that there are proteins on the surface of the cancer cells which make it harder for the body to identify them and this can make the cancer harder to treat. Patients with PD-L1+ metastatic colorectal cancer have limited treatment options resulting in high mortality rates.

Co-formulated favezelimab-pembrolizumab is a fixed-dose combination therapy where both drugs work together to target PD-1 proteins and lymphocyte activation gene-3 (LAG3) proteins on the immune cell, helping the body to identify and kill the cancer cells more effectively than if given alone. Favezelimab-pembrolizumab is administered via intravenous infusion (into the vein) once every three weeks. If licensed, favezelimab-pembrolizumab will provide a new treatment option for patients with previously treated metastatic PD-L1+ colorectal cancer, who currently have limited options.

Proposed Indication

Adults with previously treated metastatic programmed death-ligand 1 (PD-L1) positive colorectal cancer.[1]

Technology

Description

Favezelimab (MK-4280A) is a humanised, immunoglobulin G4 (IgG4) monoclonal antibody directed against the inhibitory receptor lymphocyte activation gene-3 protein (LAG3).[2] LAG-3 is an immunomodulatory receptor that regulates T effector cell homeostasis, proliferation, and activation and has a role in T regulatory cell suppressor activity.[3]

Pembrolizumab (Keytruda) is a humanised IgG4 antibody directed against programmed death receptor-1 (PD-1), binding to this ligand results in the activation of T-cell-mediated immune responses against tumour cells.[4]

Favezelimab-pembrolizumab (MK-4280A) is a fixed-dose coformulation (800mg/200mg) in development for the treatment of adult patients with previously treated metastatic colorectal cancer. In the phase III trial (NCT05064059), favezelimab-pembrolizumab is administered via intravenous (IV) infusion every three weeks for up to 35 infusions.[1]

Key Innovation

Several unmet needs have been reported by cancer survivors with sexual, urinary and bowel problems occurring as some of the common side effects from colorectal cancer treatment.[5] Favezelimab-pembrolizumab may provide a safer and more effective treatment for patients with previously treated metastatic PD-L1+ colorectal cancer who have failed standard treatment options. In phase I/II trials the new formulation of favezelimab-pembrolizumab had a 40% disease control rate, significantly higher than favezelimab alone (17%).[6] Studies have shown that blockade of both LAG-3 and PD-1 can improve antitumour activity.[3] If licensed, favezelimab-pembrolizumab will provide a new treatment option for patients who have failed standard treatment options available for metastatic colorectal cancer and have few therapeutic options available.

Regulatory & Development Status

Favezelimab-pembrolizumab does not currently have Marketing Authorisation in the EU/UK for any indication. Favezelimab as a monotherapy or in combination does not have Marketing Authorisation in the EU/UK for any indication. Pembrolizumab has Marketing Authorisation in the EU/UK as:[7]

Monotherapy for:

- Breast cancer
- Classical Hodgkin lymphoma
- Head and neck squamous cell carcinoma
- Melanoma
- Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer
- MSI-H or dMMR endometrial carcinoma
- MSI-H or dMMR gastric, small intestine, or biliary cancer
- Non-small cell lung cancer (monotherapy and combination)
- Renal cell carcinoma

- Urothelial carcinoma

Chemotherapy for:

- Breast cancer
- Cervical cancer
- Endometrial cancer
- Head and neck squamous cell carcinoma
- Non-small cell lung cancer
- Oesophageal carcinoma
- Renal cell carcinoma

Favezelimab-pembrolizumab is also in a phase III clinical trial for the treatment of Hodgkin lymphoma.[8]

Patient Group

Disease Area and Clinical Need

Colorectal cancer is a type of cancer that affects the large bowel which is made up of the colon and the rectum.[9] It is one of the most encountered cancer diagnoses in the UK. The three most commonly reported symptoms of colorectal cancer included persistent bloody stool, persistent loose watery stool, and persistent lower abdominal pain.[10] Several risk factors have been linked to colorectal cancer such as age, with older adults of age 60 and above more at risk. Also, diets high in red or processed meat, and low in fibre have been implicated in colorectal cancer. Similarly, smoking and drinking, being overweight, lack of physical exercise and a known family history of colorectal cancer are known risk factors.[10,11] Metastatic colorectal cancer occurs when the cancer spreads to other part of the body such as the liver, lung, or the peritoneum.[12] PD-L1 is an immunoinhibitory molecule that suppresses the activation of T cells, leading to the progression of tumours.[13] PD-L1 expression on tumour cells has been linked to a weakened host immune response and consequent poor prognosis in several malignancies, although links to prognosis are still unclear in colorectal cancer.[14]

Bowel cancer is the 4th most common cancer in the UK, accounting for 11% of all new cancer cases (2016-18).[15] The age standardised incidence rate of colorectal cancer in England is 83.6 and 55.8 per 100,000 amongst males and females respectively.[16] In England (2021-22) there were 178,203 finished consultant episodes (FCEs) and 162,089 admissions for colorectal cancer (ICD-10 code C18-20), which resulted in 125,188 day cases and 331,176 FCE bed days.[17] In England (2017), there were 34,825 patients diagnosed with colorectal cancer (ICD-10 code C18-C20) and 13,566 deaths registered where colorectal cancer was the underlying cause.[18] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates for stage IV (metastatic) colorectal cancer were 43.9% and 10.3% respectively.[19] PD-L1 expression has been found in roughly 82% of metastatic colorectal cancers.[20]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for the treatment of previously treated metastatic colorectal cancer:[21]

- Trifluridine–tipiracil

- Regorafenib

Clinical Trial Information

Trial	**MK-4280A-007; NCT05064059, EudraCT 2021-001309-60;** A Study of Coformulated Favezelimab/Pembrolizumab (MK-4280A) Versus Standard of Care in Subjects with Previously Treated Metastatic PD-L1 Positive Colorectal Cancer (MK-4280A-007) **Phase III –** Active, not recruiting **Location(s):** Five EU countries, UK, US, Canada, and other countries **Primary completion date:** February 2024
Trial Design	Randomised, parallel assignment, open label, active comparator controlled
Population	N= 432; Patients with previously treated PD-L1+ metastatic colorectal cancer; aged 18 years and older
Intervention(s)	Favezelimab-pembrolizumab (800 mg/200 mg), IV administration every three weeks for a maximum of 35 infusions
Comparator(s)	Regorafenib (160 mg) and TAS-102 (35 mg/m^2) oral administration
Outcome(s)	Primary outcome measures: - Overall survival: Time from randomization to death due to any cause with time frame up to approximately 26 months. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of favezelimab-pembrolizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Pembrolizumab with lenvatinib for previously treated metastatic colorectal cancer (TA11020). Expected publication date to be confirmed.
- NICE technology appraisal. Regorafenib for previously treated metastatic colorectal cancer (TA866). February 2023.
- NICE technology appraisal guidance. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016.
- NICE guideline. Colorectal cancer (NG151). January 2020. Last updated December 2021.
- NICE quality standard. Colorectal cancer (QS20). August 2012. Last updated February 2022.
- NICE diagnostics guidance in development. Quantitative faecal immunochemical tests to guide colorectal cancer pathway referral in primary care (DG10036). Expected November 2023.

- NICE diagnostics guidance. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care (DG30). July 2017.

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

- The American Society of Colon and Rectal Surgeons. Clinical Practice Guidelines for the Management of Colon Cancer.[22]
- Healthcare Improvement Scotland. Diagnosis and management of colorectal cancer: A national clinical guideline.[23]
- London Cancer Alliance (LCA). LCA Colorectal Cancer Clinical Guidelines. 2014.[24]
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Additional Information

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