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Newcastle University

Health Technology Briefing
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Favezelimab-Pembrolizumab for treating relapsed or refractory classical Hodgkin Lymphoma after 2 or more therapies

Company/Developer	Merck Sharp & Dohme Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35842	NICE ID: Not available	UKPS ID: 671809

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Co-formulated favezelimab-pembrolizumab is in clinical development for patients with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have exhausted all available treatment options and whose disease has progressed on treatment with an anti-PD-(L)1 monoclonal antibody. Hodgkin lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout your body. cHL is the most common type of Hodgkin lymphoma. The relapsed form of disease means the cancer has come back, while refractory disease means the cancer has stopped responding to treatment. Some lymphoma patients progress after chemotherapy and immunotherapy, and as such have fewer available treatment options. Therefore, there is an unmet need for effective therapies for patients with resistant cHL.

Favezelimab is a monoclonal antibody (a type of protein) which shuts off the protein (LAG-3) that suppresses an immune response to tumours, thereby enhancing tumour cell death which leads to a reduction in tumour growth. Pembrolizumab is a monoclonal antibody that has been designed to recognise and block a receptor ('target') called PD-1. By blocking PD-1, pembrolizumab stops the cancer switching off immune cells, thereby increasing the immune system's ability to kill the cancer cells. Co-formulated favezelimab-pembrolizumab is administered via intravenous (IV) infusion. If licensed, co-formulated favezelimab-pembrolizumab would offer an additional treatment option for patients with relapsed or refractory cHL.

Proposed Indication

For the management of patients with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have exhausted all available treatment options with known clinical benefit and whose disease has progressed on treatment with an anti-PD-(L)1 monoclonal antibody.[1]

Technology

Description

Favezelimab (MK-4280) is a humanised, immunoglobulin G4 (IgG4) monoclonal antibody directed against the inhibitory receptor lymphocyte activation gene-3 protein (LAG3), with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, favezelimab binds to LAG3 expressed on tumour-infiltrating lymphocytes (TILs) and blocks its binding with major histocompatibility complex (MHC) class II molecules expressed on tumour cells. This activates antigen-specific T-lymphocytes and enhances cytotoxic T-cell-mediated tumour cell lysis, which leads to a reduction in tumour growth.[2]

Pembrolizumab (Keytruda, MK-3475) 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.[3]

Co-formulated favezelimab-pembrolizumab is in clinical development for the treatment of patients with relapsed or refractory cHL that is PD-(L)1-refractory. In the phase III clinical trial (KEYFORM-008; NCT05508867), co-formulated favezelimab-pembrolizumab (800 mg/200 mg) is administered by intravenous (IV) infusion on day 1, then every three weeks, for up to 35 infusions.[1]

Key Innovation

PD-1 inhibitors, such as pembrolizumab, are highly effective in patients with relapsed or refractory cHL, but treatment options are limited for patients who have progressed after or not responded to PD1 blockade.[4] There is an unmet need for effective therapies for anti-PD1 resistant cHL.[4] Upregulation of lymphocyte-activation gene 3 (LAG-3) expression in cHL is proposed to contribute to resistance to anti PD-1 therapies.[4,5] The anti–LAG3 antibody favezelimab plus the anti-PD-1 therapy pembrolizumab has shown promising antitumor activity and manageable safety in patients with relapsed or refractory cHL after anti-PD1 therapy.[4,6]

Initial results from the multicohort phase I/II efficacy and safety study (MK-4280-003; NCT03598608) in patients with relapsed or refractory haematologic malignancies showed favezelimab plus pembrolizumab combination therapy demonstrated sustained antitumour activity and acceptable safety in patients with relapsed or refractory cHL whose disease progressed while on anti-PD-1 therapy.[7] If licensed, co-formulated favezelimab-pembrolizumab will offer an additional treatment option for patients with relapsed or refractory cHL that is PD-(L)1-refractory.

Regulatory & Development Status

Co-formulated favezelimab-pembrolizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Co-formulated favezelimab-pembrolizumab is in phase II/III clinical development for treatment of:[8]

- Colorectal cancer
- Solid tumours such as cutaneous squamous cell carcinoma and endometrial cancer

- Urothelial carcinoma
- Bladder cancer
- Small-cell lung cancer
- Esophageal cancer
- Renal cell carcinoma

Patient Group

Disease Area and Clinical Need

Hodgkin lymphoma (HL) is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout the body.[9] In HL, B-lymphocytes (a particular type of lymphocyte) start to multiply in an abnormal way and begin to collect in certain parts of the lymphatic system, such as the lymph nodes (glands). The affected lymphocytes lose their infection-fighting properties, making the patient more vulnerable to infection.[9] There are two types of HL and the most common type is classical Hodgkin lymphoma (cHL).[10] Relapsed cHL is defined as disease progression after most recent therapy, while refractory cHL is cHL that has failed to achieve complete or partial response to most recent therapy.[1,11] The most common symptom of HL is a painless swelling in the neck, armpit or groin. Other symptoms include night sweats, unintentional weight loss, a high temperature (fever), persistent cough or feeling of breathlessness, or persistent itching of the skin all over the body.[9] HL is rare and slightly more common in males than females in the UK. Other risk factors include: lowered immunity, obesity, smoking, family history, previous history of non-Hodgkin lymphoma, and Epstein Barr virus (EBV) infection.[12]

HL is not among the 20 most common cancers in the UK, accounting for less than 1% of all new cancer cases (2016-2018). There are around 2,100 new HL cases in the UK every year (2016-2018). The age standardised incidence rate of HL in England is 3.9 and 2.7 per 100,000 amongst males and females respectively.[13] In England (2022-23), there were 10,852 finished consultant episodes (FCEs) and 10,537 admissions for Other (classical) Hodgkin Lymphoma (ICD-10 code C817), which resulted in 9,713 day cases and 7,179 FCE bed days.[14] In England (2017), there were 1,802 patients diagnosed with Hodgkin's disease and 275 deaths registered where Hodgkin's disease was the underlying cause.[15] For patients diagnosed between 2013 and 2017, followed up to 2018, the age-standardised 1-year and 5-year survival rates were 90.6% and 82.2% respectively.[16]

Recommended Treatment Options

The NICE recommended treatment options for treating relapsed or refractory cHL include:[17]

- pembrolizumab after autologous stem cell transplant or at least 2 previous therapies
- nivolumab after autologous stem cell transplant and treatment with brentuximab vedotin

Clinical Trial Information

Trial	**KEYFORM-008**; NCT05508867, 2022-000371-39; A Phase 3 Randomized Clinical Study of MK-4280A (Co-formulated Favezelimab [MK-4280] Plus Pembrolizumab [MK-3475]) Versus Physician's Choice Chemotherapy in PD-(L)1-refractory, Relapsed or Refractory Classical Hodgkin Lymphoma. **Phase III** – Recruiting **Location(s)**: Six EU countries, UK, USA, and other countries **Primary completion date**: June 2031
Trial Design	Randomised, open label, parallel assignment
Population	N = 360 (estimated); subjects with relapsed or refractory cHL; aged 18 years and older

Intervention(s)	Co-formulated favezelimab/pembrolizumab (IV) 800 mg/200 mg on day 1, then every three weeks (Q3W), for up to 35 infusions
Comparator(s)	• Bendamustine (IV), dose between 90 and 120 mg/m^2 on day 1 and day 2 of either a 3- or 4-week cycle for up to 6 cycles • Gemcitabine (IV), dose between 800 and 1200 mg/m^2 on day 1 and day 8 of a 3-week cycle for up to 6 cycles
Outcome(s)	Progression Free Survival (PFS) per Lugano Response Criteria as assessed by Blinded Independent Central Review (BICR) [Time frame: up to approximately 43 months]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of co-formulated favezelimab-pembrolizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies (TA772). February 2022
- NICE technology appraisal guidance. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (TA540). September 2018
- NICE technology appraisal guidance. Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (TA462). July 2017
- NICE quality standard. Haematological Cancers (QS150). June 2017

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Statement: Bendamustine for relapsed/refractory classical Hodgkin lymphoma (all ages). 200701P. July 2020
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult), B15/S/a.

Other Guidance

- George A. et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. 2022.[18]
- Eichenauer DA. et al. Hodgkin Lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2018.[19]

Additional Information

References

1 ClinicalTrials.gov. *A Study of Coformulated Favezelimab/Pembrolizumab (MK-4280A) Versus Physician's Choice Chemotherapy in PD-(L)1-refractory, Relapsed or Refractory Classical Hodgkin Lymphoma (MK-4280A-008)*. *Trial ID: NCT05508867*. 2022. Status: Recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05508867 [Accessed 1 Nov 2023].

2 My Cancer Genome. *favezelimab*. Available from: https://www.mycancergenome.org/content/drugs/favezelimab/ [Accessed 1 Nov 2023].

3 Electronic Medicines Compendium (eMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2021. Available from: https://www.medicines.org.uk/emc/product/2498 [Accessed 1 Nov 2023].

4 Lavie D, Timmerman J, Garcia Sanz R, Kim WS, Kim TM, Avigdor A, et al. KEYFORM-008: Coformulated favezelimab and pembrolizumab (MK4280A) versus chemotherapy in relapsed/refractory classical Hodgkin lymphoma. *Journal of Clinical Oncology*. 2023;41(16_suppl):TPS7585-TPS. Available from: https://doi.org/10.1200/JCO.2023.41.16_suppl.TPS7585.

5 Veldman J, Visser L, Berg AVD, Diepstra A. Primary and acquired resistance mechanisms to immune checkpoint inhibition in Hodgkin lymphoma. *Cancer Treat Rev*. 2020;82:101931. Available from: https://doi.org/10.1016/j.ctrv.2019.101931.

6 Timmerman J, Lavie D, Johnson NA, Avigdor A, Borchmann P, Andreadis C, et al. Updated Results from an Open-Label Phase 1/2 Study of Favezelimab (anti-LAG-3) Plus Pembrolizumab in Relapsed or Refractory Classical Hodgkin Lymphoma after Anti-PD-1 Treatment. *Blood*. 2022;140(Supplement 1):768-70. Available from: https://doi.org/10.1182/blood-2022-166670.

7 Timmerman J, Lavie D, Johnson NA, Avigdor A, Borchmann P, Andreadis C, et al. Favezelimab (anti–LAG-3) plus pembrolizumab in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after anti–PD-1 treatment: An open-label phase 1/2 study. *Journal of Clinical Oncology*. 2022;40(16_suppl):7545-. Available from: https://doi.org/10.1200/JCO.2022.40.16_suppl.7545.

8 ClinicalTrials.gov. *15 Studies found for: favezelimab, pembrolizumab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Phase 2, 3 | Industry*. Available from: https://classic.clinicaltrials.gov/ct2/results?cond=&term=favezelimab%2C+pembrolizumab&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=f&type=Intr&phase=1&phase=2&fund=2 [Accessed 1 Nov 2023].

9 NHS UK. *Overview - Hodgkin lymphoma*. Available from: https://www.nhs.uk/conditions/hodgkin-lymphoma/ [Accessed 1 Nov 2023].

10 Cancer Research UK. *Types of Hodgkin lymphoma*. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/types [Accessed 1 Nov 2023].

11 Fox Chase Cancer Center. *Relapsed and Refractory Disease: What It Means for Blood Cancer Patients*. 2020. Available from: https://www.foxchase.org/blog/relapsed-and-refractory-disease-what-it-means-for-blood-cancer-patients#:~:text=Relapsed%20disease%20means%20a%20cancer%20has%20come%20back.,

means%20a%20cancer%20has%20stopped%20responding%20to%20treatment. [Accessed 1 Nov 2023].

12 Cancer Research UK. *Risks and causes*. Available from: https://www.cancerresearchuk.org/about-cancer/hodgkin-lymphoma/risks-causes [Accessed 1 Nov 2023].

13 Cancer Research UK. *Hodgkin lymphoma incidence statistics | Hodgkin lymphoma incidence by gender and UK country*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma/incidence#heading-Zero [Accessed 1 Nov 2023].

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 1 Nov 2023].

15 Office for National Statistics. *Cancer registration statistics, England*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 1 Nov 2023].

16 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 1 Nov 2023].

17 National Institute for Health and Care Excellence. *Showing 1 to 8 of 8 results for classical hodgkin lymphoma*. Available from: https://www.nice.org.uk/search?q=CLASSICAL%20HODGKIN%20LYMPHOMA [Accessed 1 Nov 2023].

18 Follows GA, Barrington SF, Bhuller KS, Culligan DJ, Cutter DJ, Gallop-Evans E, et al. Guideline for the first-line management of Classical Hodgkin Lymphoma — A British Society for Haematology guideline. *British Journal of Haematology*. 2022;197(5):558-72. Available from: https://doi.org/10.1111/bjh.18083.

19 Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, Illidge T, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2018;29(Suppl 4):iv19-iv29. Available from: https://doi.org/10.1093/annonc/mdy080.

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