

Health Technology Briefing November 2021

Pembrolizumab in combination with pemetrexed and cisplatin for previously untreated advanced malignant pleural mesothelioma

Company/Developer

Merck Sharp & Dohme Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 30374

NICE ID: 10557

UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II/III clinical development

Summary

Pembrolizumab in combination with pemetrexed and cisplatin is in clinical development for the treatment of adult patients with advanced malignant pleural mesothelioma (MPM). MPM is a rare variation of cancer that affects the internal chest wall and the outer linings of the lungs. Mesothelioma is often diagnosed at an advanced stage and surgery is not always possible. Treatment is usually given to manage the symptoms such as fatigue and shortness of breath caused by MPM, although patients tend to respond poorly to current chemotherapy and radiation therapy.

Pembrolizumab is a monoclonal antibody that has been designed to increase the immune system's ability to kill cancer cells by binding to, and blocking the PD-1 receptor that facilitates cancer cell death. Pembrolizumab is currently used in adults for cancers that are advanced, have spread to other parts of the body or are not responding to other treatments. In its development for MPM, Pembrolizumab is administered with pemetrexed and cisplatin intravenously and preliminary studies have shown that this combination may offer promising disease control rates and sustained disease stability. If licensed, pembrolizumab will offer an additional first-line treatment option for adults with advanced MPM.

Proposed Indication

Treatment of adult patients with advanced malignant pleural mesothelioma (MPM).¹

Technology

Description

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 primarily expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.^{2,3}

Pembrolizumab in addition to cisplatin and pemetrexed is currently in phase II/III clinical development for the treatment of adult patients with advanced malignant pleural mesothelioma. In the phase II/III clinical trial (NCT02784171), pembrolizumab is administered intravenously once every 21 days for a total of 2 years.¹

Key Innovation

Currently, approved therapies for MPM include radiotherapy, chemotherapy and surgery.^{4,5} Preliminary studies have shown pembrolizumab may offer promising disease control rates and sustained disease stability when added to the standard combination. In these studies, pembrolizumab has demonstrated antitumor activity in previously treated participants with advanced mesothelioma, regardless of PD-L1 status.⁶⁻⁸

If licensed, pembrolizumab will offer an additional first-line combinational immune checkpoint inhibitor treatment option for adult patients with advanced MPM.

Regulatory & Development Status

Pembrolizumab is currently licensed in the UK as a monotherapy or in combination with various medicinal products for the treatment of various cancers including:²

- Melanoma
- Non-small cell lung carcinoma (NSCLC)
- Classical Hodgkin lymphoma (cHL)
- Urothelial carcinoma
- Head and neck squamous cell carcinoma (HNSCC)
- Renal cell carcinoma (RCC)
- Colorectal cancer (CRC)

Pembrolizumab is currently in phase II/III clinical development for the treatment of various types of cancer some of which include:⁹

- Nasopharyngeal Carcinoma
- Locally Advanced Adenocarcinoma of Esophagogastric Junction
- Thymic Carcinomas
- Muscle-Invasive Bladder Cancer
- Non-small-cell Lung Cancers
- Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Patient Group

Disease Area and Clinical Need

Mesothelioma (malignant mesothelioma) is a type of cancer that affects the mesothelium, which is the lining that covers the outer surface of some of the organs in the human body. Mesothelioma that affects the pleura which is the outer lining of the lungs and internal chest wall is known as pleural mesothelioma.^{4,10} Approximately 9 out of 10 (90%) mesotheliomas occur in the chest.¹¹ Asbestos exposure is the leading cause of mesothelioma. It is a group of minerals made of microscopic fibres that used to be widely used in construction. These microscopic fibres easily get trapped in the lungs consequently, damaging the lungs over time. The effects of asbestos exposure is not instant but rather gradual with obvious adverse events showing more than 20 years after an individual is exposed to asbestos.⁴

Pleural mesothelioma leads to a thickening of the pleura. The thickened pleura may then begin to press onto the lungs or attach itself to the inside of the chest wall. In either case the expansion of the lung becomes progressively restricted by the tumour. Fluid, which can sometimes be several litres, can gather between the two layers of the pleura; this affects the lungs ability to expand and causes the affected individual to feel breathless. This is known as a pleural effusion.¹⁰ Symptoms of pleural mesothelioma include chest pain, shortness of breath, fatigue, fever and sweating, persistent cough, loss of appetite and unexplained weight loss, and swollen fingertips.^{4,10}

More than 2,600 people are diagnosed with the condition each year in the UK. Most cases are diagnosed in people aged 60 to 80, and men are affected more commonly than women.⁴ On average each year, 55% people diagnosed with mesothelioma are aged 75 and over.¹¹ There were 2,369 deaths in Great Britain due to mesothelioma in 2019 and although some deaths that happened in 2019 took longer to be registered due to the COVID-19 pandemic in 2020, the number of late registrations by March 2021 was comparable to the estimated number based on patterns of late registrations in previous years.¹² Estimates of the likely burden of disease of mesothelioma suggest that the numbers of cases in the UK are likely to peak between 2020 and 2025.¹³ In England in 2020 there were 8,566 finished consultant episodes (FCEs) of mesothelioma (ICD-10 code C45) resulting in 14,005 FCE bed days.¹⁴

Recommended Treatment Options

Current treatment options available for malignant pleural mesothelioma include:

- Ipilimumab for the treatment of MPM (in combination with nivolumab).¹⁵
- Pemetrexed for the treatment of unresectable MPM which has not previously been treated with chemotherapy (in combination with cisplatin).¹⁶

NICE recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate. Patients currently receiving pemetrexed who do not fall into the patient population as defined above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.¹⁷

Clinical Trial Information

Trial

[NCT02784171](#); [2016-002286-60](#); A Phase II/III Randomized Study of Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma
Phase II/III: Active, not recruiting
Location(s): Italy, France, and Canada

	Primary completion date: July 2022
Trial Design	Randomised, parallel assignment, open label
Population	N= 520 (actual); participants 18 years and older who have histologically confirmed malignant pleural mesothelioma; Patients must have unresectable advanced and/or metastatic disease, incurable by standard therapies.
Intervention(s)	Participants received pembrolizumab 200 mg for 2 years in combination with pemetrexed 500 mg for 6 cycles and cisplatin 75 mg intravenously once every 21 days for 6 cycles
Comparator(s)	Pemetrexed 500 mg once every 21 days for 6 cycles and cisplatin 75 mg once every 21 days for 6 cycles Pembrolizumab 200 mg once every 21 days for 2 years (phase II only)
Outcome(s)	<ul style="list-style-type: none"> - Phase II: Progression free survival measured as time from randomization to first observation of objective disease relapse or progression [Time Frame: 32 months] - Phase III: Overall Survival defined as time from randomization to the date of death from any cause [Time Frame: 32 months] <p>See trial record for full list of all outcomes</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The list price of pembrolizumab is £2,630 per 100-mg/4-ml vial.¹⁸

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531). July 2018.
- NICE technology appraisal. Pemetrexed for the treatment of malignant pleural mesothelioma (TA135). January 2008.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma (GID-TA10498). Expected date of issue: December 2021.
- NICE technology appraisal (suspended). Nintedanib for untreated malignant pleural mesothelioma (ID1424). Expected date of issue to be confirmed.
- NICE technology appraisal (suspended). NGR-TNF for previously treated advanced malignant pleural mesothelioma (GID-TA10183). Expected date of issue to be confirmed.
- NICE technology appraisal (suspended). Listeria monocytogenes vaccine for previously treated malignant pleural mesothelioma (GID-TA10320). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pegargiminase with pemetrexed and cisplatin for untreated advanced malignant pleural mesothelioma (GID-TA10486). Expected date of issue to be confirmed.

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.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Malignant Mesothelioma (Adult). B10/S/a.
- NHS England. Clinical Guidelines for the Management of Lung Cancer and Mesothelioma: Radiotherapy (SABR) West Midlands Expert Advisory Group for Lung Cancer and Mesothelioma. 2017.

Other Guidance

- Woolhouse I, Bishop L, Darlison L et al. BTS guideline for the investigation and management of malignant pleural mesothelioma. 2018.¹⁹
- Zandwijk NV, Clarke C, Henderson D et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. 2013.²⁰

Additional Information

References

- 1 Clinical Trials.gov. *Pembrolizumab in Patients With Advanced Malignant Pleural Mesothelioma*. Trial ID: NCT02784171. 26 May 2016. Status: Active. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02784171> [Accessed 20 October 2021].
- 2 Electronic medicines compendium (eMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2021. Available from: https://www.medicines.org.uk/emc/product/2498/smpc#PHARMACOLOGICAL_PROPS [Accessed 21 October 2021].
- 3 (NIH) NIOH. *Pembrolizumab*. 2014. Available from: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/pembrolizumab?redirect=true> [Accessed 21 October 2021].
- 4 National Health Services (NHS). *Mesothelioma*. Available from: <https://www.nhs.uk/conditions/mesothelioma/> [Accessed 21 October 2021].
- 5 Nicolini F, Bocchini M, Bronte G, Delmonte A, Guidoboni M, Crinò L, et al. Malignant pleural mesothelioma: state-of-the-art on current therapies and promises for the future. *Frontiers in oncology*. 2020;9:1519. Available from: <https://doi.org/https://dx.doi.org/10.3389/fonc.2019.01519>.
- 6 Yap TA, Nakagawa K, Fujimoto N, Kuribayashi K, Guren TK, Calabrò L, et al. Efficacy and safety of pembrolizumab in patients with advanced mesothelioma in the open-label, single-arm, phase 2 KEYNOTE-158 study. *The Lancet Respiratory Medicine*. 2021;9(6):613-21. Available from: [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30515-4/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30515-4/fulltext).
- 7 Marabelle A, Le DT, Ascierio PA, Di Giacomo AM, De Jesus-Acosta A, Delord J-P, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite

- instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. *Journal of Clinical Oncology*. 2020;38(1):1. Available from: <https://doi.org/https://doi.org/10.1200/jco.19.02105>.
- 8 The ASCO Post. *Use of Pembrolizumab in Advanced Pleural Mesothelioma: Results From KEYNOTE-158*. 2020. Available from: <https://ascopost.com/issues/november-25-2020/use-of-pembrolizumab-in-advanced-pleural-mesothelioma-results-from-keynote-158/> [Accessed 21 October 2021].
- 9 Clinical Trials.gov. *Pembrolizumab | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=Pembrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 21 October 2021].
- 10 Mesothelioma UK. *Pleural Mesothelioma*. Available from: <https://www.mesothelioma.uk.com/pleural-mesothelioma/> [Accessed 21 October 2021].
- 11 Cancer Research UK. *What is mesothelioma?* Available from: <https://www.cancerresearchuk.org/about-cancer/mesothelioma/about> [Accessed 21 October 2021].
- 12 Health and Safety Executive (HSE). *Mesothelioma statistics for Great Britain, 2021*. 2021. Available from: <https://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma.pdf> [Accessed 21 October 2021].
- 13 Royal College of Physicians. *National Lung Cancer Audit pleural mesothelioma report 2016*. 2016. Available from: <https://www.rcplondon.ac.uk/projects/outputs/national-lung-cancer-audit-pleural-mesothelioma-report-2016> [Accessed 21 October 2021].
- 14 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21> [Accessed 21 October 2021].
- 15 National Institute for Health and Care Excellence (NICE) BNF. *IPILIMUMAB*. Available from: <https://bnf.nice.org.uk/drug/ipilimumab.html#indicationsAndDoses> [Accessed 21 October 2021].
- 16 NICE BNF. *Pemetrexed*. Available from: <https://bnf.nice.org.uk/drug/pemetrexed.html#indicationsAndDoses> [Accessed 21 October 2021].
- 17 NICE Guidance. *Pemetrexed for the treatment of malignant pleural mesothelioma*. 2008. Available from: <https://www.nice.org.uk/guidance/ta135> [Accessed 21 October 2021].
- 18 NICE BNF. *Pembrolizumab*. Available from: <https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html> [Accessed 25 October 2021].
- 19 Woolhouse I, Bishop L, Darlison L, De Fonseka D, Edey A, Edwards J, et al. BTS guideline for the investigation and management of malignant pleural mesothelioma. *BMJ open respiratory research*. 2018;5(1):e000266. Available from: <https://doi.org/http://dx.doi.org/10.1136/bmjresp-2017-000266>.
- 20 Van Zandwijk N, Clarke C, Henderson D, Musk AW, Fong K, Nowak A, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. *Journal of thoracic disease*. 2013;5(6):E254. Available from: <https://doi.org/https://dx.doi.org/10.3978%2Fj.issn.2072-1439.2013.11.28>.

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