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Newcastle University

Health Technology Briefing
August 2023

Pembrolizumab with chemotherapy for platinum-resistant recurrent ovarian cancer after 1 or 2 therapies

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34384	NICE TSID: Not available	UKPS ID: 670305

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in combination with paclitaxel with or without bevacizumab is in clinical development for the treatment of platinum-resistant recurrent ovarian cancer after one or two prior therapies. Ovarian cancer occurs when abnormal cells in the ovary begin to grow and divide in an uncontrolled way to eventually form a growth (tumour). Some of the symptoms include bloating or a swollen tummy, discomfort in the tummy or pelvic area, and a frequent urge to urinate. Ovarian cancer has poor survival rates due to a combination of late diagnosis and disease recurrence owing to platinum chemotherapy resistance. While there are therapeutic advances in ovarian cancer generally, platinum-resistant recurrent ovarian cancer remains an area of high unmet clinical need and new treatments to further improve clinical outcomes are needed.

Pembrolizumab is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. By blocking PD-1, pembrolizumab stops the cancer switching off the activity of certain cells of the immune system, thereby increasing the immune system's ability to kill the cancer cells. Pembrolizumab is administered via intravenous infusion. If licenced, pembrolizumab in combination with paclitaxel with or without bevacizumab will provide an additional treatment option for platinum-resistant recurrent ovarian cancer patients.

Proposed Indication

Treatment of platinum-resistant recurrent ovarian cancer after one or two prior lines of systemic therapy, including at least 1 prior platinum-based therapy.[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 expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2]

Pembrolizumab in combination with paclitaxel with or without bevacizumab is in clinical development for the treatment of platinum-resistant recurrent ovarian cancer. In the phase III clinical trial (KEYNOTE-B96/ENGOT-ov65; NCT05116189), patients will be administered pembrolizumab 400mg via intravenous infusion (IV) for eighteen 6-week cycles plus paclitaxel (IV) 80mg/m2 on days 1, 8 and 15 of each 3-week cycle until intolerance or disease progression. Patients may also be administered bevacizumab (IV) 10mg/kg for each 2-week cycle.[1]

Key Innovation

Despite therapeutic advances in ovarian cancer, platinum-resistant recurrent ovarian cancer (PROC) remains an area of high unmet clinical need and there is an pressing need for new treatments to further improve clinical outcomes.[3] In a phase II clinical trial (NCT02674061), single-agent pembrolizumab showed modest activity in patients with recurrent ovarian cancer whereas in another single-arm phase II study, the combination of the of the anti-PD-1 antibody pembrolizumab with weekly paclitaxel showed antitumour activities and manageable toxicity in patients with PROC.[3,4] Combination cancer therapy tends to be more effective because the combined cancer drugs work by different mechanisms, thereby reducing the likelihood of development of resistant cancer cells. In addition, each combined drug can be used at its optimal dose, without intolerable side effects.[5]

If licenced, pembrolizumab in combination with paclitaxel with or without bevacizumab will provide an additional treatment option for platinum-resistant recurrent ovarian cancer patients.

Regulatory & Development Status

Pembrolizumab has Marketing Authorisation in the EU/UK as monotherapy and combination therapy for the following indications:[2]

- Non-small cell lung carcinoma (NSCLC)
- Melanoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma (HNSCC)
- Renal cell carcinoma
- Colorectal and non-colorectal cancers
- Oesophageal carcinoma
- Triple-negative breast cancer
- Endometrial carcinoma
- Cervical cancer

Pembrolizumab in combination with paclitaxel is currently in phase II and III clinical trials for multiple indications, including but not limited to:[6]

- NSCLC
- Breast cancer
- Cervical cancer
- HNSCC
- Metastatic malignant melanoma

Patient Group

Disease Area and Clinical Need

Ovarian cancer occurs when abnormal cells in the ovary begin to grow and divide in an uncontrolled way to eventually form a growth (tumour). There are different types of ovarian cancer depending on the type of cell the cancer starts in.[7] Epithelial ovarian cancer is the most common type of ovarian cancer and starts in the surface layer covering the ovary.[8] The symptoms of ovarian cancer can be very vague, and include bloating or a swollen tummy, discomfort in the tummy or pelvic area, feeling full quickly, needing to urinate more often, unexplained tiredness, unexplained weight loss, and changes in the bowel habit or symptoms of irritable bowel syndrome.[9,10] Some risk factors of ovarian cancer include age (around 45 years, and greatest in those aged between 75 and 79 years), inherited faulty genes, previous history of cancers, smoking, using hormone replacement therapy (HRT), being obese or overweight, contact with asbestos, and certain medical conditions such as endometriosis or diabetes.[11]

Ovarian cancer is the 6th most common cancer in women in the UK, accounting for 4% of all new cancer cases in females (2016-2018).[12] According to statistical analysis, ovarian cancer incidence rates are projected to rise by 5% in the UK between 2023-2025 and 2038-2040.[12] In England in 2021-22, there were 33,860 admissions and 36,418 finished consultant episodes (FCE) for primary diagnosis of malignant neoplasm of ovary (ICD-10 codes C56.X) which resulted in 45,542 FCE bed days and 27,232 day cases.[13]

Recommended Treatment Options

NICE recommends the following treatment options for recurrent ovarian cancer.[14]

- Paclitaxel in combination with platinum or as monotherapy.
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy
- PLDH in combination with platinum

Clinical Trial Information

Trial	**KEYNOTE-B96/ENGOT-ov65**; NCT05116189; **EudraCT** 2020-005027-37; A phase 3, randomized, double-blind study of pembrolizumab versus placebo in combination with paclitaxel with or without bevacizumab for the treatment of platinum-resistant recurrent ovarian cancer. **Phase III**- Active, not recruiting. **Location(s):** 10 EU countries, UK, US, Canada Australia and other countries **Primary completion date**: August 2027
Trial Design	Randomised, parallel assignment, triple masking
Population	N=616 (estimated); Patients with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who have received 1 or 2 prior lines of systemic therapy for ovarian cancer, including at least 1 prior platinum-based therapy.
Intervention(s)	Pembrolizumab (IV) 400mg for eighteen 6-week cycles + paclitaxel (IV) 80mg/m2 on day 1, 8 and 15 of each 3-week cycle ± bevacizumab (IV) 10mg/kg for each 2-week cycle.
Comparator(s)	Placebo + paclitaxel (IV) 80mg/m2 on day 1, 8 and 15 of each 3-week cycle ± bevacizumab (IV) 10mg/kg for each 2-week cycle.
Outcome(s)	Primary outcome measure: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1) by Investigator [Time frame: up to ~38 months]. See the trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml (25 mg per 1 ml) solution for infusion vial costs £2,630.[15]

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. [GID-TA11033] Olaparib with cediranib for treating platinum-resistant recurrent ovarian cancer after 1 or 2 therapies [ID4065]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. [GID-TA10313]. Lurbinectedin for treating advanced platinum-resistant ovarian cancer. [ID1340] Expected date of issue to be confirmed.
- NICE technology appraisal in development. [GID-TA10446]. Cositecan for treating platinum or taxane resistant advanced, mucinous, epithelial ovarian cancer. Expected date of issue to be confirmed.

- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer [TA389]. April 2016.
- NICE clinical guidelines. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Ovarian cancer (QS18). May 2012

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers. E10/S/f.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B14/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 135: Management of epithelial ovarian cancer. 2013. Revised 2018.[16]
- Capoluongo E, et al. Guidance Statement on BRCA1/2 Tumour Testing in Ovarian Cancer Patients. 2017.[17]
- Santaballa A, et al. SEOM Clinical guideline in ovarian cancer. 2016.[18]
- National Comprehensive Cancer Network (NCCN). Ovarian cancer, version 1, NCCN clinical practice guidelines in oncology. 2016.[19]

Additional Information

References

1 Clinicaltrials.gov. *A Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer (KEYNOTE-B96/ENGOT-ov65)*. Available from: https://clinicaltrials.gov/study/NCT05116189 [Accessed 12 July 2023].

2 Electronic Medicine Compendium (emc). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/product/2498 [Accessed 12 July 2023].

3 Colombo N, Coleman RL, Wu X, Köse F, Wenham RM, Sebastianelli A, et al. ENGOT-ov65/KEYNOTE-B96: Phase 3, randomized, double-blind study of pembrolizumab versus placebo plus paclitaxel with optional bevacizumab for platinum-resistant recurrent ovarian cancer. *Journal of Clinical Oncology*. 2022;40(16_suppl):TPS5617-TPS. Available from: https://doi.org/10.1200/JCO.2022.40.16_suppl.TPS5617.

4 Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian

cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol*. 2019;30(7):1080-7. Available from: https://doi.org/10.1093/annonc/mdz135.

5 MSD Manual. *Combination Cancer Therapy*. 2022. Available from: https://www.msdmanuals.com/home/cancer/prevention-and-treatment-of-cancer/combination-cancer-therapy [Accessed 23 August 2023].

6 Clinicaltrials.gov. *Phase II and III trials multiple indications for pembrolizumab and paclitaxel combination.* Available from: https://classic.clinicaltrials.gov/ct2/results?term=Pembrolizumab+and+Paclitaxel&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&phase=3&Search=Apply [Accessed 12 July 2023].

7 Cancer Research UK. *What is ovarian cancer?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/what-is-ovarian-cancer [Accessed 19 July 2023].

8 National Health Service (NHS). *Ovarian cancer: overview*. 2022. Available from: https://www.nhs.uk/conditions/ovarian-cancer/ [Accessed 13 July 2023].

9 Cancer Research UK. *Symptoms of ovarian cancer*. 2021. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms [Accessed 19 July 2023].

10 National Health Service (NHS). *Ovarian cancer: symptoms*. 2022. Available from: https://www.nhs.uk/conditions/ovarian-cancer/symptoms/ [Accessed 19 July 2023].

11 Cancer Research UK. *Risks and causes of ovarian cancer*. 2022. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/ovarian-cancer/risks-causes [Accessed 19 July 2023].

12 Cancer Research UK. *Ovarian cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Zero [Accessed 13 July 2023].

13 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 13 July 2023].

14 National Institute for Health and Care Excellence (NICE). *Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer*. 2016. Available from: https://www.nice.org.uk/guidance/ta389/chapter/1-Recommendations [Accessed 13 July 2023].

15 British National Formulary (BNF). *Medicinal forms: Keytruda 100mg/4ml concentrate for solution for infusion vials Merck Sharp & Dohme (UK) Ltd*. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab-specialist-drug/medicinal-forms/ [Accessed 13 July 2023].

16 Healthcare Improvement Scotland. *Management of epithelial ovarian cancer*. Available from: https://www.sign.ac.uk/media/2010/sign135_oct2022.pdf [Accessed 13 July 2023].

17 Capoluongo E, Ellison G, López-Guerrero JA, Penault-Llorca F, Ligtenberg MJL, Banerjee S, et al. Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients. *Semin Oncol*. 2017;44(3):187-97. Available from: https://doi.org/10.1053/j.seminoncol.2017.08.004.

18 Santaballa A, Barretina P, Casado A, García Y, González-Martín A, Guerra E, et al. SEOM Clinical Guideline in ovarian cancer (2016). *Clinical and Translational Oncology*. 2016;18(12):1206-12. Available from: https://doi.org/10.1007/s12094-016-1588-8.

19 Morgan RJ, Jr., Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Behbakht K, Chen LM, et al. Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(9):1134-63. Available from: https://doi.org/10.6004/jnccn.2016.0122.

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