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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Pembrolizumab addition to chemotherapy, followed by maintenance with olaparib for BRCA non-mutated advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer – First-line

NIHRIO ID	26974	**NICE ID**	10223
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	651297

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pembrolizumab in addition to chemotherapy, followed by maintenance with olaparib is in clinical development for the first line treatment of Breast Cancer Gene (BRCA) non-mutated advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Ovarian cancer includes a group of tumours that arise from diverse types of tissue contained in the ovary and can often spread from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. While current treatments exist for these advanced cancers of the female reproductive system, significant unmet medical need remains for more effective treatment options with manageable safety profiles for patients in the first line setting.

Pembrolizumab delivered via intravenous infusion is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells by targeting specific proteins that stimulate an immune response. Olaparib is administered orally in tablet form and can lead to cancer cell death by blocking DNA repair by an enzyme (protein) called PARP. If licensed, pembrolizumab in addition to chemotherapy, followed by maintenance with olaparib will provide a new regimen for BRCA non-mutated advanced ovarian cancer.

PROPOSED INDICATION

Pembrolizumab and chemotherapy followed by maintenance with olaparib for the first-line treatment of BRCA non-mutated advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.[1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody which binds to the 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]

Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, PARP-3) shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.[3]

In the phase III clinical trial (NCT03740165), patients receive carboplatin/paclitaxel intravenously (IV) for five 3–week cycles along with pembrolizumab 200mg IV infusion on day 1 of each 3-week cycle for up to 35 cycles and olaparib 300mg oral tablet twice each day (BID) starting with cycle 7. Participants may also receive bevacizumab IV infusion on day 1 of each 3-week cycle.[1]

INNOVATION AND/OR ADVANTAGES

There is a significant unmet need to develop new regimens for BRCA1/2-non-mutated advanced ovarian cancer. The PARP inhibitor olaparib is approved for women with platinum-sensitive, recurrent ovarian cancer regardless of BRCA1/2 status and, more recently, for newly diagnosed women with BRCA-mutated ovarian cancer. Pembrolizumab is not indicated as monotherapy or in combination for this indication but in the TOPACIO/KEYNOTE-162 study, the combination of the PD-1–blocking antibody pembrolizumab and niraparib demonstrated efficacy in platinum-resistant relapsed ovarian cancer irrespective of BRCA1/2 status.[4]

In this trial olaparib is given with pembrolizumab as maintenance therapy. Maintenance therapy is given to help keep cancer from coming back after it has disappeared following the initial therapy, the initial therapy being pembrolizumab and chemotherapy.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab in combination with chemotherapy and followed by olaparib is not currently recommended in the EU/ UK for the treatment of ovarian cancer.

Pembrolizumab is currently licenced as a monotherapy in the UK for:[2]

- The treatment of advanced (unresectable or metastatic) melanoma in adults.
- Adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection.

- First-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ⩾ 50% tumour proportion score (TPS) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.
- The treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ⩾ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
- The treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.
- The treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- The treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ⩾ 10.
- As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ⩾ 1.
- The treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ⩾ 50% TPS and progressing on or after platinum-containing chemotherapy.

Pembrolizumab is also licensed in the UK in combination with:[2]

- Pemetrexed and platinum chemotherapy is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- Carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- Axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.

The most common adverse events of pembrolizumab monotherapy or in combination with chemotherapy or other anti-tumour medicines include anaemia, neutropenia, thrombocytopenia, hypothyroidism, hyperthyroidism, decreased appetite, hypokalaemia, headache, dizziness, peripheral neuropathy, dysgeusia, hypertension, dyspnoea, cough, dysphonia, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, alopecia, palmar-plantar erythrodysaesthesia syndrome, musculoskeletal pain, arthralgia, pain in extremity, fatigue, asthenia, oedema, pyrexia, blood creatinine increased, alanine aminotransferase increased, and aspartate aminotransferase increased.[2]

Olaparib is currently licenced as a monotherapy in the UK as follows:[3]

- As maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- As maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
- The treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo) adjuvant or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with

hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.
- As maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy ($\geqslant$ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.[3]

Pembrolizumab with olaparib is currently in phase III clinical trials for non-small cell lung cancer; prostate cancer and triple negative breast neoplasms. Pembrolizumab in combination with olaparib is currently in phase II clinical trials for solid tumours, cholangiocarcinoma, and advanced gastric adenocarcinoma.[5]

PATIENT GROUP

DISEASE BACKGROUND

Epithelial ovarian cancers start in the cells covering the ovaries and are the most common type of ovarian cancer. Around 90 out of 100 (90%) of ovarian tumours are this type. Primary peritoneal cancer and fallopian tube cancer are similar to epithelial ovarian cancer and are treated in the same way.[6] Advanced ovarian cancer falls within stages III and IV. Stage III denotes that the cancer is locally advanced and has spread outside the pelvis into the abdominal cavity. Stage IV denotes that distant metastasis to other body organs such as the liver and lungs has occurred.[7]

Symptoms of ovarian cancer include loss of appetite, abdominal pain, bloating and frequent urination.[8] The risk of developing ovarian cancer increases with age and it is most common in women aged between 75 and 79. Inherited gene mutations are another major risk factor and between 5 to 15% of ovarian cancer cases are caused by mutated BRCA 1 or 2 genes. Other risk factors include: a history of breast or bowel cancer, using hormone replacement therapy, smoking, having endometriosis or diabetes and being overweight or obese.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017 there were 6,236 registrations of newly-diagnosed malignant neoplasm of the ovary and other unspecified female genital organs (ICD-10 code: C56-C57), equating to a directly age-standardised rate of 22.7 cases per 100,000 females.[10] Statistics from Cancer Research UK report that in 2017, ovarian cancer was the 6th most common cancer in the UK and accounted for 4% of all new cancer cases. Incidence rates for ovarian cancer in the UK are highest in females aged between 75 to 79 years (2015 to 2017). More ovarian cancer cases are diagnosed in late stage than an early stage and between 17% and 21% of females have metastases at diagnosis (stage IV).[11]

In England in 2018-2019 there were 41,865 finished consultant episodes, and 38,857 hospital admissions with a primary diagnosis of malignant neoplasm of female genital organs (ICD-10 code C56-C57), resulting in 30,049 day cases and 59,746 bed days.[12]

In females in the UK, ovarian cancer is the 6th most common cause of cancer death, with around 4,100 deaths in 2017. Mortality rates for ovarian cancer in the UK are highest in females aged 85 to 89 years (2015 to 2017). Mortality rates are projected to fall by 37% in the UK between 2014 and 2035, to 10 deaths per 100,000 females by 2035.[13] Almost three-quarters (71.7%) of women diagnosed with ovarian cancer in England survive their disease for one year or more (2013-2017) and 42.6% survive their disease for 5 years or more (2013-2017).[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of advanced ovarian cancer involves a multidisciplinary team. Usually it includes primary surgery with the objective of complete resection of all macroscopic disease. This can be preceded by neoadjuvant chemotherapy and followed by chemotherapy and maintenance therapy.[15]

CURRENT TREATMENT OPTIONS

NICE approved first-line therapy of advanced ovarian cancer includes:[15]

- Paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery)

Bevacizumab in combination with paclitaxel and carboplatin is not recommended for NICE but is available via the UK Cancer Drugs Fund.[16]

PLACE OF TECHNOLOGY

If licensed, pembrolizumab with chemotherapy followed by maintenance with olaparib will offer an additional first-line treatment of BRCA non-mutated advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.

CLINICAL TRIAL INFORMATION

Trial	**MK-7339-001;** NCT03740165, 2018-001973-25; Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43) **Phase III** - Recruiting **Location(s):** EU countries (not inc UK), US, Canada and other countries **Primary completion date:** Aug 2025
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N = 1086 (planned), aged 18 years and older, Stage III or Stage IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
Intervention(s)	Intravenous pembrolizumab with chemotherapy, oral olaparib, patients may also receive intravenous bevacizumab

Comparator(s)	• Intravenous pembrolizumab with chemotherapy, oral olaparib placebo, patients may also receive intravenous bevacizumab • Intravenous pembrolizumab placebo with chemotherapy, oral olaparib placebo, patients may also receive intravenous bevacizumab
Outcome(s)	• Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by the investigator [Time frame: up to approximately 6 yrs] • Overall Survival (OS) [Time frame: up to approximately 6 yrs] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab and olaparib are already marketed in the UK. The NHS indicative price for a vial of pembrolizumab (50 mg) is £1315.00 (hospital only).[17]

For olaparib, the NHS indicative price is £2317.50 for 56 x 100 and 150mg tablets and £3,550 for 448 x 50 mg capsules.[18]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.
- NICE technology appraisal. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). May 2005.
- NICE Clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.

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). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- British Gynaecological Cancer Society (BGCS). Epithelial Ovarian /Fallopian Tube /Primary Peritoneal Cancer Guidelines: Recommendations for Practice. 2017.[19]
- Comprehensive Cancer Network (NCCN). Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. 2016.[20]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43)*. Trial ID: NCT03740165. 2018;Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03740165?term=Pembrolizumab+%2B+Olaparib&phase=12&draw=2&rank=5

2 electronic Medicines Compendium. *KEYTRUDA 50 mg powder for concentrate for solution for infusion*. 2015. Available from: https://www.medicines.org.uk/emc/product/6947/smpc#PHARMACODYNAMIC_PROPS [Accessed 10 July 2020].

3 electronic Medicines Compendium. *Lynparza 100mg Film-Coated Tablets*. 2019. Available from: https://www.medicines.org.uk/emc/product/9204/smpc [Accessed 10 July 2020].

4 Vergote, I., Sehouli J., Salutari V., Zola P., Madry R., Wenham R. M., et al. *ENGOT-OV43/KEYLYNK-001: A phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer*. Journal of Clinical Oncology. 2019;37(15_suppl):TPS5603-TPS. Available from: https://doi/abs/10.1200/JCO.2019.37.15_suppl.TPS5603

5 Clinicaltrials.gov. *Search: Pembrolizumab + Olaparib | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Pembrolizumab+%2B+Olaparib&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 10 July 2020].

6 Cancer Research UK. *Epithelial ovarian cancer*. 2018. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers [Accessed 15 July 2020].

7 Cancer Research UK. *Ovarian cancer - Stages and grades*. 2019. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades [Accessed 15 July 2020].

8 Cancer Research UK. *Symptoms of ovarian cancer*. 2018. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms [Accessed 15 July 2020].

9 Cancer Research UK. *Risk factors for ovarian cancer*. 2018. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/risks-causes [Accessed 15 July 2020].

10 Office for National Statistics. *Cancer Registration Statistics, England*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

11 Cancer Research UK. *Ovarian cancer incidence statistics*. 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence#heading-Three [Accessed 10 July 2020].

12 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19

13 Cancer Research UK. *Ovarian cancer statistics*. 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-One [Accessed 10 July 2020].

14 Office for National Statistics. *Cancer survival in England - adults diagnosed*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

15 National Institute for Health and Care Excellence. *Managing advanced (stage II-IV) ovarian cancer*. 2020. Available from: https://pathways.nice.org.uk/pathways/ovarian-cancer#content=view-node%3Anodes-first-line-chemotherapy&path=view%3A/pathways/ovarian-cancer/managing-advanced-stage-ii-iv-ovarian-cancer.xml [Accessed 15 July 2020].

16 NHS England. *National Cancer Drugs Fund list.* 2020. Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ [Accessed 20 August 2020].
17 British National Formulary (BNF). *PEMBROLIZUMAB.* 2015. Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 7 July 2020].
18 British National Formulary (BNF). *Olaparib.* 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/olaparib.html [Accessed 7 July 2020].
19 Fotopoulou, C., Hall M., Cruickshank D., Gabra H., Ganesan R., Hughes C., et al. *British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice.* European journal of obstetrics, gynecology, and reproductive biology,. 2017 Jun;213:123-39. Available from: https://doi.org/10.1016/j.ejogrb.2017.04.016
20 Morgan, R. J., Armstrong D. K., Alvarez R. D., Bakkum-Gamez J. N., Behbakht K., Chen L.-m., et al. *Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology*. 2016;14(9):1134. Available from: https://doi.org/10.6004/jnccn.2016.0122

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