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Newcastle University

Health Technology Briefing
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Dostarlimab with chemotherapy and niraparib for treating advanced epithelial ovarian cancers – first line

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Dostarlimab in combination with chemotherapy and niraparib is currently in clinical development for the first-line treatment of newly diagnosed, stage III/IV, non-mucinous advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. These cancers arise from the same type of tissue and so exhibit many similar symptoms. These include pain and swelling in the abdominal area, constipation, and a frequent urge to urinate. In advanced ovarian cancers, where the cancer has spread beyond the ovary to surrounding areas such as the pelvis and abdomen, reappearance after chemotherapy is over 70% in the first two years with few therapeutic options.

Dostarlimab is a type of protein known as a monoclonal antibody, that has been designed to block a receptor (target) called programmed death -1 (PD-1) on certain cells of the immune system. Some cancers can make proteins (PD-L1 and PD-L2) that combine with PD-1 to switch off the activity of the immune cells, preventing them from attacking the cancer. By blocking PD-1, dostarlimab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. If licensed, dostarlimab, administered via intravenous injection, in combination with chemotherapy and niraparib will offer an additional first-line treatment for advanced ovarian cancers.

Proposed Indication

First-line treatment for newly diagnosed, stage III/IV, advanced, non-mucinous epithelial ovarian (EOC), fallopian tube or primary peritoneal cancer in female patients aged 18 years and older.[1]

Technology

Description

Dostarlimab (Jemperli) is a humanised monoclonal antibody of the IgG4-κ isotype that binds with high affinity to programmed death -1 (PD-1) receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in inhibition of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immune responses through blockade of PD-1 binding to PD-L1 and PD-L2, thereby increasing the immune system's ability to kill the cancer cells.[2,3]

Dostarlimab in combination with chemotherapy and niraparib is currently in clinical development for the treatment of advanced, non-mucinous EOC, fallopian tube or primary peritoneal cancer. In the phase III clinical trial (FIRST, NCT03602859), patients receive one cycle of standard of care followed by standard of care (SOC) with dostarlimab +/- bevacizumab (physician choice). Dostarlimab is administered via intravenous infusion at a dose of 1000mg for 30 minutes on Day 1 every 3 weeks. This is then followed by maintenance treatment of +/- bevacizumab with niraparib and dostarlimab, where the bevacizumab treatment duration is per current clinical practice and dostarlimab is administered every 6 weeks.[1]

Key Innovation

In advanced ovarian cancer, prognosis is poor as the recurrence rate after chemotherapy is over 70% in the first two years with few therapeutic options. Research shows that the combination with agents with different mechanisms of action appears a promising strategy to increase efficacy. The combinations of immune checkpoint inhibitors (ICIs) with poly-ADP ribose polymerase (PARP) inhibitors such as niraparib represent potentially very effective associations.[4] PARP is an enzyme that repairs DNA when it becomes damaged. Blocking these enzymes prevents DNA repair in cancerous cells, causing them to die.[5] Chronic PARP inhibition leads to sustained DNA damage that promotes several cellular mechanisms, such as increasing genomic instability, immune pathway activation, and PD-L1 expression on cancer cells, which might promote responsiveness to ICIs.[6]

If licensed, dostarlimab in combination with SOC +/- bevacizumab and niraparib will offer an additional treatment option for people with newly diagnosed, advanced ovarian cancers.

Regulatory & Development Status

Dostarlimab currently has Marketing Authorisation in the UK and EU as a monotherapy for the treatment of adult patients with mismatch repair deficient /microsatellite instability-high recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[2]

Dostarlimab is currently in phase II and III trials for the treatment of several indications, some of which include:[7]

- Non-small cell lung cancer
- Colorectal cancer
- Melanoma
- Endometrial cancer

- Liver cancer

Patient Group

Disease Area and Clinical Need

Ovarian cancer is a growth of cells that forms in the ovaries. The cells multiply quickly and can invade and destroy healthy body tissue.[8] EOC is the most common type of ovarian cancer and EOC tumours start from the cells that line or cover the ovaries and fallopian tubes (the epithelium).[9,10] EOC can be further divided into five histologic subtypes, with mucinous ovarian cancer being very rare.[11] It is characterised by the cancer cells being large and filled with fluid so that most of the tumour is made up of cells which are coated in mucus.[12] Non-mucinous EOC encompasses the four other subtypes which are: serous, endometrioid, clear cell and transitional cell tumours.[11] Advanced ovarian cancers are characterised by the cancer cells having spread outside the ovary to other parts of the body such as the pelvis, abdomen, or even the lungs.[13] The symptoms of ovarian cancer can include: bloating, discomfort in the tummy or pelvic area, feeling full quickly, needing to pee more often, back pain, vaginal bleeding after the menopause, unexplained tiredness, unexplained weight loss, and constipation or diarrhoea.[14] Fallopian tube cancer is similar to ovarian cancer with similar symptoms and can also include vaginal bleeding unrelated to menstruation and a watery vaginal discharge that may contain blood.[15] Peritoneal cancer is a rare cancer of the peritoneum and is similar to EOC. Similarly to the other types of ovarian cancer, symptoms are unclear and include: painful and swollen abdomen, constipation or diarrhoea, nausea and vomiting, indigestion, bloating and loss of appetite.[16] Factors that can increase the risk of ovarian cancer include age - most ovarian cancers develop after menopause - obesity, a family history of ovarian cancer, hereditary conditions (e.g., breast cancer type 1 susceptibility protein (BRCA) 1 and BRCA2 mutations), hormone replacement therapy and smoking.[17]

Around 7,500 women are diagnosed with ovarian cancer in the UK each year (2016-2018), making ovarian cancer the 6th most common cancer in women. It mostly affects women over 50, but the risk is greatest in those aged between 75 and 79.[18-20] Ovarian cancer accounts for 4% of all new cancer cases in females in the UK (2016-2018). Incidence rates for ovarian cancer are projected to rise by 5% in the UK between 2023-2025 and 2038-2040.[20] In England (2020), there were 3,016 patients diagnosed with stage III or IV ovarian cancer, accounting for 62% of ovarian cancers diagnosed with a known stage at diagnosis.[21] In England in 2021-2022, there were 42,173 finished consultant episodes (FCE), and 39,296 hospital admissions with a primary diagnosis of malignant neoplasm of ovary, fallopian tube and peritoneum (ICD-10 codes C48.2, C56.X, C57), resulting in 51,634 FCE bed days and 31,770 day cases.[22] In England and Wales (2021), there were 3,330 deaths caused by ovarian cancer, with 35% of patients surviving ovarian cancer for 10 years or more (based on data from 2013-2017).[20,23]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommend primary surgery, either before chemotherapy or after neoadjuvant chemotherapy, as a first-line treatment of advanced ovarian cancer and/or fallopian tube or primary peritoneal cancer.[24] Maximal cytoreductive surgery is recommended which uses additional surgical procedures, including upper abdominal surgery, with the aim of achieving no residual disease. The most important factors affecting outcomes after surgery are responsiveness to platinum-based chemotherapy and the amount of residual disease.[25]

Clinical Trial Information

Trial	**FIRST;** NCT03602859; EudraCT 2018-000413-20**;** A Randomized, Double-blind, Phase 3 Comparison of Platinum-based Therapy With dostarlimab and Niraparib Versus Standard of Care Platinum-based Therapy as First-line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancer **Phase III** – Active, not recruiting **Location(s):** 13 EU countries, UK, USA, and other countries **Primary completion date:** Q3 2023[a]
Trial Design	Randomised, parallel assignment, double-blinded
Population	N=1403 (actual); females aged 18 years and older with newly diagnosed, stage III or IV non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer.
Intervention(s)	See trial record for intervention details
Comparator(s)	See trial record for comparator details
Outcome(s)	Primary outcome measures: • Progression-free survival (PFS) for PD-L1 positive participants [time frame: up to 5 years]. • PFS for all participants [time frame: up to 5 years]. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The National Health Service (NHS) indicative price for 1 vial of dostarlimab (500mg/10ml) is £5,887.33.[26]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer (TA693). April 2021.
- NICE interventional procedures guidance. Ultra-radical (extensive) surgery for advanced ovarian cancer (IPG470). November 2013.
- NICE quality standard. Ovarian Cancer (QS18). May 2012.
- NICE clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Ovarian Cancer (QS18). May 2012.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2018/19 Manual for Prescribed Specialised Services.
- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers. E10/S/f.

[a] Information provided by GlaxoSmithKline UK Ltd

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- National Comprehensive Cancer Network. NCCN Guidelines® Insights: Ovarian Cancer, Version 3.2022.[27]
- The British Gynecological Cancer Society and the British Association of Gynecological Pathologists. British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumour testing for BRCA 1/2 variants in ovarian cancer in the United Kingdom. 2021.[28]
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- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 135: Management of epithelial ovarian cancer. 2013. Revised: 2018.[31]
- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice. 2017.[32]

Additional Information

The company terminated clinical trial (NCT03955471) which was evaluating the efficacy and safety of the combination of niraparib and dostarlimab in participants with platinum resistant ovarian cancer. This was based on the results of a planned interim analysis that showed futility.

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