NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2023

Niraparib as maintenance therapy for treating recurrent or primary-advanced endometrial cancer after chemotherapy in combination with dostarlimab.

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35715	NICE TSID: 11872	UKPS ID: 667586

Licensing and Market Availability Plans

Currently in Phase III trials.

Summary

Niraparib in combination with dostarlimab is in clinical development for patients with recurrent or primary-advanced endometrial cancer. Endometrial cancer occurs when cancer cells form in the tissues of the endometrium – the lining of the uterus. Symptoms may include irregular vaginal bleeding, painful urination, and pelvic pain. Advanced cancer means that the cancer has spread to other parts of the body; recurrent cancer means the cancer has come back after treatment. There is a need to develop new treatments and combinations that can produce longer-lasting positive outcomes for women with advanced/recurrent endometrial cancer.

Niraparib acts as an inhibitor of enzymes (proteins) called PARP-1 and PARP-2, both of which help with DNA repair when cells divide to make new cells. By blocking the activity of these enzymes, Niraparib prevents DNA repair of cancerous cells, eventually causes cell death. Dostarlimab is a type of immunotherapy (therapy that targets the immune system) that is administered intravenously (IV) and targets a receptor (protein) for PD-1. Blockage of PD-1 allows for the body's own immune cells (called T-cells) to attack and kill the cancer cells. If licensed, niraparib as maintenance therapy in combination with dostarlimab will offer an additional maintenance treatment option for primary-advanced / recurrent endometrial cancer after the chemotherapy treatment phase.

Proposed Indication

Treatment of females, 18 years and older with recurrent or primary-advanced endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination.[1]

Technology

Description

Niraparib (Zejula)[2] belong to a class of anti-cancer drugs known as PARP-inhibitors.[3] It acts as an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes called PARP-1 and PARP-2, both of which help with DNA repair when cells divide to make new cells.[2,4] By blocking the activity of these enzymes, Niraparib prevents DNA repair of cancerous cells, which results in apoptosis and eventual cell death.[2,4] Niraparib-induced cell damage described above was observed in tumour cell lines with or without mutations in the Breast Cancer (*BRCA)* 1 and 2 tumour suppressor genes.[2]

Dostarlimab (TSR-042, Jemperli)[1,5] is a monoclonal antibody, a protein that has been designed to block a receptor called PD-1 on certain cells of the immune system (the body's natural defences).[6] 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 cells.[6] This results in the inhibition of the T-cell function such as proliferation, cytokine production, and cytotoxic activity against cancer cells, which will allow cancer cells to thrive and further compromise the immune system.[5] Instead, dostarlimab increases the immune system's ability to kill cancer cells by activating the T-cell response (including anti-tumour immune response).[5,6] By blocking PD-1, dostarlimab stops cancer cells from switching off these immune cells.[6]

In the ongoing phase III clinical trial (RUBY, NCT03981796), in one of the intervention arms, participants were first administered dostarlimab and carboplatin-paclitaxel, followed by dostarlimab and niraparib in specified dosages.[1,7]

Key Innovation

By the time endometrial cancer has reached stages III and IV, the cancer has spread too far for it all to be removed through a hysterectomy (surgery). Many chemotherapy drugs especially combinations like carboplatin-paclitaxel can help women but oftentimes, only for a period of time before recurrence because cancer cells can survive chemotherapy/radiation and even become resistant to it.[8,9] There is therefore a need for treatments that can offer longer lasting outcomes for women with advanced/recurrent endometrial cancer.

In the phase III trial, RUBY (NCT03981796), dostarlimab in combination with chemotherapy produced significant survival benefits in the treatment of advanced/recurrent endometrial cancer[10] and produced a safety profile consistent with past clinical trials.[11] These results are encouraging and shows dostarlimab as a promising choice for the treatment of advanced/recurrent endometrial cancer.

Niraparib's ability to prevent DNA repair of cancer cells through PARP-inhibition will lead to a reduction in cancer cell proliferation.[2] The synergistic effect of the combination of niraparib's 'cancer cell destroyer' activity and dostarlimab's immunotherapeutic abilities[12,13] could therefore offer better outcomes for women with advanced/recurrent endometrial cancer. A recent study showed that niraparib alone showed modest results with a 20% clinical benefit rate at 16 weeks for the treatment of platinum-resistant recurrent endometrial cancer (EC). The combination of niraparib and dostarlimab showed a 31.8% clinical

benefit rate at 16 weeks.[14] If licensed, niraparib in combination with dostarlimab will offer an additional treatment option for women with advanced/recurrent endometrial cancer.

Regulatory & Development Status

Niraparib in combination with dostarlimab does not currently have Marketing Authorisation in the EU/UK for any indication.

Niraparib is licensed in the EU[15]/UK and has marketing authorization in the UK[2] for:

- maintenance treatment of advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Niraparib in combination with dostarlimab is in phase II/III clinical development for the treatment of brain metastases, bladder cancer, gastric adenocarcinoma, fallopian tube cancer, amongst other indications.[16]

Dostarlimab was granted conditional marketing authorisation in the EU[6] and in the UK[5] (subject to additional monitoring) for:

- treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen.[5]

Patient Group

Disease Area and Clinical Need

Endometrial cancer occurs when cancer cells form in the tissues of the endometrium - the lining of the uterus.[17] Symptoms may include irregular vaginal bleeding, painful urination, and pelvic pain. [17] Factors that increase the risk of having endometrial cancer are metabolic syndrome, obesity, type II diabetes, polycystic ovarian syndrome, family history via an immediate family member, taking hormone replacement therapy, taking tamoxifen for breast cancer, certain genetic conditions, and exposure of endometrial tissue to oestrogen made by the body.[17] Advanced endometrial cancers can be stage III and IV cancers that have spread outside of the uterus to neighbouring regions like the ovaries, vagina, pelvis (stage III), or further away to the bowel, bladder, liver or lungs (Stage IV).[8,17] The cancer stage is critical in determining treatment methods and chance of survival.[17] Recurrent endometrial cancer is cancer that returns after treatment either at or near the same place it started or at a distant part of the body, which determines treatment.[8]

Uterine cancer is the 4th most common cancer in females in the UK, accounting for 5% of all new cancer cases in females (2016-2018).[18] 96% of uterine cancer cases are cancers occurring in the endometrium (endometrial cancer).[18] The European Age-Standardised (AS) incidence rates for uterine cancer in England is 15.5 per 100,000 and 15.6 for the entire United Kingdom (2016 – 18),[18] while the mortality rate is 3.8 per 100,000 (2017 – 19).[19] Uterine cancer is the 8th most common cause of cancer death in females in the UK, accounting for 3% of all cancer deaths in females (2017-2019).[19] 89.5% of females survive uterine cancer for at least one year, this falls to 75.6% surviving for five years or more, as shown by age-standardised net survival for patients diagnosed with uterine cancer during 2013-2017 in England. 71.6% of females are predicted to survive their disease for ten years or more, as shown by age-standardised net survival for patients diagnosed with uterine cancer during 2013-2017 in England.[20] In England 2021-2022, there were 18,420 finished consultant episodes (FCEs), and 17,317 hospital admissions with a primary

diagnosis of malignant neoplasm of the endometrium (ICD-10 code C54.1) resulting in 27,566 FCE bed days.[21]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following treatment options for advanced or recurrent endometrial cancer:

- Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency and have had platinum-based chemotherapy [22]
- Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer [23]

Clinical Trial Information

Trial	**RUBY;** NCT03981796, **EudraCT** 2019-001576-11. A Phase 3, Randomized, Double-blind, Multicentre Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer **Phase III**: Active, not recruiting **Locations**: UK, EU countries, United States and Canada **Primary completion date**: September 28, 2022
Trial Design	Randomised, parallel assignment, quadruple-masked.
Population	N = 785; females aged 18 and older with histologically or cytologically proven endometrial cancer with recurrent or advanced disease
Intervention(s)	Part 1: Active Comparator: Arm 1 Participants receiving dostarlimab + Carboplatin-paclitaxel followed by dostarlimab Part 2: Active Comparator: Arm 3 Participants receiving dostarlimab + carboplatin-paclitaxel followed by dostarlimab+niraparib
Comparator(s)	Part 1: Placebo Comparator: Arm 2 Participants receiving placebo + carboplatin-paclitaxel followed by placebo Part 2: Placebo Comparator: Arm 4 Participants receiving placebo + carboplatin-paclitaxel followed by placebo
Outcome(s)	Primary outcome measures: 1. Parts 1 and 2: Progression-Free Survival (PFS) - investigator assessment [Time Frame: Up to 6 years] 2. Part 1: Overall survival [Time Frame: Up to 6 years] See trial record for a full list of other outcomes
Results (efficacy)	Part 1: Of the 494 patients who underwent randomization, 118 (23.9%) had mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumours. In the dMMR–MSI-H population, estimated progression-free survival at 24 months was 61.4% (95% confidence interval [CI], 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (hazard ratio for progression or death, 0.28; 95% CI, 0.16 to 0.50; P<0.001). In the

	overall population, progression-free survival at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87).[10] Part 2: no results yet reported
Results (safety)	Part 1: The most common adverse events that occurred or worsened during treatment were nausea (53.9% of the patients in the dostarlimab group and 45.9% of those in the placebo group), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). Severe and serious adverse events were more frequent in the dostarlimab group than in the placebo group. The safety profile of dostarlimab–carboplatin–paclitaxel was consistent with that of the individual components of the regimen.[10] Part 2: no results yet reported.

Estimated Cost

Dostarlimab is already marketed in the UK for the treatment of endometrial cancer.[24] The NHS indicative price for 1 vial of Dostarlimab is £5887.33 (hospital use only).[25]

Niraparib is marketed in the UK for the treatment of advanced/relapsed ovarian, fallopian tube, and peritoneal cancers respectively.[26] For Niraparib, it costs £4,500 for 56 capsules and £6,750 for 84 capsules.[27]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Dostarlimab with carboplatin-paclitaxel for treating recurrent or advanced endometrial cancer [ID 3968]. Expected Publication Date TBC.
- NICE technology appraisal in development. Pembrolizumab with Lenvatinib for previously treated advanced or recurrent endometrial cancer [ID 3811]. Expected Publication Date. 31 May 2023.
- NICE technology appraisal in development. Endometrial cancer (high risk, newly diagnosed) - pembrolizumab (with chemotherapy, adjuvant) [ID6207]. Awaiting development [GID-TA11235]. Expected publication date: TBC
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015; updated: December 2021.
- NICE interventional procedures guidance. Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer (IPG356). September 2010.
- NICE Interventional procedures guidance. Laparoscopic techniques for hysterectomy. November 2007.

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 Complex Gynaecology: specialist gynaecological cancers. E10/S/f

Other Guidance

- European Society of Gynaecological Oncology (ESGO). ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. 2021.[28]
- British Gynaecological Cancer Society (BGCS) Uterine Cancer Guidelines: Recommendations for Practice. 2021.[29]
- European Society for Medical Oncology (ESMO). Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2022.[30]
- Postoperative Radiation Therapy for Endometrial Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline.[31]

Additional Information

References

1 Clinicaltrials.gov. *A Study to Evaluate Dostarlimab Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Participants With Recurrent or Primary Advanced Endometrial Cancer (RUBY). Trial ID: NCT03981796*. 2019. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03981796 [Accessed 10th March 2023].

2 Electronic Medicines Compendium (eMC). *Zejula 100 mg hard capsules - Summary of Product Characteristics (SmPC)*. 2021. Available from: https://www.medicines.org.uk/emc/product/8828#companyDetails [Accessed February 28th, 2023].

3 Massachusetts General Hospital. *Researchers pinpoint how PARP inhibitors combat BRCA1 and BRCA2 tumor cells*. 2021. Available from: https://www.massgeneral.org/news/press-release/researchers-pinpoint-how-parp-inhibitors-combat-brca1-and-brca2-tumor-cells#:~:text=PARP%20%28poly%20%5BADP-ribose%5D%20polymerase%29%20inhibitors%20such%20as%20olaparib,in%20the%20BRCA1%20and%20BRCA2%20tumor%20suppressor%20genes. [Accessed February 28th, 2023].

4 Ovarian Cancer Action. *Ovarian cancer drug Niraparib approved for NHS use*. 2018. Available from: https://ovarian.org.uk/news-and-blog/news/ovarian-cancer-drug-niraparib-approved-nhs-use/#:~:text=Niraparib%20is%20a%20PARP%20inhibitor.%20This%20means%20it,cells%20cannot%20be%20repaired%2C%20and%20the%20cells%20die. [Accessed February 28th, 2023].

5 Electronic Medicines Compendium (eMC). *JEMPERLI 500 mg concentrate for solution for infusion*. 2021. Available from: https://www.medicines.org.uk/emc/product/12669 [Accessed February 28th, 2023].

6 European Medicines Agency (EMA). *Jemperli (dostarlimab)*. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/jemperli [Accessed February 28 2023].

7 M.R. Mirza RLC, L. Hanker, B. Slomovitz, G. Valabrega, L. DeMars, M. Walker, T. Duan, M. Powell. 820TiP - ENGOT-EN6/GOG-3031/NSGO-CTU-RUBY part 2: A phase III, randomized, double-blind, study of dostarlimab + carboplatin-paclitaxel followed by dostarlimab + niraparib versus placebo (PBO) + carboplatin-paclitaxel followed by PBO in recurrent or advanced endometrial cancer (EC). *ESMO Congress*. Annals of Oncology 2021.

8 American Cancer Society. *Treatment Choices for Endometrial Cancer, by Stage*. 2019. Available from: https://www.cancer.org/cancer/endometrial-cancer/treating/by-stage.html#:~:text=Stage%20IV%20cancers,%2C%20omentum%2C%20or%20other%20organs [Accessed March 6th 2023].

9 City of Hope. *What is cancer recurrence?* Available from: https://www.cancercenter.com/cancer-recurrence#:~:text=Cancer%20may%20return%20weeks%20to%20years%20after%20initial,cancer%20could%20be%20found%20with%20scans%20or%20tests. [Accessed March 6th 2023].

10 Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. *N Engl J Med*. 2023. Available from: https://doi.org/10.1056/NEJMoa2216334.

11 Russ Conroy; Cancer Network. *Dostarlimab/Chemotherapy Combo Elicits Significant Survival Benefit in Advanced/Recurrent Endometrial Cancer*. 2022. Available from: https://www.cancernetwork.com/view/dostarlimab-chemotherapy-combo-elicits-significant-survival-benefit-in-advanced-recurrent-endometrial-cancer [Accessed March 6th, 2023].

12 American Cancer Society. *Immunotherapy for Endometrial Cancer*. 2022. Available from: https://www.cancer.org/cancer/endometrial-cancer/treating/immunotherapy.html [Accessed March 6th, 2023].

13 Rubio-Pérez J, Hernández R, Hernández T, Doger B, Casado V, Moreno V. Dostarlimab for the treatment of endometrium cancer and other solid tumors. *Drugs Today (Barc)*. 2021;57(3):187-97. Available from: https://doi.org/10.1358/dot.2021.57.3.3233363.

14 Madariaga A, Garg S, Tchrakian N, Dhani N, Jimenez W, Welch S, et al. Phase II trial assessing niraparib with or without dostarlimab (anti-PD-1) in recurrent endometrial carcinoma. *Journal of Clinical Oncology*. 2021;39:5574-. Available from: https://doi.org/10.1200/JCO.2021.39.15_suppl.5574.

15 European Medicines Agency (EMA). *Zejula (Niraparib)*. 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zejula#authorisation-details-section [Accessed March 6th, 2023].

16 Clinicaltrials.gov. *Search of: niraparib, dostarlimab | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3 - List Results - ClinicalTrials.gov*. 2023. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=niraparib%2C+dostarlimab&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&recrs=d&recrs=f&phase=1&phase=2 [Accessed March 6th, 2023].

17 National Cancer Institute. *General Information About Endometrial Cancer : Endometrial Cancer Treatment (PDQ®)–Patient Version:* . Available from: https://www.cancer.gov/types/uterine/patient/endometrial-treatment-pdq#_92 [Accessed March 6th, 2023].

18 Cancer Research UK. *Uterine cancer incidence statistics | Cancer Research UK*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-

statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-Zero [Accessed March 6th, 2023].

19 Cancer Research UK. *Uterine cancer mortality statistics | Cancer Research UK*. 2022. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/mortality#heading-Zero [Accessed March 6th, 2023].

20 Cancer Research UK. *Uterine cancer survival statistics | Cancer Research UK*. 2020. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/survival#heading-Zero [Accessed March 6th, 2023].

21 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis*. 2022. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2F0E%2FE70963%2Fhosp-epis-stat-admi-diag-2021-22-tab.xlsx&wdOrigin=BROWSELINK.

22 National Institute for Health and Care Excellence. *Overview | Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency | Guidance | NICE* (*TA779)*. Available from: https://www.nice.org.uk/guidance/ta779 [Accessed March 6th, 2023].

23 National Institute for Health and Care Excellence. *Guidance | Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer | Guidance | NICE* (*IPG356)*. Available from: https://www.nice.org.uk/guidance/ipg356/chapter/1-Guidance [Accessed March 6th, 2023].

24 British National Formulary (BNF) | National Instititute for Health and Care Excellence (NICE). *Dostarlimab, Indications and Dose*. Available from: https://bnf.nice.org.uk/drugs/dostarlimab/#indications-and-dose [Accessed March 8th, 2023].

25 British National Formulary (BNF) | National Instititute for Health and Care Excellence (NICE). *Dostarlimab Medicinal Forms*. Available from: https://bnf.nice.org.uk/drugs/dostarlimab/medicinal-forms/ [Accessed March 8th, 2023].

26 British National Formulary (BNF) | National Instititute for Health and Care Excellence (NICE). *Niraparib Indications and Dose*. Available from: https://bnf.nice.org.uk/drugs/niraparib/#indications-and-dose [Accessed March 8th, 2023].

27 British National Formulary (BNF) | National Instititute for Health and Care Excellence (NICE). *Niraparib Medicinal Forms*. Available from: https://bnf.nice.org.uk/drugs/niraparib/medicinal-forms/ [Accessed March 8th, 2023].

28 Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *International Journal of Gynecologic Cancer*. 2021;31(1):12. Available from: https://doi.org/10.1136/ijgc-2020-002230.

29 British Gynaecological Cancer Society (BGCS). *Uterine Cancer Guidelines: Recommendations for Practice, Version 2.1*. Available from: https://www.bgcs.org.uk/wp-content/uploads/2021/11/British-Gynaecological-Cancer-Society-v13-for-website-with-figure1.pdf [Accessed March 8th, 2023].

30 European Society For Medical Oncology (ESMO). *Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up*. Available from: https://www.annalsofoncology.org/article/S0923-7534(22)01207-8/fulltext [Accessed March 8th, 2023].

31 Meyer LA, Bohlke K, Powell MA, Fader AN, Franklin GE, Lee LJ, et al. Postoperative Radiation Therapy for Endometrial Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. *Journal of Clinical Oncology*. 2015;33(26):2908-13. Available from: https://doi.org/10.1200/jco.2015.62.5459.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.