National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: January 2018

AT406 (Debio 1143) for ovarian cancer – neoadjuvant therapy

NIHRIO (HSRIC) ID: 13220 NICE ID: 9667

LAY SUMMARY

Ovarian cancer is the sixth most common cancer in women in the UK. The ovaries are a pair of small organs located in the lower abdomen and are part of the female reproductive system. Usually women who have been through menopause and aged 65 years and over are more likely to be affected by ovarian cancer. The exact cause is not known but most cases are caused by gene changes that develop during a woman's life and are not inherited. The main treatment options for ovarian cancer are surgery and chemotherapy. Most patients with ovarian cancer are diagnosed at an advanced stage and have a combination of both surgery and chemotherapy. Chemotherapy may be prescribed before and/or after surgery. Chemotherapy before surgery is called 'neoadjuvant chemotherapy'.

AT406 is a medicine under development to be added to standard neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer. AT406 is a small molecule that induces cancer cell death through a dual mode of action. If licensed, AT406 may offer an additional neoadjuvant treatment option for patients with epithelial ovarian cancer especially those who develop drug resistance and relapse to other standard chemotherapy.

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

TARGET GROUP

Ovarian cancer (epithelial) – neoadjuvant; in addition to carboplatin and paclitaxel

TECHNOLOGY

DESCRIPTION

AT406 (Debio 1143) is a small molecule mimetic of the second mitochondria-derived activator of caspase C. It blocks a highly conserved 70 amino acid domain on the N-terminal end of inhibitors of apoptosis proteins (IAPs) known as the Baculovirus IAP Repeat (BIR) domain. In vivo and in vitro studies have demonstrated that AT406 induces cell death in several tumour models by inhibiting X-chromosome associated IAP (XIAP) and cellular IAPs (cIAPs) 1 and 2.[1]

In the phase II trial in patients with ovarian cancer (EudraCT Number: 2015-005137-42), subjects in the experimental arm were given AT406 capsule at a dose of 100 mg/150 mg/200 mg orally in combination with standard of care (carboplatin (5 mg/ml) and paclitaxel (135 mg/m2)) chemotherapy intravenously.[2]

AT406 does not currently have Marketing Authorisation in the EU for any indication.

Besides ovarian cancer, AT406 is in phase II trials for the following indications:[3]

- Fallopian Tube cancer
- Endometrial cancer
- Peritoneal cancer
- Head and Neck cancers

INNOVATION and/or ADVANTAGES

If licensed, AT406 will offer an additional neoadjuvant treatment option for patients with epithelial ovarian cancer.

DEVELOPER

Debiopharm

AVAILABILITY, LAUNCH or MARKETING

AT406 received an orphan drug designation in the EU in December 2015 and in the US in June 2016 for epithelial ovarian cancer.[4]

PATIENT GROUP

BACKGROUND

Ovarian cancer is a malignancy of the ovary. The most common type of ovarian cancer is epithelial ovarian cancer.[5] The pathology in these cancers lies in the lining that covers the surface of the ovary.[6] Over 90% of ovarian cancers arise from the epithelial surface of the ovary, the rest from germ cells or

stromal cells.[7] The epithelial ovarian cancers are classified as serous (30–70%), endometrioid (10–20%), mucinous (5–20%), clear cell (3–10%), and undifferentiated (1%).[7]

Main symptoms of ovarian cancer include feeling of bloating, swollen abdomen, discomfort in the abdominal or pelvic area, loss of appetite, frequent urination. Other symptoms include persistent indigestion, dyspareunia, change in bowel habits, back pain, vaginal bleeding, lethargy and weight loss.[8]

Risk factors of ovarian cancer include increasing age, family history, hormone replacement therapy and endometriosis. Other factors include being overweight, smoking and using talcum powder.[9]

Because treatment involves radical surgery and intense courses of chemotherapy, health-related quality of life (HRQOL) is often compromised.[10]

CLINICAL NEED and BURDEN OF DISEASE

Overall survival for women diagnosed with ovarian cancer was 70.4% in 2015 in England. This was the third lowest overall survival for women with cancers when calculated by stage at diagnosis.[11] There was a steadily decreasing survival with increasing stage, but survival for those diagnosed at stage 1 was high (98.1% for 2015).[11]

According to Cancer Research UK, ovarian cancer was the 15th most common cancer in the UK in 2014 and accounted for 2% of all new cases.[12] Ovarian cancer was the sixth most common cancer in females, with around 7,400 cases diagnosed in 2014.[12] It was the 14th most common cause of cancer death in the UK in 2014 and accounts for 5% for all cancer deaths in the UK.[12]

More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for ten years or more (2010-11). Almost half (46%) of women diagnosed with ovarian cancer in England and Wales survive their disease for five years or more (2010-11). Almost three-quarters (73%) of women diagnosed with ovarian cancer in England and Wales survive their disease for one year or more (2010-11).[12]

If ovarian cancer is found (and treated) before the cancer has spread outside the ovary (stages IA and IB), the 5-year relative survival rate is 92%. However, only 15% of all ovarian cancers are found at this early stage.[13]

The 2016/2017 Hospital Episodes Statistics (HES) Data recorded 39,380 finished consultant episodes (FCEs), 36,667 admissions and 59,041 FCE bed days due to malignant neoplasm of the ovary (ICD-10 code: C56).[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ovarian (epithelial), fallopian and peritoneal cancer - pazopanib (maintenance) [ID545]. Expected date of issue: TBC.
- NICE technology appraisal in development. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (TA381). January 2016.
- NICE technology appraisal. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.

- NICE technology appraisal. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (TA285). May 2013.
- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016.
- NICE clinical guideline. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE diagnostic guidance. Tests in secondary care to identify people at high risk of ovarian cancer (DG31). November 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers.E03/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

- Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, Kehoe S, Ledermann J, Morrison J, Naik R, Rolland P, and Sundar S. *British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice.* British Gynaecological Cancer Society. [15]
- European Society for Medical Oncology. ESMO clinical practice guidelines: gynaecological cancers.[16]
- Scottish Intercollegiate Guidelines Network. Management of epithelial ovarian cancer - A national clinical guideline.[17]

CURRENT TREATMENT OPTIONS

The main treatment option for ovarian cancer is surgery. It combines surgical removal of all disease and a staging procedure. Neoadjuvant chemotherapy is used in surgically unresectable disease. Thereafter, depending on the tumour response, interval surgery might be employed. Chemotherapy is commonly prescribed as determined by the specialist multidisciplinary team following removal of the primary tumour and pathological assessment.[18]

Greater than 50% of patients with ovarian cancer are diagnosed at an advanced stage. Despite cytoreductive surgery and platinum (e.g. carboplatin)- and taxane-based (e.g. paclitaxel) chemotherapies, greater than 70% of patients with advanced ovarian cancer who achieve remission ultimately experience relapse. Because there are few effective treatments for these patients, the development of new treatment strategies is urgently required.[19]

EFFICACY and SAFETY

Trial	EudraCT-2015-005137-42; Debio1143-EOC-203, AT406, Debio 1143, in combination, ovarian cancer, epithelial, adult, female, phase II
Sponsor	Debiopharm
Status	Ongoing
Source of Information	Global Data[2], Company website[20]
Location	3 EU countries (excl UK)
Design	Randomised, active-controlled, double blind

Participants	n=84 (planned); aged 18-70 years; females; ovarian cancer; epithelial
Schedule	Subjects in the experimental arm receive AT406 capsule at a dose of 100 mg/150 mg/200 mg orally in combination with standard of care (carboplatin (5 mg/ml) and paclitaxel (135 mg/m2)) chemotherapy intravenously. Subjects in the active-controlled arm receive carboplatin at a dose of 5 mg/ml and paclitaxel at a dose of 135 mg/m2 only
Follow-up	Approximately 46 months
Primary Outcomes	• To evaluate the efficacy of AT406 when given in combination with carboplatin and paclitaxel when compared to carboplatin and paclitaxel alone • To identify the biomarkers that to be used for subjects' stratification in pivotal studies • To assess the safety and tolerability of AT406 • Response Rate (RR) according to RECIST 1.1 criteria at the end of 4 cycles of neoadjuvant treatment and prior to interval debulking surgery as determined by central independent radiology committee
Secondary Outcomes	• Rate of complete pathological response (pCR) defined as no residual invasive cancer at the time of debulking • Incidence of adverse events (AEs) and severe adverse events (SAEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v 403 criteria and extent of treatment exposure • Safety and tolerability of Debio 1143 when given in combination with paclitaxel + carboplatin as assessed by laboratory values, vital signs, ECG, and ECOG PS • Rate of perioperative serious complications within the first 28 • Rate of postoperative death (< 28 days) • Duration of hospitalisation for debulking surgery (from day of surgery to day of discharge) • Duration of surgical intervention
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

The cost of AT406 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

REFERENCES

[1] DiPersio JF, Erba HP, Larson RA, Luger SM, Tallman MS, Brill JM, Vuagniaux G, Rouits E, Sorensen JM, and Zanna C. Oral Debio1143 (AT406), an antagonist of inhibitor of apoptosis proteins, in combination with daunorubicin and cytarabine in patients with poor-risk acute myeloid leukemia - results of a phase I dose escalation study. *Clin Lymphoma Myeloma Leuk*. 2015 July ; 15(7): 443–449.

[2] Global Data. *A Clinical Trial to Test the Effect of Carboplatin and Paclitaxel, with or Without Debio 1143 in Patients with Newly Diagnosed Advanced Epithelial Ovarian Cancer.* Available from: https://pharma.globaldata.com/ClinicalProductsView.aspx?ClinicalID=jW@YCKGuap6ZGruZTrQU0g== [Accessed on 12 December 2017]

[3] Global Data. *Debio-1143*. Available from: https://pharma.globaldata.com/ProductsView.aspx?id=CT&ProductId=16838&ProductType=0,1 [Accessed on 12 December 2017]

[4] Debiopharm Group. EMA grants Orphan Drug Designation to Debiopharm International SA's IAP inhibitor Debio 1143 in the treatment of Ovarian Cancer. Available from: https://www.debiopharm.com/medias/press-release/item/3600-ema-grants-orphan-drug-designation-to-debiopharm-international-sa-s-iap-inhibitor-debio-1143-in-the-treatment-of-ovarian-cancer [Accessed on 19 December 2017]

[5] Cancer Research UK. *Ovarian Cancer.* Available from: http://www.cancerresearchuk.org/about-cancer/ovarian-cancer?_ga=2.145047924.1746957806.1513087282-

1291739923.1505917245&_gac=1.36949780.1510308590.EAIaIQobChMI_ffl9OGz1wIVipXtCh3b2gTBEAAYASAAEgK4LPD_BwE [Accessed on 12 December 2017]

[6] Macmillan Cancer Support. *Understanding ovarian cancer*. Available from: https://www.macmillan.org.uk/information-and-support/ovarian-cancer/understanding-cancer [Accessed on 12 December 2017]

[7] Rosen DG, Liu GYG, Mercado-Uribe I, Chang B, Xiao X, Zheng J, Xue F, and Liu J. Ovarian cancer: pathology, biology, and disease models. *Front Biosci*. 2009 Jan 1; 14: 2089–2102.

[8] NHS choices. *Ovarian cancer symptoms*. Available from: https://www.nhs.uk/conditions/ovarian-cancer/symptoms/ [Accessed on 12 December 2017]

[9] NHS Choices. *Ovarian cancer causes*. Available from: https://www.nhs.uk/conditions/ovarian-cancer/causes/ [Accessed on 12 December 2017]

[10] Chase DM, and Wenzel L. Health-related quality of life in ovarian cancer patients and its impact on clinical management. *Expert Rev Pharmacoecon Outcomes Res*. 2011 Aug; 11(4): 421–431.

[11] Office for National Statistics. *Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/adultstageatdiagnosisandchildhoodpatientsfollowedupto2016 [Accessed on 12 December 2017]

[12] CancerResearchUK. *Ovarian Cancer Statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Zero [Accessed on 12 December 2017]

[13] American Cancer Society. *Survival Rates for Ovarian Cancer, by Stage*. Available from: https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html [Accessed on 12 December 2017]

[14] Office of National Statistics. Hospital Episodes Statistics 2015-2016. Primary diagnosis: 3 character. NHS Digital. Available from: http://digital.nhs.uk/catalogue/PUB300988/hosp-epis-stat-admi-diag-2016-17-tab [Accessed on 12 December 2017]

[15] Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, Kehoe S, Ledermann J, Morrison J, Naik R, Rolland P, and Sundar S. *British Gynaecological Cancer Society (BGCS) Epithelial Ovarian / Fallopian Tube / Primary Peritoneal Cancer Guidelines: Recommendations for Practice. British Gynaecological Cancer Society.* Available from: https://bgcs.org.uk/BGCS%20Guidelines%20Ovarian%20Guidelines%202017.pdf [Accessed on 12 December 2017]

[16] European Society for Medical Oncology. *ESMO clinical practice guidelines: gynaecological cancers*. Available from: http://www.esmo.org/Guidelines/Gynaecological-Cancers. [Accessed on 12 December 2017]

[17] Scottish Intercollegiate Guidelines Network. *Management of epithelial ovarian cancer - A national clinical guideline.* Available from: http://www.sign.ac.uk/assets/sign135.pdf [Accessed on 12 December 2017]

[18] NHS England. *2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers.E03/S/f*.

[19] Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, and Murayama A. Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. *Clinical Oncology* 33, no. 34 (December 2015) 4015-4022.

[20] Debiopharm Group. *Debiopharm International SA initiates clinical phase II study evaluating Debio 1143 in Ovarian Cancer.* Available from: https://www.debiopharm.com/our-business/pipeline/item/3664-debiopharm-international-sa-initiates-clinical-phase-ii-study-evaluating-debio-1143-in-ovarian-cancer [Accessed on 12 December 2017]