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Lurbinectedin for platinum resistant ovarian cancer

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LAY SUMMARY

Ovarian cancer is one of the most common types of cancer. It is the fifth most common cancer in women in the UK. The ovaries are a pair of small organs located in the lower tummy and are part of the female reproductive system. Usually women who have been through menopause are more likely to be affected by ovarian cancer. 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. The chemotherapy drugs used to treat ovarian cancer are relatively standard. Typically doctors combine a platinum-based drug with a taxane (which inhibits cancer cell division). Platinum resistant ovarian cancer is defined as progression during or within 6 months after completing platinum- based chemotherapy. More than half of patients with advanced disease develop platinum resistant ovarian cancer. Treatment options for these patients are sparse. Hence, lurbinectedin administered intravenously, if licenced, might be of significant benefit for patients with ovarian cancer who are platinum resistant.

TARGET GROUP

Ovarian cancer (unresectable, platinum resistant)

TECHNOLOGY

DESCRIPTION

Lurbinectedin (PM 01183; Zepsyre) is a synthetic tetrahydroisoquinolone with a novel mechanism of action. Lurbinectidin inhibits the active transcription (irreversible stalling of elongation RNA polymerase II and its degradation), induces double strand DNA breaks and affect the tumour microenvironment reducing the tumour associated macrophages and the production of inflammatory/trophic mediators by mononuclear phagocytes.[1,2,3]

Currently, lurbinectedin is not licenced for use for ovarian cancer anywhere in the EU or elsewhere.[4] It is not marketed for any other indication, however, it is globally in phase II/III development for

- non-small cell lung cancer
- Ewing family of tumours
- germ cell cancer
- fallopian tube cancer
- soft tissue sarcoma
- neuroendocrine tumours
- metastatic breast cancer
- epithelial ovarian cancer
- small-cell lung cancer
- endometrial cancer
- head and neck carcinoma
- biliary tract
- primary peritoneal cancer.[5]

Lurbinectedin is administered intravenously at 3.2mg/m2 from day 1 to every three weeks.[6]

INNOVATION and/or ADVANTAGES

If licensed, lurbinectedin will offer an additional treatment option for patients with unresectable, platinum resistant ovarian cancer. The company has provided sufficient information to show that lurbinectedin might be of significant benefit for patients with ovarian cancer as early studies in experimental model show that it might slow down the growth of the cancer when used on its own.[4]

DEVELOPER

PharmaMar

AVAILABILITY, LAUNCH or MARKETING

Lurbinectedin is a designated orphan drug in the EU/ US for ovarian cancer.[7,4]

PATIENT GROUP

BACKGROUND

Ovarian cancer is one of the most common types of cancer.[10] It is the fifth most common cancer in women in the UK.[8] The ovaries, a pair of small organs, are located in the lower abdomen and are connected to the womb. They store a woman's supply of eggs[10] and are hence part of the female reproductive system, which is made up of the ovaries, fallopian tubes, womb (uterus), cervix and vagina. The ovaries also produce the female hormones oestrogen and progesterone.[9] Usually women, who have been through menopause (aged over 50), are affected by ovarian cancer, it can, however, occur at an earlier stage as well.[10] In most cases ovarian cancer is caused by gene changes that develop during a woman's life and are not inherited. Only about 5 to 15 out of 100 ovarian cancers are due to an inherited faulty gene. These inherited genes include BRCA1 and BRAC2, which also increase the risk of breast cancer.[11]

There are several types of ovarian cancer. These affect woman of different ages and are treated in different ways. Epithelial ovarian cancer is the most common type, affecting 90% of patients with ovarian cancer. This cancer develops in the cells that line the ovaries and fallopian tubes. Non-epithelial ovarian cancer is much less common and usually affects younger women.[8] 5-8% come from stromal cells. The stroma is the supportive tissue of the ovary. Stromal cell tumours may occur in women of any age, although certain tumours, such as androblastomas, may be more common in adolescence. 3-5% of ovarian cancer are developed in germ cells. These are the cells in the body that develop into sperm and eggs. Germ cell tumours usually occur in younger women.[12]

Platinum resistant ovarian cancer is defined as progression during or within 6 months after completing platinum- based chemotherapy.[13] At first relapse, approximately 25% of patients have platinum-resistant ovarian cancer. Almost all patients with recurrent disease ultimately develop platinum resistance.[14]

CLINICAL NEED and BURDEN OF DISEASE

Ovarian cancer is the fifteenth most common cancer in the UK. It accounts for 2% of all new cases in the UK. There were around 7,400 new cases of ovarian cancer in the UK in 2014, which accounts to 20 cases diagnosed every day.[11] In England, the crude rates per 100,000 female populations are 22.3 for ovarian cancer.[15] More than half (53%) of ovarian cancer cases in the UK each year are diagnosed in females aged 65 and over and incidence rates are highest in females aged 75-79 years. 1 in 52 women will be diagnosed with ovarian cancer during their lifetime. In the UK, there were around 4,100 ovarian cancer deaths in 2014. More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for ten years or more and almost half (46%) survive their disease for one year or more.[16]

In the UK, there were 35,935 hospital admissions for malignant neoplasm of the ovary and 38,514 finished consultant episodes.[17]

In 2012, ovarian cancer affected approximately 2.8 in 10,000 people in the European Union, which accounts to 142 people. The ceiling for orphan designation is 5 in 10,000 people.[4]

Trends over the last 10 years show a reduction in the proportion of unclassified epithelial cases, and a rise in the proportions of serous carcinoma, borderline and miscellaneous & unspecified cases.

Besides, there is little evidence of any geographical patterns in the incidence and mortality of ovarian cancer.[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ovarian cancer (platinum sensitive) – cediranib (ID790). TBC
- NICE technology appraisal in development. Ovarian cancer - vintafolide (with pegylated liposomal doxorubicin) (ID564). TBC
- NICE technology appraisal. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (TA389). April 2016
- 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. 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
- NICE Quality standard. Ovarian cancer (QS18). May 2012
- NICE interventional procedures guidance (IPG470). November 2013

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers. E10/S/f
- NHS England. Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations. E01/P/b. July 2015

OTHER GUIDANCE

- Vidal A, Munoz C, Guillen MJ et al. Lurbinectedin (PM01183), a New DNA Minor Groove Binder, Inhibits Growth of Orthotopic Primary Graft of Cisplatin-Resistant Epithelial Ovarian Cancer. *Clin Cancer Res* 2012.
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CURRENT TREATMENT OPTIONS

The main treatment option for ovarian cancer (including fallopian tube cancer and primary peritoneal 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.[15]

More than 50% of patients with ovarian cancer are diagnosed at an advanced stage. Despite cytoreductive surgery and platinum- and taxane – based chemotherapies, greater than 70% of patients with advanced ovarian cancer who achieve remission ultimately experience relapse. Effective treatment options for these patients are sparse[19] and its main goal has been palliative care and symptom improvement.

Patients with recurrent ovarian cancer are typically categorized as having either platinum resistant or platinum sensitive disease, which is based on a platinum free interval of less or greater than 6 months. Individuals who relapse within 6 months of completing platinum based therapy, and are hence platinum resistant, typically have low response rates to subsequent chemotherapy (<15%). Bevacizumab, a recombinant humanized monoclonal antibody has shown encouraging activity in platinum resistant ovarian cancer (PROC) when combined with oral cyclophosphamide or weekly paclitaxel. Paclitaxel chemotherapy combined with trebananib has also shown improvement in phase III trials, as well as liposomal doxorubicin, topotecan, gemcitabine and etoposide.[20] The response rates with these agents is about 10-15% and overall survival is around 12 months.[21]

EFFICACY and SAFETY

Trial	NCT02421588, EudraCT-2014-005251-39, CORAIL; adults with platinum-resistant ovarian cancer; Lurbinectedin versus pegylated liposomal doxorubicin or topotecan; phase III trial
Sponsor	PharmaMar
Status	Ongoing
Source of Information	Trial registry[22], Company[6]
Location	USA
Design	Randomized, controlled
Participants	n=420; aged 18+ years; unresectable epithelial ovarian, fallopian tube or primary peritoneal cancer; platinum resistant; no more than three prior systemic chemotherapy regimens;
Schedule	Randomized to lurbinectedin 3.2mg/m2 from day 1 to every three weeks intravenously; or active comparator pegylated liposomal doxorubicin at a dose of 50mg/m2 from day 1 to every four weeks intravenously or topotecan at a dose of 1.5mg/m2 from day 1 to day 5 every three weeks intravenously;
Follow-up	Not reported

Primary Outcomes	Difference in progression-free-survival between lurbinectedin and pegylated liposomal doxorubicin or topotecan
Secondary Outcomes	Overall survival; antitumor activity, safety, pharmacokinetic, and quality of life
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary endpoint is expected Q4 2017- Q1 2018. Estimated study completion date is October 2018

ESTIMATED COST and IMPACT

COST

The cost of lurbinectedin 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: uncertain unit cost compared to existing treatments
- ☐ None identified

OTHER ISSUES

- ☐ Clinical uncertainty or other research question identified
- ☒ None identified

INFORMATION FROM

PharmaMar

UK PharmaScan ID: 643682

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