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Mirvetuximab soravtansine for platinum-resistant ovarian cancer

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LAY SUMMARY

Ovarian cancer is the 6th most common cancer in women in the UK, with around 5,800 new cases every year in England. Just over half of all ovarian cancer cases in the UK each year are diagnosed in women aged 65 years and over. The symptoms of the disease are vague, including loss of appetite and tummy pain. This can mean that the cancer is diagnosed when the disease is advanced and more difficult to treat. Most patients have the cancer removed by surgery and also receive chemotherapy, which usually includes platinum-based drugs. However, the disease often comes back (recurs), and the platinum-based chemotherapy drugs may be less effective at treating this recurrence. If the cancer recurs within 6 months of the previous treatment, and platinum-based chemotherapy does not work, the disease is called “platinum-resistant”.

Mirvetuximab soravtansine has been developed to treat ovarian cancer that is platinum-resistant. The drug is administered by intravenous infusion and works in two stages. First, it recognises a receptor on the cancer cells, attaches itself to the cancer cell and then enters it. When it is inside the cancer cell the drug releases a toxic substance that kills the cancer cell when it tries to grow. This toxic substance can spread to other nearby cancer cells, killing them as well. If licensed, this drug would provide an additional treatment option to women with ovarian cancer when other treatments have stopped working.

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TARGET GROUP

Ovarian cancer (platinum-resistant, folate receptor alpha positive (FRα)) – second/third/fourth line

TECHNOLOGY

DESCRIPTION

Mirvetuximab soravtansine (IMGN853) is an immunoconjugate consisting of the humanized monoclonal antibody M9346A against folate receptor 1 (FOLR1) conjugated, via the disulphide-containing cleavable linker sulfo-SPDB, to the cytotoxic maytansinoid DM4, with potential antineoplastic activity. The anti-FOLR1 monoclonal antibody moiety of mirvetuximab soravtansine targets and binds to the cell surface antigen FOLR1. After antibody-antigen interaction and internalization, the immunoconjugate releases DM4, which binds to tubulin and disrupts microtubule assembly/disassembly dynamics, thereby inhibiting cell division and cell growth of FOLR1-expressing tumour cells. FOLR1, a member of the folate receptor family is overexpressed on a variety of epithelial-derived cancer cells. The sulfo-SPDB linker prevents cleavage in the bloodstream and may improve this agent's efficacy in multidrug resistant tumour cells.[1]

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

Mirvetuximab soravtansine is in phase III development for the treatment of folate receptor alpha positive, platinum-resistant epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer in women. In the phase III clinical trial (NCT02631876), mirvetuximab soravtansine is administered as an intravenous (IV) infusion at 6mg/kg calculated using adjusted ideal body weight (AIBW) on day 1 of a 21-day cycle. The treatment phase extends from randomization until disease progression, development of unacceptable toxicity or withdrawal of consent.[2]

Mirvetuximab soravtansine is phase II clinical trials for triple-negative breast cancer,[3] and is in phase Ib trials for ovarian cancer in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin or pembrolizumab.[4]

INNOVATION and/or ADVANTAGES

Mirvetuximab soravtansine is an anti-drug conjugate (ADC), and a key feature of ADCs is that they are designed to deliver cytocidal amounts of therapeutic agents direct to the site of tumours, including compounds that, on their own, are too toxic to be clinically useful. A majority of ADCs in development, including mirvetuximab soravtansine, use highly cytotoxic tubulin-targeting compounds as their payload. The cytotoxin used in mirvetuximab soravtansine, DM4, inhibits microtubule assembly in a manner similar to that of vinca alkaloids but with up to 1,000-fold greater potency. Results from early trials confirm that conjugation of this antimitotic agent to a tumour-selective antibody affords a means of achieving a meaningful therapeutic window, evidenced by low systemic toxicities and robust anti-tumour activity.[5] In addition, the cleavable linker incorporated into mirvetuximab soravtansine allows active DM4 metabolites to diffuse into proximal tumour cells and kill them, an effect termed bystander killing.[6]

If licensed, mirvetuximab soravtansine will offer an additional treatment option for patients with platinum-resistant ovarian cancer, who currently have few effective durable therapies available.

DEVELOPER

ImmunoGen Inc.

REGULATORY INFORMATION/ MARKETING PLANS

Mirvetuximab soravtansine was designated an orphan drug in the EU for ovarian cancer in March 2015.[7]

Mirvetuximab soravtansine was designated an orphan drug in the USA for ovarian cancer in July 2014.[8]

The company has been contacted about UK licensing/marketing plans, but has not responded.

PATIENT GROUP

BACKGROUND

Ovarian cancer is the 6th most common cancer in women in the UK.[9] About 53% of ovarian cancer cases in the UK each year are diagnosed in women aged 65 years and over. The causes of ovarian cancer are not known, but factors that increase the risk of developing the condition include family history, inheriting faulty genes, older age and prior hormone replacement therapy.[10] Factors that may reduce risk include taking the contraceptive pill, having children and breastfeeding.[11]

Symptoms of ovarian cancer can be very vague, particularly when the disease is in its early stages. Symptoms can include feeling full quickly, loss of appetite, abdominal pain or bloating, and urinary frequency or urgency.[12]Most women with ovarian cancer are diagnosed with advanced disease, and their treatment involves a combination of surgery and platinum-based chemotherapy (after surgery, or both before and after surgery).[13] The majority of patients experience disease recurrence and receive further lines of treatment. Platinum resistance (relapse within 6 months of treatment) eventually occurs in virtually all patients with recurrent ovarian cancer.[5]

Folate receptor alpha (FRα) is a cell-surface transmembrane glycoprotein that facilitates the unidirectional transport of folates into cells. This receptor shows a restricted distribution pattern in normal tissues, with expression limited to a variety of polarized epithelia. Aberrant FRα overexpression is a characteristic of a number of epithelial tumours. In epithelial ovarian cancer approximately 80% of tumours constitutively express FRα10. Elevated receptor expression may be a negative prognostic factor with respect to chemotherapeutic response in this malignancy.[5]

CLINICAL NEED and BURDEN OF DISEASE

In England in 2016 there were 5,895 registrations of newly diagnosed cases of malignant neoplasm of the ovary (ICD-10 code C56).[14] Across the UK, the incidence rate for ovarian cancer (ICD-10 codes C56-C57.4) is expected to increase from 27.67 per 100,000 European age-standardised rate (EASR) (7,367 cases) in 2014 to 31.89 per 100,000 EASR (10,501 cases) in 2035.[15]

In England and Wales in 2016 there were 3,693 deaths with malignant neoplasm of ovary (ICD-10 code C56) recorded as the underlying cause.[16] The latest published survival statistics for ovarian cancer

(2016, patients diagnosed in 2011-2015, ICD-10 codes C56-C57.7) report 1-year survival rate of 70.9% and 5-year survival rate of 42.9% (age-standardised).[17]

In England in 2016/2017 there were 36,667 hospital admissions with a primary diagnosis of malignant neoplasm of ovary (ICD-10 code C56), resulting in 59,041 bed days and 27,763 day cases.[18]

Although a significant percentage of ovarian cancer tumours respond to initial chemotherapy, between 55% and 75% of those tumours that respond recur within 2 years of completing treatment.[19] It is estimated that a quarter of patients who relapse after initial treatment will have platinum-resistant cancer.[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Bevacizumab in combination with carboplatin, gemcitabine and paclitaxel for treating the first recurrent of platinum-sensitive advanced ovarian cancer (GID-TA10246). Expected publication date to be confirmed.
- NICE technology appraisal in development. Lurbinectidin for treating advanced platinum-resistant ovarian cancer (GID-TA10313). Expected publication date to be confirmed.
- NICE technology appraisal in development. Ovarian, fallopian tube and peritoneal cancer - rucaparib (GID-TA10168). Expected publication date to be confirmed.
- NICE technology appraisal in development. Lurbinectidin for treating advanced platinum-resistant ovarian cancer (GID-TA10313). Expected publication date to be confirmed.
- NICE technology appraisal in development. Ovarian cancer (platinum sensitive) - cediranib (GID-TA10018). Expected publication date to be confirmed.
- NICE technology appraisal in development. Niraparib for ovarian cancer (GID-TA10135). Expected July 2018.
- 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 recurrent of platinum-sensitive advanced ovarian cancer (TA285). May 2013.
- NICE quality standard. Ovarian cancer (QS18). May 2012.
- NICE interventional procedure guidance. Ultra-radical (extensive) surgery for advanced ovarian cancer (IP470). November 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.

OTHER GUIDANCE

- British Gynaecological Cancer Society (BGCS). Epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: Recommendations for practice. June 2017.[21]

- Scottish Intercollegiate Guidelines Network (SIGN). Management of epithelial ovarian cancer. November 2013.[22]
- European Society for Medical Oncology (ESMO). Clinical Practice Guidelines: Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma. October 2013.[23]

CURRENT TREATMENT OPTIONS

The main treatments for ovarian cancer are surgery and chemotherapy. Surgery usually involves bilateral salpingo-oophorectomy, total abdominal hysterectomy and omentectomy. Potentially curative surgery requires resection of all macroscopic disease. More commonly the goal is to reduce the diameters of the remaining pieces of tumour tissues to less than 1cm (optimal debulking). Advanced ovarian cancer is also sometimes treated by radiotherapy to shrink the tumour and reduce pain.[24]

NICE guidelines recommend that current evidence on the safety and efficacy of ultra-radical (extensive) surgery for advanced ovarian cancer is inadequate. Therefore this procedure should not be done except with special arrangements for clinical governance, consent and audit or research.[24]

NICE technology appraisal guidance TA389 (April 2016) states:

- Paclitaxel in combination with platinum or as a monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.[25]
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.[25]

- The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:
  - gemcitabine in combination with carboplatin
  - trabectedin in combination with PLDH
  - topotecan

  The Appraisal Committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.[25]

- Topotecan is not recommended within its marketing authorisation for treating recurrent platinum-resistant or platinum-refractory ovarian cancer.[25]
- People whose treatment with gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, or topotecan is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.[25]

NICE technology appraisal TA285 states that bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents. People currently receiving bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer should be able to continue treatment until they and their clinician consider it appropriate to stop.[26]

For platinum-resistant ovarian cancer, the British Gynaecological Cancer Society (BGCS) recommendations for practice guideline states that there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. If the patient cannot tolerate chemotherapy and/or symptoms are not requiring a rapid response to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited.[21]

EFFICACY and SAFETY

Trial	FORWARD I, NCT02631876, IMGN853-0403; mirvetuximab soravtansine vs selected single-agent chemotherapy (investigator's choice); phase III
Sponsor	ImmunoGen Inc.
Status	Ongoing
Source of Information	Trial Registry[2] Publication[10]
Location	EU (incl UK), USA, Canada and Russia
Design	Randomised, open label, uncontrolled study
Participants	n=333; aged ≥ 18 years; females; advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer; folate receptor alpha positive tumour expression, platinum-resistant ovarian cancer defined as progression within 6 mths from completion of a minimum of 4 cycles of platinum-containing therapy; received at least 1 but no more than 3 prior systemic treatment regimens and for whom single-agent chemotherapy is appropriate as the next line of treatment
Schedule	Randomised to mirvetuximab soravtansine IV infusion at 6mg/kg calculated using AIBW on day 1 of a 21-day cycle; or paclitaxel, pegylated liposomal doxorubicin or topotecan (investigator's choice)
Follow-up	The treatment phase extends from randomization until disease progression, development of unacceptable toxicity or withdrawal of consent. A safety follow-up visit will occur 30 days after the last treatment and all patients are followed every 3 months until death, lost to follow-up or withdrawal of consent for survival follow-up.
Primary Outcomes	Progression free survival in all pts randomised to the study and in patients with high folate receptor alpha expression [Time Frame: Up to 2 yrs]
Secondary Outcomes	Objective response rate per RECIST1.1 [Time Frame: Up to 2 yrs] Overall survival as measured from the date of randomisation until the date of death [Time Frame: Up to 2 yrs] Quality of life [Time Frame: Up to 2 yrs]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Nov 2018. Study completion date reported as Feb 2019.

ESTIMATED COST and IMPACT

COST

The cost of mirvetuximab soravtansine 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

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