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HEALTH TECHNOLOGY BRIEFING
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Atezolizumab in addition to paclitaxel, carboplatin and bevacizumab for epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer – first-line

NIHRIO ID	15113	**NICE ID**	10117
Developer/Company	Roche Products Ltd	**UKPS ID**	645032

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Atezolizumab in addition to carboplatin, paclitaxel and bevacizumab, is in clinical development for epithelial ovarian, fallopian tube or primary peritoneal cancer. Ovarian cancer includes a group of tumours that arise from the ovary. The most common type of ovarian cancer arises from the outside layer of cells on the surface of the ovary. Fallopian tube and primary peritoneal cancer are histologically equivalent diseases to ovarian cancer. These cancers are more often diagnosed at an advanced stage and treatment may consistent of surgery and/or chemotherapy.

Atezolizumab is a cancer medicine given by intravenous injection that works to enhance part of the immune system (T-cells) against tumours. Atezolizumab prevents DNA repair of cancer cells and is expected to enhance the activity of chemotherapy and targeted therapy such as bevacizumab when used in this combination. If licensed, atezolizumab in addition to bevacizumab, carboplatin and paclitaxel will offer an additional treatment option for women with newly diagnosed stage III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

PROPOSED INDICATION

Treatment of advanced (stage III or IV) newly diagnosed epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer.[1]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the anti-tumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.[2]

Atezolizumab is in clinical development in addition to paclitaxel, carboplatin and bevacizumab for epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. In the phase III clinical trial (NCT03038100; IMagyn050), participants in the primary tumour-reductive surgery group will receive paclitaxel, carboplatin, atezolizumab intravenous (IV) infusion on day 1 of each 21-day cycle for a total of 6 cycles, and bevacizumab IV infusion starting with cycle 2 for a total of 5 cycles, followed by maintenance therapy bevacizumab with atezolizumab for a total of 22 cycles of atezolizumab and 21 cycles of bevacizumab. Participants in the neoadjuvant therapy group will receive paclitaxel, carboplatin and atezolizumab for 6 cycles and bevacizumab for 4 cycles. Interval surgery will occur between cycles 3 and 4. Each cycle is 21 days long. After 6 cycles, participants will start maintenance therapy of bevacizumab and atezolizumab for additional 16 cycles.[1]

INNOVATION AND/OR ADVANTAGES

There is mounting pre-clinical and clinical evidence that combinations of immunotherapy, specifically programed cell death-1 (PD-1) inhibition, with chemotherapy and anti-angiogenesis agents, such as bevacizumab, result in markedly improved outcomes across a variety of tumour types including endometrial cancer, renal cell cancer, and non-small cell lung cancer. NCT03038100 (IMagyn050) is the first, randomised, phase III clinical trial to evaluate the potential impact of this combination on both progression-free survival and overall survival in patients presenting with advanced epithelial ovarian cancer.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is licensed in the UK for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.[2]

Very common (≥ 20%) adverse events associated with atezolizumab in combination with other agents include: decreased appetite, cough, dyspnoea, nausea, constipation, diarrhoea, peripheral neuropathy, rash, arthralgia, fatigue, anaemia and musculoskeletal pain.[2]

Atezolizumab, in combination with bevacizumab, paclitaxel and platinum based chemotherapy, is in phase III clinical trials for metastatic carcinoma of the cervix.[4]

Atezolizumab, in combination with bevacizumab, is in phase III clinical trials for metastatic hepatocellular carcinoma, renal cell carcinoma, ovarian cancer, mesothelioma and colorectal cancer.[5]

PATIENT GROUP

DISEASE BACKGROUND

Ovarian cancer represents a group of tumours that arise from diverse types of tissue contained in the ovary and is classified from stage I to IV. Advanced ovarian cancer falls within stages III and IV. Stage III denotes that the cancer is locally advanced and has spread outside the pelvis into the abdominal cavity. Stage IV denotes that distant metastasis to other body organs such as the liver and lungs has occurred.[6] Epithelial ovarian cancer means the cancer started in the surface layer covering the ovary. There are different types of epithelial ovarian cancer.[7] Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to ovarian cancer. Most people are diagnosed with advanced stage disease.[6]

The exact cause of ovarian cancer is unknown but risk factors include a family history of breast cancer, being over 50 years of age, hormone replacement therapy (although any increase in risk is likely to be small), endometriosis and being overweight. Common symptoms of ovarian cancer include feeling constantly bloated, a swollen tummy, discomfort in your tummy or pelvic area, feeling full quickly when eating and needing to pee more often than normal.[8]

Fallopian tube cancer is rare - around 1 - 2% of the female reproductive system cancers occur in the fallopian tubes.[9] Symptoms can be similar to those of ovarian cancer, and can also include vaginal bleeding unrelated to menstruation, a watery vaginal discharge that may contain blood, and abdominal pain which is often colicky.[10]

Peritoneal cancer is a rare cancer of the peritoneum and is similar to epithelial ovarian cancer. Again, symptoms are unclear and are similar to other conditions: painful and swollen abdomen, constipation or diarrhoea, nausea, bloating and loss of appetite.[11]

Women who undergo treatment for, or survive, ovarian cancer are at risk of several complications that may persist for a long time and negatively impact the quality of life. These include the early onset of menopausal symptoms and gynaecological problems leading to sexual dysfunction. These in turn can lead to psychological symptoms in addition to those caused by a distortion of body image after hysterectomy and abdominal scarring.[12]

CLINICAL NEED AND BURDEN OF DISEASE

There are around 7,500 new ovarian cancer cases in the UK every year (2014 to 2016). In 2016, ovarian cancer was the 6th most common cancer in the UK and accounted for 4% of all new cancer cases. Incidence rates for ovarian cancer in the UK are highest in females aged 75 to 79 years (2014 to 2016). Directly age standardised incidence rate of malignant neoplasm of ovary and other unspecified female genital organs (ICD 10 code: C56 – C57) in England in 2017 were 22.7 per 100,000 females.[13]

Almost 6 in 10 ovarian cancer cases were diagnosed in late stage in England in 2014. In 2016, the number of patients diagnosed with stage III and stage IV ovarian cancer was 1,809 and 1,167 respectively.[14] Incidence rates for ovarian cancer are projected to rise by 15% in the UK between 2014 and 2035, from 28 cases per 100,000 in 2014 to 32 cases per 100,000 females by 2035.[15,16]

There are 4,100 ovarian cancer deaths in the UK annually (2014 to 2016).[15] In females in the UK, ovarian cancer caused 3,472 deaths in 2016.[17] Mortality rates for ovarian cancer in the UK are highest in females aged 85 to 89 years (2014 to 2016). Mortality rates are projected to fall by 37% in the UK between 2014 and 2035, from about 15 deaths per 100,000 in 2014 to 10 deaths per 100,000 females by 2035.[15,18]

More than a third (35%) of women diagnosed with ovarian cancer in England and Wales survive their disease for 10 years or more (2010 to 2011), 46% survive their disease for five years or more (2010 to 2011) and 73% survive for one year more (2010 to 2011). Ovarian cancer survival in England is the highest for women diagnosed under 40 years in the UK (2009 to 2013). One-year and five-year age-standardised survival rates in England for all stages were 71.3% and 42.1% respectively. One-year age-standardised survival rates were 71.6% and 52.8 for women diagnosed at stage 3 and stage 4 respectively. Five-year age-standardised survival rate were 26.8% and 12.2% for women diagnosed at stage 3 and stage 4 respectively.[19]

1 in 50 females in the UK will be diagnosed with ovarian cancer in their lifetime. About 11% of ovarian cancer cases in the UK are preventable.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The current NICE treatment pathway for managing advanced stage II to IV ovarian cancer includes primary surgery followed by first-line then second-line chemotherapy.[20] The aim of treatment is to cure the cancer if possible. If the cancer is too advanced to be cured, treatment aims to relieve symptoms and control the cancer for as long as possible.[8]

CURRENT TREATMENT OPTIONS

The following are recommended first-line pharmacological treatment options for women (stage II-IV):[20]

- It is recommended that paclitaxel in combination with a platinum-based compound or platinum based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer.
- Bevacizumab in combination with paclitaxel and carboplatin is licenced (but not recommended by NICE), for first-line treatment of advanced ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV epithelial ovarian, fallopian tube or primary peritoneal cancer). NICE states that people currently receiving bevacizumab for first-line treatment of advanced ovarian cancer should be able to continue treatment until they and their clinicians consider it appropriate to stop.

PLACE OF TECHNOLOGY

If licensed, atezolizumab in addition to bevacizumab, carboplatin and paclitaxel will offer an additional first line treatment option for women with newly diagnosed stage III or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

CLINICAL TRIAL INFORMATION

Trial	**IMagyn050, NCT03038100, YO39523, EudraCT 2016-003472-52; patients aged 18 yrs and older; atezolizumab vs placebo, both in combination with paclitaxel, carboplatin and bevacizumab; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[1,21]
Location	EU (not UK), USA and other countries
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=1300 (planned); aged 18 yrs and older; females; epithelial ovarian cancer, peritoneal primary carcinoma, or fallopian tube cancer; newly-diagnosed; stage III or IV
Schedule	Participants were randomised to: • Experimental arm: o Stage 3 and 4: participants in the primary tumour-reductive surgery group will receive paclitaxel, carboplatin, atezolizumab intravenous (IV) infusion on day 1 of each 21-day cycle for a total of 6 cycles, and bevacizumab IV infusion starting with cycle 2 for a total of 5 cycles, followed by maintenance therapy bevacizumab with atezolizumab for a total of 22 cycles of atezolizumab and 21 cycles of bevacizumab. o Neoadjuvant: Participants in the neoadjuvant therapy group will receive paclitaxel, carboplatin and atezolizumab for 6 cycles and bevacizumab for 4 cycles. Interval surgery will occur between cycles 3 and 4. Each cycle is 21 days long. After 6 cycles, participants will start maintenance therapy of bevacizumab and atezolizumab for additional 16 cycles. • Placebo comparator arm: o Stage 3 and 4: participants in the primary tumour-reductive surgery group will receive paclitaxel, carboplatin, placebo IV infusion on day 1 of each 21-day cycle for a total of 6 cycles, and bevacizumab IV infusion starting with cycle 2 for a total of 5 cycles, followed by maintenance therapy bevacizumab with placebo for a total of 22 cycles of placebo and 21 cycles of bevacizumab. o Neoadjuvant: Participants in the neoadjuvant therapy group will receive paclitaxel, carboplatin and placebo for 6 cycles and bevacizumab for 4 cycles. Interval surgery will occur between cycles 3 and 4. Each cycle is 21 days long. After 6 cycles, participants will start maintenance therapy of bevacizumab and placebo for additional 16 cycles.
Follow-up	The expected study treatment duration for an individual patient is approximately 66 wks for patients randomised after primary surgery and

	70 wks for patients randomised prior to neoadjuvant therapy. Patients will be followed up for 60 mths.[a]
Primary Outcomes	• Progression-Free Survival (PFS) assessed by investigator as per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) - Intent-to-Treat (ITT) Population [Time frame: From randomisation until disease progression or death from any cause (up to approximately 55 mths)] • PFS assessed by investigator as per RECIST v1.1 - PD-L1–Positive Subpopulation [Time frame: From randomisation until disease progression or death from any cause (up to approximately 55 mths)] • Overall Survival - ITT Population [Time frame: From randomisation up to death from any cause (up to approximately 60 mths)] • Overall Survival - PD-L1–Positive Subpopulation [Time frame: From randomisation up to death from any cause (up to approximately 60 mths)]
Secondary Outcomes	• Percentage of participants with Objective Response (OR) assessed by investigator as per RECIST v1.1 - primary tumour-reductive surgery (having residual measurable disease) group [Time frame: From randomisation until disease progression or death from any cause (up to approximately 55 mths)] • Duration of response assessed by investigator as per RECIST v1.1 - primary tumour-reductive surgery (having residual measurable disease) group [Time frame: From the date of first occurrence of a confirmed complete or partial response until disease progression or death from any cause (up to approximately 55 mths)] • Percentage of participants who achieve a clinically-meaningful improvement in patient-reported abdominal pain or bloating - neoadjuvant group [Time frame: From randomisation to the end of treatment/discontinuation (up to approximately 70 wks), and during follow-up period (up to approximately 60 mths)] • Percentage of participants who achieve a clinically-meaningful improvement in patient-reported function and Health Related Quality of Life (HRQoL) - neoadjuvant group [Time frame: From randomisation to the end of treatment/discontinuation (up to approximately 70 wks), and during follow-up period (up to approximately 60 mths)] • Percentage of participants who achieve a clinically-meaningful improvement, remain stable or deterioration in patient-reported function and HRQoL - primary tumour-reductive surgery group [Time frame: From randomisation to the end of treatment/discontinuation (up to approximately 66 wks), and during follow-up period (up to approximately 60 mths)] • Percentage of participants with adverse events [Time frame: From randomisation up to 90 days after last dose of study treatment or until initiation of new anti-cancer therapy (up to approximately 82 wks)] • Maximum serum concentration (Cmax) of atezolizumab [Time frame: Pre-infusion (0 hr), 30 min after end of infusion (EOI) on cycle 1 day 1(cycle length=21 days) up to approximately 82 wks] • Minimum serum concentration (Cmin) of atezolizumab [Time frame: Pre-infusion (0 hr), 30 min after EOI on cycle 1 day 1(cycle length=21 days) up to approximately 82 wks]

[a] Information provided by Roche Products Ltd

	• Percentage of participants with anti-drug antibodies (ADAs) to atezolizumab [Time frame: Pre-infusion (0 hr) on cycle 1 day 1(cycle length=21 days) up to approximately 82 wks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as April 2020. Study completion date reported as Dec 2021.

ESTIMATED COST

The NHS indicative price of one vial of Tecentriq 1200mg/20ml concentrate for solution for infusion vials (atezolizumab 60mg per 1 ml) is £3,807.69.[22] A confidential Patient Access Scheme is available to the NHSE.[b]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Ovarian, fallopian tube and peritoneal cancer - rucaparib (ID1184). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Veliparib with carboplatin and paclitaxel for untreated epithelial ovarian, fallopian tube or primary peritoneal cancer (ID1561). Expected publication date: TBC.
- NICE technology appraisal guidance in development. Ovarian cancer - vintafolide (with pegylated liposomal doxorubicin) (ID564). Expected publication date: TBC.
- NICE technology appraisal guidance. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (TA284). May 2013.
- NICE technology appraisal guidance. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (TA263). August 2012.
- NICE technology appraisal guidance. Guidance on the use of paclitaxel in the treatment of ovarian cancer (TA55). January 2003. Updated May 2005.
- NICE clinical guidelines. Ovarian cancer: recognition and initial management (CG122). April 2011.
- NICE quality standard. Ovarian cancer (QS18). May 2012.
- NICE interventional procedures guidance. Ultra-radical (extensive) surgery for advanced ovarian cancer (IPG470). November 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology – Specialist Gynaecological Cancers. E10/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.

[b] Information provided by Roche Products Ltd

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network. SIGN 135: Management of epithelial ovarian cancer. 2013. Revised 2018.[23]
- British Gynaecological Cancer Society. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. 2017.[24]
- European Society for Medical Oncology. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2013.[25]
- NICE Evidence summary. Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment (ESUOM21). October 2013.[26]

ADDITIONAL INFORMATION

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