Paclitaxel poliglumex (Xyotax) for advanced ovarian cancer – maintenance therapy

SUMMARY

Paclitaxel poliglumex is intended for the maintenance treatment of advanced (stage III or IV) epithelial ovarian, peritoneal or fallopian tube cancer, following first line chemotherapy in patients who have no evidence of residual disease. If licensed, it will offer an additional treatment option for this patient group. Paclitaxel poliglumex consists of a biodegradable polyglutamate polymer linked to paclitaxel. Paclitaxel is activated and released once inside tumour tissue by the action of cathepsin B. It does not currently have a Marketing Authorisation in the EU for any indication.

Ovarian cancer is the fifth most common cancer in women in the UK with an overall 5-year survival rate of 38.2%. Approximately 75% of tumours are sensitive to first line platinum-based chemotherapy, however this falls to 50% on recurrence, if the duration of the platinum-free interval is >12 months. Although most patients respond to initial treatment, 70-80% with advanced-stage ovarian cancer subsequently develop recurrent disease. The annual numbers of new diagnoses of ovarian cancer in England is around 5,500. It is estimated that around 82% of these women have stage IIIB to IV ovarian cancer; chemotherapy will be unsuitable for about 10% of these. In 2012-13, there were 35,939 admissions for ovarian and fallopian tube cancer resulting in 62,477 bed days and 38,186 finished consultant episodes in England, (there was also an additional 4,861 finished consultant episodes for peritoneal cancer in females). There were 3,769 deaths registered in England and Wales in 2012.

First line chemotherapy is invariably a platinum-based therapy alone or in combination with paclitaxel. For recurrent ovarian cancer, decisions are based upon the platinum-free interval. Paclitaxel poliglumex is currently in one phase III clinical trial comparing its effect on overall survival against treatment with paclitaxel or clinical observation. This trial is expected to complete in January 2022.
TARGET GROUP

- Epithelial ovarian, peritoneal or fallopian tube cancer: stage III or IV – maintenance therapy, following first line chemotherapy in patients who have no evidence of residual disease.

TECHNOLOGY

DESCRIPTION

Paclitaxel poliglumex (Xyotax; CT-2103; CT-2103; poly(L-glutamic acid)-paclitaxel conjugate; PPX) consists of a biodegradable polyglutamate polymer linked to paclitaxel. By linking paclitaxel to a biodegradable amino acid carrier, the conjugated chemotherapeutic agent is inactive in the bloodstream, sparing normal tissues the toxic side effects of chemotherapy. Paclitaxel is activated and released once inside tumour tissue by the action of cathepsin B. Paclitaxel poliglumex is intended for the maintenance treatment of stage III or IV epithelial ovarian, peritoneal or fallopian tube cancer, following first line chemotherapy in patients who have no evidence of residual disease. It is administered by intravenous (IV) infusion over 10 minutes at 175mg/m² on day 1 of a 28 day cycle. Treatment cycles are repeated monthly for 12 months and continued indefinitely.

Paclitaxel poliglumex does not currently have Marketing Authorisation in the EU for any indication. Paclitaxel poliglumex is in phase III clinical trials for locally advanced head and neck cancer (first line – in combination with rituximab and radiotherapy). It is also in phase II/III development for glioblastoma multiforme with unmethylated MGMT status (first line – in combination with radiotherapy).

INNOVATION and/or ADVANTAGES

If licensed, paclitaxel poliglumex will offer an additional treatment option for this patient group.

DEVELOPER

Cell Therapeutics, Inc (cti).

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Primary ovarian, fallopian and peritoneal cancers arise from the epithelial tissues of the ovary, fallopian tube and peritoneal lining of the abdomen. Almost 90% of adult ovarian tumours are epithelial cancers. The serous subtype of ovarian epithelial carcinoma accounts for approximately 60-80% of ovarian cancer cases and has the most aggressive clinical course¹. Regardless of its origin, ovarian cancer leads to similar symptoms and is treated in a similar way². Symptoms can be vague and non-specific initially, but include abdominal
distension; feeling full and/or loss of appetite; pelvic or abdominal pain; and increased urinary urgency and/or frequency\(^3,4\). At the time of diagnosis 60% of patients will have FIGO\(^a\) stage III disease (abdominal or lymph node metastases) and 10% will have metastatic disease in the liver or outside of the abdomen and pelvis (stage IV). For patients with advanced (stage III or IV) disease, initial treatment results are generally favourable, but the clinical course commonly involves relapse, which is ultimately fatal\(^5\). The remaining minority of patients have disease confined to the ovaries (stage I) and/or pelvis (stage II), where cure is a realistic goal of treatment\(^5\).

Several risk factors have been associated with the development of ovarian cancer, such as obesity, certain fertility drugs, reproductive history and duration of reproductive career\(^6\). Genetic predisposition also plays a role; women who carry \textit{BRCA1} mutations have an estimated lifetime risk of between 26% and 54% of developing ovarian cancer, and women who carry \textit{BRCA2} mutations have an estimated lifetime risk of between 10% and 23%\(^6\). \textit{BRCA}-associated ovarian cancer carcinomas are usually high grade, poorly differentiated, serous adenocarcinomas\(^7\).

### NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


### CLINICAL NEED and BURDEN OF DISEASE

Ovarian cancer is the fifth most common cancer in women in the UK\(^5\) with an overall 5-year survival rate of 38.2%\(^9\). Most women (approximately 75%) present with advanced disease and undergo a combination of debulking surgery and 6 cycles of platinum-based chemotherapy\(^10,11,12\). Approximately 75% of tumours are sensitive to first line platinum-based chemotherapy, however this falls to 50% on recurrence if the duration of the platinum-free interval is >12 months\(^5\). Although most patients respond to initial treatment, 70-80% with advanced-stage ovarian cancer subsequently develop recurrent disease\(^5,13\). Most patients receive platinum-based therapy a second or third time before developing resistance\(^5\). The cure rate for stage III disease is approximately 30% while treatments for stage IV are usually palliative\(^5\). The median time to progression after primary treatment (surgery and chemotherapy) is 15-18 months\(^5\), and the median overall survival in patients with advanced ovarian cancer is 31-51 months\(^9,14\).

The annual numbers of new diagnoses of ovarian cancer in England is around 5,500\(^15\). It is estimated that around 82% of these women have stage IIB to IV ovarian cancer; chemotherapy will be unsuitable for about 10% of these patients. The highest incidence rates occur in women aged 50 years and over, with approximately 80% of cases occurring in this age group\(^16\). In 2012-13, there were 35,939 admissions for ovarian and fallopian tube cancer (ICD-10 C56 and C57 respectively) resulting in 62,477 bed days and 38,186 finished consultant episodes in England (there was also an additional 4,861 finished consultant episodes for peritoneal cancer [ICD-10 C48] in females)\(^17\). There were 3,769 deaths due to ovarian and fallopian tube cancer registered in England and Wales in 2012\(^18\).

\(^a\) FIGO – International Federation of Obstetricians and Gynaecologists staging for ovarian cancer.
PEGYLATED LIPOSOMAL DOXORUBICIN HYDROCHLORIDE, PACLITAXEL, TRABECTEDIN AND GEMCITABINE FOR ADVANCED RECURRENT DISEASE ONLY (REVIEW OF TA91) (ID468). EXPECTED DATE OF ISSUE TO BE CONFIRMED.

- NICE TECHNOLOGY APPRAISAL. BEVACIZUMAB IN COMBINATION WITH PACLITAXEL AND CARBOPLATIN FOR FIRST-LINE TREATMENT OF ADVANCED OVARIAN CANCER (TA284). MAY 2013.
- NICE QUALITY STANDARD. QUALITY STANDARD FOR OVARIAN CANCER (QS18). MAY 2012.

OTHER GUIDANCE

- EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY. NEWLY DIAGNOSED AND RELAPSED EPITHELIAL OVARIAN CARCINOMA: ESMO CLINICAL PRACTICE GUIDELINES FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP. 2010.
- NATIONAL COMPREHENSIVE CANCER NETWORK. CLINICAL PRACTICE GUIDELINES IN ONCOLOGY. OVARIAN CANCER. CLINICAL PRACTICE GUIDELINES IN ONCOLOGY. 2008.
- SCOTTISH INTERCOLLEGiate GUIDELINES NETWORK. EPITHELIAL OVARIAN CANCER (SIGN 75). 2003.

CURRENT TREATMENT OPTIONS

First line chemotherapy is invariably a platinum-based therapy alone or in combination with paclitaxel (PAC). The addition of bevacizumab to patients with high-risk disease who have not achieved optimal debulking has been shown to improve progression-free survival (PFS). Single-agent PAC, followed less frequently by topotecan (TOP) or liposomal doxorubicin (PLD), are recommended for the second line (or subsequent) treatment of women with platinum-refractory or platinum-resistant advanced ovarian cancer, and for women who are allergic to platinum-based compounds. For recurrent ovarian cancer, decisions are based upon the platinum-free interval. In patients whose disease has relapsed more than 6 months after previous platinum-based therapy, first choice is usually carboplatin, either alone or in combination with PAC, gemcitabine or PLD until platinum-resistance develops; at which point chemotherapy options include: gemcitabine, PLD, PAC alone, TOP and trabectedin (neither of the last two options are widely used in the UK). Tamoxifen or an aromatase inhibitor may be considered in patients for whom chemotherapy is not appropriate; however this is unlicensed for this indication.
# EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00108745, GOG-0212, NCI-2009-00586, CDR0000422427, U10CA027469; paclitaxel poliglumex vs paclitaxel or clinical observation; phase III.</th>
<th>NCT00045682, CDR0000257039, GOG-01186C; paclitaxel poliglumex; phase II.</th>
<th>NCT00017017, CTI-1071, MSKCC-01024, CDR000068642, NCI-G01-1947; paclitaxel poliglumex; phase I/II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry.</td>
<td>Publication, trial registry.</td>
<td>Trial registry and company.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Participants</td>
<td>n=1,100 (planned); aged 18 years or older; epithelial ovarian, fallopian tube or primary peritoneal carcinoma; stage III or IV; optimal or suboptimal residual disease following initial surgery; received at least 5, but not more than 8 courses, of a platinum and paclitaxel or docetaxel-based combination chemotherapy.</td>
<td>n=78; aged 18 year and older; epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; received 1 or 2 prior chemotherapy regimens, with no more than 1 non-platinum, non-taxane regimen.</td>
<td>n=99; epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; recurrent disease following prior initial therapy with platinum-based regimen; no more than 2 prior cytotoxic chemotherapy regimens; no more than 1 prior non-platinum, non-taxane regimen.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to: paclitaxel poliglumex 135mg/m² IV over 10-20 minutes on day 1 of a 28 day cycle; or paclitaxel 175mg/m² IV over 3 hours on day 1 of a 21 day cycle; or no further anti-cancer treatment until evidence of disease progression.</td>
<td>Randomised to paclitaxel poliglumex 235mg/m² (cohort 1) or 175mg/m² (cohort 2) IV over 10 minutes on day 1 of a 21 day cycle.</td>
<td>Participants receive paclitaxel poliglumex 175mg/m² IV on day 1 of a 21 day cycle.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 12 cycles, follow-up every 3 months for 2 years then every 6 months for 10 years.</td>
<td>Active treatment period until disease progression or unacceptable toxicity.</td>
<td>Follow-up every 3 months.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Overall survival (OS).</td>
<td>Overall response rate (ORR).</td>
<td>Response rate (RR); time to treatment failure.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Progression free survival (PFS), safety, quality of life (QoL).</td>
<td>PFS, OS, safety.</td>
<td>Safety.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>For paclitaxel poliglumex 235mg/m² vs 175mg/m² respectively: complete</td>
<td>For paclitaxel poliglumex 175mg²: RR, 10%; SD, 32%.</td>
</tr>
</tbody>
</table>

b Assessed by Functional Assessment of Cancer Therapy Ovarian Trial Outcome Index (FACT-O-TOI) and Functional Assessment of Cancer Therapy Gynaecologic Oncology Group/Neurotoxicity version 4 (FACT-GOG/NTX4).
response, 4% vs 0%; partial response, 16% vs 16%; stable disease (SD), 40% vs 41%. The Kaplan-Meier estimate of PFS and OS for cohort 2: median OS, 15.4 months; median PFS, 2.8 months (95% CI 1.48-4.8 months).

Adverse effects (AEs)  
AEs (grade II, III and IV) for cohort 1 and cohort 2 respectively: thrombocytopenia, 4% vs 2%; neutropenia, 88% vs 59%; anaemia, 20% vs 16%; allergy, 8% vs 6%; dermatologic, 12% vs 10%; endocrine, 8% vs 0%; gastrointestinal symptoms, 40% vs 24%; constitutional symptoms, 56% vs 35%; musculoskeletal symptoms, 8% vs 2%; neuropathy, 48% vs 39%; pain, 40% vs 26%; alopecia, 4% vs 4%.

Expected reporting date  
Primary completion date, reported as January 2022.

ESTIMATED COST and IMPACT

COST

The cost of paclitaxel poliglumex 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:**
  
  *Ongoing maintenance therapy.*

- **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

recurrent disease only (Review of TA91). Technology appraisal in development ID468. Expected date of issue to be confirmed.


