Orteronel for metastatic hormone-relapsed prostate cancer following chemotherapy

SUMMARY

Orteronel is intended to be used as therapy for the treatment of hormone-relapsed prostate cancer following progression despite docetaxel-containing chemotherapy. If licensed, it will provide an additional treatment option for this patient group. Orteronel is a reversible, non-steroidal androgen biosynthesis inhibitor that selectively inhibits the 17,20 lyase enzyme, suppressing the production of testosterone.

Prostate cancer is the most common cancer in men in the UK, accounting for 25% of all male cancers. The main risk factor is increasing age, with an average of 75% of cases diagnosed in men aged 65 years and over. In 2010, there were 37,354 new diagnoses registered in England and Wales and in 2011, there were 9,671 deaths.

Current treatment options include hormonal therapies, (glucocorticoids, low-dose oestrogens, selective 17,20 lyase inhibitors, or novel androgen receptor antagonists), chemotherapies (docetaxel, mitoxantrone) and immunotherapies (sipuleucel-T). Orteronel is currently in phase III clinical trials comparing its effect on overall survival and event-free survival against treatment with placebo. These trials are expected to complete in 2013 and 2015.
TARGET GROUP

- Prostate cancer: metastatic; hormone-relapsed (mHRPC) - in combination with prednisolone, following disease progression during or after docetaxel-based therapy.

TECHNOLOGY

DESCRIPTION

Orteronel (TAK-700) is a reversible, non-steroidal androgen biosynthesis inhibitor that selectively inhibits the 17,20 lyase enzyme, suppressing the production of testosterone. The progression and growth of prostate cancer cells are initially driven by testosterone via a signalling cascade that begins with the secretion of gonadotropin-releasing hormone and luteinising hormone in the pituitary gland. Orteronel targets the testes and the adrenal cortex where testosterone is synthesised in the mitochondrial membrane by a series of enzymes, including 17-alpha-hydroxylase. Previous agents known to inhibit this pathway have blocked other key enzymatic pathways in the adrenal glands, affecting the synthesis of cortisol. Selective blockade of the 17,20 lyase enzyme, but not the synthesis of cortisol, has the potential to offer a benefit over less selective agents. Orteronel is administered orally, twice daily, in combination with prednisolone.

Orteronel is in phase III clinical trials for the treatment of mHRPC pre-chemotherapy, and in phase II trials for non-metastatic HRPC.

INNOVATION and/or ADVANTAGES

If licensed, orteronel will provide an additional treatment option for this patient group.

DEVELOPER

Takeda UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

HRPC is defined clinically as a failure of medical or surgical castration to prevent an increase in circulating hormones which are associated with worsening prostate cancer. The mainstay of prostate cancer treatment is hormone therapy, which aims to suppress endogenous androgens and thus slow tumour growth. Most men eventually become resistant to this therapy and the cancer will progress and metastasise, which is variously termed HRPC, castration-resistant prostate cancer (CRPC), or androgen-resistant prostate cancer.
NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

CLINICAL NEED and BURDEN OF DISEASE

Prostate cancer is the most common cancer in men in the UK, accounting for 25% of all male cancers\(^2\). The lifetime risk of being diagnosed with prostate cancer is approximately 1 in 8 for men in the UK\(^3\). The main risk factor is increasing age, with an average of 75% of cases diagnosed in men aged 65 years and over\(^2\). In 2010, there were 37,354 new cases registered in England and Wales, resulting in an age-standardised incidence rate of around 110 per 100,000 population\(^3\). Estimates suggest that most prostate cancer deaths occur in men with metastatic disease\(^4\), which develops in approximately 55-65% of patients\(^5\). In 2011-12, there were 56,027 hospital admissions in England due to prostate cancer (ICD-10 C61), accounting for 60,650 finished consultant episodes and 118,393 bed days\(^6\). In 2011, 9,671 deaths were registered in England and Wales\(^7\).

PATIENT PATHWAY

RELEVANT GUIDANCE

**NICE Guidance**

- **NICE technology appraisal in development.** Sipuleucel-T for the first line treatment of metastatic hormone relapsed prostate cancer. Expected February 2014\(^8\).
- **NICE technology appraisal in development.** Radium-223 for the treatment of bone metastases in hormone relapsed prostate cancer. Expected January 2014\(^9\).
- **NICE technology appraisal in development.** Bone metastases (hormone refractory prostate cancer) – denosumab (ID405). Expected November 2013\(^10\).
- **NICE technology appraisal in development.** Abiraterone acetate for the treatment of metastatic castration-resistant prostate cancer not previously treated with chemotherapy (ID503). Expected November 2013\(^11\).
- **NICE technology appraisal.** Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA259). June 2012\(^12\).
- **NICE technology appraisal.** Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA255). May 2012\(^13\).
- **NICE technology appraisal.** Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006\(^14\).
- **NICE clinical guideline in development.** Prostate cancer: diagnosis and management (CG58). Expected January 2014\(^15\).
- **NICE clinical guideline.** Prostate cancer: diagnosis and treatment (CG58). 2008\(^16\).
- **NICE interventional procedure guidance.** Focal therapy using cryoablation for localised prostate cancer (IPG423). April 2012\(^17\).
- **NICE interventional procedure guidance.** Focal therapy using high-intensity focused ultrasound for localised prostate cancer (IPG424). April 2012\(^18\).
- **NICE interventional procedure guidance.** Transperineal template biopsy and mapping of the prostate (IPG364). October 2010\(^19\).
- **NICE interventional procedure guidance.** High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer (IPG174). May 2006\(^20\).
• NICE interventional procedure guidance. Cryotherapy as a primary treatment for prostate cancer (IPG145). November 2005\textsuperscript{21}.
• NICE interventional procedure guidance. Low dose rate brachytherapy for localised prostate cancer (IPG132). July 2005\textsuperscript{22}.
• NICE interventional procedure guidance. Cryotherapy for recurrent prostate cancer (IPG119). May 2005\textsuperscript{23}.
• NICE interventional procedure guidance. High-intensity focused ultrasound for prostate cancer (IPG118). March 2005\textsuperscript{24}.
• NICE cancer service guidance. Improving outcomes in urological cancers (CSGUC). September 2002\textsuperscript{25}.

Other Guidance

• National Comprehensive Cancer Network. NCCN guideline prostate cancer. 2013\textsuperscript{26}.
• European Association of Urology. Guidelines on prostate cancer. 2012\textsuperscript{27}.
• European Society for Medical Oncology. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2010\textsuperscript{28}.
• American Society of Clinical Oncology. American Society of Clinical Oncology endorsement of the cancer care Ontario practice guideline on nonhormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer. 2007\textsuperscript{29}.

EXISTING COMPARATORS and TREATMENTS

Hormone relapsed disease generally develops around 18-24 months from the start of hormone therapy\textsuperscript{30}. Treatment options for HRPC include\textsuperscript{14,15,25,30,a}:

• Additional hormonal therapy
  o Non-steroidal anti-androgens, i.e. bicalutamide, flutamide.
  o Glucocorticoids, i.e. dexamethasone, prednisolone
  o Low dose oestrogens, i.e. diethylstilboestrol
  o Non-selective adrenal inhibitors, i.e. ketoconazole
  o Selective 17,20-lyase inhibitors, i.e. abiraterone (Zytiga) in minimally symptomatic chemotherapy naïve patients with low burden or slowly progressive disease, or after progression on docetaxel.
  o Novel androgen receptor antagonists, i.e. enzalutamide – second line after progression on docetaxel (not yet licensed for this indication).

• Chemotherapy
  o Docetaxel in combination with prednisolone.
  o Mitoxantrone with prednisolone – second line after progression on docetaxel (not licensed for this indication).
  o Cabazitaxel (Jevtana) – second line after progression on docetaxel.

• Immunotherapy
  o Sipuleucel-T, asymptomatic chemotherapy naïve patients, or after progression on docetaxel (not yet licensed for these indications).

• Supportive care, given in combination with the above
  o External beam radiotherapy.
  o Bisphosphonates.
  o Systemic radioisotopes, i.e. radium-223 (Alpharadin) – chemotherapy naïve patients, after progression on docetaxel, or symptomatic patients with bone metastases (not yet licensed for this indication) - samarium-153 or strontium-89.

\textsuperscript{a} Expert personal communication.
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
<th>Follow-up</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01193257, C21005, 2010-018662-23; orteronel vs placebo, both in combination with prednisolone; phase III.</td>
<td>Millenium Pharmaceuticals, Inc.</td>
<td>Ongoing.</td>
<td>Trial registry 31.</td>
<td>EU, USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=1,083 (planned); aged 18 years and older; males; prostate cancer; metastatic; prior surgical castration or concurrent use of an agent for medical castration; progressive disease during or following 1 or 2 cytotoxic chemotherapy regimens, 1 of which must have included docetaxel.</td>
<td>Randomised to orteronel, oral, twice daily, or placebo, oral, twice daily; both in combination with prednisolone.</td>
<td>Active treatment until disease progression, unacceptable toxicity, or death; follow-up until 80% of participants have died or lost to follow-up.</td>
<td>Overall survival (OS).</td>
<td>Prostate specific antigen (PSA) response; pain response; radiographic progression-free survival (rPFS); health-related AEs; PSA response; rPFS; QoL and pain response; OS; FACT-P.</td>
</tr>
<tr>
<td>NCT01707966, SAKK 08/11, 2011-002965-39; orteronel vs placebo; phase III.</td>
<td>Swiss Group for Clinical Cancer Research.</td>
<td>Ongoing.</td>
<td>Trial registry 32.</td>
<td>EU (incl UK).</td>
<td>Randomised, placebo-controlled.</td>
<td>n=192 (planned); aged 18 years and older; males; prostate cancer; metastatic; castration resistant, tumour progression following orchiectomy or during treatment with gonadotropin-releasing hormone (GnRH) analogues; non-progressive disease following first line treatment with docetaxel.</td>
<td>Randomised to orteronal, oral, 300mg twice daily, or placebo, twice daily; both with best supportive care.</td>
<td>Active treatment until disease progression; follow-up until death.</td>
<td>Event free survival (EFS).</td>
<td>PSA response; circulating tumour cell counts; time to pain progression; HRQoL.</td>
</tr>
<tr>
<td>NCT01193244, C21004, 2010-018661-35; orteronel vs placebo, both in combination with prednisolone; phase III.</td>
<td>Millenium Pharmaceuticals, Inc.</td>
<td>Ongoing.</td>
<td>Trial registry 33.</td>
<td>EU, USA, Canada and other countries.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=1,454 (planned); aged 18 years and older; males; prostate cancer; metastatic; progressive; prior surgical castration or concurrent use of an agent for medical castration; no pain or pain not requiring use of any opioid or narcotic analgesia in 2 weeks prior to entry.</td>
<td>Randomised to orteronel, oral, twice daily; or placebo, twice daily; both in combination with prednisolone and concomitant GnRH analogue therapy unless previously undergone orchiectomy and have testosterone concentration of &lt;50ng/dL.</td>
<td>Active treatment until disease progression, unacceptable toxicity or death; follow-up until 80% of participants have died or lost to follow-up.</td>
<td>rPFS; OS.</td>
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b FACT-P: Functional Assessment of Cancer Therapy-Prostate, a questionnaire measuring health-related quality of life in men with prostate cancer.

c Measured by Brief Pain Inventory-Short Form (BPI-SF), a validated questionnaire to measure pain.
ESTIMATED COST and IMPACT

COST

The cost of orteronel is not yet known. The costs of selected treatments for HRPC are summarised below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (Zytiga)</td>
<td>1g, oral, once daily (taken as 250mg tabs, with prednisolone)</td>
<td>£2930.00 per 120-tab pack</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75mg/m(^2), IV, once every 3 weeks (with prednisolone)</td>
<td>£1,069.50 per cycle</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5mg, oral, twice daily</td>
<td>£9.65 per 30-tab pack</td>
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IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified

Impact on Services
- Increased use of existing services: additional therapeutic option
- Decreased use of existing services: oral administration
- Need for new services
- None identified

Impact on Costs
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- None identified

Other Issues
- Clinical uncertainty or other research question identified: Expert opinion highlights that trials will not currently address the relative efficacy of different agents acting on the same hormonal axis, whether this agent may be active following failure of new agents, or has potential synergies with other newer agents. Future work should consider the optimal agent for individual patients.
- None identified

\(^d\) Based on an average adult surface area of 1.88m\(^2\), assumes wastage.
REFERENCES