Sipuleucel-T (Provenge) for metastatic castration resistant prostate cancer – first line

April 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Sipuleucel-T (Provenge) for metastatic castration resistant prostate cancer – first line

Target group
- Castration resistant prostate cancer (CRPC): metastatic – first line.

Technology description
Sipuleucel-T (Provenge, APC 8015, APC-8015) is an autologous cell-based vaccine, designed to stimulate a T-cell response against prostatic acid phosphatase (PAP), an antigen expressed in the majority of prostate cancers but not in non-prostate tissue. Sipuleucel-T is composed of autologous peripheral blood mononuclear cells including antigen presenting cells (APCs), which have been cultured with a recombinant human antigen. Sipuleucel-T is administered by 3 intravenous (IV) infusions at weeks 0, 2 and 4 and treatment is usually completed within one month. Each dose of sipuleucel-T contains a minimum of 5 million autologous CD54+ cells, activated with PAP granulocyte-macrophage colony-stimulating factor, suspended in 250ml of Lactated Ringer’s Solution.

Sipuleucel-T is in phase III clinical trials for early stage and recurrent prostate cancer and in phase II trials for patients with early stage prostate cancer as neoadjuvant therapy following radical prostatectomy.

Innovation and/or advantages
If licensed, sipuleucel-T will be the first therapeutic cancer vaccine for this patient group, which may prolong survival and offer an improved tolerability profile over existing therapies.

Developer
Dendreon Corporation.

Availability, launch or marketing dates, and licensing plans
In phase III trials.

NHS or Government priority area
This topic is relevant to the NHS Cancer Plan (2000) and Cancer Reform Strategy (2007).

Relevant guidance
- In development. Dutasteride for reducing the risk of developing prostate cancer in men who are considered to be at increased risk of developing the disease. Expected date of issue to be confirmed\(^1\).
- In development. Cabazitaxel for the treatment of hormone refractory prostate cancer previously treated with docetaxel chemotherapy regimens. Expected date of issue to be confirmed\(^2\).
- Docetaxel for the treatment of hormone refractory prostate cancer. 2006\(^3\)
- Prostate Cancer: diagnosis and treatment. 2008\(^4\).

NICE Interventionsal Procedure Guidance
- Cryotherapy as a primary treatment for prostate cancer. 2005\(^5\).
- Cryotherapy for recurrent prostate cancer. 2005\(^6\).
- High-intensity focused ultrasound for prostate cancer. 2005\(^7\).
Clinical need and burden of disease

Prostate cancer is the most common cancer in men in the UK, accounting for around 24% of all male cancers. The main risk factor is increasing age, with more than 60% of cases diagnosed over the age of 70. In 2007, there were 30,201 new cases registered in England and 2,552 in Wales, resulting in age standardised rates of 97.2 and 126.1 per 100,000 populations respectively. There were 9,222 deaths from prostate cancer in England and Wales in 2007, approximately 13% of all male cancer deaths. The lifetime risk of being diagnosed with prostate cancer is 1 in 9 for men in the UK. Although epidemiological data on metastatic CRPC is limited, it is estimated that most deaths occur in patients with metastatic CRPC. Metastatic disease occurs in 55-60% of men with prostate cancer, the majority of whom eventually become resistant to hormone therapy, at which point survival is not expected to exceed between 9 and 12 months.

Existing comparators and treatments

There is no curative therapy for CRPC. Treatment is aimed at improving symptoms, slowing progression of the disease and prolonging life. Clinical management is multimodal rather than sequential, and patients may receive a combination of palliative treatments.

Management options include:
- Docetaxel in combination with prednisolone.
- Mitoxantrone with or without steroids (not licensed for this indication).
- Additional hormonal therapy.
- Supportive care with radiotherapy, bisphosphonates, and/or steroids.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Participants and schedule</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>D9901, NCT00005947; adults; sipuleucel-T vs placebo; phase III.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=127; adults; metastatic CRPC; tumour progression following hormonal therapy; baseline prostate specific antigen (PSA) of &gt;5ng/mL; expected survival &gt;3 months. Randomised to sipuleucel-T at weeks 0, 2 and 4 for a total of 3 infusions, or IV placebo.</td>
<td>36 month follow-up period.</td>
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<td>D9902A, NCT01133704; adults; sipuleucel-T vs placebo; phase III.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=98; adults; metastatic CRPC; progressive disease; expected survival &gt;3 months. Randomised to sipuleucel-T at weeks 0, 2 and 4 for a total of 3 infusions or IV placebo.</td>
<td>Survival until death or 36 months following</td>
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<td>D9902B, NCT00065442; adults; sipuleucel-T vs placebo; phase III.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=512; adults; metastatic CRPC. Randomised to sipuleucel T at weeks 0, 2 and 4 for a total of 3 infusions or IV placebo.</td>
<td>Median follow-up 36.5 months.</td>
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<tr>
<td>Primary outcome</td>
<td>Time to disease progression (TTP).</td>
<td>OS.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Disease related pain, AEs, response rate and duration of response. No quality of life (QoL) outcome measures included in trial outcomes.</td>
<td>Overall survival (OS). No quality of life (QoL) outcome measures included in trial outcomes.</td>
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<td>Key results</td>
<td>Sipuleucel-T group vs placebo respectively: median TTP, 11.7 vs 10.0 weeks (p= 0.052; 95% = CI 0.99-2.11); median survival, 25.9 vs 21.4 months (p=0.010; 95% CI 1.13-2.58). Median ratio of T-cell stimulation at 8 weeks higher in sipuleucel-T group (16.91 vs 1.99; p=0.001).</td>
<td>TTP not statistically significant between treatment groups (hazard ratio (HR), 1.09; 95% CI 0.69-1.70). There was a 21% reduction in risk of death in sipuleucel-T vs placebo, not statistically significant (HR, 1.27; 95% CI 0.78-2.07). In overall integrated analysis of NCT01133704 and NCT00005947 patients randomised to sipuleucel-T demonstrated 33% reduction in risk of death (95% CI 1.10-2.05).</td>
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<td>Relative reduction of 22% in risk of death in sipuleucel-T group vs placebo. In sipuleucel-T group vs placebo respectively: median OS. 25.8 months vs 21.7 (p= 0.03); median time to objective disease progression 14.6 weeks vs 14.4 weeks (p=0.63); 36 month survival probability 31.7% vs 23%; T-cell proliferation responses in 46 of 63 patients vs 4 of 33. Responses to immunising antigen were observed in patients who received sipuleucel- T. At 36.5 month follow-up median survival benefit remained at 4.1 mths favouring sipuleucel-T arm.</td>
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</table>
### Adverse effects (AEs)

Statistically significantly different rates of AEs (p ≥0.05) between sipuleucel-T group and placebo groups included: rigors (59.8% vs 8.9%), pyrexia (29.3% vs 2.2%), tremor (9.8% vs 0%) and feeling cold (8.5% vs 0%). Majority of AEs grade 1 or 2. 95% of patients received all 3 infusions and there were no withdrawals due to AEs.

AEs more frequently reported in sipuleucel-T group included: chills (57.8% vs 7.9%), pyrexia (32.0% vs 6.7%), headache (19.0% vs 6.6%), asthenia (14.3% vs 3.9%), dyspnoea (10.9% vs 2.6%) and vomiting (10.9% vs 2.6%). No grade 3 or 4 AEs reported in ≥5% of patients in either arm and no significant differences in incidence of grade 3 or 4 AEs between arms. Increased risk of cerebrovascular events observed in sipuleucel-T group vs placebo (7.5% vs 2.6%).

AEs more frequently reported in sipuleucel-T group vs placebo (NCT00005947 and NCT01133704 combined) included: chills (54.1% vs 12.5%), pyrexia (29.3% vs 13.7), headache (16.0% vs 4.8%), influenza-like illness (9.8% vs 3.6%), myalgia (9.8% vs 4.8%), hypertension (7.4% vs 3.0%) hyperhydrosis (5.3% vs 0.6%) and groin pain (5.0% vs 2.4%). 6.8% of sipuleucel-T group and 1.8% placebo experienced grade 3 or 4 AEs within 1 day of infusion. 3 patients in sipuleucel-T group unable to receive all infusions due to infusion-related AE. Cerebrovascular events reported in 2.4% of sipuleucel-T group vs 1.8% in placebo.

### Trial Details

<table>
<thead>
<tr>
<th>Trial</th>
<th>PB01, NCT00849290; adults; sipuleucel-T; phase III extension.</th>
<th>ProACT, P07-21, NCT00715078; adults; sipuleucel-T; phase II.</th>
<th>P09-1, NCT00901342; adults; sipuleucel-T; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of information</td>
<td>Manufacturer, trial registry\textsuperscript{20}, abstract\textsuperscript{21}</td>
<td>Trial registry\textsuperscript{22}.</td>
<td>Trial registry\textsuperscript{23}.</td>
</tr>
<tr>
<td>Location</td>
<td>USA and Canada.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Design</td>
<td>Uncontrolled, open-label.</td>
<td>Randomised.</td>
<td>Uncontrolled.</td>
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<td>Participants and schedule</td>
<td>n=113; adults; objective disease progression; previously enrolled in placebo arm of NCT0065442. Sipuleucel-T, 3 infusions at 2 week intervals.</td>
<td>n=120 (planned); adults; metastatic CRPC; PSA &gt;5.0ng/dL; castration level of testosterone &lt;50ng/dL. Randomised to sipuleucel-T with 1 of 3 different concentrations of PA2024 antigen for 3 infusions at 2 week intervals.</td>
<td>n=80; adults; metastatic CRPC; castration level of testosterone &lt;50ng/dL. Sipuleucel-T, 3 infusions at 2 week intervals.</td>
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<td>Follow-up</td>
<td>24 month treatment period.</td>
<td>6 month follow-up.</td>
<td>30 day follow-up period.</td>
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<tr>
<td>Primary outcome</td>
<td>Safety.</td>
<td>Cumulative CD54 upregulation ratio.</td>
<td>Immune response.</td>
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<tr>
<td><strong>Secondary outcome</strong></td>
<td>Efficacy. No quality of life (QoL) outcome measures included in trial outcomes.</td>
<td>Immune response, OS, QoL measured using Functional Assessment of Cancer Therapy-Prostate (FACT-P) and European Quality of Life – 5 dimensions (EQ-5D) instruments.</td>
<td>Safety. No QoL outcome measures included in trial outcomes.</td>
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<td><strong>Key results</strong></td>
<td>In a combined analysis of NCT01133704 and NCT00849290 sipuleucel-T vs placebo respectively: OS following disease progression was 20.7 vs 20.0 mths. After adjusting for baseline age, PSA, lactate dehydrogenase and post-randomisation docetaxel use HR= 0.55 (95 CI 0.39-078). CD54 upregulation and total nucleated cell count product parameters correlated with survival.</td>
<td>Not yet reported.</td>
<td>Not yet reported.</td>
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<tr>
<td><strong>Adverse effects (AEs)</strong></td>
<td>Combined analysis demonstrated that any grade AEs occurred in 43.0% of sipuleucel-T arm vs 51.6% in placebo.</td>
<td>Not yet reported.</td>
<td>Not yet reported.</td>
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</table>

**Estimated cost and cost impact**

The cost of sipuleucel-T is not yet known.

**Claimed or potential impact – speculative**

**Patients**

- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

**Services**

- Increased use
- Service organisation
- Staff requirements: training and IV infusion facilities required.
- None identified

**Costs**

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- None identified
Other issues
- Clinical uncertainty or other research question identified: ☐ Yes ☐ No
- None identified

References

1 National Institute for Health and Clinical Excellence. Dutasteride for reducing the risk of developing prostate cancer in men who are considered to be at increased risk of developing the disease. Expected date of issue to be confirmed.
2 National Institute for Health and Clinical Excellence. Cabazitaxel for the treatment of hormone refractory prostate cancer previously treated with docetaxel chemotherapy regimens. Expected date of issue to be confirmed.