### Emerging Drug List

**VACCINES FOR METASTATIC HORMONE-REFRACTORY PROSTATE CANCER**

<table>
<thead>
<tr>
<th>Generic (Trade Name):</th>
<th>Sipuleucel-T [Provenge® (formerly APC8015)]; granulocyte macrophage-colony stimulating factor (GM-CSF) gene-transduced tumour vaccine (GVAX®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer:</td>
<td>Dendreon Corporation (Provenge®); Cell Genesys (GVAX®)</td>
</tr>
<tr>
<td>Indication:</td>
<td>Provenge® and GVAX® are being investigated as therapeutic vaccines in men with metastatic hormone-refractory prostate cancer (HRPC).</td>
</tr>
<tr>
<td>Current Regulatory Status:</td>
<td>On November 7, 2005, the US Food and Drug Administration (FDA) granted Fast Track review status to Provenge® for the treatment of men with asymptomatic, metastatic HRPC, based on its potential to improve survival in this population.1</td>
</tr>
<tr>
<td>Description:</td>
<td>Prostatic acid phosphatase (PAP) is a unique protein that is overexpressed in 95% of prostate cancer cells. Provenge® is a patient-specific vaccine designed to stimulate a T-cell-mediated immune response against PAP. The vaccine is made by isolating antigen presenting cells (APCs) from the patient’s blood, and combining the sample with a recombinant fusion protein containing PAP and granulocyte macrophage-colony stimulating factor (GM-CSF), another immune-stimulating protein. The mixture is returned to the patient over one hour, starting two days after each harvest, for a total of three infusions. The vaccine stimulates other cells of the immune system to seek and destroy PAP-containing prostate cancer cells.3,4</td>
</tr>
<tr>
<td>Current Treatment:</td>
<td>Options for men with metastatic HRPC include hormonal therapy, radiation therapy, chemotherapy, or the use of investigational agents. The combination of Taxotere® (docetaxel) plus prednisone, which was approved by Health Canada in May 2005, has been shown to improve survival in this population. Adjunctive therapies include the use of zoledronic acid, which is a bisphosphonate that may relieve the skeletal complications associated with metastatic disease.8</td>
</tr>
<tr>
<td>Cost:</td>
<td>There is no cost information on Provenge® or GVAX®, because they are not yet marketed in any country.</td>
</tr>
</tbody>
</table>

---

1. Provenge® and GVAX® are being investigated as therapeutic vaccines in men with metastatic hormone-refractory prostate cancer (HRPC).
2. Cell Genesys has received Special Protocol Assessment (SPA) provision from the US FDA for two Phase III clinical trials being conducted for GVAX® in men with advanced prostate cancer: VITAL 1, granted May 2004; and VITAL 2, granted May 2005.
3. Prostatic acid phosphatase (PAP) is a unique protein that is overexpressed in 95% of prostate cancer cells. Provenge® is a patient-specific vaccine designed to stimulate a T-cell-mediated immune response against PAP. The vaccine is made by isolating antigen presenting cells (APCs) from the patient’s blood, and combining the sample with a recombinant fusion protein containing PAP and granulocyte macrophage-colony stimulating factor (GM-CSF), another immune-stimulating protein. The mixture is returned to the patient over one hour, starting two days after each harvest, for a total of three infusions. The vaccine stimulates other cells of the immune system to seek and destroy PAP-containing prostate cancer cells.
4. GVAX® is a prostate cancer vaccine composed of irradiated whole tumour cells from two cell lines that have been genetically modified to secrete GM-CSF. GVAX® is administered intradermally on an outpatient basis. Patients receive an initial dose of GVAX®, in millions of cells, followed by boost vaccinations every 14 days for up to six months.
5. The genetically modified cells secrete GM-CSF and activate a systemic anti-tumour immune response.
6. Options for men with metastatic HRPC include hormonal therapy, radiation therapy, chemotherapy, or the use of investigational agents. The combination of Taxotere® (docetaxel) plus prednisone, which was approved by Health Canada in May 2005, has been shown to improve survival in this population. Adjunctive therapies include the use of zoledronic acid, which is a bisphosphonate that may relieve the skeletal complications associated with metastatic disease.
The efficacy and safety of Provenge® were evaluated in two Phase III clinical trials (D9901, D9902A). Men with asymptomatic, metastatic HRPC [n=127 (study D9901), n=98 (study D9902A)] were randomized to receive Provenge® or placebo, administered in three intravenous infusions over four weeks. The outcome measures were time to disease progression and time to development of disease-related pain. Survival was also evaluated at the three-year follow-up.10,11

The final three-year data from study D9901, presented at the American Society of Clinical Oncology (ASCO) meeting in May 2005, indicated a statistically significant survival benefit for Provenge®.10 Patients who received Provenge® had a median survival of 25.9 months compared with 21.4 months for patients in the placebo arm, a survival benefit of 4.5 months or 21% (p=0.01). Patients who received placebo had a 70% higher relative risk of dying during the study period compared with the group receiving Provenge®. Among patients receiving Provenge®, 34% were alive at 36 months compared with 11% in the placebo group.10,12

Final three-year follow-up data from study D9902A were presented on October 31, 2005, at the 13th European Cancer Conference (ECCO). A non-statistically significant 3.3 month or 21% improvement in survival for Provenge®-treated patients (p=0.332) was reported.11,13 An integrated analysis of data from studies D9901 and D9902A showed a statistically significant survival benefit in the overall intent-to-treat population of 225 patients, with a 4.3 month or 23% improvement in median survival in patients treated with Provenge® compared with patients who received placebo (23.2 months versus 18.9 months; p=0.011). Among the men who received Provenge®, 33% were alive at three-year follow-up, compared with 15% of the men who received placebo. It was not stated whether this difference was statistically significant.13

Provenge® is being used in a pivotal double-blind placebo-controlled Phase III trial, D9902B, which was designed to evaluate the time to disease progression and time to development of disease-related pain in patients and metastatic HRPC with a Gleason score—a measure of the degree of tumour differentiation—of <8. Tumours with Gleason scores of <8 are considered to be less aggressive than those with Gleason scores of ≥8.14 D9902B has been granted SPA, indicating that the trial may serve as the basis for a Biologics License Application for Provenge®.

GVAX® is being evaluated in two Phase III trials in men with metastatic HRPC. VITAL-1 will compare GVAX® with Taxotere® plus prednisone, and VITAL-2 will compare GVAX® plus Taxotere® with Taxotere® plus prednisone. Both trials will assess survival benefit and are expected to enrol 600 patients across North America and Europe. In two previously reported Phase II trials,5,15 the combined overall median survival of patients with metastatic HRPC treated with GVAX® was comparable to the 18.9 months reported for metastatic HRPC patients treated with Taxotere® plus prednisone.6
Adverse Effects: Provenge® and GVAX® are generally well tolerated. Mild to moderate infusion-related fever and chills lasting one to two days are reported in clinical trials.4,16

Commentary: There are no therapeutic vaccines approved for use for prostate cancer in Canada or the US. To be effective, a therapeutic vaccine must demonstrate the ability to elicit an appropriate tumour-specific response, and have a favourable safety profile.17 Provenge® is safe and well-tolerated. It targets a specific protein for prostate cancer and demonstrates a statistically significant survival benefit. Further clinical trials should compare Provenge® with the current treatment standard (Taxotere® plus prednisone), as is being done in the GVAX® clinical trials. GVAX® is safe and well-tolerated. Because it is not patient-specific, it will be available on an outpatient basis to any patient. If GVAX® makes it to the market, it could prove to be a convenient addition to the limited treatment arsenal that is available for men with metastatic HRPC.18

References:


