**Emerging Drug List**

**METASTATIC MELANOMA VACCINES**

<table>
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<tr>
<th><strong>Generic (Trade Name):</strong></th>
<th>HLA-B7 and β2 microglobulin plasmid DNA-lipid complex (Allovectin-7®); autologous DNP-conjugated tumour vaccine (M-Vax™); vitespen [Oncophage® (formerly HSPPC-96)]</th>
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<td><strong>Manufacturer:</strong></td>
<td>Vical (Allovectin-7®); AVAX Technologies (M-Vax™); Antigenics (Oncophage®)</td>
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<td><strong>Indication:</strong></td>
<td>Allovectin-7®, M-Vax™, and Oncophage® are being evaluated for the treatment of patients with metastatic melanoma (stage III or IV), or patients with recurrent metastatic disease.</td>
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<td><strong>Current Regulatory Status:</strong></td>
<td>Allovectin-7® was granted Orphan Drug Status by the US Food and Drug Administration (FDA) in October 1999 for the treatment of stage III or IV metastatic melanoma.¹</td>
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<td>M-Vax™ was granted Orphan Drug Status by the FDA for the treatment of stage III melanoma in January 1999.² In 2001, the FDA halted two pivotal phase III trials because of manufacturing violations at the company’s US plant. AVAX Technologies successfully resubmitted a new Investigational New Drug (IND) application in 2002.³ M-Vax™ was approved in Switzerland in October 2005 for the treatment of stages III and IV melanoma.⁴</td>
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<td>Oncophage® was granted Fast Track designation in February 2002⁵ and Orphan Drug Status in July 2002⁶ by the FDA for the treatment of metastatic melanoma.</td>
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<td><strong>Description:</strong></td>
<td>Allovectin-7® is a gene-based immunotherapeutic vaccine composed of plasmid DNA encoding the genes HLA-B7 and β2-microglobulin complexed with a cationic lipid mixture, which aids in the uptake of DNA by the tumour. HLA-B7 and β2 microglobulin proteins together form a class I major histocompatibility complex (MHC-I) antigen. MHC-I antigens are usually displayed on cell surfaces. They are responsible for lymphocyte recognition and the subsequent immune response. Tumour cells, including melanoma cells, often demonstrate absent or reduced levels of MHC-I expression on their cell surfaces. Allovectin-7® is injected into the tumour, where it is taken up by the melanoma cells. The cells subsequently express the HLA-B7 antigen, triggering an immune response at the primary tumour and metastatic sites.⁷</td>
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<td>M-Vax™ is a patient-specific vaccine. Melanoma cells are taken from the patient’s tumour at the time of lymph node resection, and are modified with the addition of dinitrophenyl (DNP). DNP stimulates a T-cell-based immune response, and a delayed-type hypersensitivity to the patient’s tumour cells. Vaccination starts after recovery from surgery, and involves multiple intradermal injections of M-Vax™.⁸</td>
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Oncophage® is a patient-specific vaccine based on heat shock protein (HSP) technology. HSPs are induced in diseased cells, where they play a role in the presentation of antigens on the cell surface for immune system recognition. Because HSPs and associated peptides are unique to each person’s disease, they act as an antigenic “fingerprint.” Oncophage® is made by extracting and purifying the HSP gp96 and its associated proteins from the patient’s surgically resected tumour. After recovery from surgery, the vaccine is injected into the patient, where it stimulates the immune system to attack only cells bearing the cancer fingerprint. Oncophage® is designed to be given on an outpatient basis, with patients receiving one injection once a week for four weeks, then one injection every other week.

Depending on the location and extent of the metastases, treatment options for metastatic melanoma include surgery to remove the tumour and any involved lymph nodes, chemotherapy, immunotherapy, or radiation therapy. Chemotherapy with dacarbazine remains the gold standard for the treatment of patients with metastatic disease. Immunotherapy with high-dose interferon alfa-2b (IL-2b) therapy (e.g., Intron® A) is used to stimulate the immune system and is standard therapy for those patients at high risk for recurrence after surgery. High-dose IL-2b can be associated with significant toxicity (e.g., chronic fatigue, elevated liver enzymes, neurologic symptoms), which can lead to treatment discontinuation. Chemotherapy and immunotherapy are usually administered as monotherapy, but may be combined in some cases.

For patients with recurrent metastatic disease—those with disease progression despite an initial response to therapy—treatment options are limited, and depend on factors such as prior treatment, site of recurrence, and individual patient considerations.

Cost: Costing information for Allovectin-7®, M-Vax™, and Oncophage® is unavailable.

Evidence: A phase II trial evaluated the safety and efficacy of Allovectin-7® in 133 patients with stage III or IV metastatic melanoma that was recurrent or unresponsive to therapy. Patients with two or more injectable lesions were randomized to receive single or multiple injections of Allovectin-7® weekly for six weeks (total 2 mg per week). Of 127 patients evaluated for efficacy, overall clinical responses were observed in 11.8% of patients (n=15), including four complete responses and 11 partial responses. The Kaplan-Meier estimated median duration of response was 12.7 months, and the estimated median survival was 21.3 months. Based on end-of-phase-II meetings with the FDA, Vical announced in February 2005 that it had successfully completed a Special Protocol Assessment (SPA) for an open-label, multicentre phase III trial (LX01-315). The phase III trial is expected to enrol 375 patients with recurrent metastatic melanoma.
Patients will be randomized on a 2:1 basis to treatment with Allovectin-7® (2 mg) or the physician’s choice of chemotherapeutic agent (i.e., dacarbazine or temozolomide). Patients in the Allovectin-7® group will receive the full 2 mg dose per week injected into one lesion. The primary endpoint is overall response ≥24 weeks after randomization using Response Evaluation Criteria in Solid Tumor (RECIST) (e.g., complete or partial tumour response).15

In a phase II study involving 214 patients with stage III melanoma, patients who received adjuvant therapy with M-Vax™ after a standard lymphadenectomy had a five-year overall survival rate of 44% (p<0.035), which compared favourably with the reported surgical rate of 20% to 25%.17 AVAX Technologies announced in July 2005 that it has initiated enrolment in a phase II multicentre trial evaluating M-Vax™ for the treatment of stages III and IV melanoma.18

In a phase II study of 28 patients with residual measurable stage IV melanoma after surgery, two patients had a complete response and three had stable disease after treatment with Oncophage®. The two patients with a complete response remained disease-free for at least two years.9 Oncophage® is being evaluated in a phase III trial of 322 patients with stage III metastatic melanoma. Preliminary results indicate that patients randomized to receive Oncophage® (n=133) have a greater, but not statistically significant, median survival of 20.9 months compared with 12.8 months in patients randomized to receive the physician’s choice of chemotherapy (i.e., dacarbazine or temozolomide), immunotherapy (i.e., IL-2), or surgery (n=107).19 The trial began in 2002, but was not intended to be used to file for FDA approval. The company has announced plans to initiate a phase III trial with the aim of filing for FDA approval.19

High dose (2 mg) Allovectin-7® has been reported to be well tolerated, with no grade 3 or grade 4 adverse events.15 Treatment with M-Vax™ was well tolerated in a phase II study, although injection site reactions were common.17 Oncophage® was well tolerated in phase II trials, with no serious adverse events observed.9,20

Although treatable in its early stages, cure rates fall dramatically once melanoma has spread from its site of origin.21 Treatment strategies for metastatic melanoma are limited, especially for recurrent metastatic disease. In this case, treatment is associated with disappointing outcomes and unpleasant side effects that adversely affect patients’ quality of life.15 With the exception of high dose interferon as adjuvant therapy in stage III disease, there have been no new treatment developments for metastatic melanoma over the last 20 years.22 Effective therapies are needed for this patient population.
Although vaccine therapies for metastatic melanoma have shown promise, there have been disappointments. For example, CancerVax Corporation has discontinued all development and manufacturing of its melanoma vaccine, Canvaxin™, after the data safety monitoring board recommended discontinuation of two phase III trials because of a lack of survival benefit.23 Melacine®, the first melanoma vaccine approved for use in Canada (January 2000),24 was delisted on September 23, 2005, when the manufacturer, Corixa Corporation, inactivated the drug identification number (DIN) for Melacine® post-market.25 Although Allovectin-7®, M-Vax™, and Oncophage® have led to encouraging preliminary results, the evidence is limited, and results from phase III trials are required before these vaccines are considered as viable treatment options.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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