Melanoma Vaccines

Description

Tumor vaccines are a type of active immunotherapy that attempts to stimulate the patient’s own immune system to respond to tumor antigens. There are a number of different tumor vaccines for the treatment of malignant melanoma in various stages of development.

Background

Vaccines using crude preparations of tumor material were first studied by Ehrlich over 100 years ago, (1) but the first modern report suggesting benefit using these in cancer patients did not appear until 1967. (2) Melanoma has been viewed as a particularly promising tumor for this type of treatment because of its immunologic features, which include the prognostic importance of lymphocytic infiltrate at the primary tumor site, the expression of a wide variety of antigens, and the occasional occurrence of spontaneous remissions. (3) Melanoma vaccines can be generally categorized or prepared in the following ways (4):

- **Whole-cell vaccines** prepared using melanoma cells or crude sub-cellular fractions of melanoma cell lines
  - **Autologous whole-cell vaccines** in which tumor cells are harvested from the tissue of excised cancers, irradiated, and potentially modified with antigenic molecules to increase immunogenicity and made into patient-specific vaccines (e.g., M-Vax, AVAX Technologies)
  - **Autologous heat-shock protein-peptide complexes vaccines** in which a patient’s tumor cells are exposed to high temperatures and then purified to make patient-specific vaccines (e.g., Oncophage®, Vitaspin, Antigenics, Inc.), and
  - **Allogeneic whole-cell vaccines** in which intact or modified allogeneic tumor cell lines from other patients are lysed by mechanical disruption or viral infection and used to prepare vaccine (e.g., Canvaxin®, CancerVaxCorp. or Melacine®, University of Southern California)
- **Dendritic cell vaccines** in which autologous dendritic cells are pulsed with tumor-derived peptides, tumor lysates, or antigen encoding RNA or DNA to produce immunologically enhanced vaccines.
- **Peptide vaccines** consisting of short, immunogenic peptide fragments of proteins (e.g., melanoma antigen E or MAGE; B Melanoma antigen or BAGE) used alone or in different combinations to create vaccines of varying antigenic diversity, depending on the peptide mix.

- **Ganglioside vaccines** in which glycolipids present in cell membranes are combined with an immune adjuvant (e.g. GM2) to create vaccines.

- **DNA vaccines** created from naked DNA expression plasmids.

- **Viral vectors** in which DNA sequences are inserted into attenuated viruses for gene delivery to patient immune systems.

- **Anti-idiotype vaccines** made from monoclonal antibodies with specificity for tumor antigen-reactive antibodies.

**Regulatory Status**

At the present time, no melanoma vaccine has received approval from the U.S. Food and Drug Administration (FDA).

**Related Policies**

8.01.01 Adoptive Immunotherapy

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Melanoma vaccines are considered **investigational**.

**Rationale**

The Technology Evaluation Center (TEC) evaluated the use of vaccines to treat melanoma in a 2001 TEC Special Report, “Vaccines for the Treatment of Malignant Melanoma.” (5) In spite of the fact that the literature contained hundreds of publications on this treatment at this time, there was a striking paucity of completed Phase III clinical trials available for evaluation. The 2001 report highlighted the importance of such studies to control for patient characteristic, disease and treatment confounders. It also highlighted the value of long-term outcomes that measure disease progression or mortality instead of the use of less reliable surrogate measures of immune response. Of note, several Phase I or II studies of melanoma vaccines (Canvaxin®, Melacine®) have not been replicated in subsequent Phase II or III studies. (4)

In an article in *Nature Medicine* in 2004, Rosenberg et al. (6) noted that looking at the experience at the National Cancer Institute’s Surgery Branch in evaluating 450 patients treated for metastatic cancer with vaccines (the majority—422—with metastatic melanoma), only 2.6% exhibited a positive treatment response. Reviewing 35 carefully selected representative reports from the literature (one-third in melanoma patients) involving 765 patients, the objective response rate to this treatment was again surprisingly low (only 3.8%).
Rosenberg et al. (6) suggested that an important reason for this poor performance was the inability of T-cells generated by cancer vaccines to infiltrate tumors and become activated after an encounter with tumor antigen in vivo. He concluded “the lack of clinical effectiveness of currently available cancer vaccines should not be interpreted to mean that cancer vaccine approaches are at an investigational dead end. Rather, it emphasizes the need for profound changes in the application of this approach.” Among several suggestions proposed were mechanisms to increase the yield and activity of CD4+ cells and to eliminate tumor induced or normally occurring lymphocyte-mediated immune suppressive mechanisms.

While more than 1,700 publications on melanoma vaccine use in both animals and humans have appeared since the 2001 TEC Special Report, there are currently only 12 Phase III clinical studies evaluating melanoma vaccines (7-18): 4 using allogeneic vaccines, 2 autologous whole-cell vaccines, 2 ganglioside vaccines, one autologous heat shock protein, and 3 peptide vaccines—one pulsed with dendritic cells, one administered with ipilimumab and one administered with concomitant IL-2. In 2 studies, (7,10) vaccine treatments appeared to demonstrate superior performance in unique populations identified during post hoc data evaluation. However, no published study to date has shown a statistically significant survival benefit in the general population selected for study. In two reports, (9,12) outcomes using vaccines appeared inferior to those observed in controls. A summary of trials showing lack of efficacy are provided in Table 1.

Hodi et al. (17) performed a Phase III study of ipilimumab, an agent that blocks cytotoxic T-lymphocyte-associated antigen 4 to potentiate an antitumor T cell response. This agent was administered in a 3-arm study comparing ipilimumab to ipilimumab with gp100 peptide vaccine to gp100 peptide vaccine alone. Ipilimumab, when used alone or with gp100, exhibited improved overall survival compared to gp100 alone in patients with previously treated melanoma. Ipilimumab has subsequently been approved by the FDA for this use.

Schwartzentruber et al. (15, 18) reported the initial findings of their Phase III trial of gp100:209-217(210M) peptide vaccine plus high-dose IL-2 (vaccine) versus high-dose IL-2 alone (control). The vaccine arm showed significant improvement in response rate (p=0.03) and progression-free survival (PFS; p=0.008) but not median overall survival (OS; p=0.06). The authors reached the guarded conclusion that “additional data are needed to ascertain whether the finding in our study was due to a direct effect of the vaccine or to the possibility that vaccinated patients were more responsive to salvage regimens or that the nature of progression differed between the two groups or that other factors were involved.”

In a recent systematic review and meta-analysis of 4,375 patients in 56 Phase II and Phase III studies, no evidence was found that vaccine therapy provides better overall disease control or overall survival compared with other treatments. (19) However, in a second review of medical treatments in melanoma, 2 pending studies were highlighted. (20) The first is a Phase III vaccine trial of patients with stage IIIIB melanoma whose tumors express MAGE-A3 antigen in lymph node metastasis. This allogeneic vaccine is unique in targeting a specific cancer germline family antigen. The second is a Phase III trivalent vaccine prepared using 3 peptides (GP100, MART-1/Melan, and tyrosine HLA-A2). Preliminary reports suggest patients exhibiting antibodies to any of the 3 peptides had insignificantly improved survival. More definitive results from both studies are pending.
There are a variety of explanations as to why melanoma vaccines have not been able to date to produce clinically significant improvements in treatment outcomes. (21) One possible mechanism is immune ignorance and the ability of melanoma cells to escape detection through loss of antigens or loss of HLA expression. A second mechanism is immune tolerance. This may result from the ability of the melanoma tumor to prevent a local accumulation of active helper and/or effector T cells as a result of high interstitial pressure in the tumor or lack of appropriate adhesion molecular on tumor vasculature. This may also occur as a result of normal down-regulation of the immune system at the site of T cell tumor interaction. A wide range of immune-modulating techniques are being explored to find mechanisms for enhancing the immune response induced by tumor vaccines.

Gajewski (22) published a preliminary or exploratory report on the value of molecular profiling to identify relevant immune resistance in the tumor microenvironment. This approach toward identifying subsets of patients likely to benefit from specific treatment choices, if confirmed in future studies, may help improve treatment outcomes with the use of tumor vaccines.

**Ongoing Clinical Trials**

A review of online site, ClinicalTrials.gov on April 23, 2014 identified 2 active phase 3 studies on melanoma vaccines. In the MAVIS trial, a polyvalent melanoma vaccine will compare a placebo in stage IIb, IIC and III melanoma patients at high risk of recurrence after surgical resection (NCT01546571). This multicenter, double blind, phase 3 trial is estimated to enroll 1059 patients and be completed in 2018. In a single-center, randomized, open label, phase 2/3 trial of 108 stage IIb, IIC, and III melanoma patients, an allogeneic, irradiated melanoma vaccine will be compared with alpha interferon 2b after surgical melanoma resection (NCT01729663). An estimated completion date was not provided. The search of ClinicalTrials.gov also identified 39 open and active phase 1 and 2 studies.

**Practice Guidelines and Position Statements**

The National Comprehensive Cancer Network guidelines on the treatment of melanoma do not reference the use of vaccines in clinical trials in any of its treatment algorithms. (23) The guidelines do discuss clinical trials that have reported inferiority in melanoma vaccine treatment arms.

**Summary**

Tumor vaccines are a type of active immunotherapy that attempts to stimulate the patient’s own immune system to respond to tumor antigens. There are a number of different tumor vaccines for the treatment of malignant melanoma in various stages of development.

A wide range of vaccine choices are available including use of autologous tumor cells, allogeneic tumor cells, and tumor-specific moieties including peptides, gangliosides, and DNA plasmids. A variety of mechanisms appear to exist as possible obstacles to successful active immunotherapy using vaccines. Current studies are focused on the use of new and different vaccine preparations, as well as on various forms of immune-modulation as potential techniques for enhancing vaccine effectiveness.

Despite considerable interest and numerous studies over the past 20 years, to date no melanoma vaccine has been shown to demonstrate safety and efficacy in a well-controlled published Phase III
clinical trial and no vaccine treatment for this cancer has been approved by FDA. Current studies are focused on the use of new and different vaccine preparations, as well as on various forms of immune-modulation as potential techniques for enhancing vaccine effectiveness. Consequently, vaccinations for the immunization against melanoma are considered investigational.

Table 1. Phase III randomized, controlled, clinical trials of vaccine therapy evaluating cancer outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Population</th>
<th>Vaccine</th>
<th>Control</th>
<th>Results</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Livingston et al.,</td>
<td>Stage III</td>
<td>GM2/BCG (bacille Calmette-Guerin)</td>
<td>BCG</td>
<td>Disease-free survival (DFS) and overall survival (OS) showed no statistically significant differences</td>
<td>Patients with no pre-treatment anti-GM2 antibody showed improved PFS with vaccine</td>
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<tr>
<td>1994 (7)</td>
<td>n=122</td>
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<tr>
<td>Wallack et al.,</td>
<td>Stage III</td>
<td>Vaccinia melanoma oncolysate</td>
<td>Vaccinia oncolysate from normal cell</td>
<td>DFS and OS showed no statistically significant differences</td>
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<tr>
<td>1998 (8)</td>
<td>n=217</td>
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<tr>
<td>Kirkwood et al.,</td>
<td>Stage IIB/III</td>
<td>Ganglioside GM2-KLH21 (GMK [guanylate kinase])</td>
<td>Interferon alpha</td>
<td>Trial closed after interim analysis indicated GMK inferiority</td>
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<td>2001 (9)</td>
<td>n=774</td>
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<td></td>
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<tr>
<td>Sondak et al.,</td>
<td>Stage II</td>
<td>Allogeneic melanoma vaccine (Melacine®)</td>
<td>Observation</td>
<td>No evidence of DFS</td>
<td>Patients with 2 or more HLA matches showed improved PFS</td>
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<td>2002 (10)</td>
<td>n=600</td>
<td></td>
<td></td>
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<tr>
<td>Hersey et al.,</td>
<td>Stage IIB/III</td>
<td>Vaccinica melanoma oncolysate</td>
<td>Observation</td>
<td>Recurrence-free and overall survival not statistically improved in vaccine patients</td>
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<tr>
<td>2002 (11)</td>
<td>n=700</td>
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<tr>
<td>Morton et al.,</td>
<td>Stage III</td>
<td>Canvaxin® + BCG + placebo</td>
<td>BCG + placebo</td>
<td>Trial closed after interim analysis indicated Canvaxin® inferiority</td>
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<tr>
<td>2006 (12)</td>
<td>n=1,160</td>
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<tr>
<td>Morton et al.,</td>
<td>Stage IV</td>
<td>Canvaxin® + BCG + placebo</td>
<td>BCG + placebo</td>
<td>Trial closed after interim analysis</td>
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<td>2006 (12)</td>
<td>n=496</td>
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<thead>
<tr>
<th>Mitchell et al., 2007 (13)</th>
<th>Stage III n=604</th>
<th>Allogeneic whole-cell lysate administered with Detox™ (Melacine®) + interferon alpha</th>
<th>Interferon alpha</th>
<th>No survival advantage but fewer adverse events in patients on vaccine</th>
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<td>Testori et al., 2008 (14)</td>
<td>Stage IV n=322</td>
<td>Heat shock protein gp96 complex vaccine (Oncophage®)</td>
<td>Physician’s choice of dacarbazine, temozolomide, IL-2 and/or resection</td>
<td>No survival advantage in patients on vaccine</td>
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<tr>
<td>Schadendorf et al., 2006 (16)</td>
<td>Stage IV n=108</td>
<td>Peptide-pulsed dendritic cells</td>
<td>Dacarbazine</td>
<td>Trial closed after interim analysis showed lack of efficacy</td>
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<td>Hodi et al., 2010 (17)</td>
<td>Stage III or IV n=676</td>
<td>Ipilimumab alone or with GP100</td>
<td>GP100 peptide alone</td>
<td>Ipilimumab showed improved overall survival with or without GP100 compared to GP100 treatment alone</td>
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<tr>
<td>Schwarzentruber et al., 2011 (18)</td>
<td>Stage III/IV n=185</td>
<td>GP100 peptide + IL2</td>
<td>High-dose IL2</td>
<td>Objective response and increased in patients on vaccine and IL2 treatment</td>
</tr>
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</table>

**Medicare National Coverage**

There is no National Coverage determination.

**References**


16. Schadendorf D, Ugurel S, Schuler-Thurner B et al. Dacarbazine (DTIC) versus vaccination with autologous peptide-pulsed dendritic cells (DC) in first-line treatment of patients with


**Policy History**

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<td>Update Policy</td>
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<td>September 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search. Reference 23 added; no change to policy statement.</td>
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**Keywords**

Melanoma Vaccine  
Vaccine, Melanoma  
Vaccine, Tumor

This policy was approved by the FEP Pharmacy and Medical Policy Committee on September 12, 2014 and is effective October 15, 2014.

**Signature on File**

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