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. A wide range of vaccine types 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.

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 target for vaccine treatments 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 (eg, 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 (eg, Oncophage®, 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 (eg, 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 (eg, melanoma antigen E [MAGE]; B Melanoma antigen [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 (eg 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 marketing 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 BCBSA 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) At that time, the literature contained hundreds of publications on this treatment, but only a few reports of phase 3 clinical trials. 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 1 or 2 studies of melanoma vaccines (Canvaxin®, Melacine®) have not been replicated in subsequent phase 2 or 3 studies. (4)

In 2004, Rosenberg et al noted that looking at the experience of the National Cancer Institute’s Surgery Branch in evaluating 450 patients treated for metastatic cancer with vaccines, (422 with metastatic melanoma), a positive treatment response occurred in 2.6%. (6) Further a review of 35 carefully selected representative reports from the literature (one-third in melanoma patients) involving 765 patients showed and overall 3.8% objective response rate to this treatment.
Rosenberg et al 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. (6) He proposed the use of mechanisms to increase the yield and activity of CD4+ cells and to eliminate-tumor induced or normally occurring lymphocyte-mediated immune suppressive mechanisms.

Although more than 1700 publications on melanoma vaccine use in both animals and humans have appeared since the 2001 TEC Special Report, only 12 phase 3 clinical studies evaluated melanoma vaccines: 4 using allogeneic vaccines, 2 autologous whole-cell vaccines, 2 ganglioside vaccines, 1 autologous heat shock protein, and 3 peptide vaccines—1 pulsed with dendritic cells, 1 administered with ipilimumab, and 1 administered with concomitant IL-2. In 2 studies, vaccine treatments appeared to demonstrate superior performance in unique populations identified during post hoc data evaluation. (7, 10) However, no published study to date has shown a statistically significant survival benefit in the general population selected for study. In 2 reports, outcomes using vaccines appeared inferior to those observed in controls. (9, 12) Table 1 provides a summary of trials that showed lack of efficacy of melanoma vaccines.

In a 2011 systematic review and meta-analysis of 4375 patients in 56 phase 2 and phase 3 studies, no evidence was found that vaccine therapy yields better overall disease control or OS 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 3 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 3 trivalent vaccine prepared using 3 peptides (gp100, MART-1/Melan, tyrosine HLA-A2). Preliminary reports suggest patients who develop antibodies to any of the 3 peptides had insignificantly improved survival. More definitive results from both studies are pending.

Several explanations have been offered as to why melanoma vaccines have not produced clinically significant improvements in clinical 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.

In 2011, Gajewski published a preliminary report on the use of molecular profiling to identify relevant immune resistance in the tumor microenvironment. (22) If confirmed in future studies, this approach toward identifying subsets of patients likely to benefit from specific treatment choices may help improve treatment outcomes with the use of tumor vaccines.
### Table 1. Phase 3 Randomized Controlled 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>
</tr>
</thead>
<tbody>
<tr>
<td>Livingston et al (1994)</td>
<td>Stage III (N=122)</td>
<td>GM2/BCG</td>
<td>BCG</td>
<td>DFS and OS showed no statistically significant differences</td>
<td>Patients with no pretreatment anti-GM2 antibody showed improved PFS with vaccine</td>
</tr>
<tr>
<td>Wallack et al (1998)</td>
<td>Stage III (N=217)</td>
<td>Vaccinia melanoma oncolysate</td>
<td>Vaccinia oncolysate from normal cell</td>
<td>DFS and OS showed no statistically significant differences</td>
<td></td>
</tr>
<tr>
<td>Sondak et al (2002)</td>
<td>Stage II (N=600)</td>
<td>Allogeneic melanoma vaccine (Melacine®)</td>
<td>Observation</td>
<td>No evidence of DFS</td>
<td></td>
</tr>
<tr>
<td>Hersey et al (2002)</td>
<td>Stage III/II (N=700)</td>
<td>Vaccinia melanoma oncolysate</td>
<td>Observation</td>
<td>Recurrence-free and OS not statistically improved in vaccine patients</td>
<td></td>
</tr>
<tr>
<td>Morton et al (2006)</td>
<td>Stage III (N=1160)</td>
<td>Canvaxin® + BCG + placebo</td>
<td>BCG + placebo</td>
<td>Trial closed after interim analysis indicated Canvaxin® inferiority</td>
<td></td>
</tr>
<tr>
<td>Morton et al (2006)</td>
<td>Stage IV (N=496)</td>
<td>Canvaxin® + BCG + placebo</td>
<td>BCG + placebo</td>
<td>Trial closed after interim analysis showed lack of efficacy</td>
<td></td>
</tr>
<tr>
<td>Mitchell et al (2007)</td>
<td>Stage III (N=604)</td>
<td>Allogeneic whole-cell lysate administered with Detox™ (Melacine®) + interferon alfa</td>
<td>Interferon alfa</td>
<td>No survival advantage but fewer adverse events in patients on vaccine</td>
<td></td>
</tr>
<tr>
<td>Testori et al (2008)</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>
<td></td>
</tr>
<tr>
<td>Schadendorf et al (2006)</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>
<td></td>
</tr>
<tr>
<td>Hodi et al (2010)</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 OS with or without GP100 vs GP100 treatment alone</td>
<td></td>
</tr>
<tr>
<td>Schwarzentruber et al (2011)</td>
<td>Stage III/IV (N=185)</td>
<td>GP100 peptide + IL-2</td>
<td>High-dose IL-2</td>
<td>Objective response and increased in patients on vaccine and IL-2 treatment</td>
<td></td>
</tr>
</tbody>
</table>

BGS: bacille Calmette-Guérin; DFS: disease-free survival; GMK: guanylate kinase; HLA: human leukocyte antigen; IL-2: interleukin-2; OS: overall survival.

No new phase 3 RCT evidence has been published in the period since the last evidence review for this Policy. In recent single-arm series, combinations of immunotherapeutic agents (nivolumab, pegylated interferon) and study vaccines have been investigated in patients with unresectable or resected stage III and IV malignant melanoma. (23-25) Results from these studies suggest combined immunotherapeutic approaches are tolerable and may have clinical efficacy reflected by tumor regression. However, no valid conclusions can be drawn from this evidence as to the effectiveness of the combinations relative to other treatments.
A randomized, phase 2 clinical trial published in 2014 evaluated the activity of interleukin-2 (IL-2) alone or IL-2 in combination with allogeneic large multivalent immunogen (LMI) vaccine in patients with stage IV melanoma. (26) The primary objective of this trial was to evaluate the effect of the treatments on progression-free survival (PFS), with a secondary objective to evaluate median OS and 1- and 2-years rates of OS. The study was halted after enrolling 21 patients after a preplanned analysis established that it was unlikely to meet its primary objective of improved PFS with additional accrual. Per-protocol analysis of data from the 21 accrued patients showed median PFS of 2.20 months in the IL-2 plus LMI group versus 1.95 months in the IL-2 controls (p=NS). Median OS was 11.89 months in the IL-2 plus LMI group and 9.97 months in the IL-2 group (p=NS).

Ongoing Clinical Trials

Ongoing clinical trials that might influence this policy are listed in Table 2.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01546571</td>
<td>A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients With a High Risk of Recurrence (MAVIS)</td>
<td>1059</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT01729663</td>
<td>Randomized, Comparative Phase II/III Study Between Treatment With CSF470 Vaccine (Allogeneic, Irradiated) Plus BCG and MOLGRAMOSTIN (rhGM-CSF) as Adjuvants and Interferon-alfa 2b (IFN-ALPHA), in Stages IIB, IIC and III Post Surgery Cutaneous Melanoma Patients</td>
<td>108</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network guidelines on the treatment of melanoma (v.3.2015) do not reference the use of vaccines in clinical trials in any of its treatment algorithms. (27) The guidelines do discuss clinical trials that have reported inferiority in melanoma vaccine treatment arms.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary

The evidence for melanoma vaccines in patients who have stage II-IV melanoma is 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 activity in numerous studies over the past 20 years, no melanoma vaccine has received U.S. Food and Drug Administration marketing approval. One randomized controlled trial (RCT) of a gp100 melanoma vaccine has reported a significant increase in response rate and progression-free survival. However, several other RCTs have reported no improvements in disease-free survival or overall survival rates with the use of study vaccines. Additionally, other RCTs were closed early due to inferiority of results with study vaccines.
Other phase 3 RCTs are underway or in the planning stages to further investigate vaccine preparations to treat malignant melanoma. For use of melanoma vaccines for treatment of patients with stage II-IV melanoma, the body of evidence is insufficient to conclude that antimelanoma vaccines of any type alone or in combination with immunomodulating agents significantly improve survival outcomes compared with nonvaccine therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Medicare National Coverage**

There is no national coverage determination (NCD).

**References**


