



# Louisiana

## Melanoma Vaccines

**Policy #** 00368

Original Effective Date: 06/25/2013

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## Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers melanoma vaccines to be **investigational**.\*

## Background/Overview

Vaccines using crude preparations of tumor material were first studied by Ehrlich over 100 years ago. However, the first modern report to suggest benefit in cancer patients did not appear until 1967. Melanoma has been viewed as a particularly promising target for vaccine 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. Melanoma vaccines can be generally categorized or prepared in the following ways:

- Whole-cell vaccines prepared using melanoma cells or crude subcellular 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<sup>®</sup>‡, 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<sup>®</sup>‡, 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

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used to prepare vaccine (eg, Canvaxin<sup>®</sup>‡, CancerVax Corp.; or Melacine<sup>®</sup>‡, 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-idiotypic vaccines made from monoclonal antibodies with specificity for tumor antigen-reactive antibodies.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

At the present time, no melanoma vaccine has received marketing approval from the U.S. FDA.

### **Centers for Medicare and Medicaid Services (CMS)**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

## **Rationale/Source**

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 overall survival (OS) compared with other treatments. Currently, there are 12 phase 3 clinical studies that have 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

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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. 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. Table 1 provides a summary of trials that showed lack of efficacy of melanoma vaccines.

Several explanations have been offered as to why melanoma vaccines have not produced clinically significant improvements in clinical outcomes. 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. One potential solution to this problem is to use molecular profiling to identify relevant immune resistance in the tumor microenvironment. 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

Author	Patient Population	Vaccine	Control	Results	Comment
Livingston et al (1994)	Stage III (N=122)	GM2/BCG	BCG	DFS and OS showed no statistically significant differences	Patients with no pretreatment anti-GM2 antibody showed improved PFS with vaccine
Wallack et al (1998)	Stage III (N=217)	Vaccinia melanoma oncolysate	Vaccinia oncolysate from normal cell	DFS and OS showed no statistically significant differences	
Kirkwood et al (2001)	Stage IIB/III (N=774)	Ganglioside GM2-KLH21 (GMK)	Interferon alfa	Trial closed after interim analysis indicated GMK inferiority	

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Sondak et al (2002)	Stage II (N=600)	Allogeneic melanoma vaccine (Melacine®)	Observation	No evidence of DFS	Patients with ≥2 HLA matches showed improved PFS
Hersey et al (2002)	Stage IIB/III (N=700)	Vaccinia melanoma oncolysate	Observation	Recurrence-free and OS not statistically improved in vaccine patients	
Morton et al (2006)	Stage III (N=1160)	Canvaxin® + BCG + placebo	BCG + placebo	Trial closed after interim analysis indicated Canvaxin® inferiority	
Morton et al (2006)	Stage IV (N=496)	Canvaxin® + BCG + placebo	BCG + placebo	Trial closed after interim analysis showed lack of efficacy	
Mitchell et al (2007)	Stage III (N=604)	Allogeneic whole-cell lysate administered with Detox™ (Melacine®) + interferon alfa	Interferon alfa	No survival advantage but fewer adverse events in patients on vaccine	
Testori et al (2008)	Stage IV (N=322)	Heat shock protein gp96 complex vaccine (Oncophage®)	Physician's choice of dacarbazine, temozolomide, IL-2, and/or resection	No survival advantage in patients on vaccine	
Schadendorf et al (2006)	Stage IV (N=108)	Peptide-pulsed dendritic cells	Dacarbazine	Trial closed after interim analysis showed lack of efficacy	
Hodi et al (2010)	Stage III or IV (N=676)	Ipilimumab alone or with GP100	GP100 peptide alone	Ipilimumab showed improved OS with or without GP100 vs GP100 treatment alone	
Schwarzentruber et al (2011)	Stage III/IV (N=185)	GP100 peptide + IL-2	High-dose IL-2	Objective response and increased in patients on vaccine and IL-2 treatment	

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

In single-arm series published in 2013-2015, 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. 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.

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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. 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 and Unpublished Clinical Trials

A search of the online site [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) in June 2015 identified a number of small phase 2 trials. Ongoing phase 3 clinical trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01546571 <sup>a</sup>	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)	1059	Oct 2018
NCT01729663	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	108	Not provided

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

### Summary of Evidence

The evidence for melanoma vaccines in patients who have stage II-IV melanoma includes studies on the use of new and different vaccine preparations, as well as on various forms of immune-



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modulation as potential techniques for enhancing vaccine effectiveness. Relevant outcomes include overall survival, disease-specific survival, and morbid events. Despite considerable activity and numerous studies over the past 20 years, no melanoma vaccine has received U.S. FDA marketing approval. One 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 anti-melanoma vaccines of any type, alone or in combination with immunomodulating agents, significantly improve survival outcomes compared with non-vaccine therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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- with high-dose IL-2 alone in patients with metastatic melanoma. A Phase III multi-institutions randomized study of immunization with the gp100.209-217 (210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma. 2009 ASCO Annual Meeting. 2009. PMID
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### **Policy History**

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06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. New policy.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2018	Medical Policy Committee review. Recommend archiving policy.
06/20/2018	Medical Policy Implementation Committee approval. Archived
03/07/2019	Medical Policy Committee review.
03/20/2019	Medical Policy Implementation Committee approval. Brought back to active status.
03/05/2020	Medical Policy Committee review.
03/11/2020	Medical Policy Implementation Committee approval. No change to coverage.
03/04/2021	Medical Policy Committee review.
03/10/2021	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2022

### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	86849
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

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