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Update on Vaccines for High-Risk Melanoma

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Opinion statement

The management of high-risk melanoma has historically included primary surgical resection with or without lymphadenectomy followed by an array of adjuvant options including radiation therapy or immunomodulatory therapies such as interferon-α, granulocyte macrophage colony-stimulating factor, and a multitude of vaccines. There has been a long-standing interest in the development of vaccines in high-risk and metastatic melanoma, and clinical trials have been ongoing for decades. Given that melanoma is identified as one of the most immunogenic solid tumors, there is continued hope that vaccine therapies will improve clinical outcomes. Despite intense interest in this field, few clinical trials to-date have demonstrated significant benefit from melanoma vaccines in high-risk disease. Several trials have even documented a detrimental effect on outcomes after vaccine administration. While the role of vaccines in the adjuvant setting of high-risk melanoma presently remains unclear, recent advances in immunotherapy for melanoma including development of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) monoclonal antibodies have demonstrated meaningful clinical responses. With further study and focus on mechanisms of immune regulation, there remains promise for the role of vaccines in combination with other immune-stimulatory agents in high-risk melanoma.

Introduction

Epidemiology

Malignant melanoma is rising in incidence. In 2012 it was projected that an estimated 76,250 new cases would be diagnosed, resulting in over 9000 deaths [1, 2]. The lifetime risk of developing melanoma may be as high as 1 in 55 in the United States

[3]. The prognosis of melanoma is dependent on the stage at presentation, with 5-year survival rates approximately 90 % in localized disease, 20 %–70 % in regional nodal involvement, and less than 10 % in metastatic disease [4]. High-risk melanoma includes American Joint Committee on Cancer TNM stages II–III, encompassing patients without nodal disease but with primary tumor thickness greater than 1 mm or patients with regional lymph node metastasis, as well as completely resected stage IV melanoma.

Current Treatment Options

Management of high-risk melanoma involves primary surgical resection with or without lymphadenectomy. Historically, adjuvant treatments have included a variety of options such as regional radiotherapy or systemic immunostimulatory therapies including interferon-α, vaccines, and granulocyte macrophage colony-stimulating factor (GM-CSF) [5]. Outside of enrollment on a clinical trial, interferon-α is presently the only FDA approved drug option for both stage II and III melanoma, and peg-interferon-alfa is approved for stage III melanoma. Although they improve relapse free survival, there is no overall survival benefit and toxicities can be significant [6, 7]. Thus, there is an ongoing urgency to develop therapies that can reduce disease recurrence in this high-risk population.

Immunogenicity of Melanoma

Melanoma is known as one of the most immunogenic cancers and can elicit a robust immunologic response. Evidence to support melanoma's immunogenic properties include (1) the absence of a primary melanoma in 5 % of patients with metastatic melanoma suggesting that the primary melanoma underwent an immune-mediated regression, (2) the finding of lymphocytes within the tumor microenvironment, (3) reports of sporadic spontaneous regression of metastatic tumors, and (4) regression of metastatic tumors in response to IL-2 and anti-CTLA-4 immune modulation [8].

Vaccine Development in Melanoma

Vaccines are a type of active immunization designed to recognize tumor-associated antigens, thereby giving them specificity to tumor cells, sparing nontumor cells, and resulting in an immune response. Vaccines have been extensively studied in melanoma clinical trials for decades. Multiple different vaccine approaches have been used in the adjuvant treatment of high-risk melanoma with the goal of harnessing the immune system to fight the presence of micrometastatic tumor cells.

Tumor-associated antigens are proteins overexpressed by tumor cells that can be used as targets for vaccine-induced immune responses. The classes of tumor-associated antigens include differentiation antigens, cancer-testis antigens, antigens with specific mutations, and viral antigens. Antigens are delivered in numerous forms including as peptides, proteins, recombinant viruses, and by loading the antigen onto dendritic cells, which serve as powerful antigen presenting cells [9, 10]. Immunologic adjuvants including Bacillus Calmette–Guérin (BCG), toll-like receptor (TLR) agonists, cytokines such as GM-CSF and IL-2, Montanide emulsions, and others are usually added to boost the chances of vaccine immunogenicity.

Protein and peptide vaccines consisting of a particular tumor-associated antigen have not been successful in eliciting vigorous immune responses and usually require coupling with an adjuvant. In addition, these vaccines have the disadvantage of requiring patients to have the correct HLA haplotype that matches with the protein or peptide's binding [9, 10]. Recombinant vector-based vaccines are another strategy of administration that incorporates gene segments into viral vectors. A third approach are whole cell-based vaccines that are either autologous, using the patient's actual tumor, or allogeneic, using cell lines or other patient's tumors, to prepare the vaccine [10].

Although trials of melanoma vaccines in the adjuvant setting have shown tolerability and safety, there has been little to no evidence suggesting significant clinical benefit. More recently, trials are also directly measuring the magnitude of patients' immune response to vaccine therapy to better understand their immunologic impact [11].

Treatment

Differentiation Antigens as Peptide Vaccines

The most well-studied tumor-associated antigens are differentiation antigens, which in melanoma include Melan-A/MART-1, gp100, tyrosinase, tyrosinase-related protein-1 (trp-1), and tyrosinase-related protein-2 (trp-2) [10, 12, 13]. Vaccines often combine multiple peptide antigens aided by adjuvants.

GM-CSF Alone and as an Adjuvant to Vaccines Targeting Differentiation Antigens

GM-CSF is a cytokine and amongst its' numerous functions, stimulates dendritic cells to present antigen to naïve T cells.

A phase II trial studied GM-CSF in the adjuvant setting, in which 48 patients with resected stage III-IV melanoma at high risk of recurrence received GM-CSF for 14 days in a 28-day cycle for 1 year or until disease recurrence. When matched to historical controls, overall survival (OS) and disease-free survival (DFS) was prolonged in patients who received GM-CSF, with median survival duration of 37.5 vs 12.2 months ($P<0.001$). One patient experienced an adverse event of a grade 2 injection site reaction [14].

Similarly, a phase III trial enrolling 735 patients with completely resected stage IIIB, IIIC, IV were randomized to GM-CSF 250 mcg or placebo SC daily for 14 days followed by every 28 days for 1 year. Median OS was 72.1 months in the GM-CSF group and 59.8 months for the placebo group but this did not reach statistical significance. Median DFS, however, was significantly improved in the GM-CSF arm at 11.8 months vs 8.8 months in the placebo group ($P=0.034$) [15]

In another phase II trial, 26 patients were randomly assigned to vaccination with dendritic cells (DCs) pulsed with peptides alone or to peptides in adjuvant plus GM-CSF. The peptides were a mixture of 4 gp100 and tyrosinase peptides that were HLA-restricted, with a tetanus helper peptide. The adjuvants Montanide ISA-51 and low-dose IL-2 were administered to both groups. T cell responses were measured in peripheral blood lymphocytes (PBL), as well as in the lymph node draining a vaccine site, ie, the sentinel immunized node (SIN). There were greater T cell responses seen in the PBLs and SINs in the GM-CSF vaccination arm vs the DC arm (42 % vs 11 % in PBLs and 80 % vs 13 % in SINs). An objective clinical response was seen in 2 patients in the GM-CSF arm, and in 1 patient in the DC arm, with a higher immune response that was statistically significant in the GM-CSF arm ($P<0.02$). Stable disease was noted in 2 patients in the GM-CSF arm, and in 1 patient in the DC arm. It appeared that vaccination with the HLA-restricted peptides led to the expansion of peptide-specific immune responses, and was associated with some clinical tumor regression [16].

Another phase II trial was initiated, in which 121 patients were vaccinated with peptides with or without GM-CSF in a vaccine emulsion to investigate whether the addition of GM-CSF to vaccine would increase immunogenicity [16]. Patients with stage IIB to IV melanoma were vaccinated with 12 MHC class I-restricted melanoma peptides to stimulate CD8+ T cells with an HLA-restricted tetanus helper peptide to stimulate CD4+ T cells, emulsified in incomplete Freund's adjuvant, with or without GM-CSF. T cell responses to the melanoma peptides with or without GM-CSF were seen in 34 % vs 73 % ($P<0.001$). Furthermore, given that CD4+ T cell responses to tetanus helper peptide were higher without addition of GM-CSF (95 % vs 77 %, $P=0.005$), it is unclear whether the addition of GM-CSF as a vaccine adjuvant in humans has any clinical benefit [17].

Most recently, a pilot study of a multi-peptide melanoma vaccine including MART-1a, gp100, and surviving antigens administered to HLA-A2-positive patients with completely resected stage II, III, or IV melanoma. The trial studied whether the addition of GM-CSF and/or IL-2 as adjuvants is safe and if these cytokines can improve the immunologic response to the vaccine. The arms of the study included 5 patients enrolled in the vaccine plus GM-CSF 300 mcg group, 5 patients in the vaccine plus GM-CSF 300 mcg plus IL-2 group, 4 patients in the vaccine plus GM-CSF 500 mcg group, and 5 patients in the vaccine plus GM-CSF 500 mcg plus IL-2 group. The vaccine was given on day 1 and IL-2 was given on days 7–20 of a 21-day cycle for a goal of 4 total cycles. Two patients had an immune response to only 1 peptide and 6 patients had an immune response to all 3 peptides. The majority of patients demonstrated cytotoxic T lymphocyte responses to the 3 peptide vaccine, but responses were at a frequency of less than 0.5 % of CD8 T cells. The addition of IL-2 did not appear to make a difference in the frequency of cytotoxic T-lymphocyte responses; however, IL-2 treatment did increase NK cells and T regulatory cells. Increasing the dose of GM-CSF beyond 300 mcg did not improve immune responses. For these reasons the authors concluded that there is not a benefit of the addition of IL-2 or high dose GM-CSF in future vaccine trials [18].

Differentiation Antigens with a Chemotherapy Adjuvant

A randomized multicenter trial of 167 resected stage IIB-IV melanoma patients studied whether melanoma-associated helper peptides could improve CD8+ T-cell responses to a melanoma vaccine and if cyclophosphamide pretreatment could improve the CD4+ or CD8+ T-cell responses. Patients were randomly assigned to receive or not receive pretreatment with cyclophosphamide and then were vaccinated with 12 class I major histocompatibility complex-restricted melanoma peptides (12MP). This was followed by randomized administration of either tetanus helper peptide (MELITAC 12.1) or a mixture of 6 melanoma-associated helper peptides (6MHP). The primary endpoint was the maximum cumulative circulating CD8+ T cell response to 12MP over the first 6 vaccines, which was assayed using ELISpot. Adding 6MHP to

12MP actually decreased CD8+ T-cell responses (P <0.001) when compared with addition of the MELITAC 12.1 vaccination, which was unexpected because previously studied 6MHP vaccination induced Th1-dominant responses. Reasons for the paradoxical decrease in CD8+ T-cell responses may be that T regulatory cells were induced, increased T-cell homing to tumor sites, or T-cell sequestration at the vaccine site. Additionally, cyclophosphamide did not improve CD4+ or CD8+ T-cell responses or clinical outcome [19].

Differentiation Antigens and Immunotherapy

There is continued interest in combining intravenous immunotherapies with vaccines. A phase I study reported in a 2013 ASCO Abstract combined nivolumab, a monoclonal antibody against programmed death-1 (PD-1), with a multi-peptide vaccine of HMB-45, NY-ESO-1, MART-1, and Montanide ISA 51 VG in 33 patients with resected stage IIIC and IV HLA-A*0201 positive melanoma. Nivolumab at doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg were administered with the multi-peptide vaccine every 2 weeks for 12 doses followed by nivolumab maintenance every 3 months for 8 doses or until disease recurrence. This combination therapy was well-tolerated. All patients had an increase in T regulatory cells (P=0.015). Seven out of 33 patients have relapsed thus far, but the nonrelapsing patients had higher pre-treatment PD-1 expression on CD4+ and CD8+ T cells and a greater increase in T regulatory cells after 12 weeks on treatment (P=0.027) [20•].

Differentiation Antigens and Toll-Like Receptors (TLR) as Immunologic Adjuvants

Another trial reported in a 2013 ASCO abstract, NCT01585350, is also studying the effect of TLR agonists (TLR3 agonist polyICLC and TLR4 agonist endotoxin) at augmenting responses to a peptide vaccine with or without incomplete Freund's adjuvant (IFA), the most common peptide vaccine adjuvant. The trial is enrolling resected stage IIB–IV melanoma patients who will receive 12 class I MHC-restricted melanoma peptides in a vaccine administered 6 times over 12 weeks along with a tetanus helper peptide and either of the 2 toll-like receptor agonists, with or without the IFA adjuvant. The study is ongoing but aims to evaluate the safety of these adjuvants and to measure the immune response within the vaccine site microenvironment and the persistence of CD4+ and CD8+ T-cell responses [21].

Cancer Testis/Germline Antigens

Cancer-testis antigens are expressed only on tumor cells and normal testicular tissue (an immune-privileged site) and in melanoma include MAGE-A3, NY-ESO-1, and PRAME. They are thought to be better vaccine targets than differentiation antigens because of their tumor-specific expression and therefore less peripheral immune tolerance [10, 12, 13].

MAGE-A3

MAGE-A3 is a cancer testis antigen that is overexpressed in an estimated 70 % of melanomas [22].

Recombinant protein vaccines such as recombinant MAGE-A3 have the advantage of targeting multiple epitopes and thereby elicit a wider range of CD4+ and CD8+ immune responses, and can also be applied to a larger patient population because they do not require specific HLA types [22]. The majority of MAGE-A3 vaccines studied in melanoma have been in the advanced and/or metastatic setting rather than the adjuvant setting.

A phase 1/2 study of 32 patients with metastatic melanoma given recombinant MAGE-A3 protein by subcutaneous and intradermal administration showed low toxicity, but only a very modest clinical response. Among 26 patients, there was 1 partial response and 4 mixed responses, with a time to progression ranging from 3.5 months to greater than 51 months. One out of the 5 responders had an anti-MAGE-3 CD4 T-lymphocyte response [23].

A phase II study was designed to assess if the immunostimulants AS02B (QS21 saponin combined with a TLR-4 agonist) or AS15 (QS21 saponin, monophosphoryl lipid A, and CpG7909, a TLR-9 agonist) when added to MAGE-3, could induce a more robust immunologic response and lead to improved clinical outcomes than MAGE-3 alone. Thirty-six patients with MAGE-A3–positive, stage III in-transit or unresectable stage III–IV melanoma were enrolled. Four responses were seen in the AS15 arm and 1 partial response in the AS02B arm. Six month PFS rates were 25 % and 14 % and median OS over 48 month median follow-up was 33 months and 19.9 months, in the AS15 and AS02B arms, respectively. MAGE-A3 antibody titers were 3-fold higher in the AS15 arm, where the addition of CpG7909 was thought to enhance T-cell responses and increase numbers of activated DCs and has led to consideration of AS15 to be studied in additional trials [24].

Based on the previous trials in metastatic melanoma, a phase III randomized, placebo-controlled trial known as the DERMA trial was conducted in MAGE-A3 positive, resected stage IIIB/C melanoma patients who were randomized in a 2 to 1 ratio to receive recombinant MAGE-A3 vaccine with AS15 adjuvant vs placebo. MAGE-A3 vaccine administered as 5 doses in 3 week intervals as induction therapy followed by 8 doses in 3 month intervals as maintenance therapy did not significantly extend DFS, the primary endpoint, when compared with placebo [25, 26••].

NY-ESO-1

NY-ESO-1 is expressed in an estimated 45 % of melanomas [27].

LUD99-008 was a placebo-controlled phase I trial that studied an NY-ESO-1 protein vaccine formulated with the saponin-based adjuvant ISCOMATRIX given to 46 patients with completely resected NY-ESO-1 positive tumors, of whom 42 had melanoma. The vaccine and adjuvant were found to be safe and capable of inducing measurable immunity [28].

A follow-up study LUD01-017 then assessed the persistence of antigen-specific immunity in 28 eligible patients who were previously vaccinated in LUD99-008 and recruited for follow-up. Out of the 14 patients that previously received NY-ESO-1 plus ISCOMATRIX adjuvant, 10 had persistent anti-NY-ESO-1 immunity, compared with only 3 out of 14 patients who

received NY-ESO-1 vaccine without the adjuvant ISCOMATRIX administration (P=0.02) [29].

A phase II trial (LUD2003-009) of NY-ESO-1 ISCOMATRIX vaccine vs ISCOMATRIX adjuvant alone was subsequently conducted in patients with NY-ESO-1 antigen-positive fully resected stage IIC, IIIB, IIIC, or IV melanoma to see if the vaccine improves RFS rates at 18 months. The trial has been completed and results are pending [30].

Resiquimod is a TLR 7/8 agonist that has been used as a vaccine adjuvant and improves immunogenicity by increasing cytokine production, activating immune cells, and inducing dendritic cell antigen presentation. In a recent phase I study reported as an ASCO Abstract in 2012, an NY-ESO-1 vaccine with resiquimod was administered with either a topical resiquimod gel or a placebo gel in 26 resected stage IIB–IV melanoma patients. Overall the combination was found to be safe with no grade 4 adverse events, 1 grade 3 injection site necrosis, and other milder toxicities including injection site reactions and flu-like symptoms [31].

Cell Surface Glycolipids

Cell surface glycolipids are another class of melanoma tumor antigens that include gangliosides GD3 and GM2 [12].

In a 1994 study of stage III melanoma patients receiving adjuvant GM2-BCG vaccine vs BCG alone, there was no difference found in DFS [32].

To further investigate the role of a GM2 vaccine, EORTC 18961, a phase III trial studied the efficacy of the adjuvant ganglioside GM2-KLH/QS-21 vaccine for 3 years vs observation in 1314 resected stage II melanoma patients. RFS was the primary outcome and OS was the secondary outcome. However, the trial was closed early at the second interim analysis for failure to show a treatment difference and because there was a trend toward decreased OS in the vaccine group [33•].

Tumor Cell-Derived Antigens

Vaccines using cell-derived antigens may be more effective than using molecularly-defined antigens; however, adjuvants are still needed in order to generate sufficient immune responses [12, 34].

Allogeneic Tumor Vaccines

Canvaxin is an allogeneic, living whole-cell melanoma vaccine comprised of three different melanoma cell lines that express 20 tumor antigens and is associated with BCG as adjuvant [35].

In a phase II study of 2602 stage III melanoma patients who underwent lymphadenectomy, 935 received Canvaxin and 1667 did not. Five-year OS for the vaccine group vs the nonvaccine group was 49 % vs 37 %, respectively, (P<.0001) [36].

OS outcomes were studied amongst 263 patients with completely resected stage IV melanoma who were enrolled onto 1 of 5 phase II protocols of adjuvant Canvaxin vaccine, comprised of 150 patients who received

adjuvant Canvaxin and 113 patients who did not. Five-year OS rates were 39 % in the vaccine group vs 19 % in the control group. In the vaccine group, there was a statistically significant delayed-type hypersensitivity response that correlated with survival [37].

Additionally, a phase II trial of Canvaxin plus BCG evaluated the prognostic impact of TA90, a tumor-associated antigen that is expressed on most melanoma cells and may be a marker of disease burden [38]. In 219 patients with resected stage II–IV melanoma, 51 patients had positive TA90 immune complex prior to Canvaxin therapy. After vaccination, all 51 patients remained positive, 79 additional patients seroconverted to positive, and 89 negative patients remained negative. Seroconverters, in comparison with those who remained negative after vaccination, had increased 2-year DFS (59 % vs 32 %, P <0.006) and OS rates (78 % vs 63 %, P <0.02) [39].

However, the 2 large randomized, double-blinded, placebo-controlled Phase III trials evaluating Canvaxin plus BCG vs placebo plus BCG for completely resected stage III (1166 patients) and IV (496 patients) melanoma were discontinued prematurely after the data and safety monitoring board determined that statistically different survival outcomes between the 2 groups would not be reached. Administration of Canvaxin resulted in a survival disadvantage. In the stage III study, 5-year OS was 59 % vs 68 % for Canvaxin vs placebo, respectively. In the resected stage IV study, median survival was 32 months vs 39 months and OS was 40 % vs 45 % for Canvaxin vs placebo, respectively, [40, 41•, 42].

The first report of an adjuvant allogeneic gene-modified melanoma vaccine was recently published in 2012. Two phase II trials studied the efficacy and toxicity of the Hyper-IL-6 (H6) gene-modified whole-cell allogeneic melanoma vaccine as adjuvant therapy in resected stage IIIB, IIIC, and IV melanoma. The phase II trial "Trial 3," enrolled 97 patients and evaluated the efficacy of Hyper-IL-6 in patients with resected melanoma. The other phase II trial "Trial 5" enrolled 99 patients using Hyper-IL-6 with the addition of GM-CSF. The vaccine was administered 8 times over 2 week intervals as induction therapy and then monthly as maintenance therapy until death. Vaccine administration was continued at disease progression, in some cases with re-induction. The median follow-up was 10.5 and 6.2 years in trials 3 and 5, respectively. Overall 5-year survival for trials 3 and 5 were 66.7 % and 56.3 % for stage IIIB, 43.8 % and 39.8 % for stage IIIC, and 26.1 % and 41.2 % for stage IV, respectively. These studies show a DFS and OS survival advantage when compared with nontreated historical controls from three other previously conducted randomized clinical trials [43•].

Dendritic Cell-Based Vaccines

Dendritic cells can prime naïve T-cells and have been used in conjunction with tumor antigens in vaccines to elicit an immune response with the goal of protective immunity in resected high-risk melanoma patients.

In a recent 2012 study, 44 high-risk stage III melanoma patients postlymph node dissection were treated with an adjuvant dendritic cell vaccine loaded with MHC-class-I-restricted melanoma peptides matched to each patient's haplotype and patients were matched to unvaccinated stage III controls. Three-year DFS rate was 40.9 % in the vaccinated group vs 14.5 % in the control group (P= 0.1083) and 3-year OS rate was 68.2 % in the vaccinated group vs 25.7 % in the control group (P=0.0290). Eight (36.4 %) of the vaccinated patients were free from disease after 85 months median follow-up [44].

Adjuvant dendritic cell vaccine therapy vs observation was studied in 108 resected stage III and IV melanoma patients as reported in a recent 2012 ASCO Abstract. The vaccine was an autologous monocyte-derived dendritic cell primed with autologous tumor lysate that was administered to 56 patients every 2–6 weeks until disease progression vs 52 patients in the control group. Median follow-up was 22 months. Toxicity was minimal. The DFS hazard ratio was 0.45 (P <0.05) and the OS hazard ratio was 0.71 (P=0.23), demonstrating significant DFS improvement in the dendritic cell vaccine group [45].

Viruses

Viruses that are engineered to replicate only in tumor cells result in lysis of the cells and are known as oncolytic viruses.

The ICP34.5 gene deleted herpes simplex virus (HSV) results in tumor selectivity. A phase I trial studied an oncolytic HSV expressing GM-CSF in 30 patients with various tumor types including melanoma, breast, and colorectal cancer in escalating and multi-dose regimens. The insertion of GM-CSF is thought to enhance the immune response to virus replication and the resulting release of tumor antigens. All patients who were seronegative for HSV all seroconverted approximately 3–4 weeks post injection. All seropositive patients had increased levels of anti-HSV antibodies. There were no complete or partial responses, but three patients had stable disease [46].

A subsequent phase II trial studied the oncolytic HSV-type 1 expressing GM-CSF, in which 50 patients including previously treated ones, with stage IIIC and IV disease, were treated with intratumoral injections every 2 weeks for up to 24 treatments. The overall response rate was 26 %, including 8 patients who had a CR, and 5 patients who had a PR, with regressions seen in injected and noninjected (including visceral) lesions suggesting a direct intratumoral effect as well as a distal immune-mediated anti-tumor response. About 92 % of patients experienced a response that lasted for 7–31 months, with 58 % experiencing a one-year OS, and 52 % with two-year OS rates [47].

Based on the phase I and II data, a randomized prospective phase III trial termed OPTIM (Oncovex Pivotal Trial in Melanoma) studied 436 patients with stage IIIB, IIIC, or IV melanoma randomized in a 2 to 1 ratio to receive intralesional T-VEC, or Talimogene laherparepvec, a type of an oncolytic immunotherapy, or subcutaneous GM-CSF. The objective response rate with T-VEC was 26 % vs 6 % in GM-CSF arm, with a durable response rate of 16 % vs 2 %. A trend toward improved OS was seen in the T-VEC arm. There was a tolerable safety profile [48••].

Conclusions

Vaccine therapy has been extensively studied in numerous malignancies in phase I, II, and III clinical trials. In the adjuvant setting in high-risk melanoma, use of vaccines derived from different peptides or proteins and their pairing with adjuvants to augment the immune response has shown only modest clinical responses at best, if any at all, and in several cases have had disadvantageous clinical outcomes. Further study to understand the mechanisms and pathways of immunization, the properties of the underlying tumor microenvironment, and how tumors escape the immune system may lead to improved design of adjuvant vaccine therapies for melanoma in the future [10]. Particularly of interest may be the recently developed monoclonal antibodies for melanoma including anti-CTLA-4 and anti-PD-1, which have revolutionized melanoma treatment paradigms. Although the role of adjuvant vaccines as single agents is unclear, there is potential to develop and deliver vaccines in conjunction with newer immunotherapies [42].

Compliance with Ethics Guidelines

Conflict of Interest
S. A. Weiss, S. Chandra, and A. C. Pavlick declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2012;62:10–29.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. CA Cancer J Clin. 2010;60:277–300.
3. National Cancer Institute Surveillance Epidemiology and End Results. Available at: http://seer.cancer.gov/. Accessed December 20, 2013.
4. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–206.
5. Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist. 2011;16:5–24.
6. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000;18:2444–58.
7. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of Eastern Cooperative Oncology Group and intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res. 2004;10:1670–7.
8. Rietschel P, Chapman PB. Immunotherapy of Melanoma. Hematol Oncol Clin North Am. 2006;20:751–66.

9. Oble DA, Loewe R, Yu P, et al. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun. 2009;9:1–20.
10. Kaufman HL. Vaccines for melanoma and renal cell carcinoma. Semin Oncol. 2012;39:263–75.
11. Zarour HM, Kirkwood JM. Melanoma vaccines: early progress and future promises. Semin Cutan Med Surg. 2003;22:68–75.
12. Klein O, Schmidt C, Knights A, et al. Melanoma vaccines: developments over the past 10 years. Expert Rev Vaccines. 2011;10:853–73.
13. Kawakami Y, Robbins PF, Wang RF, Parkhurst M, Kang X, Rosenberg SA. The use of melanosomal proteins in the immunotherapy of melanoma. J Immunother. 1998;21:237–46.
14. Spitler LE, Grossbard ML, Ernstoff MS, et al. Adjuvant therapy of stage III and IV malignant melanoma using granulocyte-macrophage colony-stimulating factor. J Clin Oncol. 2000;18:1614–21.
15. Lawson DH, Lee SJ, Tarhini AA, et al. E4679: Phase III cooperative group study of yeast-derived granulocyte macrophage colony-stimulating factor (GM-CSF) vs placebo as adjuvant treatment of patients with completely resected stage III-IV melanoma. ASCO Annual Meeting Abstracts. J Clin Oncol. 2010;28:8504.
16. Slingluff Jr CL, Petroni GR, Yamshchikov GV, et al. Clinical and immunologic results of a randomized phase II trial of vaccination using four peptides either administered in granulocyte-macrophage colony-stimulating factor in adjuvant or pulsed on dendritic cells. J Clin Oncol. 2003;21:4016–26.
17. Slingluff Jr CL, Petroni GR, Olson WC, et al. Effect of granulocyte/macrophage colony-stimulating factor on circulating CD8+ and CD4+ T-cell responses to a multi-peptide melanoma vaccine: outcome of a multicenter randomized trial. Clin Cancer Res. 2009;15:7036–44.
18. Block MS, Suman VJ, Nevala WK, et al. Pilot study of granulocyte-macrophage colony-stimulating factor and interleukin-2 as immune adjuvants for a melanoma peptide vaccine. Melanoma Res. 2011;21:438–45.
19. Slingluff Jr CL, Petroni GR, Chianese-Bullock KA, et al. Randomized multicenter trial of the effects of melanoma- associated helper peptides and cyclophosphamide on the immunogenicity of a multipeptide melanoma vaccine. J Clin Oncol. 2011;29:2924–32.
20.• Gibney GT, Weber JS, Kudchadkar RR, et al. Safety and efficacy of adjuvant anti-PD1 therapy (nivolumab) in combination with vaccine in resected high-risk metastatic melanoma. ASCO Annual Meeting Abstracts. J Clin Oncol. 2013;31:9056.

This trial highlights the importance of investigating combinations vaccines and newer immunotherapies such as nivolumab. Patients on this regimen who did not relapse had an increase in T-regulatory cells

21. Slingluff CL, Petroni GR, Chianese-Bullock KA, et al. A multi-peptide vaccine plus toll-like receptor agonists in melanoma patients, with evaluation of the vaccine site microenvironment and sentinel immunized node (Mel58; NCT01585350). ASCO Annual Meeting Abstracts. J Clin Oncol. 2013;31: [Abstract TPS3125].
22. Ferrucci PF, Tosti G, di Pietro A, et al. Newly identified tumor antigens as promising cancer vaccine targets for malignant melanoma treatment. Curr Top Med Chem. 2012;12:11–31.
23. Kruit WH, van Ojik HH, Brichard VG, et al. Phase I/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma. Int J Cancer. 2005;117:596–604.
24. Kruit WH, Suciu S, Dreno B, et al. Selection of immunostimulant AS15 for active immunization with MAGE-A3 protein: results of a randomized phase II study of the European Organisation for Research and Treatment of Cancer Melanoma Group in metastatic melanoma. J Clin Oncol. 2013;31:2413–21.
25. GlaxoSmithKline. The investigational MAGE-A3 antigen-specific cancer immunotherapeutic does not meet first co-primary endpoint in Phase III melanoma clinical trial. Available at: http://www.gsk.com/media/press-releases/2013/the-investigational-mage-a3-antigen-specific-cancer-immunotherap.html.
26.•• Kirkwood JM, Dreno B, Hauschild A, et al. DERMA phase III trial of MAGE-A3 antigen-specific cancer immunotherapeutic (ASCI) as adjuvant therapy in patients with MAGE-A3-positive resected stage III melanoma. ASCO Annual Meeting Abstracts. J Clin Oncol. 2011;29.

This phase III randomized trial known as the DERMA trial showed that MAGE-A3 vaccination in resected stage IIIB/C melanoma patients does not significantly extend DFS when compared with placebo.

27. Barrow C, Browning J, MacGregor D, et al. Tumor antigen expression in melanoma varies according to antigen and stage. Clin Cancer Res. 2006;12:764–71.
28. Davis ID, Chen W, Jackson H, et al. Recombinant NY-ESO-1 protein with ISCOMATRIX adjuvant induces broad integrated antibody and CD4+ and CD8+ T cell responses in humans. PNAS. 2004;101:10697–702.
29. Nicholaou T, Chen W, Davis ID, et al. Immunoediting and persistence of antigen-specific immunity in patients who have previously been

vaccinated with NY-ESO-1 protein formulated in ISCOMATRIX™. Cancer Immunol Immunother. 2011;60:1625–37.

30. Study of NY-ESO-1 ISCOMATRIX in patients with high-risk, resected melanoma. Available at: http://clinicaltrials.gov/show/NCT00199901. Accessed December 29, 2013.
31. Sabado RL, Pavlick AC, Gnjatic S, et al. Phase I/II study of resiquimod as an immunologic adjuvant for NY-ESO-1 protein vaccination in patients with melanoma. ASCO Annual Meeting Abstracts. J Clin Oncol. 2012;30: [Abstract 2589].
32. Livingston PO, Wong GYC, Adluri S, et al. Improved survival in stage III melanoma patients with GM2 antibodies: a randomized trial of adjuvant vaccination with GM2 ganglioside. J Clin Oncol. 1994;12:1036–44.
33.• Eggermont AMM, Suciu S, Rutkowski P, et al. Adjuvant ganglioside GM2-KLH/QS-21 vaccination vs observation after resection of primary tumor 1.5 mm in patients with stage II melanoma: results of the EORTC 18961 randomized phase III trial. J Clin Oncol. 2013;31:3831–40.

A phase III trial (EORTC 18961) studied the efficacy of the adjuvant ganglioside GM2-KLH/QS-21 vaccine in resected stage II melanoma patients and found that the vaccine did not improve RFS, but actually demonstrated a trend toward decreased OS, for which the trial was closed early

34. Neller MA, Lopez JA, Schmidt CW. Antigens for cancer immunotherapy. Semin Immunol. 2008;20:286–95.
35. Motl SE. Technology evaluation: Canvaxin, John Wayne Cancer Institute/CancerVax. Curr Opin Mol Ther. 2004;6:104–11.
36. Morton DL, Hseuh EC, Essner R, et al. Prolonged survival of patients receiving active immunotherapy with canvaxin therapeutic polyvalent vaccine after complete resection of melanoma metastatic to regional lymph nodes. Ann Surg. 2002;236:438–49.
37. Hsueh EC, Essner R, Foshag LJ, et al. Prolonged survival after complete resection of disseminated melanoma and active immunotherapy with a therapeutic cancer vaccine. J Clin Oncol. 2002;20:4549–54.
38. Hseuh EC, Gupta RK, Qi K, Yee R, Leopoldo ZC, Morton DL. TA90 immune complex predicts survival following surgery and adjuvant vaccine immunotherapy for stage IV melanoma. Cancer J Sci Am. 1997;3:364–70.
39. Tsioulias GJ, Gupta RK, Tisman G, et al. Serum TA90 Antigen-antibody complex as a surrogate marker for the efficacy of a polyvalent allogeneic whole-cell vaccine (CancerVax) in Melanoma. Ann Surg Oncol. 2001;8:198–203.
40. Kelland L. Discontinued drugs in 2005: oncology drugs. Expert Opin Invest Drugs. 2006;15:1309–18.
41.• CancerVax announces results of phase 3 clinical trials of canvaxin™ in patients with stage III and stage IV melanoma. Available at: http://www.marketwired.com/press-release/-675445.htm. Accessed December 29, 2013.

This press release reports that the two large randomized Phase III trials evaluating Canvaxin plus BCG vs placebo plus BCG for completely resected stage III and IV melanoma was discontinued prematurely because there was found to be no difference in survival outcomes.

42. Eggermont AMM. Immunotherapy: vaccine trials in melanoma—time for reflection. Nat Rev Clin Oncol. 2009;6:256–8.
43.• Mackiewic A, Mackiewicz J, Wysocki PJ, et al. Long-term survival of high-risk melanoma patients immunized with a Hyper-IL-6-modified allogeneic whole-cell vaccine after complete resection. Expert Opin Invest Drugs. 2012;21:773–83.

This is the first report of an adjuvant allogeneic gene-modified melanoma vaccine studied in two phase II trials as adjuvant therapy in resected stage IIIB, IIIC, and IV melanoma that was found to have a DFS and OS survival advantage when compared with non-treated historical controls

44. Markowicz S, Nowecki ZI, Rutkowski P, et al. Adjuvant vaccination with melanoma antigen-pulsed dendritic cells in stage III melanoma patients. Med Oncol. 2012;29:2966–77.
45. Petenko NN, Mikhaylova IN, Chkadua GZ, et al. Adjuvant dendritic cell (DC)-based vaccine therapy of melanoma patients. ASCO Annual Meeting Abstracts. J Clin Oncol. 2012;30: [Abstract 2524].
46. Hu JC, Coffin RS, Davis CJ, et al. A phase I study of OncoVEXGM-CSF, a second generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. Clin Cancer Res. 2006;15:6737–47.
47. Senzer NN, Kaufman HL, Amatruda T, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpes virus in patients with unresectable metastatic melanoma. J Clin Oncol. 2009;27:5763–71.
48.•• Andtbacka RHI, Collichio F, Amatruda T, et al. OPTIM: a randomized phase 3 trial of talimogene laherparepvec (T-VEC) vs subcutaneous granulocyte-macrophage colony-stimulating factor for the treatment of unresectable stage IIIB/C and IV melanoma. ASCO Annual Meeting Abstracts. J Clin Oncol. 2013;31: [Abstract LBA9008].

This is a prospective phase III trial (OPTIM) that studied patients with stage IIIB, IIIC or IV melanoma that compared administration of an oncolytic vaccine with GM-CSF and a trend toward improved OS vaccine arm.