The new paradigm of systemic therapies for metastatic melanoma

Virginia O. Volpe, MD,[a] Daniel M. Klufas, BS,[b] Upendra Hegde, MD,[a] and Jane M. Grant-Kels, MD[b]
Farmington, Connecticut

New treatments for metastatic melanoma work through distinct mechanisms: enhancing the immune response and blocking cellular proliferation. Agents that enhance the immune response include ipilimumab, pembrolizumb, and nivolumab; agents that block cellular proliferation include vemurafenib, dabrafenib, trametinib, cobimetinib, binimetinib, and selumetinib. The translational impact of laboratory discoveries has revolutionized management of metastatic melanoma and enhanced the prognosis of affected patients. (J Am Acad Dermatol 2017;77:356-68.)

Key words: immune therapy; metastatic melanoma; targeted therapy.

Elucidation of the mechanisms that contributed to the inefficacies of previous melanoma therapies led to the discovery of molecules (referred to as checkpoints) expressed by activated T cells. These molecules mediated the inhibition of T cells so that immune homeostasis was preserved and the harm caused to the body by uncontrolled inflammation prevented. The characterization of these checkpoints and their blockade by monoclonal antibodies resulted in the evolution of immune checkpoint inhibitor treatments of metastatic melanoma (MM) (Fig 1). Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) receptor represent 2 inhibitory molecules expressed on activated T cells that regulate their growth, proliferation, and survival and potentially compromise melanoma immunity.

Abbreviations used:

APC:	antigen presenting cells
BRAF:	v-RAF murine sarcoma viral oncogene
CRR:	complete response rate
CTLA-4:	cytotoxic T-lymphocyte–associated antigen 4
irAEs:	immune related adverse events
KA:	keratoacanthoma
LDH:	lactate dehydrogenase
MAPK:	mitogen-activated protein kinase
MHC:	means of antigen presenting
MM:	metastatic melanoma
OS:	overall survival
PD-1:	programmed cell death 1
PFS:	progression-free survival
PI3K:	phosphatidylinosital-3-kinase
SCC:	squamous cell carcinoma

IMMUNE CHECKPOINTS AND THEIR INHIBITION

A melanoma-specific immune response is generated when melanoma antigen on the major histocompatibility complexes of antigen-presenting cells (APCs) is presented to the T-cell receptors of T cells. The antigen-primed T cell becomes activated by engagement of its CD28 molecule with the costimulatory molecules CD80 and CD86 present on APCs (Fig 2). The resulting tight synapse between the T cell and APC leads to proliferation and survival of T cells that help eliminate tumor cells.[1] The CTLA-4 pathway regulates this reaction through rapid expression of CTLA-4 antigens on activated naïve and memory T cells. By virtue of their superior affinity for the costimulatory molecules on the APC, CTLA-4 antigens outcompete the CD28 molecule for binding and thereby abrogate T-cell antitumor activity.[2]

From the Department of Internal Medicine, Division of Oncology's Neag Cancer Center, University of Connecticut Health Center, Farmington[a]; and the Department of Dermatology, University of Connecticut Health Center, Farmington.[b]
Dr Volpe and Mr Klufas contributed to this work equally.
Drs Hegde and Grant-Kels contributed to this work equally.
Funding sources: Supported by Jane and Richard Lublin.
Conflicts of interest: None declared.

Accepted for publication April 25, 2017.
Reprints not available from the authors.
Correspondence to: Jane M. Grant-Kels, MD, UConn Health Department of Dermatology, 21 South Rd, Suite 200, Farmington, CT 06030-6231. E-mail: grant@uchc.edu.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.04.1126

Anti–CTLA-4 antibody ipilimumab

Ipilimumab is a human monoclonal antibody of IgG1 type developed to inhibit CTLA-4 activity and to allow for T-cell activation and proliferation (Fig 3). Phase 1 and 2 clinical trials demonstrated antitumor activity leading to durable responses in patients including those with unfavorable characteristics (M1c melanoma subclass and elevated lactate dehydrogenase [LDH]) but also revealed autoimmune side effects.[3-6] In a large prospective multicenter randomized phase 3 clinical trial, patients diagnosed with unresectable stage III or IV melanoma failing previous treatments were randomly assigned in 3:1:1 ratio to receive ipilimumab plus gp100 (vaccine derived from melanosomal glycoprotein 100), ipilimumab alone, or gp100 alone at a dose of 3 mg/kg body weight every 3 weeks for ≤4 treatments. The results showed similar median survival of 10 months among patients in the ipilimumab groups compared with 6.4 months in patients receiving gp100 alone. Grade III/IV toxicities occurred in 10%-15% of the patients receiving ipilimumab, and 14 deaths occurred including 7 deaths from autoimmune side effects. Overall survival for ipilimumab plus gp100, ipilimumab alone, and gp100 alone at 12 months was 43.6%, 45.6%, and 25.3%, respectively; at 18 months it was 30.0%, 33.2% and 16.3%, respectively; and at 2 years was 21.6%, 23.5%, and 13.7%, respectively.[7] In a pooled analysis, overall survival for patients who received ipilimumab appeared to plateau after 3 years. This analysis, however, reflects the survival status, not the disease status, of survivors.[8]

Anti–PD-1 antibody pembrolizumab and nivolumab

PD-1, like CTLA-4, is an immune checkpoint receptor that regulates a different point in the immune response and can be found on activated effector T cells in tumor microenvironments (Fig 2). The 2 ligands, PDL1 (B7H1) and PDL2 (B7DC), are found on a variety of cells including APCs and tumor tissues. This bond results in downregulation of the immune response that protects the host against autoimmunity.[9] This mechanism can be used by tumors to circumvent antitumor immunity and develop immune tolerance. Interruption of the PD-1–PDL1/2 axis is accomplished by generating monoclonal antibodies against PD-1 receptor or PDL1 leading to blockade of T-cell inhibition and activation of antimelanoma immune responses in animal studies. Pembrolizumab and nivolumab are 2 humanized monoclonal antibodies of the IgG4 subtypes that are FDA approved to treat unresectable stage III or IV disease.

CAPSULE SUMMARY

- Metastatic melanoma historically has been associated with a poor prognosis.
- Emerging treatments have resulted from knowledge of mechanisms to enhance the immune response against tumors and molecular characterization of mutated gene products important for cellular proliferation.
- The new treatments discussed herein have revolutionized management of metastatic melanoma.

Nivolumab. Nivolumab is a fully human monoclonal IgG4 antibody against PD-1. A pilot study on nivolumab in patients with treatment-refractory solid tumors demonstrated a promising safety profile and evidence of antitumor activity.[10] A larger phase 1 study reinforced this finding showing a durable objective response (28%) with nivolumab.[11]

Further studies were undertaken in previously treated advanced melanoma patients who had not received CTLA-4 antibody treatment. An overall response rate of 30.8% was obtained across all doses of nivolumab, with median progression-free survival (PFS) of 3.7 months, median overall survival (OS) of 16.8 months, and an OS of 62% and 43% at 1 and 2 years, respectively.[12] This led to 2 large, randomized, open-label, phase 3 clinical trials. One trial compared nivolumab versus dacarbazine in treatment-naïve, *BRAF* (v-RAF murine sarcoma viral oncogene) wild-type tumors; this trial demonstrated a higher OS with the nivolumab treatment than with the dacarbazine treatment (73% vs 42%) at 1 year. Other studies showed a similar benefit regardless of *BRAF* mutation status. The survival benefit associated with nivolumab was also noted irrespective of PDL1 status; in those negative for PDL1, survival was improved in the nivolumab group in comparison with the dacarbazine group.[13]

Another study compared nivolumab versus investigator-choice chemotherapy in previously treated MM patients who progressed after treatment with CTLA-4 or BRAF inhibitor. Objective responses were 31.7% with the CTLA-4 inhibitor and 10.6% with the BRAF inhibitor, suggesting ipilimumab is an efficacious treatment option after progression.[14]

Pembrolizumab. Pembrolizumab (initially called labrolizumab) is another highly selective humanized monoclonal antibody of the IgG4 isotype that was designed to block PD-1 receptor expressed on activated effector T lymphocytes. In a phase 1 study, patients with MM previously