Combination Immunotherapy for Melanoma

Howard L. Kaufman, MD

Advances in precision medicine and immunology have led to major paradigm shifts in the general approach to treating patients with metastatic cancer. This is perhaps best exemplified by malignant melanoma, an aggressive tumor characterized by alterations in defined cell signaling pathways and susceptibility to recognition by the immune system. Over the past 4 years, there have been 7 new drugs approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma.1 There has been considerable excitement focused on the immunotherapy of melanoma based on several randomized clinical trials (RCTs) demonstrating an improvement in overall survival with immunotherapy agents and also on emerging data supporting the use of immunotherapy in a variety of other types of cancer. In contrast to cytotoxic chemotherapy or targeted therapy, immunotherapy is often characterized by a relatively slow onset of action, lack of drug resistance, and induction of durable therapeutic responses, at least in a subset of patients. In fact, results in patients with metastatic melanoma treated with high-dose interleukin-2 (IL-2), which has been available since 1998, suggest that most patients who achieve an objective complete response remain free of melanoma recurrence 15 years later and are likely cured of metastatic disease.2 More recently, a monoclonal antibody that blocks the cytolytic T lymphocyte antigen 4 (CTLA-4) and prevents T-cell unresponsiveness (ipilimumab) demonstrated an overall survival benefit in an RCT in patients with metastatic melanoma and was approved by the FDA. Other T-cell checkpoint inhibitors targeting the programmed cell death 1 (PD-1) pathway have also shown considerable promise with 2 anti–PD-1 antibodies achieving FDA approval for metastatic melanoma over the past 12 months.3,4

A logical strategy that has been used in cancer pharmacology is to consider combinations of 2 or more agents to expand the therapeutic activity of a particular class of drugs or to use drugs from different classes that may have independent mechanisms of action. In

**JAMA**

**Ipilimumab Plus Sargramostim vs Ipilimumab Alone for Treatment of Metastatic Melanoma: A Randomized Clinical Trial**

F. Stephen Hodi, MD; Sandra Lee, ScD; David F. McDermott, MD; Uma N. Rao, MD; Lisa H. Butterfield, PhD; Ahmad A. Tarhini, MD, PhD; Philip Leming, MD; Igor Puzanov, MD; Donghoon Shin, SM; John M. Kirkwood, MD


**OBJECTIVE** To compare the effect of ipilimumab plus sargramostim vs ipilimumab alone on overall survival (OS) in patients with metastatic melanoma.

**DESIGN, SETTING, AND PARTICIPANTS** The Eastern Cooperative Oncology Group (ECOG) conducted a US-based phase 2 randomized clinical trial from December 28, 2010, until July 28, 2011, of patients (N = 245) with unresectable stage III or IV melanoma, at least 1 prior therapy, no central nervous system metastases, and ECOG performance status of 0 or 1.

**INTERVENTIONS** Patients were randomized to receive ipilimumab, 10 mg/kg, intravenously on day 1 plus sargramostim, 250 μg subcutaneously, on days 1 to 14 of a 21-day cycle (n = 123) vs ipilimumab alone (n = 122). Ipilimumab treatment included induction for 4 cycles followed by maintenance every fourth cycle.

**MAIN OUTCOMES AND MEASURES** Primary end point: comparison of length of OS. Secondary end point: progression-free survival (PFS), response rate, safety, and tolerability.

**RESULTS** Median follow-up was 13.3 months (range, 0.03-19.9). As of December 2012, median OS and 1-year survival for the ipilimumab plus sargramostim group vs ipilimumab alone were significantly different. A planned interim analysis was conducted at 69.8% of expected events (104 observed of 149 expected deaths) and the O’Brien-Fleming boundary was crossed for improvement in OS. There was no difference in PFS. Adverse events were more common in the ipilimumab-only group.

**CONCLUSION AND RELEVANCE** Among patients with unresectable stage III or IV melanoma, treatment with ipilimumab plus sargramostim vs ipilimumab alone resulted in longer OS and lower toxicity, but no difference in PFS. These findings require confirmation in larger studies with longer follow-up.

JAMA. 2014;312(17):1744-1753
a recent issue of *JAMA*. Hodi et al reported an RCT that compared combination ipilimumab, and sargramostim (recombinant granulocyte-macrophage colony-stimulating factor [GM-CSF]) with ipilimumab alone in 245 patients with metastatic melanoma. After a median follow-up of 13.3 months, they found that combination immunotherapy was associated with an improvement in overall survival (17.5 vs 12.7 months; *P* = .01) and improved 1-year survival (68.9% vs 52.9%; *P* = .01). Surprisingly, there were significantly fewer adverse events seen in patients receiving combination therapy (*P* = .04). Although the trial had several limitations, including the use of a nonstandard, higher dose of ipilimumab (10 mg/kg) and lack of blinding between treatment arms and no data on subsequent therapy, the study supports further investigation of the combination. The decrease in toxicity observed in the combination arm was unexpected, and the reason for this was not clear. GM-CSF is known to have both activating and suppressive properties on T cells and has been associated with inconsistent results in both monotherapy and combination therapy studies in melanoma. While it is possible that GM-CSF did augment antigen presentation and promote T-cell responses, the suppressive effects of GM-CSF may have allowed more ipilimumab to be given, which would explain the therapeutic and toxicity outcomes, but Hodi et al did not report on the total number of ipilimumab doses across treatment arms.

In addition to T-cell checkpoint inhibitors, other approaches in clinical development include cytokines, oncolytic viruses, tumor vaccines, Toll-like receptor agonists, recombinant bacteria, chemokine regulators, and adoptive and chimeric antigen receptor-modified T cells. This provides numerous combinations to consider, and early-phase clinical studies are supporting the potential of this approach. In a small phase 1/2 study,6 patients with metastatic melanoma were treated with standard high-dose IL-2 and escalating doses of ipilimumab. In the initial report6 of this trial there was a 22% objective response rate, which was not considered a significant improvement from treatment with IL-2 alone. In further follow-up8 of the patients, however, the response rate improved to 25%, with a remarkable 17% of patients becoming complete responders. More recently, Wolchok et al8 reported data on 53 patients with metastatic melanoma treated in a phase 1 clinical trial using increasing doses of ipilimumab and nivolumab given concurrently to patients with melanoma. In this trial, an objective response rate of 40% was reported with a disease control rate of 65% and many patients experiencing rapid and profound regression.

While combination immunotherapy seems promising, there are major challenges that will need to be considered as the field moves forward. The large number of possible combinations need to have a more rational method for selecting the optimal agents for evaluation in clinical trials. Clinical trial designs will need to be established for rapid testing of combinations with respect to the unique features of immunotherapy drugs, including potentially delayed kinetics of response and autoimmune-related adverse effects. In addition, regulatory and legal hurdles exist for rapid combination clinical studies, especially when agents are being developed by unrelated industry and pharmaceutical sponsors. Many of the RCTs conducted to date have been in second-line settings, and it will be important to bring the most promising regimens forward into first-line treatment to best optimize the potential for clinical benefit. These hurdles should be easily addressed by collaboration among academic institutions, government regulatory bodies, industry leaders, and professional medical societies. The potential promise of tumor immunotherapy is considerable given the increasing response rates observed with combination regimens and the characteristic durability of immunotherapy-related responses. These initial observations need to be more fully understood but are already changing the therapeutic landscape for patients with melanoma. The paradigms being established in melanoma, particularly for combination immunotherapy, will also have implications for patients with other types of cancer.

**ARTICLE INFORMATION**

**Author Affiliation:** Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey.

**Corresponding Author:** Howard L. Kaufman, MD, Rutgers Cancer Institute of New Jersey, 195 Little Albany St, Rm 2004, New Brunswick, NJ 08901 (howard.kaufman@rutgers.edu).

**Published Online:** April 16, 2015. doi:10.1001/jamaoncol.2015.0479.

**Conflict of Interest Disclosures:** Dr Kaufman has served as a consultant for Alkermes, Amgen, EMD Serono, Merck, Prometheus, and Sanofi and has received research funding from Bristol-Myers-Squibb. No other disclosures are reported.

**Funding/Support:** This work was supported, in part, by National Cancer Institute (NCI) grant U01 CA186716-01.

**Role of the Funder/Sponsor:** The NCI had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**REFERENCES**


