5 Minute JournalClub

Key ASCO Presentations
Issue 2, 2010

Ipilimumab or the gp100 Vaccine or the Combination of Both as Therapy for Patients with Metastatic Melanoma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Demonstrate knowledge of both the survival benefit and the rate of clinically significant immune-related adverse events with ipilimumab in the treatment of metastatic melanoma.

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This CME activity contains slides. To receive credit, the participant should review the slide presentation and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Key ASCO Presentations
Issue 2, 2010

Dr Steven O'Day must have had his heart in his hand as he ascended the stage at the 2010 ASCO plenary session to present some very provocative and hopeful results in a disease that has until recently been resistant to systemic management.

The focal point of this landmark presentation, which was also just published in *The New England Journal of Medicine*, was a randomized **Phase III trial evaluating the potential benefit of ipilimumab**, a fully human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), for patients with previously treated metastatic melanoma.

The study demonstrated that this innovative immune stimulant — which, as Dr O'Day explained to me during a recent interview, "blocks the brakes" on T cells — when used alone or in combination with a glycoprotein 100 (gp100) peptide vaccine resulted in a four month increase in overall survival compared to a gp100 vaccine alone. Objective responses were uncommon, and PFS was reported but not thought to be relevant with this type of treatment. In terms of toxicity, because for once investigators really were dealing with serious immune modulation, a variety of manageable but potentially serious, even life-threatening, autoimmune complications were reported, particularly in the gut and on the skin.

The highly enthused discussant, Dr Vernon Sondak, a rare surgeon at the head table at ASCO, reminded us all just how groundbreaking these findings are by reviewing a meta-analysis of 42 cooperative group Phase II trials in patients with metastatic melanoma, none of which demonstrated prolonged survival. He then sincerely and empathetically acknowledged the persistence and patience of the many investigators in the audience and beyond who, until now, had little to show for their dedication to finding a solution to this dreadful disease. In a related ASCO presentation, **evaluating "Ipi" in patients with melanoma and brain metastases**, a series of pretty remarkable MRIs illustrated some of the prolonged responses that were reported.

The other melanoma presentation profiled in this, the second in our series of email/web summaries of key ASCO data sets, is in a sense a follow-up to Keith Flaherty's stunning presentation at ASCO last year on the B-raf kinase inhibitor PLX4032 in patients with V600-mutant melanoma. This year, Dr Richard Kefford showed equally impressive findings from a **Phase I-II trial of a similar B-raf kinase inhibitor, GSK2118436**, in which 18 of 30 patients with mutant B-raf tumors had tumor responses of greater

than 20 percent by RECIST criteria, and the waterfall plots were reminiscent of the ones shown by Dr Flaherty in 2009. Minimal toxicity was observed with this oral agent.

While the data in melanoma that emerged at this year's ASCO meeting are impressive, this was hardly a home run. But for a disease for which very little has worked, these two novel strategies and others coming along provide hope that we may soon hit one out of the park.

Next up on 5-Minute Journal Club: NHL and CLL at ASCO and the long-awaited and very interesting results of the PRIMA study of rituximab maintenance in follicular lymphoma.

Neil Love, MD
Research To Practice
Miami, Florida

Ipilimumab or the gp100 Vaccine or the Combination of Both as Therapy for Patients with Metastatic Melanoma

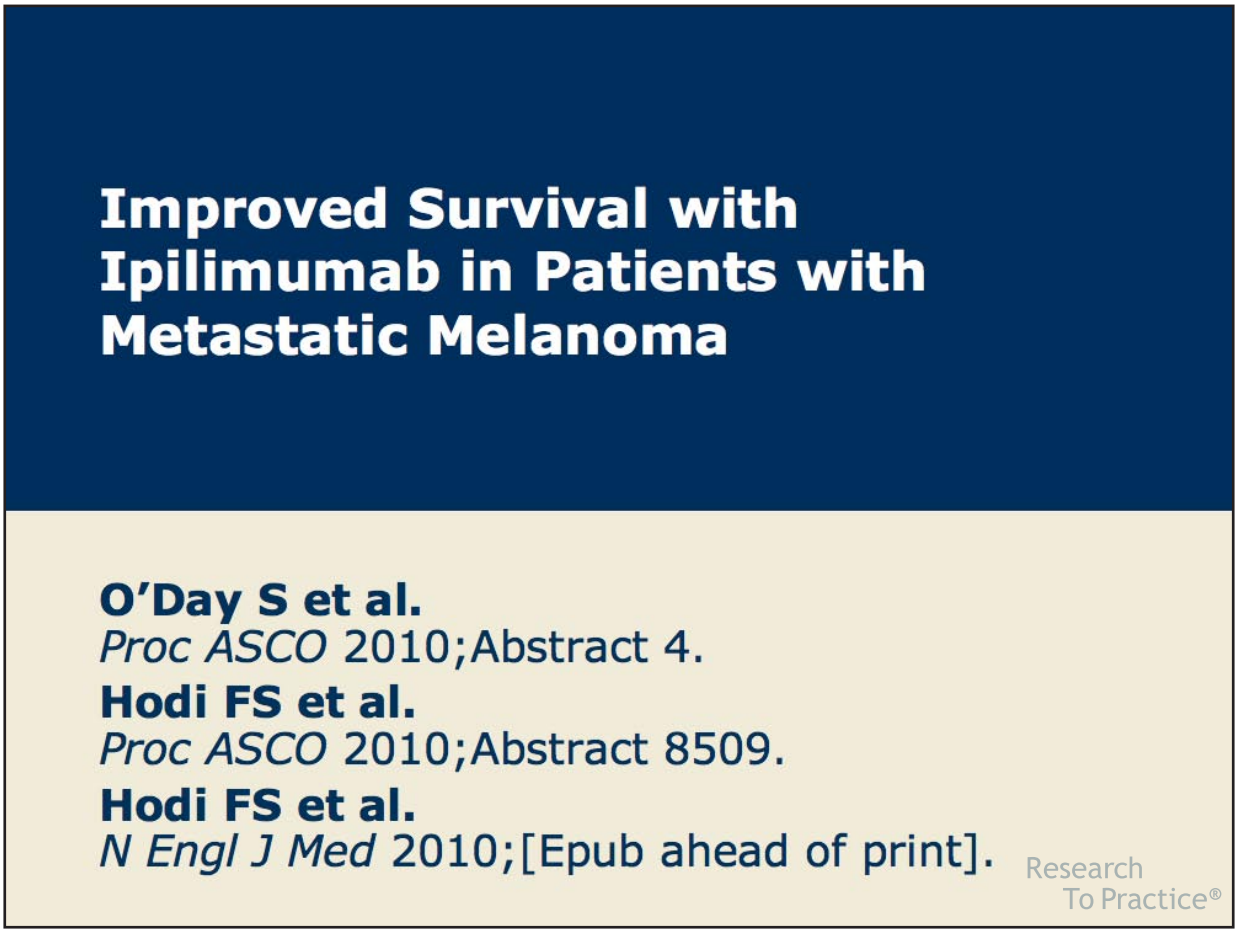
Presentations discussed in this issue

O'Day S et al. **A Phase III randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma.** *Proc ASCO* 2010;**Abstract 4**.

Hodi FS et al. **Re-induction with ipilimumab, gp100 peptide vaccine, or a combination of both from a phase III, randomized, double-blind, multicenter study of previously treated patients with unresectable stage III or IV melanoma.** *Proc ASCO* 2010;**Abstract 8509**.

Hodi FS et al. **Improved survival with ipilimumab in patients with metastatic melanoma.** *N Engl J Med* 2010;[Epub ahead of print]. **Abstract**

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Jedd D Wolchok, MD, PhD (6/16/10), Steven J O'Day, MD (6/25/10) and David F McDermott, MD (6/25/10)

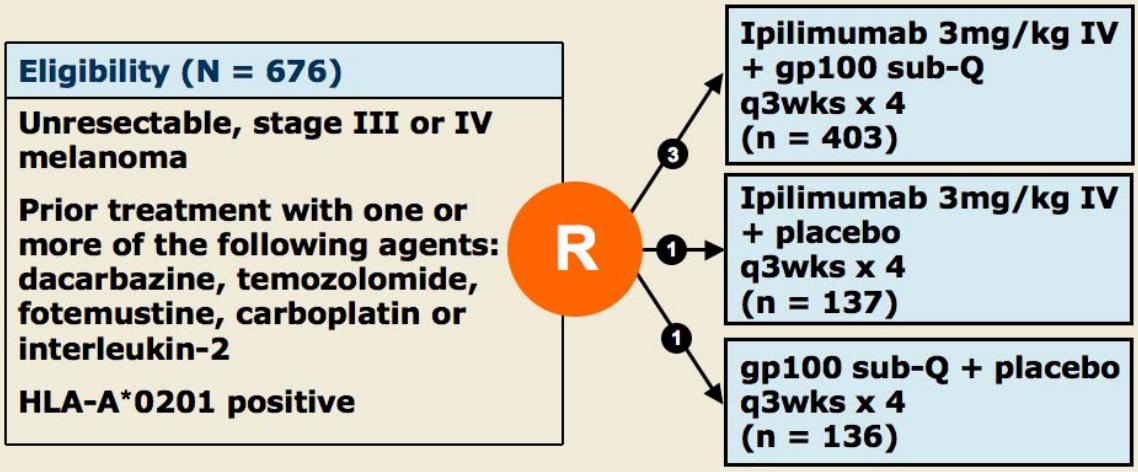


Introduction

- There are no approved therapies for metastatic melanoma in pretreated patients and enrollment in a clinical trial is the standard of care.
- Ipilimumab, a monoclonal antibody that blocks CTLA-4, has shown anti-tumor activity when used alone[1] or combined with other agents[2] ([1] *Clin Cancer Res* 2009;15:5591, [2] *Melanoma Res* 2010;20:1).
- Phase III trial data suggest that the gp100 peptide vaccine may improve the efficacy of high-dose IL-2 in patients with metastatic melanoma (*Proc ASCO* 2009;Abstract CRA9011).
- **Current study objectives:**
  - Evaluate whether ipilimumab with or without gp100 improves overall survival (OS) when compared with gp100 alone in patients with previously treated metastatic melanoma.
  - Assess incremental benefit of treatment reinduction for patients whose disease progresses after initial evidence of clinical benefit.

O'Day S et al. *Proc ASCO* 2010;Abstract 4; Hodi FS et al. *Proc ASCO* 2010; Abstract 8509; Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

MDX010-20: Study Design



Patients with stable disease for 3 months after week 12, or a confirmed partial or complete response were offered reinduction with assigned treatment regimen upon disease progression.

O'Day S et al. *Proc ASCO* 2010;Abstract 4; Hodi FS et al. *Proc ASCO* 2010; Abstract 8509; Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

Survival Data
Intent-To-Treat Population

Overall Survival (OS)	Ipilimumab + gp100 (n = 403)	Ipilimumab + placebo (n = 137)	gp100 + placebo (n = 136)
Median OS	10.0 months	10.1 months	6.4 months
Hazard ratio, versus gp100 alone (*p*-value)	0.68 (<0.001)	0.66 (0.003)	—
2-year OS rate	21.6%	23.5%	13.7%
Progression-Free Survival (PFS)			
Median PFS	2.76 months	2.86 months	2.76 months
PFS rate at week 12	49.1%	57.7%	48.5%

O'Day S et al. *Proc ASCO* 2010;Abstract 4; Hodi FS et al. *Proc ASCO* 2010; Abstract 8509; Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

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Best Overall Response Data

Induction	Ipilimumab + gp100 (n = 403)	Ipilimumab + placebo (n = 137)	gp100 + placebo (n = 136)
Complete response	0.2%	1.5%	0
Partial response	5.5%	9.5%	1.5%
Stable disease	14.4%	17.5%	9.6%
Reinduction	**(n = 23)**	**(n = 8)**	**(n = 1)**
Complete response	0	12.5%	0
Partial response	13.0%	25.0%	0
Stable disease	52.2%	37.5%	0

Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

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Select Grade 3/4 Adverse Events

Adverse Event*	Ipilimumab + gp100 (n = 380)		Ipilimumab + placebo (n = 131)		gp100 + placebo (n = 132)	
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4
Any drug-related event	16.3%	1.1%	19.1%	3.8%	11.4%	0
Diarrhea	4.2%	0.3%	5.3%	0	0.8%	0
Fatigue	5.0%	0	6.9%	0	3.0%	0
Anemia	2.9%	0	3.1%	0	8.3%	0
Any immune-related event	9.7%	0.5%	12.2%	2.3%	3.0%	0

* Listed adverse events occurred in ≥15% of patients. A total of 14 treatment-related deaths occurred (8 in ipilumumab + gp100 group, 4 in ipilumumab alone group and 2 in the gp100 alone group).

O'Day S et al. *Proc ASCO* 2010;Abstract 4; Hodi FS et al. *Proc ASCO* 2010; Abstract 8509; Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

Conclusions

- Ipilumumab alone or combined with gp100 showed a significant survival improvement with long-term effects in metastatic melanoma when compared to gp100 alone.
  - Efficacy of ipilimumab was not improved by the addition of gp100.
- The safety profile of ipilimumab was consistent with Phase II trials with the majority of adverse events being immune-related.
  - Adverse events could be severe and/or long-lasting, but many were reversible with appropriate and timely treatment.
- Reinduction with ipilimumab at the time of disease progression can result in further clinical benefit.
- Ipilimumab may be useful for treating patients with metastatic melanoma whose disease progressed while receiving one or more previous therapies.

O'Day S et al. *Proc ASCO* 2010;Abstract 4; Hodi FS et al. *Proc ASCO* 2010; Abstract 8509; Hodi FS et al. *N Engl J Med* 2010;[Epub ahead of print].

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Investigator comments on ipilimumab in metastatic melanoma

There are lots of both accelerators and brakes that moderate T-cell activity, and ipilimumab is the first in its class that's blocking the brakes. But what's so exciting about looking at this with melanoma as a prototype disease is that with this single antibody, about 30 percent of patients with widespread disease seem to have long-term benefit. Patients on the tail of the survival curve seem to be living with their cancer for years, and we have patients from earlier studies who are seven or eight years out with this agent.

I hate to use the word "cure," but clearly 20 to 25 percent of patients who had widespread metastatic melanoma experience long-term survival, and these patients had poor prognoses right from the beginning. So this is a big move forward. Once the dose and schedule of ipilimumab is more defined and optimized, trials of combinations will be important, including with the B-raf drugs in addition to other T cell-targeted antibodies — pushing the accelerator and blocking the brake at the same time.

Interview with Steven J O'Day, MD, June 25, 2010

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Investigator comments on ipilimumab in metastatic melanoma

Ipilimumab clearly enhances overall survival, and there's no precedent for that in metastatic melanoma. If and when it's approved, there will be widespread use of this agent. I have published on the need for immune-related response criteria to judge the activity of drugs like this, because the pattern of response is notably heterogeneous. Patients may stabilize for long periods of time and then have a response. Even more challenging, some patients get worse before they get better. Progression-free survival does not capture the natural history of immunologic therapy, and I believe it is an irrelevant endpoint in this setting.

Ipilimumab is easy to administer in the outpatient setting. The side effects are different, but not difficult to manage with the algorithms that have been developed. The safety profile was as expected based on the Phase II studies — tissue-specific inflammation including pruritus and rash, diarrhea that can progress to colitis, endocrinopathy including pituitary and thyroid dysfunction, and occasionally inflammatory hepatitis. The vast majority of side effects can be controlled using simple algorithms with corticosteroids, and if managed properly, last two or three weeks.

Interview with Jedd D Wolchok, MD, PhD, June 16, 2010

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Investigator comments on ipilimumab in metastatic melanoma

What's most impressive about these data is the tail of survival curves, which suggest that maybe 20 percent or more of patients who received ipilimumab are out two years without progression of their disease. That's a fair proportion of folks. There are obviously important related questions like: Who are those patients? Can we identify them? How do we decide who should receive this drug and who should receive other treatments? For the first time, though, we have an agent that truly impacts survival.

Ipilimumab has real toxicity, but a much more manageable toxicity profile than interleukin-2, and is administered intravenously in the outpatient setting. It's going to require a steep learning curve for oncologists to understand this drug, because it's quite different than many that they've used before, but it's a real ray of hope to a subset of patients with advanced melanoma. It also probably is active in other tumors that are prone to response to immune therapy and it will be interesting to see if it's developed in those areas.

Interview with David F McDermott, MD, June 25, 2010

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