5 Minute JournalClub

Key ASCO Presentations
Issue 2, 2010

Ipilimumab Monotherapy for Patients with Melanoma and Brain Metastases

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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

- Describe the efficacy and safety of ipilimumab monotherapy in patients with melanoma and brain metastases.

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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

Last review date: July 2010
Expiration date: July 2011

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Key ASCO Presentations
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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 Monotherapy for Patients with Melanoma and Brain Metastases

Presentation discussed in this issue

Lawrence DP et al. **Phase II trial of ipilimumab monotherapy in melanoma patients with brain metastases.** *Proc ASCO* 2010;**Abstract 8523**.

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

- Thirty percent of patients who present with melanoma already have brain metastases (mets) and an additional 30% will develop brain lesions within 12 to 24 months (*Cancer* 2007;110:1329).
- Whole brain irradiation is the standard of care.
  - Reported response rates are approximately 10% and median survival is approximately 3 to 6 months (*JCO* 2004;22:1293).
- Ipilimumab (Ipi) is a human monoclonal antibody that blocks CTLA-4 and its inhibitory effects on T cell-mediated immunity.
- Ipi monotherapy has shown anti-tumor activity and high one- and two-year survival rates (*Clin Cancer Res* 2009;15:5591, *Ann Oncol* 2010;[Epub Feb 10]).
- **Current study objective:**
  - Assess the safety and activity of Ipi for patients with advanced melanoma and brain mets.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) Inhibits Antitumor Activity

- CTLA-4 is a negative regulator of T-cell activation and proliferation, and anticancer immunity.
- Antigen presenting cells (APC) present tumor-specific antigens to T-cells, activating them against the tumor.
- Binding of CTLA-4 on T-cell to B7 receptor on APC promotes inhibition of T-cell activation.
- Ipi blocks CTLA-4 interaction with B7 and prevents CTLA-4-mediated block of T-cell activation.
- Although Ipi cannot cross the blood-brain barrier, activated T-cells can.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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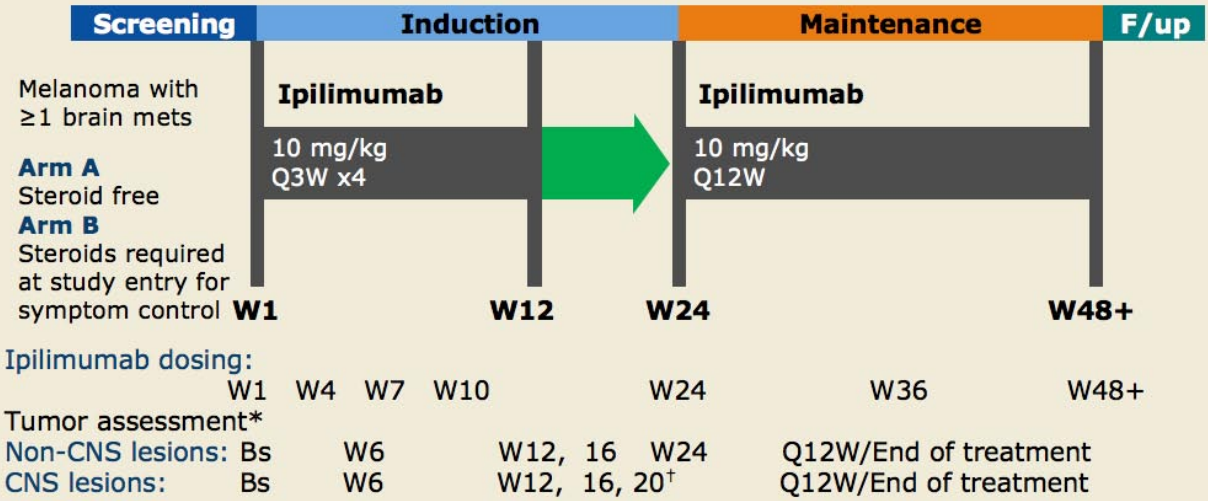
CA184-042: A Phase II Sequential Two-Arm Study Design



F/up = follow-up; W = week; Bs = baseline; * or as clinically indicated;
† confirmatory scan of Week 16 response (not PD); Arm B was sequential to Arm A.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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Immune-Related Response Criteria (irRC)

- Novel patterns of response appear to limit the ability of standard response criteria (mWHO) to fully and accurately characterize anticancer activity in patients on Ipi.
  - Tumor inflammation (desired outcome of treatment) may be mistaken for tumor progression.
- Four patterns of response in advanced melanoma are observed:
  - Shrinkage in baseline lesions, without new lesions
  - Stable disease, sometime with slow, steady decline in tumor volume
  - Response in the presence of new lesions
  - Response after an increase in total tumor volume
- All patterns listed above are associated with favorable survival.
- irRC were evolved from mWHO to more comprehensively characterize anticancer activity.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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Best Overall Response by irRC

	Arm A: Steroid free (n = 51)*			Arm B: Steroids required at study entry for symptom control (n = 21)*		
	Global	Brain	Non-CNS	Global	Brain	Non-CNS
CR	0	0	0	0	0	0
PR	9.8%	15.7%	13.7%	4.8%	4.8%	4.8%
SD	15.7%	9.8%	19.6%	4.8%	4.8%	4.8%
BORR	**9.8%**	**15.7%**	**13.7%**	**4.8%**	**4.8%**	**4.8%**
DCR	**25.5%**	**25.5%**	**33.3%**	**9.5%**	**9.5%**	**9.5%**

* Follow-up scans unavailable for some patients (may include patients who died or had disease progression prior to second scan)
CR = complete response; PR = partial response; SD = stable disease; BORR = best overall response (CR + PR); DCR = disease control rate (CR + PR +SD).

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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Survival and Duration of Response (by irRC)

Clinical Parameter	Arm A: Steroid free (n = 51)		Arm B: Steroids required at study entry for symptom control (n = 21)	
	irRC	mWHO	irRC	mWHO
Median overall survival (mos)	7.0		5.1	
Median progression-free survival (mos)	2.6	1.4	1.3	1.2
Time to onset of responses (mos)	1.2	1.2	1.2	1.2
Median duration of stable disease (mos)*	4.6	5.0	0.9	—
Median duration of response (mos)*	**15.3**	**15.3**	**NE**	**NE**

* Duration from week 12; NE = not evaluated.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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Immune-Related Adverse Events (irAE)*

Adverse Event	Arm A : Steroid free (n = 51)		Arm B: Steroids required at study entry for symptom control (n = 21)	
	Any Grade	Grade 3	Any Grade	Grade 3
Any irAE	66.7%	21.6%	61.9%	9.5%
Diarrhea	41.2%	11.8%	28.6%	4.8%
Rash	33.3%	2.0%	28.6%	4.8%
Pruritus	31.4%	0%	23.8%	0%
Colitis	11.8%	2.0%	9.5%	0%
Exfoliative rash	2.0%	2.0%	0%	0%
Increased ALT	3.9%	0%	14.3%	9.5%
Increased AST	3.9%	0%	19.0%	9.5%

* AEs occurring in >5% of pts in either arm or of Grade 3 severity

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

Conclusions

- Ipilimumab therapy can be effective for patients with advanced melanoma who have active, stable brain mets.
  - Patients on corticosteroids for symptom control may also benefit from ipilimumab treatment.
- Ipilimumab therapy is well tolerated without unique toxicities in patients with advanced melanoma who have brain mets.
- Durable responses can occur in brain mets following early evidence of progressive disease (data not shown).
- The optimal dose of ipilimumab and sequencing with surgery and radiation therapy have yet to be determined.

Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523; Koon HB. *Proc ASCO* 2010; Discussant.

Investigator comments on ipilimumab for melanoma with brain metastases

We actually saw some patients who had complete responses in the brain, which is unheard of with other agents. For example, IL-2 is almost never administered to patients with brain metastases because it worsens edema. The responses with ipilimumab appear to be durable — at least for the short time since the trial. So this works in a group of folks you'd expect would have exceedingly poor prognoses with a median survival of several months.

In terms of why this agent caused responses in the brain, the thought is that T cells enter the brain from the systemic circulation. You might ask whether the blood-brain barrier is broken down in these patients, but my sense is that the reason we talk about the blood-brain barrier may be that we simply had poor therapies and now that we have more active agents, these drugs can either get to the brain directly, as was observed with the selective B-raf inhibitor data also presented at ASCO, and/or transmit their effect into the brain, in this case through activated T cells crossing that barrier.

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

Investigator comments on ipilimumab for melanoma with brain metastases

Clearly a cohort of patients in this Phase II study had durable brain responses, and even in the presence of steroids — which you might think would nullify it — objective responses occurred in the brain.

This is encouraging and supports our clinical impressions that ipilimumab has some activity in the brain. No new side effects emerged in this study. It's certainly not a home run, but I believe it has important implications for why this drug may be working as well as it is in the group of patients that it benefits. That was reassuring.

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

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Investigator comments on ipilimumab for melanoma with brain metastases

This Phase II trial demonstrated that a subset of patients with melanoma experience regression of untreated brain metastases with ipilimumab. This is important because the brain has always been considered a sanctuary site for this disease.

This trial used the 10-mg/kg dose with maintenance therapy, whereas the Phase III trial presented by O'Day used the 3-mg/kg dose for induction alone, which reflected what was considered to be the optimal dose and schedule in 2004 when the pivotal trial launched. We recently completed a randomized study published in *Lancet Oncology* in February 2010 comparing the two doses, and 10 mg may now be considered optimal. So the O'Day results may actually have been a bit better if 10 mg/kg were administered with maintenance therapy, but obviously we won't ever be able to know that for sure.

More immune-related adverse events occur with 10 mg, but these are not different in the types of side effects. We simply saw a few more with 10 mg, but we found no difference in our ability to control them with the available algorithms.

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