5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Response and Survival with Dacarbazine and Vemurafenib for the Treatment of BRAF^{V600E}-Mutated Melanoma and Dacarbazine and Ipilimumab for the First-Line Treatment of Advanced-Stage 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 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 diverse forms of cancer.

LEARNING OBJECTIVES

- Communicate the benefits and risks of ipilimumab-based therapy to appropriately selected patients with advanced-stage melanoma.
- Recall emerging data with the BRAF inhibitor vemurafenib in the targeted treatment of melanoma, and consider how this class of agents may affect diagnosis and management of the disease.

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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Melanoma/CME.

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Keith T Flaherty, MD
Associate Professor, Harvard Medical School
Director of Developmental Therapeutics
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Eisai Inc, Genentech BioOncology; Consulting Agreements: Cephalon Inc, GlaxoSmithKline.

Jeffrey Weber, MD, PhD
Senior Member, H Lee Moffitt Cancer Center
Director, Donald A Adam Comprehensive
Melanoma Research Center
Tampa, Florida

Advisory Committee: Bristol-Myers Squibb Company, Celldex Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation; Consulting Agreement: Bristol-Myers Squibb Company; Stock Ownership: Celldex Inc.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

Neil Love, MD
Research To Practice
Miami, Florida

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

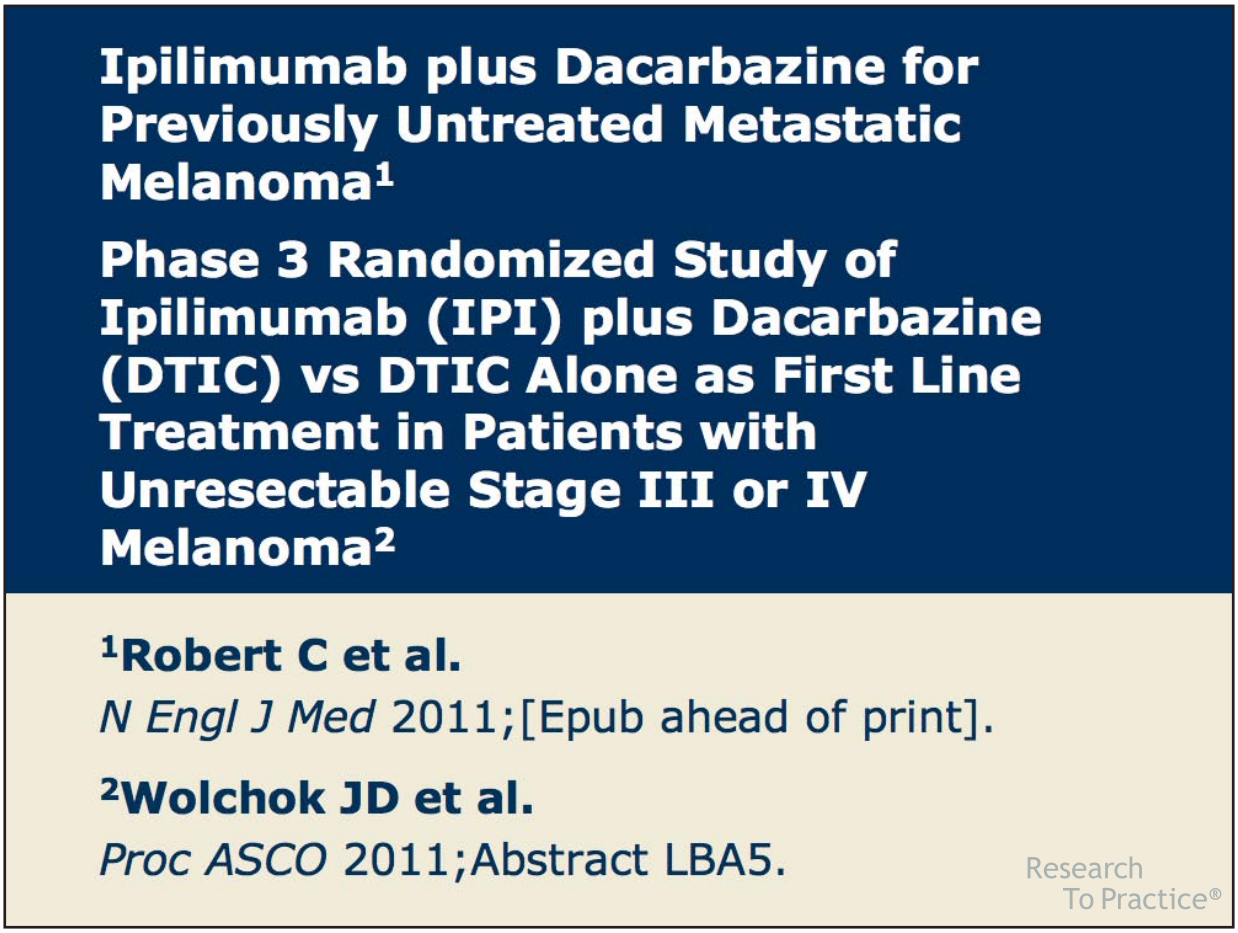
Response and Survival with Dacarbazine and Vemurafenib for the Treatment of BRAF^{V600E}-Mutated Melanoma and Dacarbazine and Ipilimumab for the First-Line Treatment of Advanced-Stage Melanoma

Presentation discussed in this issue

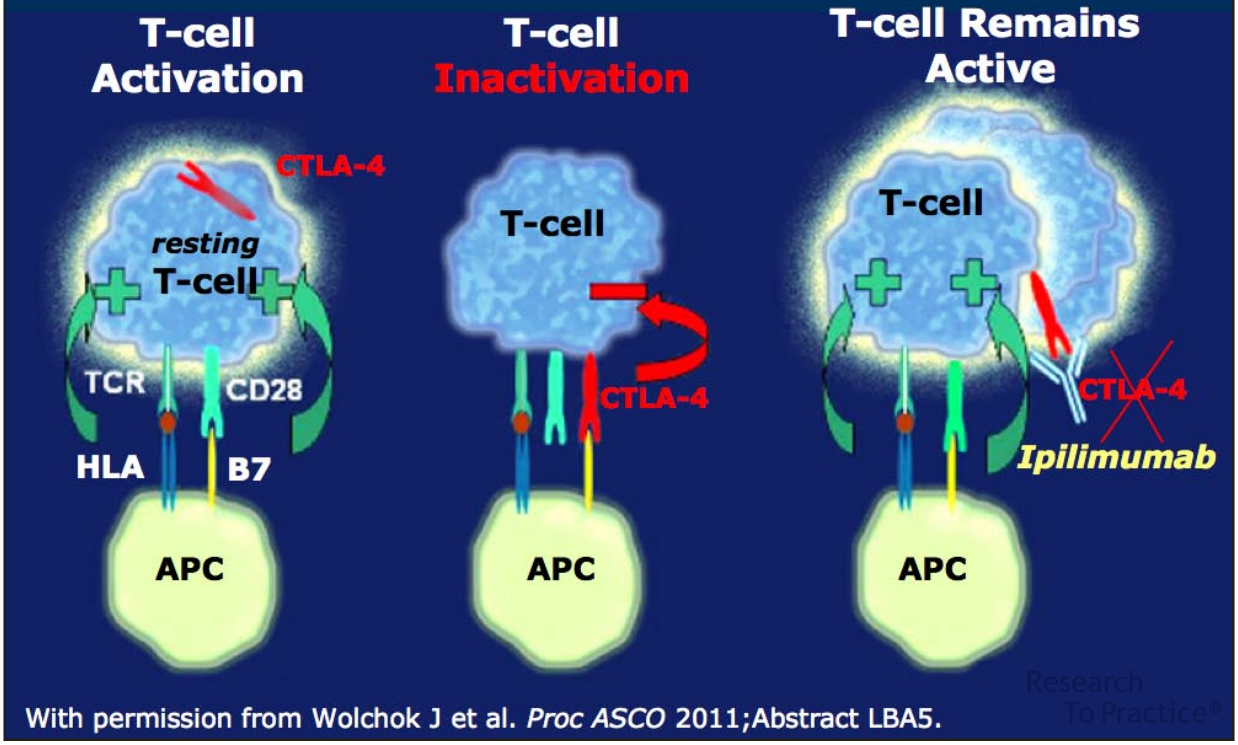
Robert C et al. **Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.** *N Engl J Med* 2011;364(26):2517-26. **Abstract**

Wolchok JD et al. **Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma.** *Proc ASCO* 2011;**Abstract LBA5**.

Slides from a presentation at ASCO 2011 and comments from Jeffrey Weber, MD



Ipilimumab, a CTLA-4 Blocking Monoclonal Antibody, Augments T-Cell Activation



With permission from Wolchok J et al. *Proc ASCO* 2011;Abstract LBA5.

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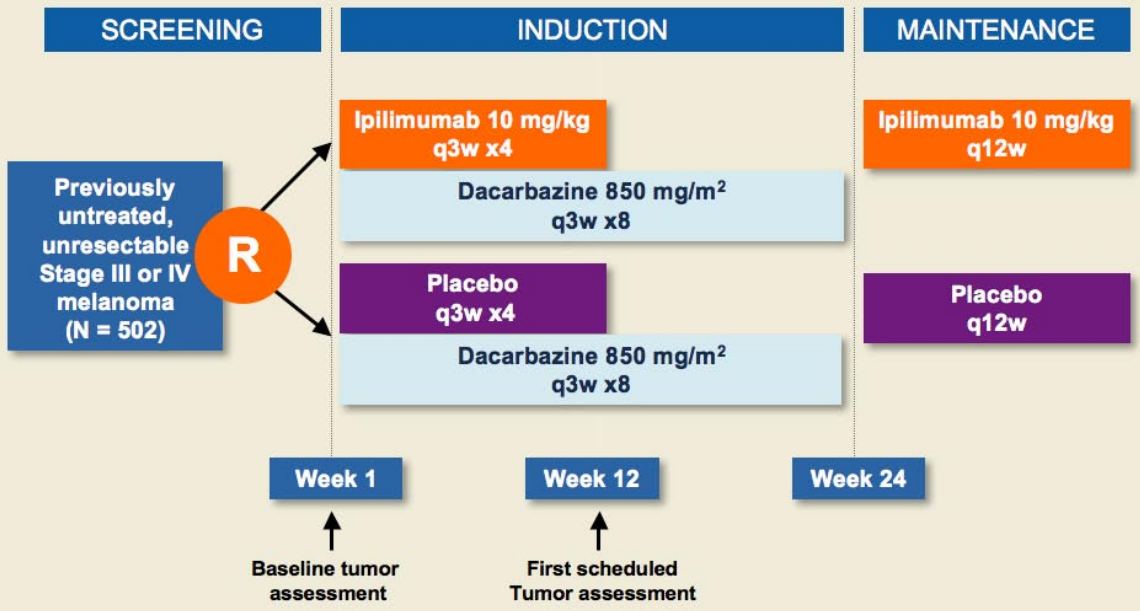
Study 024: Phase III Placebo-Controlled Trial of First-line DTIC ± IPI



Robert C et al. *N Engl J Med* 2011;[Epub ahead of print].

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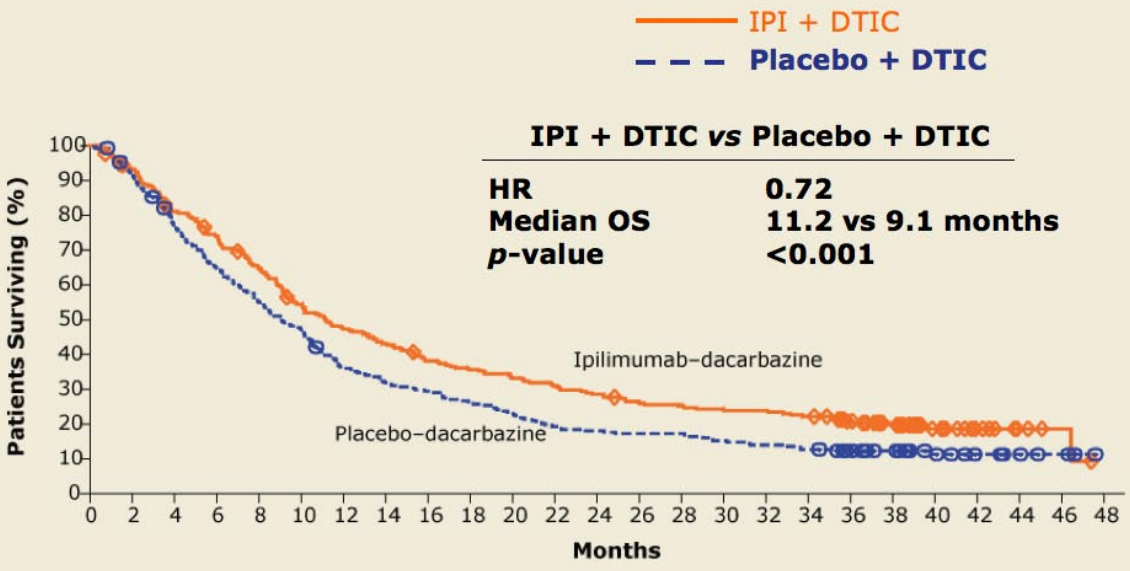
Study 024: Overall Survival



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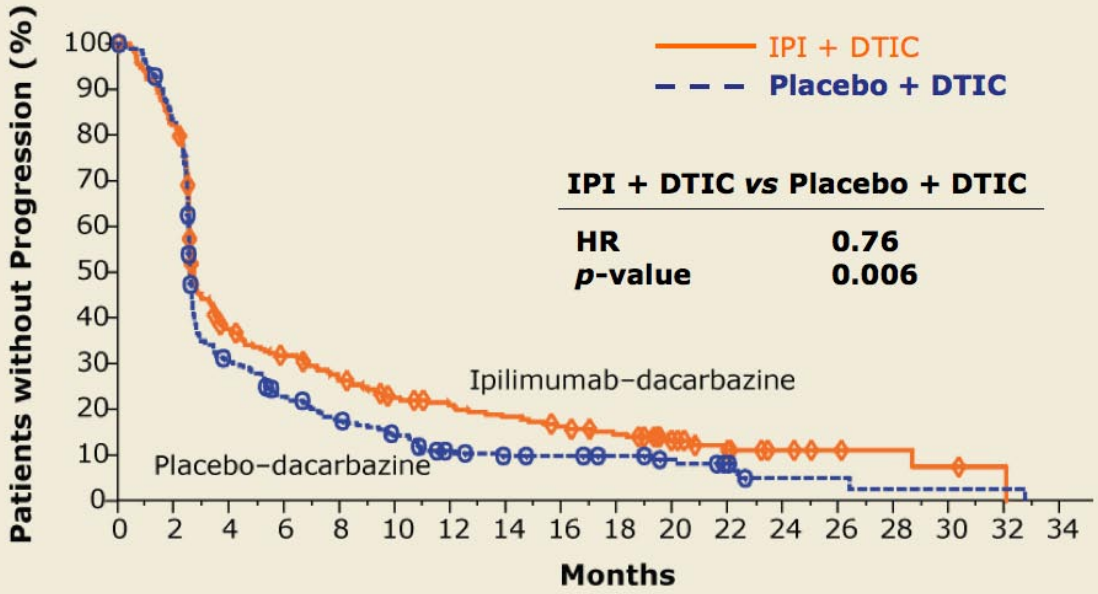
Study 024: Progression-Free Survival



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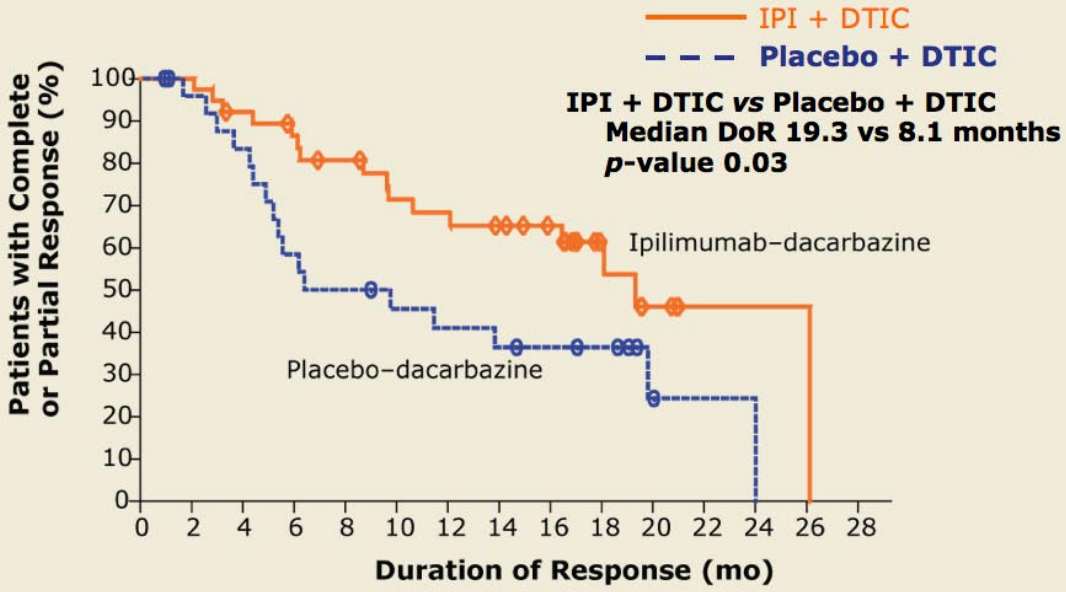
Study 024: Duration of Response (DoR)



Data shown for patients with a confirmed complete response (CR) or partial response (PR)

Robert C et al. *N Engl J Med* 2011;[Epub ahead of print]. Copyright © 2011 *Massachusetts Medical Society. All rights reserved.*

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Select Adverse Events and Immune-Related Adverse Events

All Adverse Events, Regardless of Cause	IPI + DTIC (n=247)		Placebo + DTIC (n=251)	
	Total	Gr 3/4	Total	Gr 3/4
Diarrhea	36.4%	4.0%	24.7%	0
Rash	24.7%	1.2%	6.8%	0
Increased AST	29.1%	18.2%	5.6%	1.2%
Increased ALT	33.2%	21.9%	5.6%	0.8%
Immune-Related Adverse Events				
Increased AST	26.7%	17.4%	3.2%	0.4%
Increased ALT	29.1%	20.7%	4.4%	0.8%

Robert C et al. *N Engl J Med* 2011;[Epub ahead of print].

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Conclusions

- IPI (10 mg/kg) + DTIC improved overall survival in patients with previously untreated metastatic melanoma compared to DTIC + placebo.
- Durable responses were observed in the IPI + DTIC group compared to the DTIC + placebo group.
- Adverse events observed were consistent with those seen in earlier studies of IPI.
- However, rates of the following events differed from the expected based on prior studies:
  - Higher rates of elevated ALT and AST
  - Lower rates of gastrointestinal events
  - No GI perforations

Robert C et al. *N Engl J Med* 2011;[Epub ahead of print].

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Investigator Commentary: Ipilimumab for Untreated Metastatic Melanoma

This Phase III trial was launched based on the promising pilot Phase II data published by Evan Hirsch. We have learned several things about ipilimumab. You can have progression followed by regression, stable disease for months to even a year and then a response or responses that evolve over months to about a year. Therefore, evaluating responses may not tell the whole story. Considering overall survival is more important than progression-free survival. The most encouraging result is for duration of response, which suggests that with IPI, if you get a response, you have a much higher chance of staying in remission.

Ipilumumab is a well tolerated agent. The side effects of this drug are clearly immune related, and it's extremely rare that an immune-related adverse event is not relatively rapidly reversed with proper immune suppression, such as with steroids. The study of this drug is moving into the adjuvant setting with both the EORTC and ECOG sponsoring trials.

Jeffrey Weber, MD, PhD

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