5 Minute JournalClub

Key ASCO Presentations

Issue 2, 2010

For more visit ResearchToPractice.com/5MJCMT2010

Research To Practice®

CME Information

LEARNING OBJECTIVES

- 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.
- Describe the efficacy and safety of ipilimumab monotherapy in patients with melanoma and brain metastases.
- Assess the early activity and safety of GSK2118436 in patients with V600E- and non-V600E-mutant metastatic melanoma.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

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

CME Information (Continued)

FACULTY DISCLOSURES
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:

David F McDermott, MD
Assistant Professor of Medicine, Harvard Medical School
Clinical Director, Biologic Therapy Program, Beth Israel Deaconess Medical Center
Chair, Clinical Research Subcommittee, Renal Cancer Program
Dana Farber/Harvard Cancer Center
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Eisai Inc, Genentech BioOncology, Genzyme Corporation, GlaxoSmithKline, Roche Laboratories Inc; *Consulting Agreements:* Biogen Idec, Wyeth.

CME Information (Continued)

Steven J O'Day, MD
Chief of Clinical Research
Director of the Melanoma Program
The Angeles Clinic and Research Institute
Santa Monica, California

Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Bristol-Myers Squibb Company, GlaxoSmithKline, Roche Laboratories Inc, Schering-Plough Corporation; *Consulting Agreement and Speakers Bureau:* Bristol-Myers Squibb Company; *Paid Research:* Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Bristol-Myers Squibb Company, Eisai Inc, Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Millennium — The Takeda Oncology Company, Roche Laboratories Inc.

Jedd D Wolchok, MD, PhD
Director, Immunotherapy Clinical Trials, Department of Medicine
Associate Attending Physician, Melanoma-Sarcoma Service
Associate Director, Ludwig Center for Cancer Immunotherapy
Memorial Sloan-Kettering Cancer Center
New York, New York

Advisory Committee: Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation.

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

O'Day S et al.
Proc ASCO 2010;Abstract 4.

Hodi FS et al.
Proc ASCO 2010;Abstract 8509.

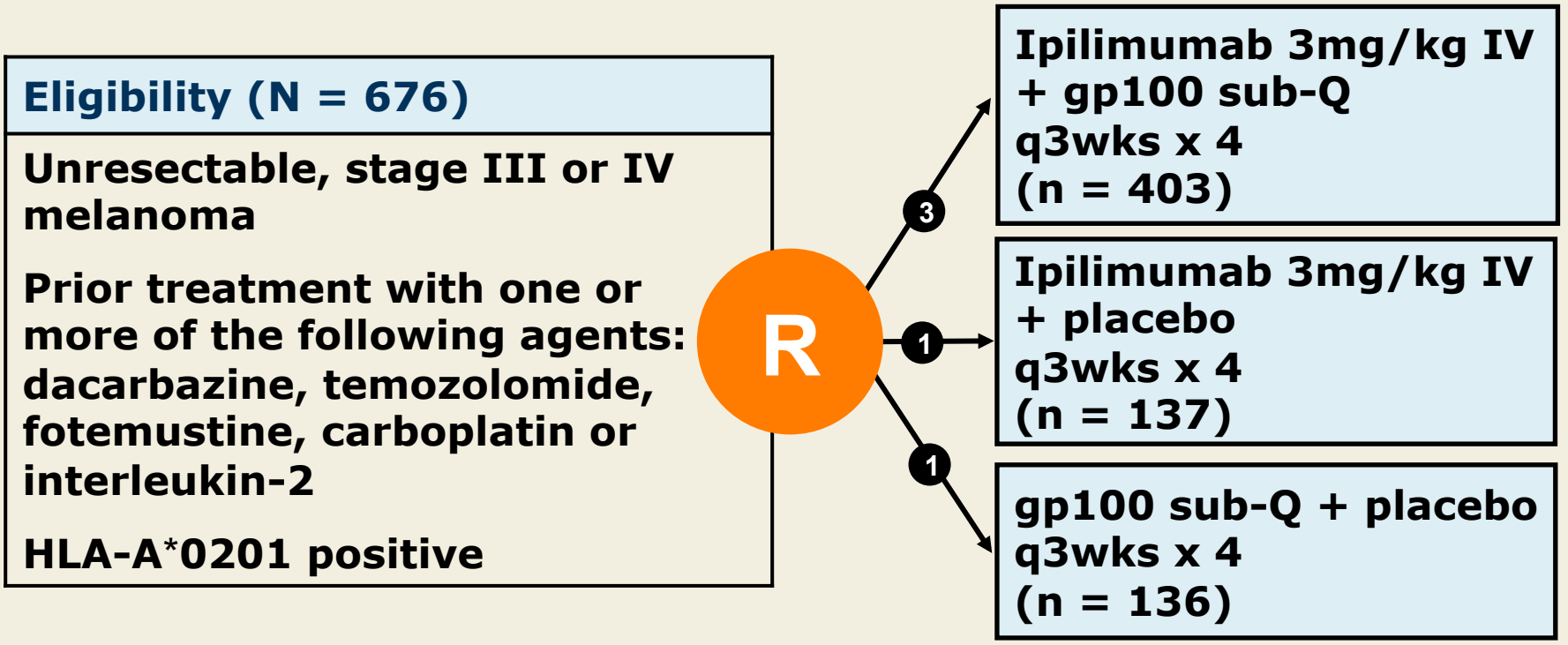
Hodi FS et al.
N Engl J Med 2010;[Epub ahead of print].

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].

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].

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].

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

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

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

Phase II Trial of Ipilimumab Monotherapy in Melanoma Patients with Brain Metastases

Lawrence DP et al.

Proc ASCO 2010;Abstract 8523.

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.

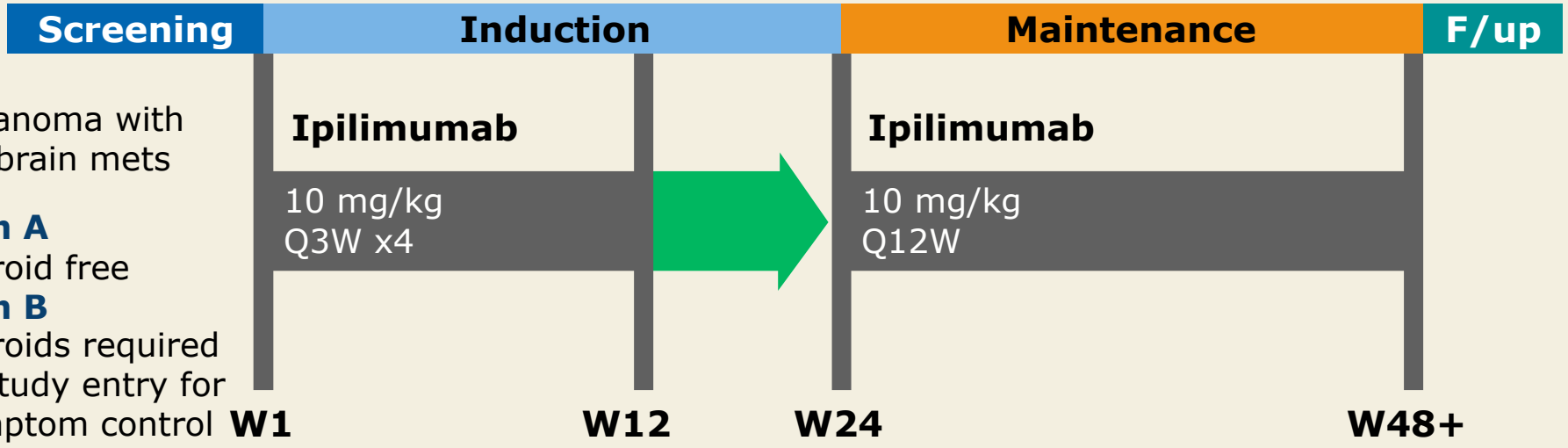
Lawrence DP et al. *Proc ASCO* 2010;Abstract 8523.

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.

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



Ipilimumab dosing:

W1 W4 W7 W10 W24 W36 W48+

Tumor assessment*

Non-CNS lesions:	Bs	W6	W12, 16	W24	Q12W/End of treatment
CNS lesions:	Bs	W6	W12, 16, 20†		Q12W/End of treatment

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.

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.

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.

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.

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

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

Phase 1/2 Study of GSK2118436, a Selective Inhibitor of Oncogenic Mutant BRAF Kinase in Patients with Metastatic Melanoma and Other Solid Tumors

Kefford R et al.

Proc ASCO 2010;Abstract 8503.

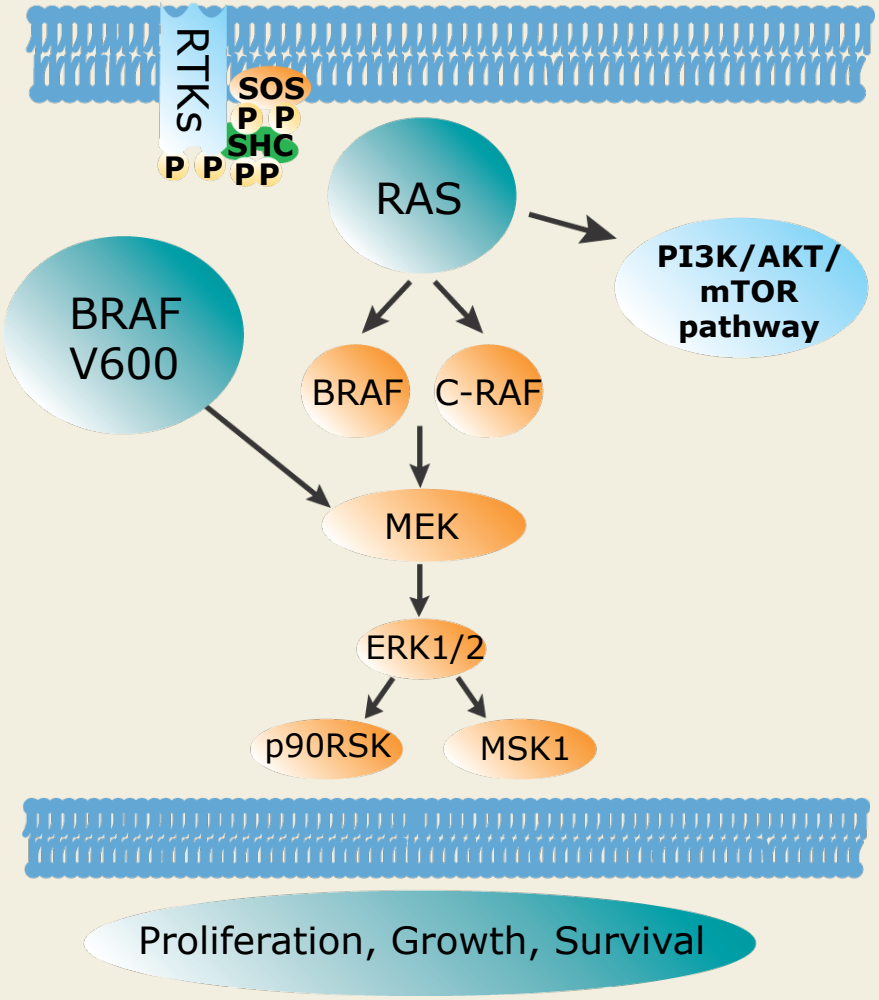
Introduction

- Activating mutations in the BRAF proto-oncogene, such as V600E, K, D, G and K601E are present in 50% of cutaneous melanomas.
  - In preclinical models, these mutations have the hallmarks of an oncogene addiction.
- The selective V600E BRAF inhibitor PLX 4032 has demonstrated clinical activity in metastatic melanoma and serves as a proof of concept for V600E BRAF mutation as a therapeutic target (Flaherty K. ASCO 2009;Abstract 9000).
- GSK2118436 is an ATP competitive, reversible inhibitor of RAF kinases, which selectively inhibits V600 mutant BRAF.
- **Current study objective:**
  - First-in-human study to evaluate the safety, dosing recommendations for future study, pharmacokinetics and pharmacodynamics and clinical activity of GSK2118436 in a Phase I study population intentionally enriched for patients with BRAF mutant tumors.

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

MAPK Pathway in Melanoma

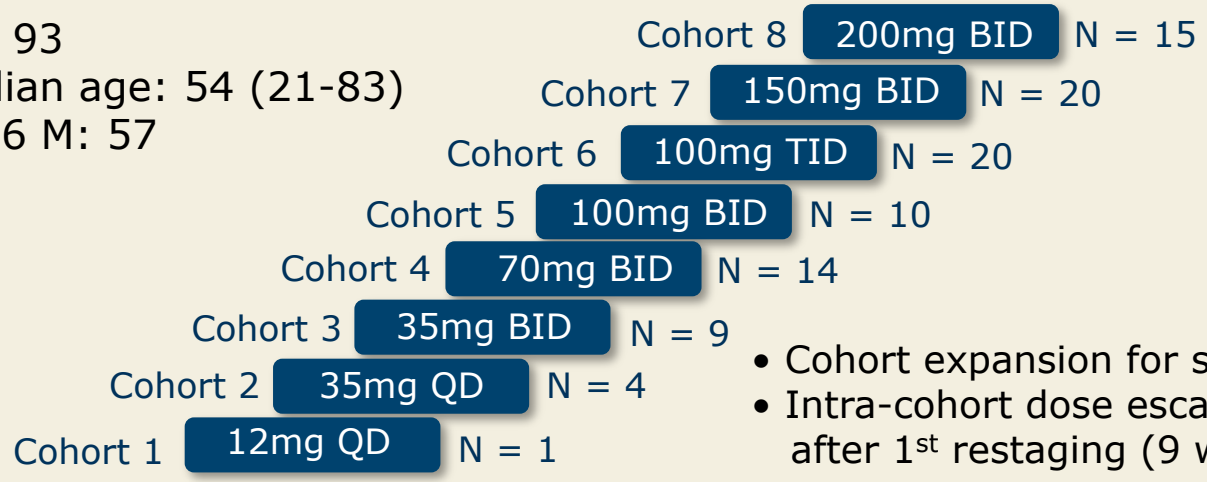
- Pathway frequently mutated
  - NRAS mutations: ~15%
  - BRAF Mutations: ~50%
- BRAF activating mutations
  - V600E most common (>80%)
  - Others include V600K/D/G; K601E
  - V600 mutant BRAF constitutively active (~500x WT)
- Preclinical oncogene addiction
- Clinical proof-of-concept
  - PLX4032 activity in V600E metastatic melanoma



Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

GSK2118436 Cohort Accrual

N = 93
Median age: 54 (21-83)
F: 36 M: 57



- Cohort expansion for safety or activity
- Intra-cohort dose escalation: allowed after 1st restaging (9 weeks)

Tumor Type	BRAF V600 mutant	BRAF WT (or other mutant)*
Melanoma	76 (82%)	9 (10%)
Papillary thyroid carcinoma	2 (2%)	0
Colorectal cancer	4 (1%)	1 (1%)
Ovarian	1 (1%)	0

* Includes subject with unknown BRAF mutation type.

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

All Cause Adverse Events GSK2118436 ≥ 150 mg BID (N = 35)

		All Grades	>Grade 3
General	Pyrexia	37%	—
	Fatigue	34%	—
	Chills	11%	—
Gastrointestinal	Nausea/vomiting	23%	—
	Diarrhea	14%	3%
Hematologic	Anemia	11%	—
	Neutropenia	11%	3%
Other	Headache	29%	3%
	Musculoskeletal pain	11%	—
	Decreased appetite	11%	—
	Oropharyngeal pain	11%	—
	Skin (any)	72%	—

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

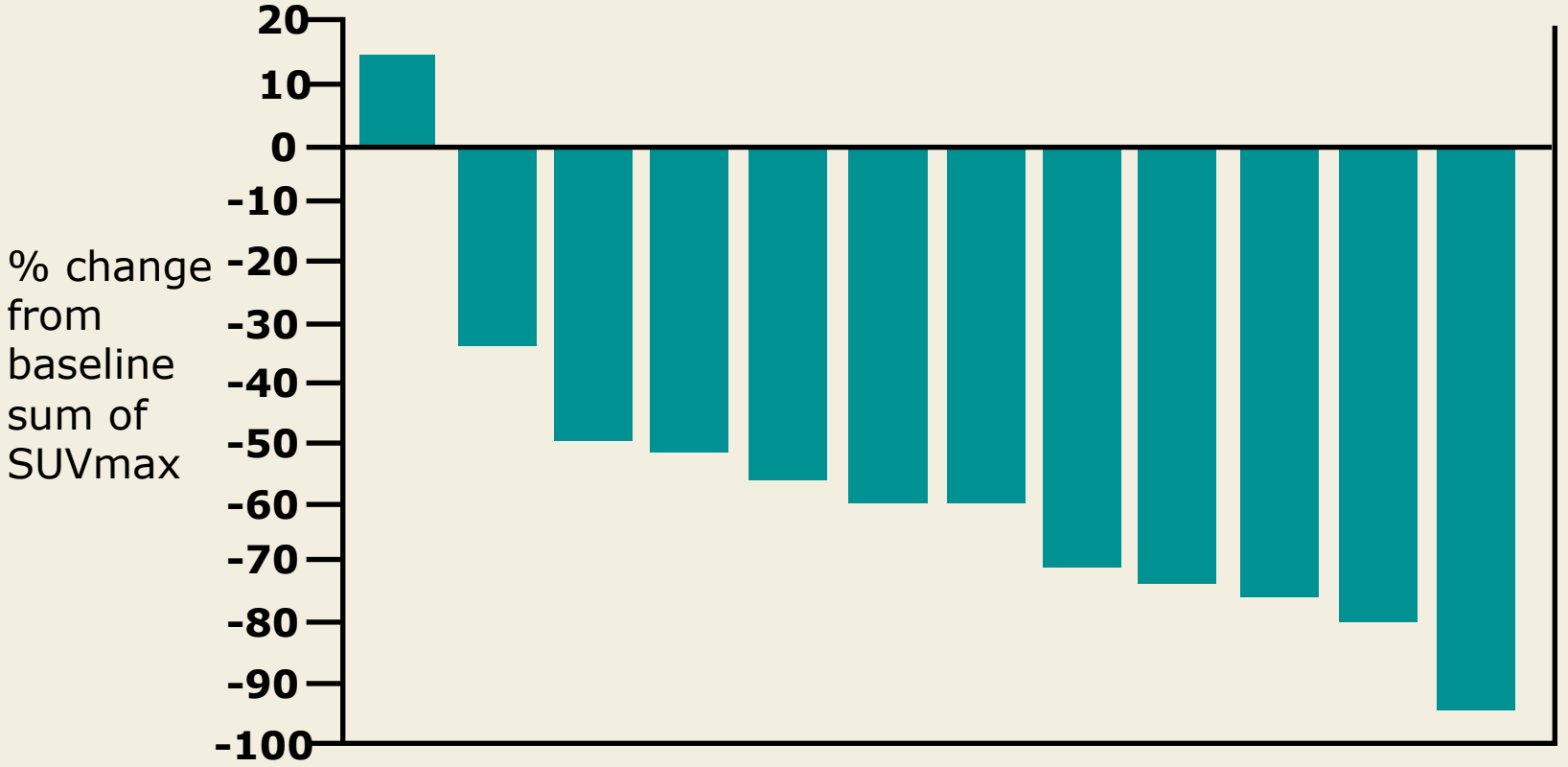
Skin Adverse Events GSK2118436 ≥ 150 mg BID

	All Grades	>Grade 3
Rash	31%	—
Skin lesions (other)	31%	—
Hyperkeratosis	11%	—
Actinic keratosis	9%	—
Palmar-plantar erythrodysesthesia (PPE)	6%	—
Squamous cell carcinoma (SCC)	—	9%*

* Incidence of SCC since data cut-off: ~15%

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

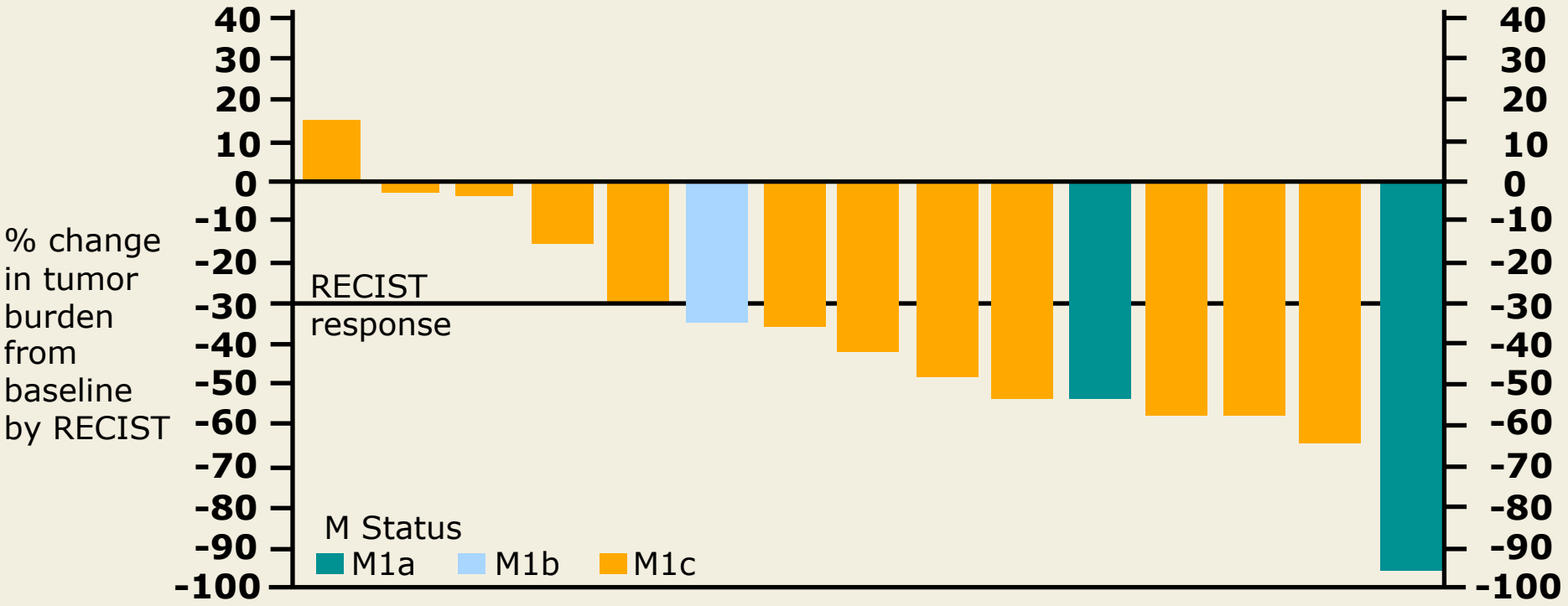
FDG-PET in V600 Mutant Melanoma (≥150 mg BID)



Mean ↓ SUVmax: 31% (70 mg BID); 58% (150 mg BID)

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

Interim Best Response: ≥150 mg BID in V600 Mutant Melanoma



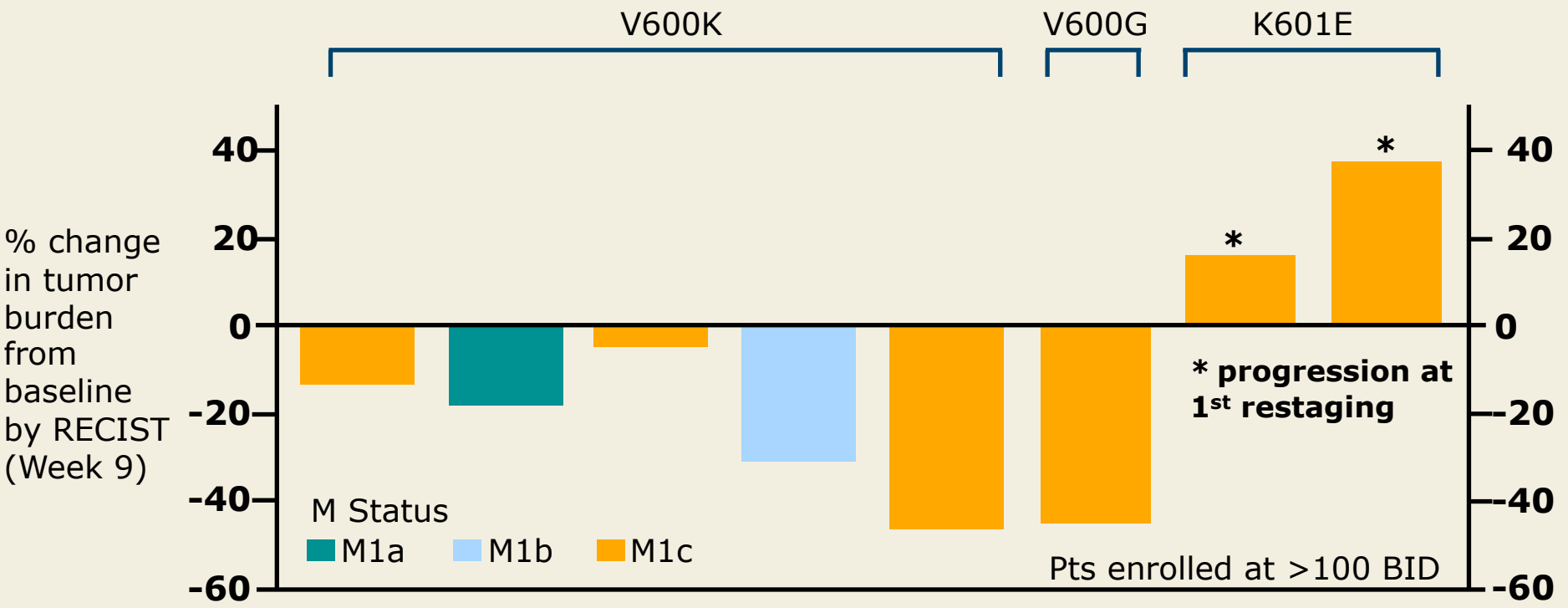
- 150 BID: 7/11
- 200 BID: 3/5

} 63% PR

- Lower dose cohorts: 16/41=39% OR, 1 CR

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

Preliminary Activity in Non-V600E BRAF Mutant Melanoma



- Evidence of activity in V600K/G mutants
- K601E: No activity to date (rapid progression)
- BRAF WT (Not shown): Rapid progression in 2/3 pts (1st restaging)

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

Clinical Activity in Evaluable Patients

- **BRAF V600 Mutant Melanoma (≥150 mg BID)**
  - Overall response rate = 63%
  - Responses in multiple sites: lung, bone, liver and brain
  - All responders still on study, with longest at 5+ months at data cut
- **BRAF Non-V600 Melanoma**
  - Wild type and K601E: 4/5 patients progressed at 1st restaging
- **V600E Mutant Tumors (Non-Melanoma)**
  - Papillary thyroid carcinoma (n = 2)
    - 100 mg TID: Partial response; 31% decrease in tumor burden
    - 150 mg BID: Progressive disease/mixed response; target lesions decreased 66%
  - Ovarian cancer (n = 1)
    - 100 mg BID: Stable disease; 14% decrease in tumor burden
  - Colorectal cancer (n = 3)
    - 100 mg TID (n = 2) and 150 mg BID (n = 1): Progressive disease

Kefford R et al. *Proc* ASCO 2010;Abstract 8503.

Conclusions

- GSK2118436 is a potent and highly selective inhibitor of BRAF V600 mutant enzyme/cell lines with excellent bioavailability and target inhibition (data not shown).
- GSK2118436 is tolerable and safe.
  - Key adverse events: Pyrexia and squamous cell carcinoma
- GSK2118436 is active in BRAF V600E mutant melanoma.
  - Emerging evidence of activity against V600K/G mutations
  - BRAF V600 mutant melanoma, ORR = 63%
  - No activity against K601E-mutant melanoma
- Recommended dose for part 2 of the study: 150 mg BID
  - Melanoma and other BRAF V600-mutant tumors
  - Specific cohort to study activity in brain

Kefford R et al. *Proc ASCO* 2010;Abstract 8503.

Investigator comment on a Phase I/II study of a selective mutant BRAF kinase inhibitor

Fifty to 60 percent of patients with melanoma have tumors with BRAF mutations, and a number of BRAF inhibitors are now being studied. The first of these agents, PLX4032, was reported on by Drs Chapman and Flaherty at ASCO last year and demonstrated a 70 to 80 percent response rate or stable disease. This caused a huge splash. It's still exciting, but with longer follow-up some concern has arisen that resistance develops to these drugs, and recurrences can be explosive, particularly in the brain.

At ASCO this year, Dr Kefford presented Phase I and II data on a similar BRAF inhibitor, GSK2118436, and they also showed dramatic response — 60 to 70 percent — with comparable side effects. So it appears that we have two highly selective BRAF drugs that are racing to obtain regulatory approval.

Some squamous cell carcinomas of the skin have occurred secondary to these agents, and we monitor the skin carefully. It may be that blocking the BRAF or MAP kinase pathways accelerates other pathways, such as MEK, which may relate to squamous cell stimulation. However, these agents are generally well tolerated and can be administered chronically.

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