5 Minute JournalClub

Key ASCO Presentations
Issue 2, 2010

B-raf Kinase Inhibitor GSK2118436 as Therapy for Patients with Metastatic Melanoma and Other Solid Tumors

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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

- Assess the early activity and safety of GSK2118436 in patients with V600E- and non-V600E-mutant metastatic melanoma.

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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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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
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Miami, Florida

B-raf Kinase Inhibitor GSK2118436 as Therapy for Patients with Metastatic Melanoma and Other Solid Tumors

Presentation discussed in this issue

Kefford R et al. **Phase I/II study of GSK2118436, a selective inhibitor of oncogenic mutant BRAF kinase, in patients with metastatic melanoma and other solid tumors.** *Proc ASCO* 2010;**Abstract 8503**.

Slides from a presentation at ASCO 2010 and transcribed comments from a recent interview with Steven J O'Day, MD (6/25/10)

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.

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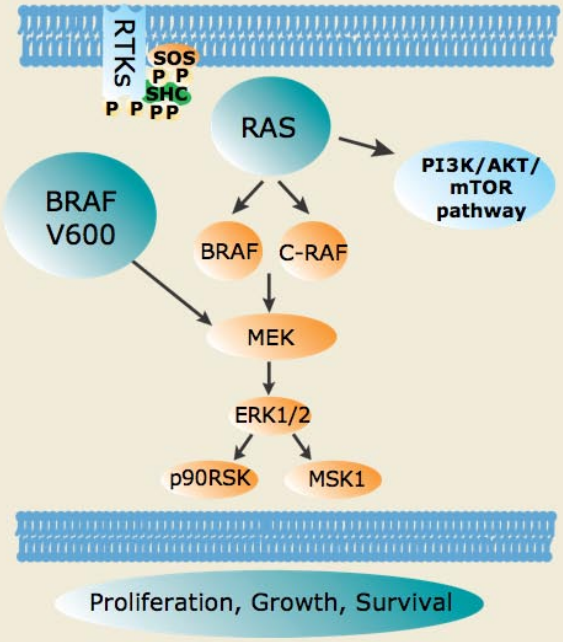
MAPK Pathway in Melanoma

- 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.

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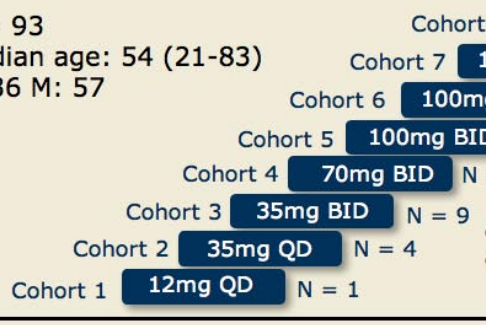
GSK2118436 Cohort Accrual

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.

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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.

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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.

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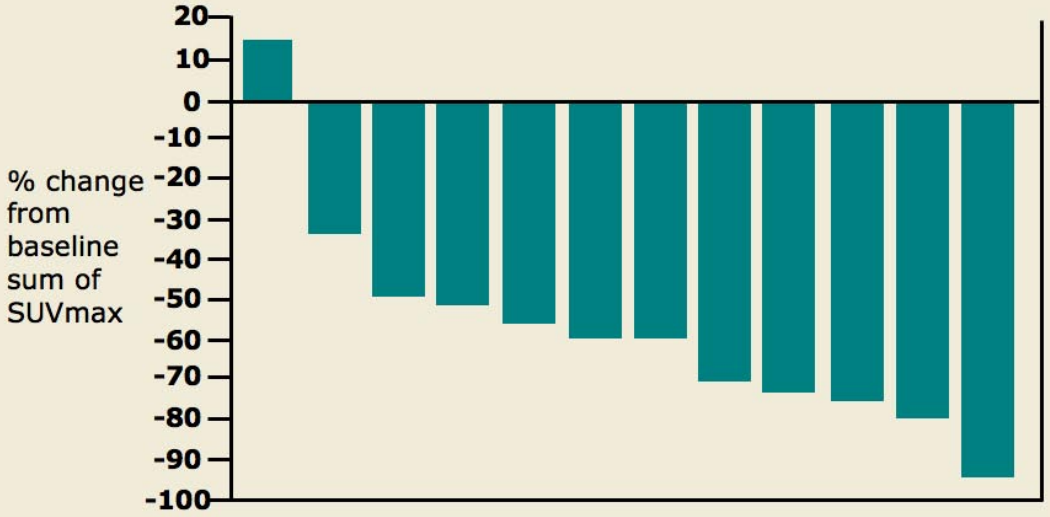
FDG-PET in V600 Mutant Melanoma (≥150 mg BID)



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

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

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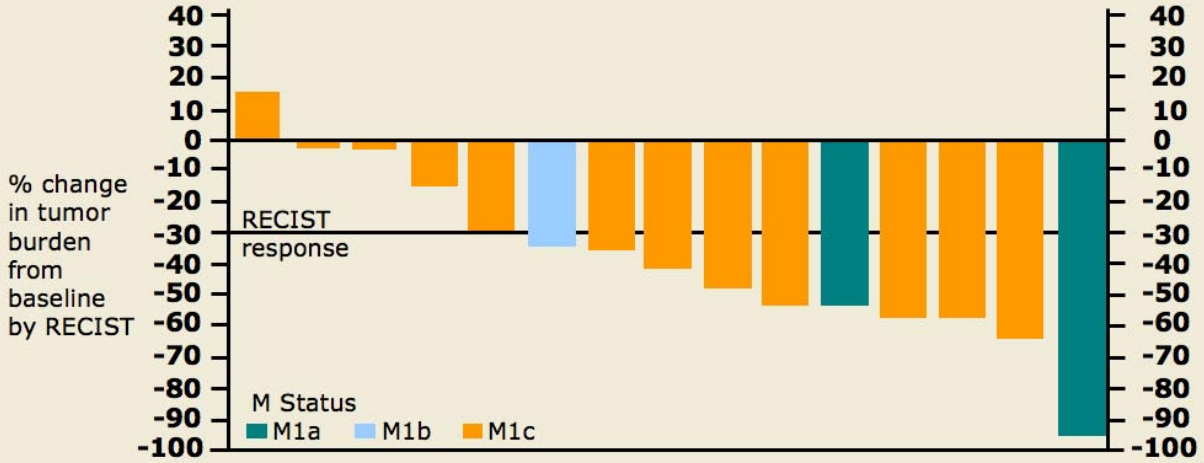
Interim Best Response: ≥150 mg BID in V600 Mutant Melanoma



- 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.

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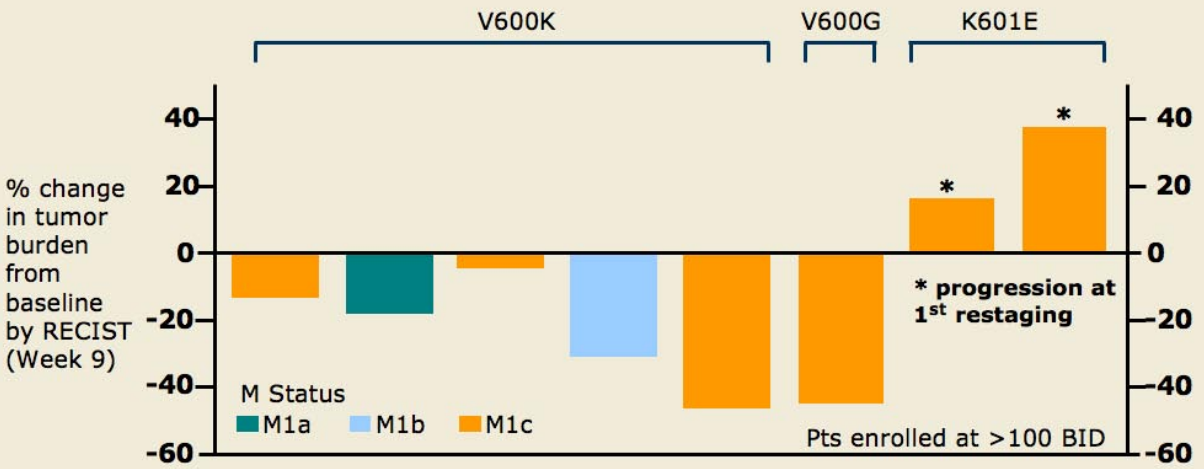
Preliminary Activity in Non-V600E BRAF Mutant Melanoma



- 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.

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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