

Hot Topic: Anti-CTLA-4: Development and Regulatory Issues

Review of Ipilimumab Clinical Development Program and Data

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**Earliest trials of ipilimumab were small phase II
pilot studies**

Initial Ipilimumab Trials: Durable Responses in Patients With Metastatic Melanoma

	Combination	mAb Dose	Dosing	ORR (%)	Duration of Response (mo)
Hodi 2003 ¹	No, but previously immunized with defined melanosomal antigens	3 mg/kg	Single	0 (n=4)	–
	No, but previously vaccinated with irradiated, autologous GM-CSF–secreting tumor cells	3 mg/kg	Single	100 “IRs” (n=3)	NA
Phan 2003 ²	gp100 peptides	3 mg/kg	q3w	21 (n=14)	11-15+
Attia 2005 ³	gp100 peptides	1-3 mg/kg	q3w	13 (n=56)	4-34+
Maker 2006 ⁵	No	3-9 mg/kg	q3w	11 (n=46)	4-16+

GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin.

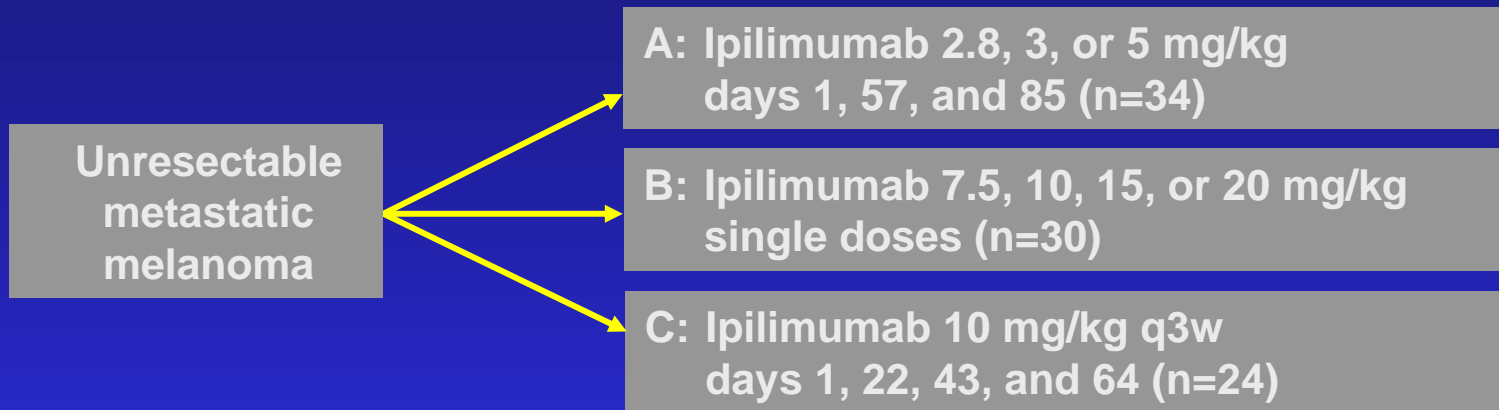
1. Hodi et al. *Proc Natl Acad Sci U S A*. 2003;100:4712;
2. Phan et al. *Proc Natl Acad Sci U S A*. 2003;100:8372;
3. Attia et al. *J Clin Oncol*. 2005;23:6043;
4. Maker et al. *Ann Surg Oncol*. 2005;12:1005;
5. Maker et al. *J Immunother*. 2006;29:455.

CTLA-4 antibody: phase II combination trial with vaccine

(Attia et al *J Clin Oncol* 2005 23:6043)

- CTLA-4 antibody at 1 to 3 mg/kg with two peptides from the melanoma antigen gp100 and Montanide ISA 51 adjuvant
- 7 responses in 56 patients (2 CR, 5 PR) in second line therapy for stage IV melanoma (13% RR)
- Five of 7 responders were sustained over 25 months and ongoing
- Unusual side effects were seen: colitis, diarrhea, hypophysitis, hepatitis, nephritis with azotemia, rash and vitiligo; they were **autoimmune or autoinflammatory**
- 5 responses in 14 who had grade III or more immune response adverse events (irAE) vs 2/42 without irAE (**p=0.008**)

Phase 1/2 Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma



Cohort	Response		Duration (d)	Disease Control Rate (%)
A (n=34)	ORR	1 PR	246	15
	SD	4	29, 61, 168, 172	
B (n=30)	ORR	1 PR	211	13
	SD	3	37, 109, 395	
C (n=24)	ORR	1 CR, 1 PR	263, 275	39
	SD	7	99, 190, 194, 194, 246, 351, 379	(Median OS 13.5 months)

Phase 2 Randomized Trial: Ipilimumab ± DTIC in Metastatic Melanoma

- Stage IV unresectable melanoma
- Chemotherapy and vaccine naive

Reassessment every 12 weeks until PD
Primary end point: Safety and activity

Arm 1: Ipilimumab 3 mg/kg
qmo × 4
(n=37)

Arm 2: Ipilimumab 3 mg/kg
qmo × 4
+
DTIC 250 mg/m² for 5 days
qmo up to 6 cycles
(n=35)

Optional
crossover if PD

Efficacy	Ipilimumab	Ipilimumab + DTIC
CR	0	2 (6%)
PR/PR unconfirmed	3 (9%)	6 (17%)
SD	4 (11%)	4 (11%)
PFS	2.7 mo	3.3 mo
OS	11.7 mo	14.8 mo
Grade 3/4 adverse event	7 (18.5%)	10 (28.6%)
Adverse event	Primarily gastrointestinal, rash, and injection site reaction	

PFS = progression-free survival.

Fischkoff et al. ASCO, 2005. Abstract 7525; Hersh et al. ASCO, 2004. Abstract 7511.

Phase II Trial of Ipilimumab \pm Vaccine at NCI

- 139 patients at differing doses (3-9 mg/kg) \pm peptide vaccine; most were in second-line therapy
- 15.7 month OS
- 17% ORR by RECIST
- 2.9 month median time to progression
- No difference in response or OS \pm peptides; most received peptides
- No impact of steroids on response or OS

NCI = National Cancer Institute; RECIST = Response Evaluation Criteria for Solid Tumors.

Downey et al. *Clin Cancer Res.* 2007;13:6681.

2 Trials Using Ipilimumab as Adjuvant Therapy Show Correlation of Autoimmunity With Benefit

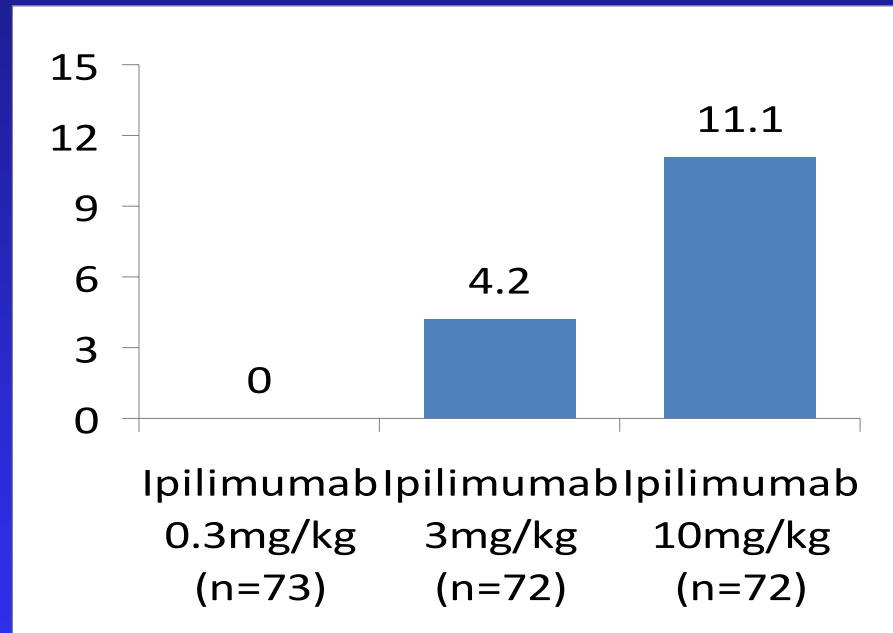
- 59 patients treated with CTLA-4 antibody ± a multipeptide vaccine
- 4/24 patients with grade 2-3 IRAEs had a relapse, vs 13/35 without an IRAE ($P < 0.03$; Fisher's exact)
- 1 death in 24 patients with IRAEs vs 3/35 without an IRAE
- These data have supported a new EORTC study of ipilimumab at 10 mg/kg vs observation in patients with resected stage III melanoma

Second-Line Ipilimumab Trials

- Registrational monotherapy program includes 487 patients with stage III-IV metastatic melanoma from 3 clinical trials
 - Trial **008**, evaluating overall response rate in patients progressing on or following standard treatment at 10 mg/kg ipilimumab times 4 every 3 weeks
 - Trial **022**, evaluating efficacy of 3 doses every 3 weeks in patients who were previously treated, relapsed or failed to respond to experimental treatment, or who were unable to tolerate currently approved therapies
 - Trial **007**, comparing the safety of ipilimumab \pm prophylactic budesonide
 - Three arm trial of ipilimumab at 3 mg/kg vs vaccine alone vs, combination
- Trial 008 did not meet the primary registration end point, to rule out a best objective response rate with lower boundary of the 95% CI of 10%
- However, the data included a clear dose-response in study 022, excellent survival in study 007 and best objective response rates across the 3 studies ranged from mid-single digits to mid-teens

Dose-finding trial of ipilimumab in unresectable stage III/IV melanoma: response rate varies with dose: trial 022

CR + PR (%)



$p=0.0015$

- Disease control rate (CR+ PR+ SD) also increased with increasing dose
- Rates of immune related adverse events increased with increasing dose

Unique Kinetics of Response: Ipilimumab Patients

- Some patients treated with ipilimumab have been shown to have unique time courses for their antitumor responses
- Patients may have prolonged SD followed by regression
- Some patients have an initial response with slow induction of a CR
- Others have new lesions, meaning PD, but then have either prolonged stability or a subsequent response
- These types of responses suggest that there may be other ways to assess clinical benefit than traditional response criteria

Disconnect Between Clinical and Regulatory Assessment of Ipilimumab in Clinical Trials: New Response Criteria?

- In some patients, efficacy continued to be measured by the irRC after PD per mWHO was assessed at Week 12
- Tumor progression by WHO is NOT a surrogate for drug failure in all patients
- Total measurable tumor burden (index + new lesions) was measured at each TA and compared to baseline to detect tumor shrinkage weeks to months after therapy initiation and immune activation: new irRC

SPD – sum of the product of the perpendicular diameters

First-Line Ipilimumab Registration Trial

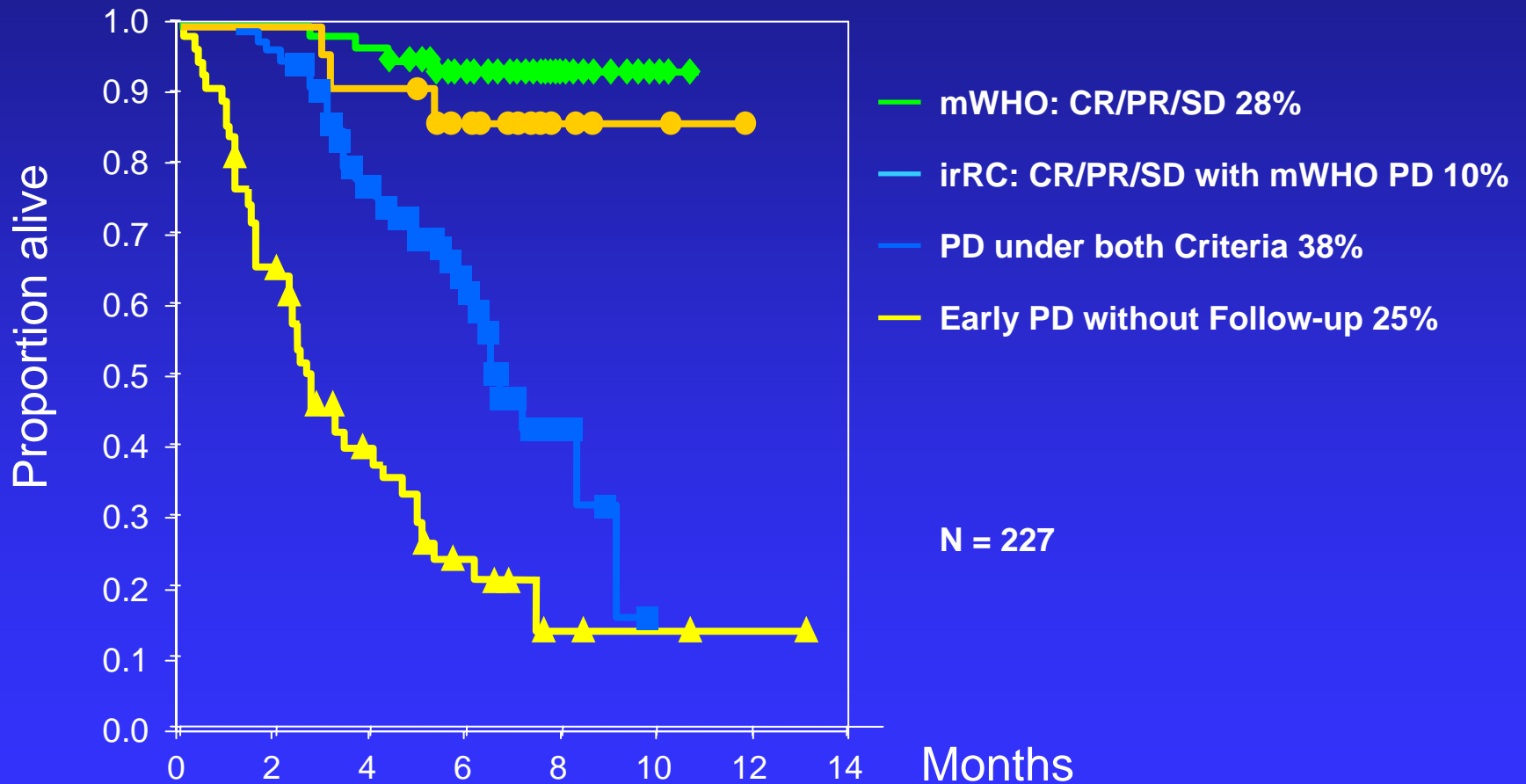
- 500 previously untreated melanoma patients were randomly allocated to receive ipilimumab at 10 mg/kg q3w × 4 with DTIC vs DTIC alone, based on the favorable median survival of 14.8 months in a randomized phase II trial
- Patients may be boosted every 3 months if they are stable or have regression
- The last patient was treated in early 2008
- The trial is ongoing, the breaking of the blind is event driven, and the predicted number of events is due ????
- By extrapolation to phase II data, median OS should be similar to 13.5, 14.8, 15.7 and 17.1 in over 250 patients

Conclusions

- Ipilimumab can produce durable clinical responses with manageable toxicity; it is an active agent in melanoma
- Responses to ipilimumab may occur with prolonged kinetics or even after progression; implicit in mechanism
- Checkpoint blockade allows for greater T-cell activation, which then leads to antitumor effect; this takes time!
- Criteria such as RECIST may be inappropriate for accurate evaluation of clinical activity of biologics like ipilimumab
- Early response assessment may impair the ability to observe clinical benefit over time

Immune-related Response Criteria (irRC) Identifies Survivors with Otherwise mWHO PD

Pooled data from Phase 2 studies CA 184-008: ipilimumab monotherapy 10 mg/kg



Hodi et al, Abstract 3008, ASCO 2008