Ipilimumab: Indications and Clinical Management

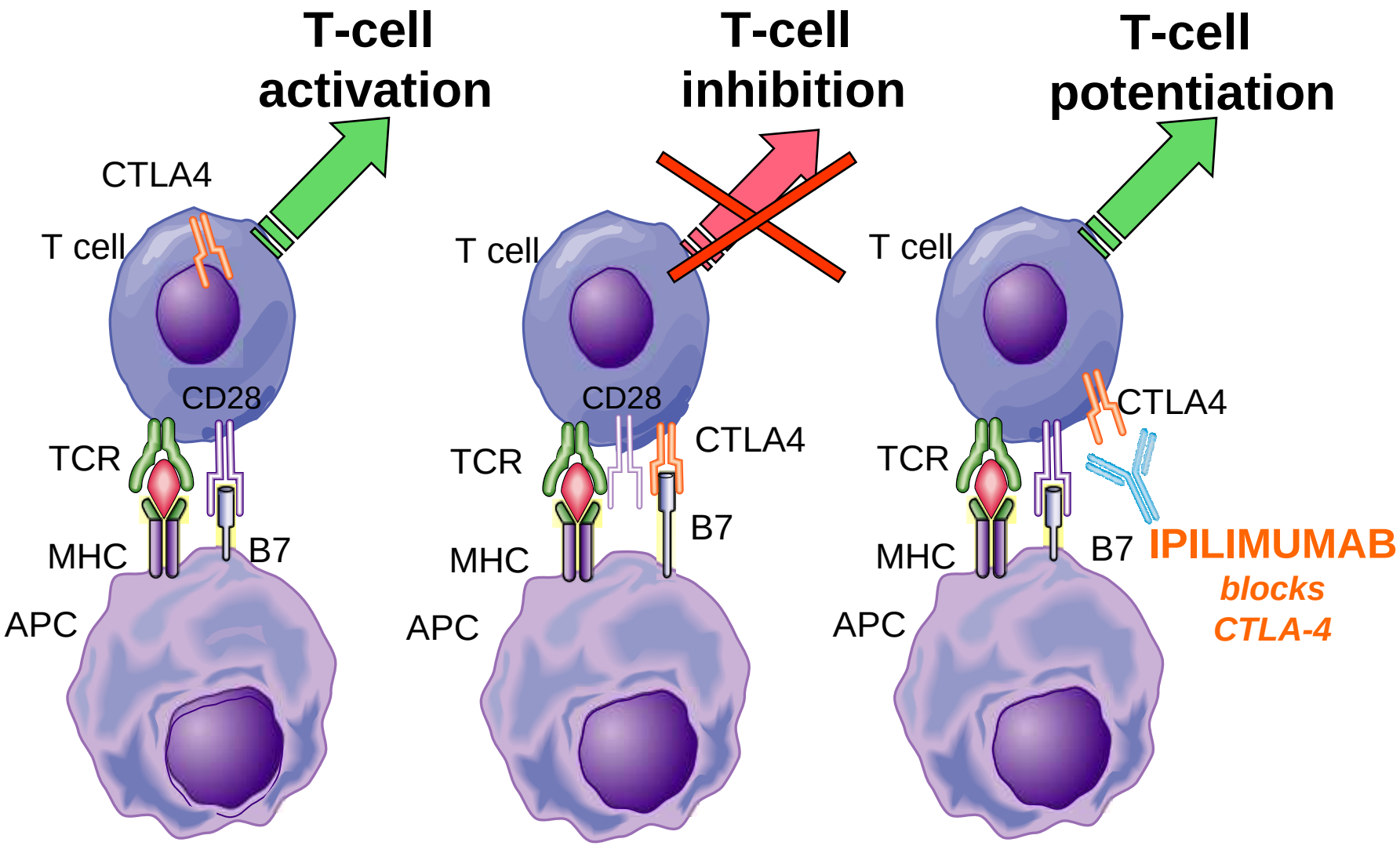
Shailender Bhatia, MD

December, 2013

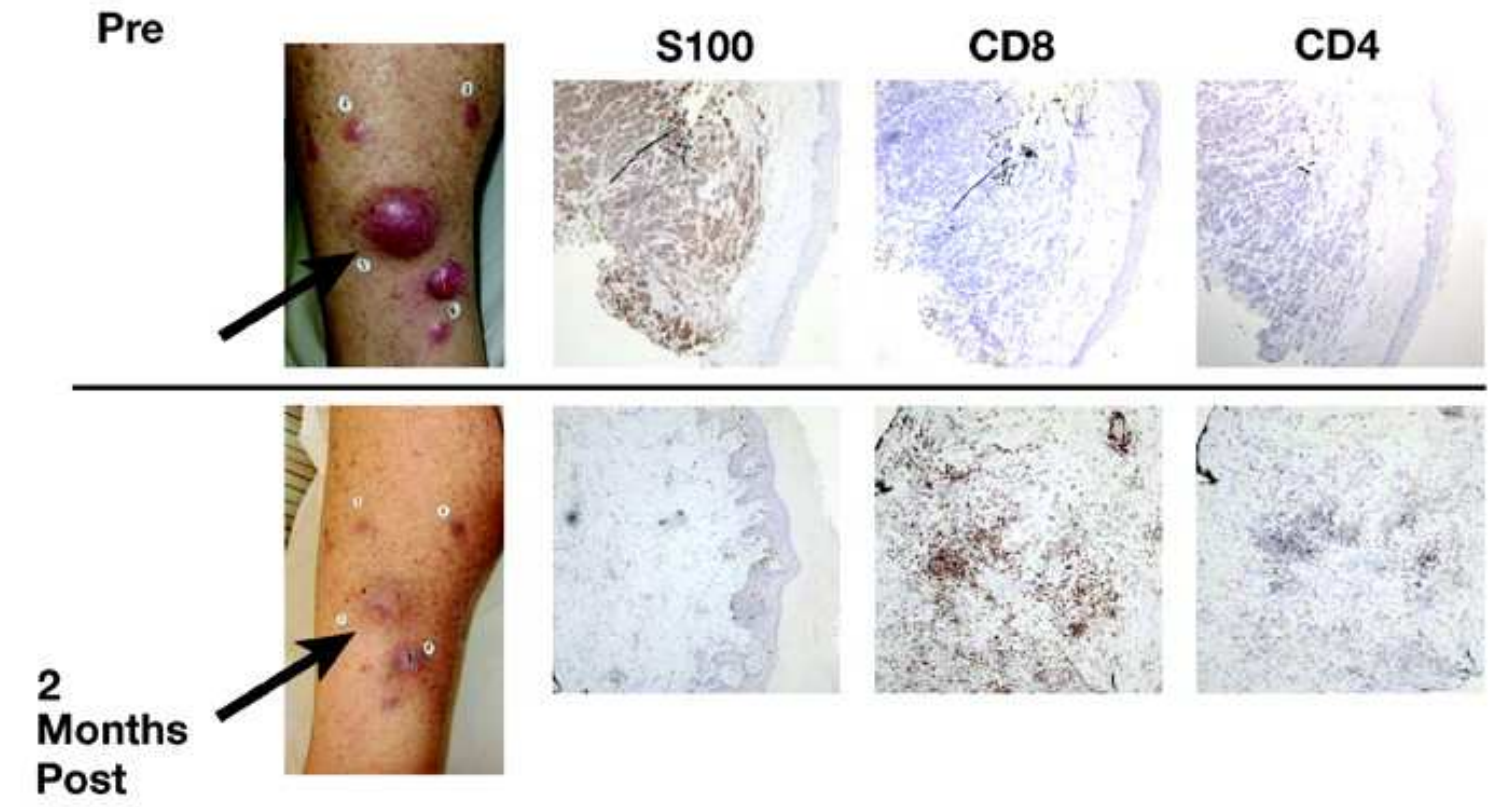
Presentation Outline

- Mechanism of action (CTLA-4)
- Clinical Indication(s) for using Ipilimumab
- Efficacy and response characteristics in melanoma
- Adverse events (AEs) and management
- Patient selection/sequencing of therapies in melanoma
- Future Directions

Ipilimumab: Mechanism of Action



Precise mechanisms of efficacy of anti-CTLA4-ab in humans are still unclear



- Clinical responses are accompanied by increased infiltration of CD8 T-cells in melanoma tumors.

[Ribas A et al. *Clin Ca Res*. 2009]

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Indication for Ipilimumab (*Yervoy*™)

Yervoy™ *was* approved by the US FDA in **2011** for "the treatment of unresectable or advanced **melanoma**"

Approved dose is **3 mg/kg** administered IV over 90 minutes every 3 weeks for a total of 4 doses.

Until recently, few standard therapy options existed for advanced melanoma.

US-FDA approved therapies for metastatic melanoma.

Dacarbazine	(1975)	No proven OS benefit
High-dose IL-2	(1998)	

Treatment of Metastatic Melanoma: An Overview
Bhatia S et al. ONCOLOGY. 2009; 23:6; 488-500

2010: The ceiling was finally broken

ORIGINAL ARTICLE

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D.,

[Hodi FS et al. NEJM. 2010]

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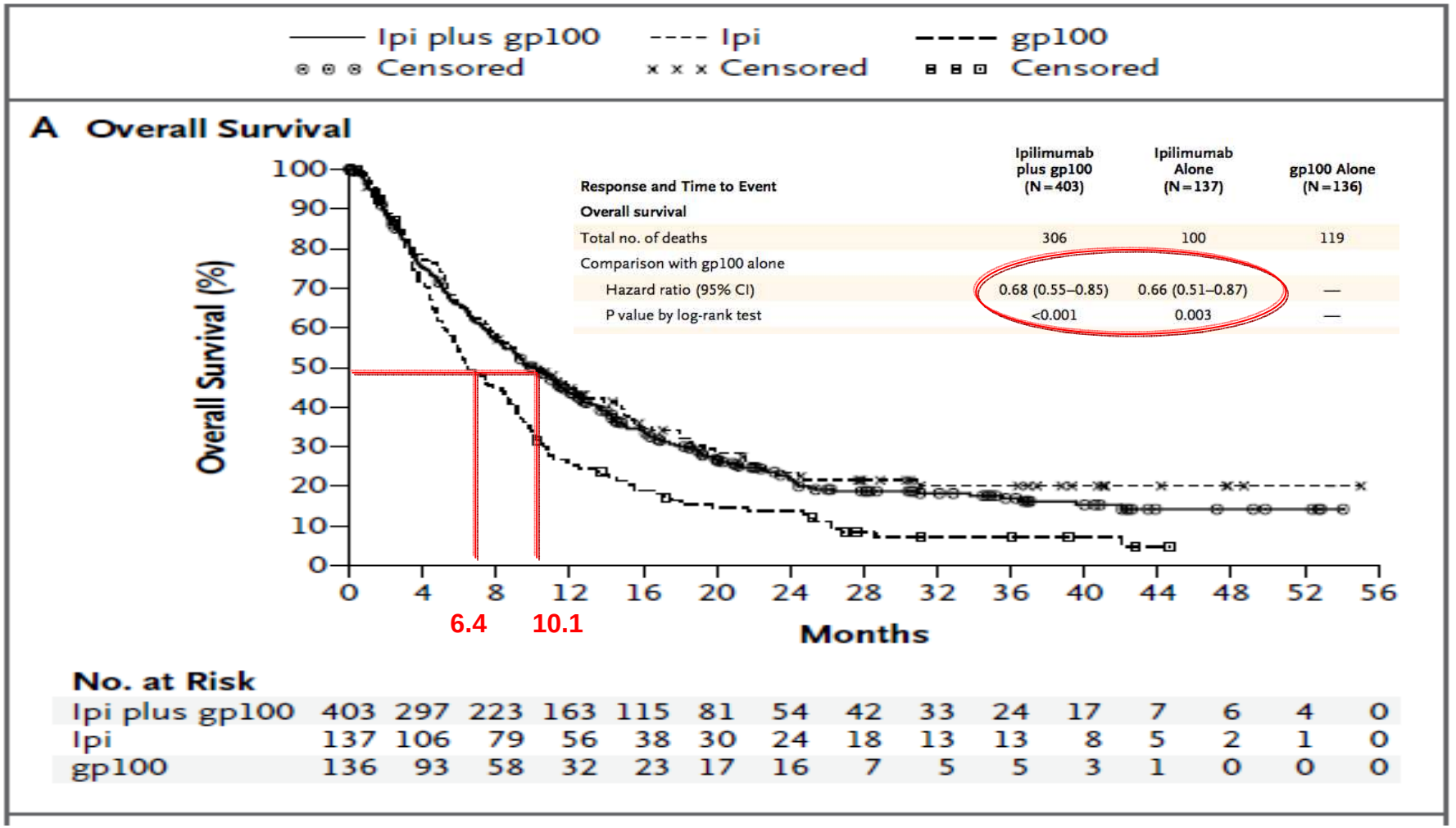
Trial Design and Patient demographics

- N = 676 melanoma patients
- 3:1:1 randomization to Ipi plus gp100, Ipi alone and gp100 alone respectively

- **Pre-treated** patient population (23% with prior IL-2)
- 7**3% M1c**; elevated LDH (38%)
- ECOG 0 (53%) or 1 (47%)

Hodi FS et al. NEJM. 2010

Improved Overall Survival was seen in both the Ipilimumab arms (3mg/kg q3 wks x4)



Hodi FS et al. NEJM. 2010

However, objective responses are infrequent, and complete remissions rare.

Response and Time to Event	Ipilimumab plus gp100 (N=403)	Ipilimumab Alone (N=137)	gp100 Alone (N=136)
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Time to event — mo			
Time to progression — median (95% CI)	2.76 (2.73–2.79)	2.86 (2.76–3.02)	2.76 (2.73–2.83)
Time to response — mean (95% CI)	3.32 (2.91–3.74)	3.18 (2.75–3.60)	2.74 (2.12–3.37)
Duration of response — median (95% CI)	11.5 (5.4–NR)	NR (28.1–NR)	NR (2.0–NR)

Responses are usually delayed (12-16 weeks), but tend to be durable.

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Ipilimumab: Delayed Onset of Responses

Acquired resistance to Ipilimumab after having an initial response may be overcome by Reinduction dosing

Reinduction‡			
Best overall response — no./total no. (%)			
Complete response	0	1/8 (12.5)	0
Partial response	3/23 (13.0)	2/8 (25.0)	0
Stable disease	12/23 (52.2)	3/8 (37.5)	0
Progressive disease	8/23 (34.8)	2/8 (25.0)	1/1 (100.0)

Hodi FS et al. NEJM. 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Dacarbazine

850 mg/m2 q 3 weeks x 8 doses

+

Ipilimumab (or placebo)

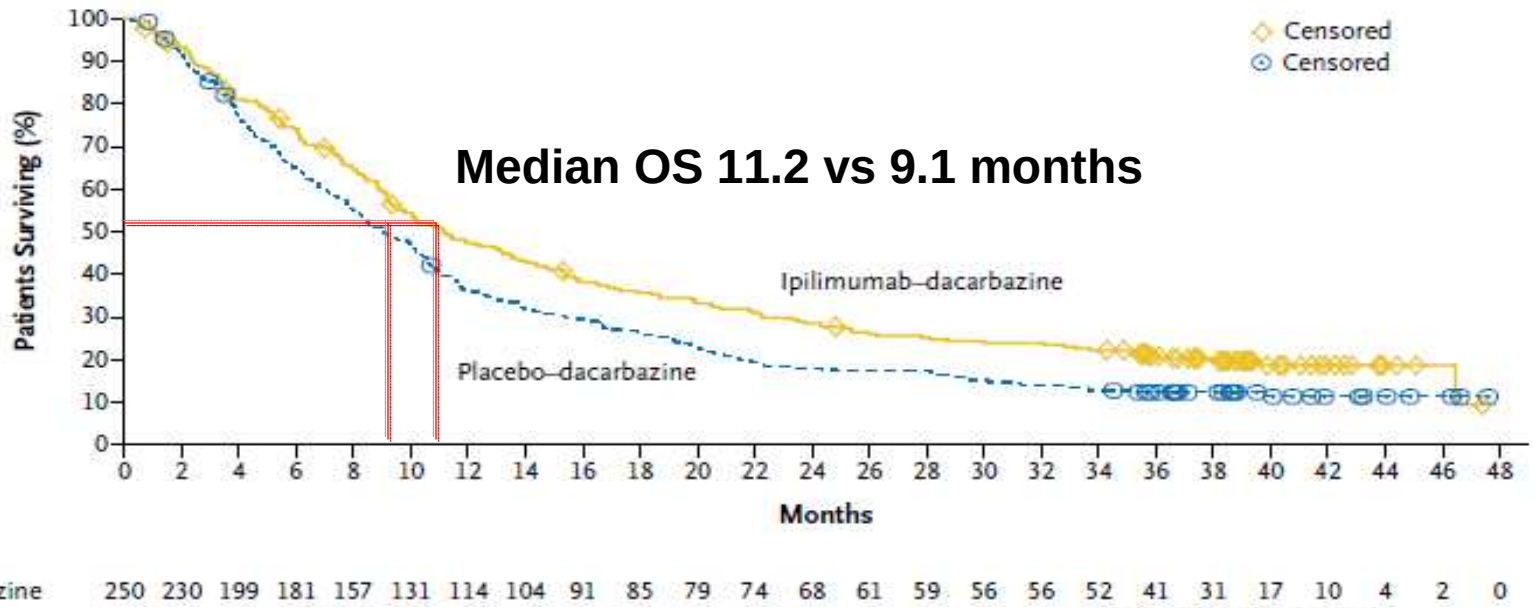
10 mg/kg q 3 weeks x 4 (**Induction**),

then q 12 wk **(Maintenance)**

[Robert C et al. NEJM. 2011]

Improved OS in the Ipilimumab+DTIC arm

A



End Point	Ipilimumab plus Dacarbazine (N=250)	Placebo plus Dacarbazine (N=252)	Hazard Ratio with Ipilimumab plus Dacarbazine (95% CI)	P Value
Primary end point: overall survival				
No. of deaths	196	218	0.72 (0.59–0.87)	<0.001
Survival — % (95% CI)				
1 yr	47.3 (41.0–53.6)	36.3 (30.4–42.4)		
2 yr	28.5 (22.9–34.2)	17.9 (13.3–22.8)		
3 yr	20.8 (15.7–26.1)	12.2 (8.2–16.5)		

Ipi mono 3mg/kg

45%

24%

[Robert C et al. NEJM. 2011]

Optimal dose and schedule still need to be determined

	Ipi 3 mg/kg alone **Re-induction allowed** **(n=137)**	**Ipi 10mg/kg + DTIC with maintenance (n=250)**
Baseline characteristics	M1c - 73% ECOG 1 - 47% Elevated LDH - 38% Pretreated	M1c - 69% ECOG 1 - 48% Elevated LDH - 49% Treatment-naive
Median OS (mos)	10.1	11.2
1 yr-OS	45%	47%
2 yr-OS	24%	28%
Best ORR	11%	15%
Grade 3-4 IRAE	15%	**41%**
Cost (Induction only) {assuming 60kg person)	~$120,000	**$400,000**
References	Hodi NEJM 2010	Robert NEJM 2011

While CR rate is low, there is a potential for long-term survival in a subset of patients

- Retrospective analysis of 1861 patients treated with Ipilimumab on several clinical trials.

  ➢OS curve begins to plateau at around 3 years and extends up to 10 years.

  ➢OS at 3 years was 21% and at 5 years was 18%

[Hodi FS et al. 2013 ESMO (abstract # LBA24)]

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Adverse Events from Ipilimumab

Immune-related AE	Any grade (%)	Grade 3 or higher (%)
Any IrAE	**60**	**15**
Dermatologic (pruritis, rash, vitiligo)	43	2
GI (Diarrhea, colitis)	29	8
Endocrine (Hypohysitis, hypothyroidism, adrenal insuff)	8	2
Hepatic	4	0
Others	5	2

[Hodi FS et al. NEJM. 2010]

Adverse Events (contd.)

- Toxicities are **manageable** and usually **reversible** with immunosuppression, when **identified and treated promptly**.

Type of Immune-Related Adverse Event	Median Time to Onset, wk	Median Time From Onset to Resolution, wk
Skin	3	5
Hepatic	3-9	0.7-2.0
Gastrointestinal reactions	8	4
Endocrine	7-20	NR

[Weber JS et al. Cancer. 2013]

Unusual (immune-mediated) AEs have also been reported, but are infrequent.

Inflammatory Enteric Neuropathy With Severe Constipation After Ipilimumab Treatment for Melanoma

A Case Report

Shailender Bhatia, Bertrand R. Huber,† Melissa P. Upton,† and John A. Thompson**

[Bhatia S et al. JIT. 2009]

- Neuropathy, meningitis, interstitial nephritis, pneumonitis, sarcoidosis, eosinophilia, pericarditis, pancreatitis, episcleritis/uveitis *et cetera* have been reported.

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How to choose amongst therapeutic options?

1. Establish goals of care
    - Durable disease-control
    - Rapid symptom palliation
    - Quality-of-life

2. Match desired goals to the safety/efficacy characteristics of the therapy
    - Rate of tumor regression (ORR) or clinical benefit
    - Kinetics of response (rapid vs delayed)
    - Duration of response
    - AEs
    - ?Cost

How to choose amongst therapeutic options?: The **SB** approach

	BRAF wild type	**BRAF mutated**
Low Volume, Asymptomatic disease	**Immunotherapy (HD IL-2 or Ipilimumab or other)**	**Immunotherapy (preferred)** **Vemurafenib (fine)**
Bulky disease, Symptomatic	**Chemotherapy** **Ipilimumab (if life expectancy >12 weeks**	**Vemurafenib followed by immunotherapy**

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True impact of Ipilimumab's success story goes far beyond Melanoma

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Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

[Topalian S et al. NEJM. 2013; Brahmer J et al. NEJM. 2013]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

[Wolchok J et al. NEJM. 2013]

Near-CRs seen in a large proportion of pts

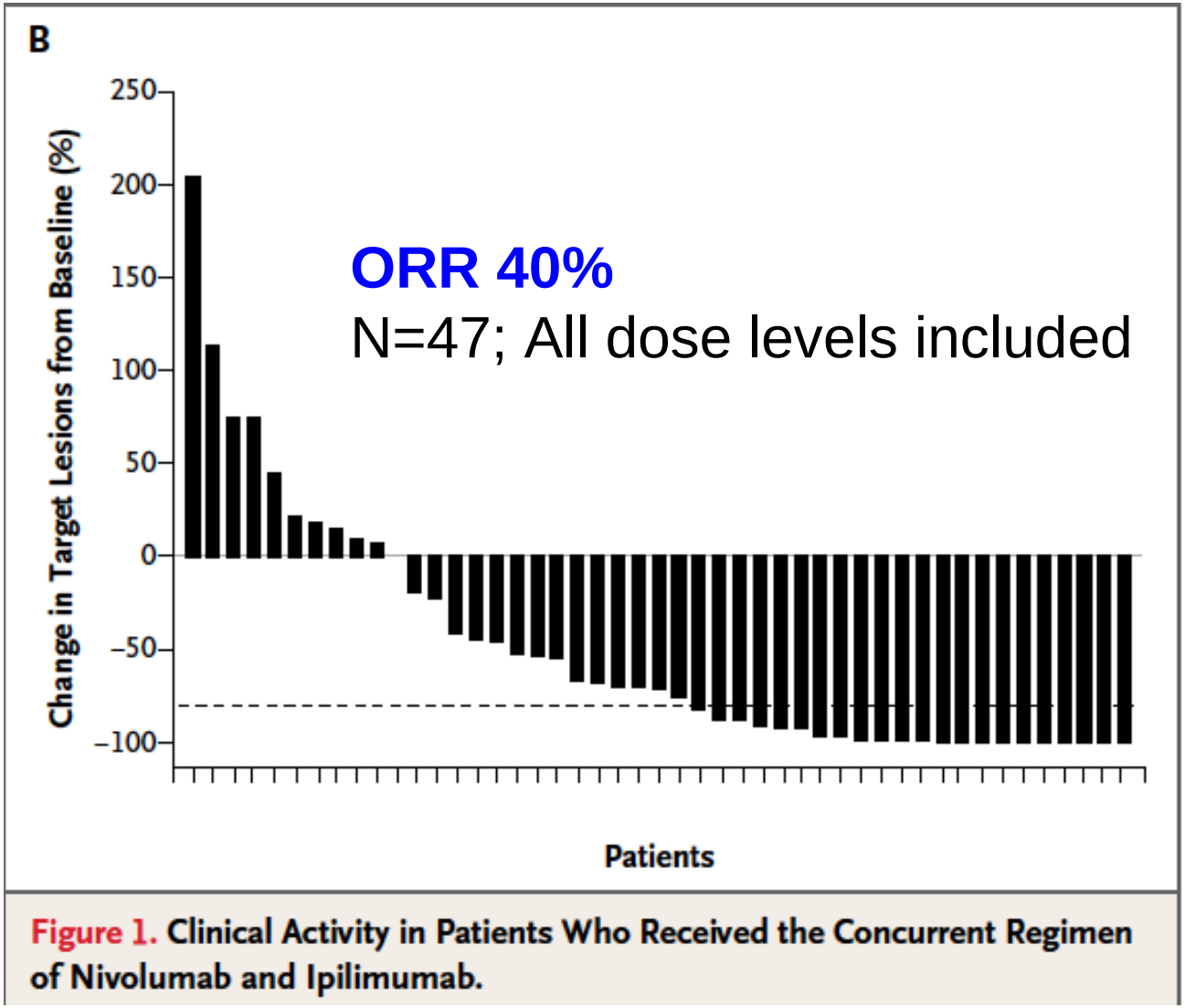
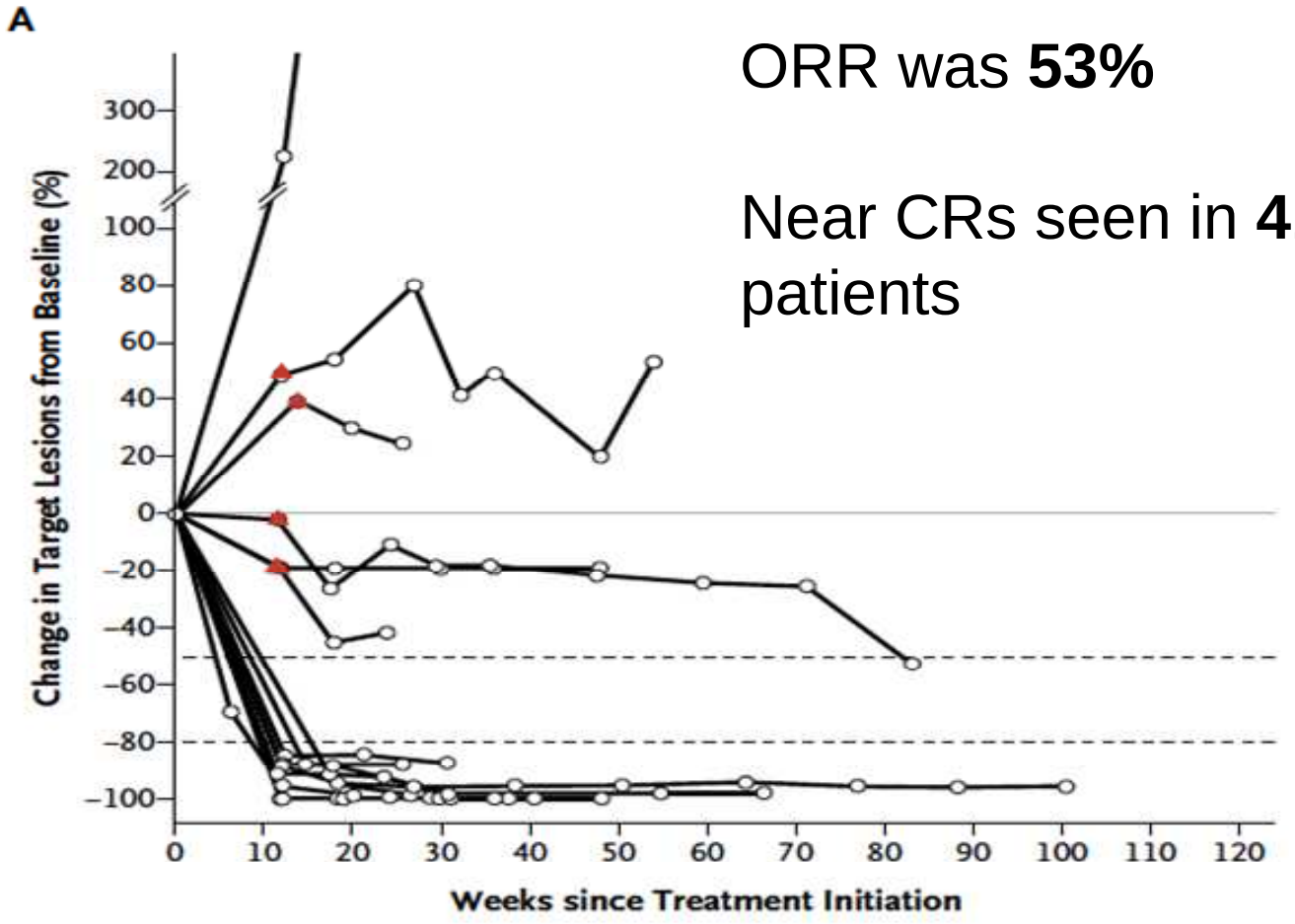


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

[Wolchok J et al. NEJM. 2013]

Tumor regression occurs faster and much more frequently than Ipilimumab



ORR was **53%**

Near CRs seen in **41%** of all patients

Nivo (1 mg/kg) and Ipi (3 mg/kg)

[Wolchok J et al. NEJM. 2013]

Safety Observations

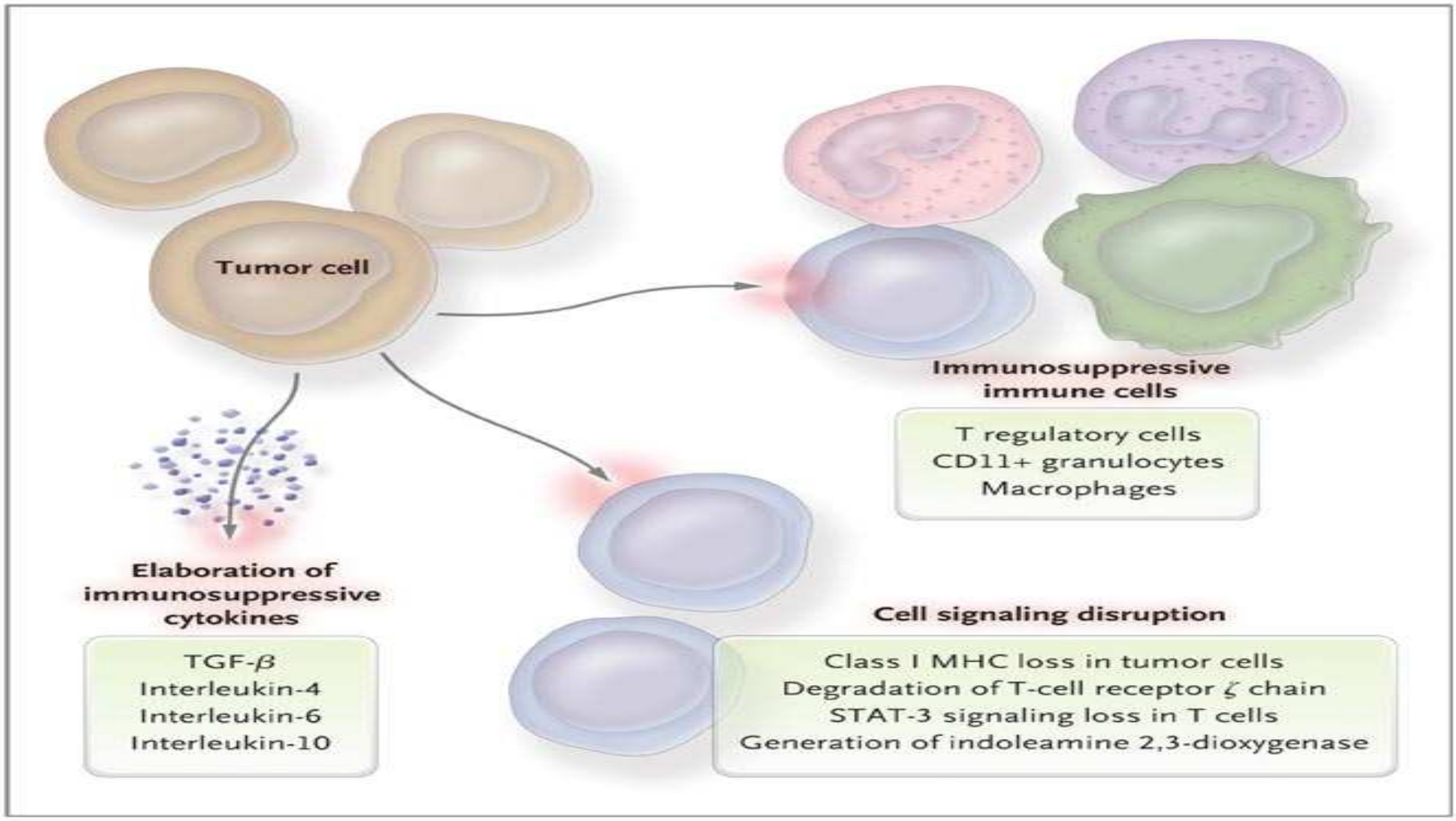
- Toxicities reported to be manageable and reversible with immunosuppression.

- Grade 3/4 treatment-related AEs: 53%
  - Elevations in Lipase (13%), AST (13%, ALT (11%)

- Cohort 3 (Nivo 3 + Ipi 3) deemed to have **unacceptable** level of toxicity
  - 3/6 patients had Gr 3 or 4 lipase elevations lasting more than 3 weeks.

[Wolchok J et al. NEJM. 2013]

Why does immunotherapy not work all the time?



[*Weiner L* NEJM *2008*]

Until CURE happens, participation in well-designed clinical trials should be considered Standard of Care

	Therapeutic Trials at SCCA (not including the T-cell Therapy trials)	
Disease Status	**Immunotherapy**	**Targeted therapy**
1st Line Metastatic	Ipi+PD1 vs Ipi vs PD1 Ipi vs PD1	BRAFi+Bevacizumab
2nd Line or NOS	PD-1 versus Chemo IL-12 Electroporation (M1a) IL-21+Ipilimumab/PD1 PD1 Biomarker	Several planned

Questions