ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

Mark R. Albertini, MD

University of Wisconsin

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosure Information

Research Funding:

- Celldex
- MedImmune
- Bristol-Myers Squibb

Conflict of Interest: None

Non-FDA indications will not be discussed apart from clinical trials

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Presentation Objectives

1. Describe clinical efficacy of approved immunotherapies
2. Recognize patient selection criteria for different immunotherapies
3. Identify factors influencing dosing and choice of immunotherapy relative to other therapies for melanoma
4. Appreciate the potential of immune system interventions to improve survival for patients with metastatic melanoma

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Types of Immunotherapies for Melanoma

- Cytokines
  - Interferon-α 2b
  - Interleukin-2
- Oncolytic Virus
  - Modified Herpes Virus (Talimogene Laharparepvec; TVEC)
- Checkpoint Antibodies
  - Anti-CTLA4 (ipilimumab)
  - Anti-PD1 (pembrolizumab, nivolumab)
    - (Avelumab for Merkel cell carcinoma – March 2017)

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Cytokines

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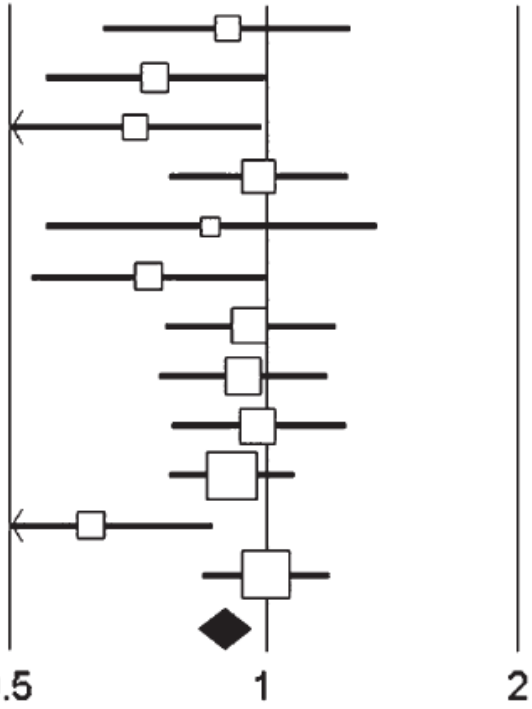
Adjuvant Treatment of High-Risk Melanoma

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



Mocellin et al. JNCI. 2010

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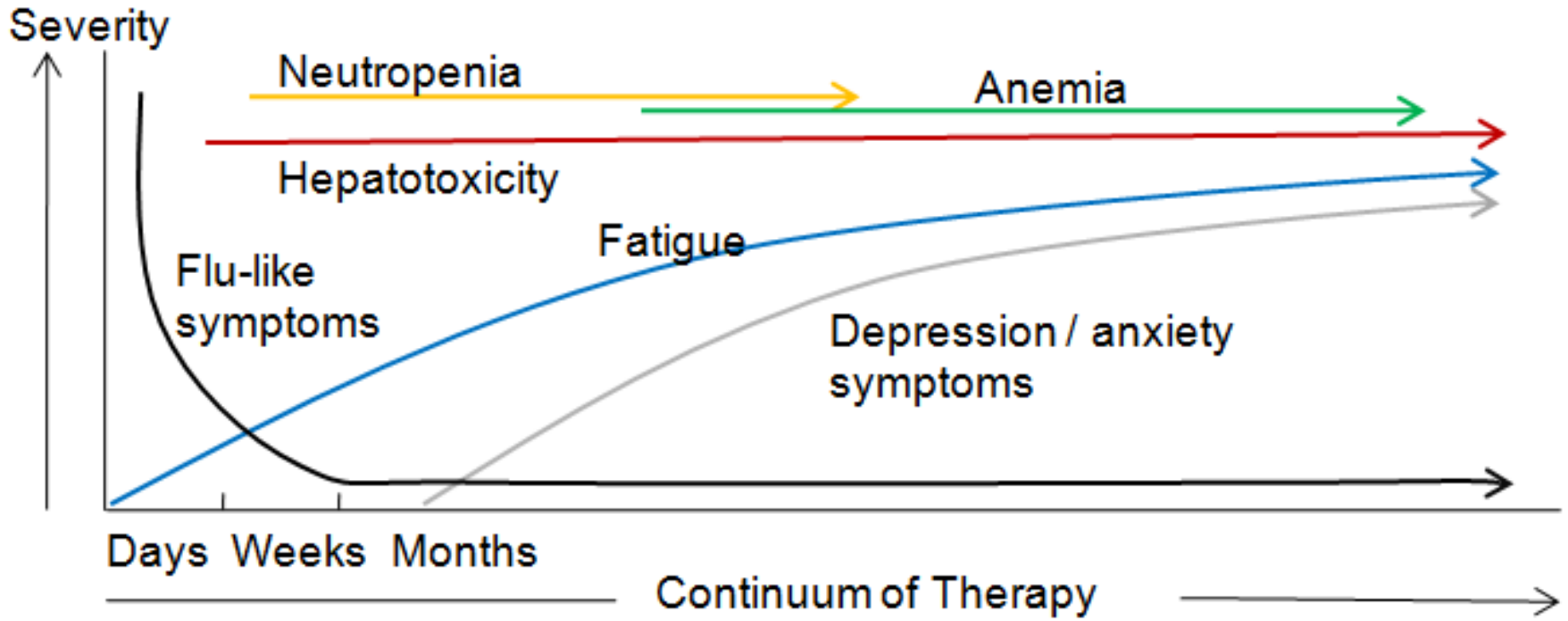
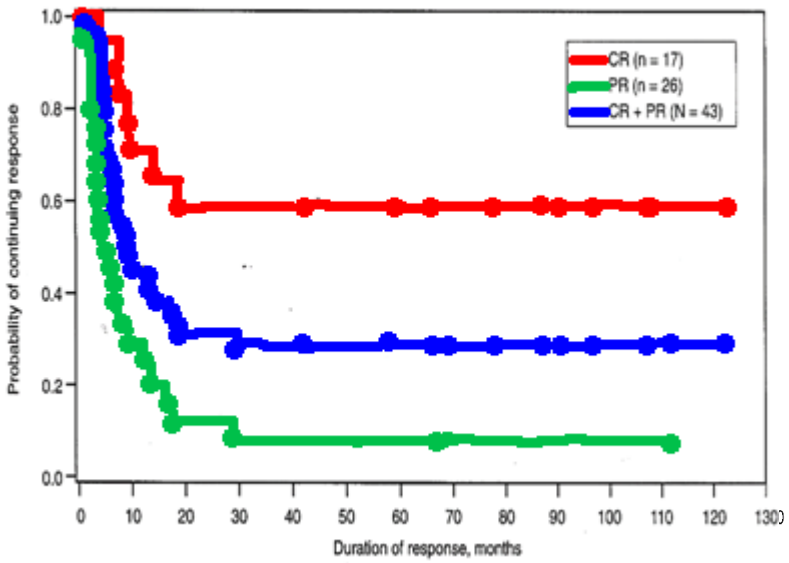
Toxicity of Adjuvant Interferon-α



http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html

High Dose Interleukin-2 Therapy (HD IL-2) : Durable Responses

- HD IL-2 produces durable responses in 6%-10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (cured?)
- FDA approval for melanoma in 1998
- High toxicity



Atkins et al. J Clin Oncol. 1999

Atkins et al. J Clin Oncol. 1999

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Oncolytic Virus

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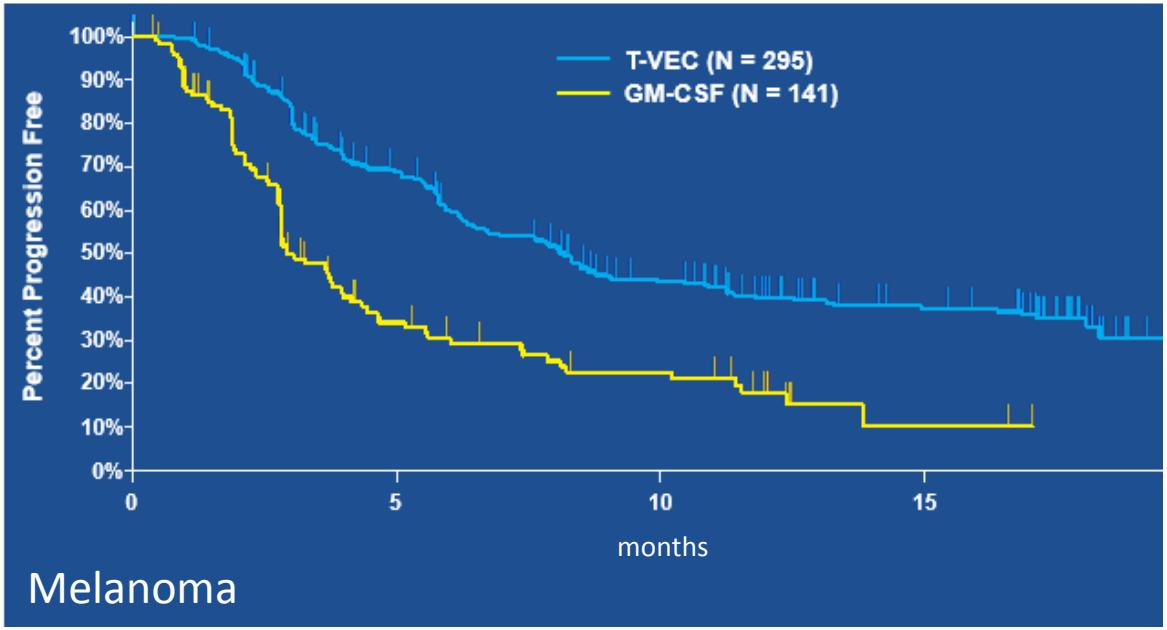
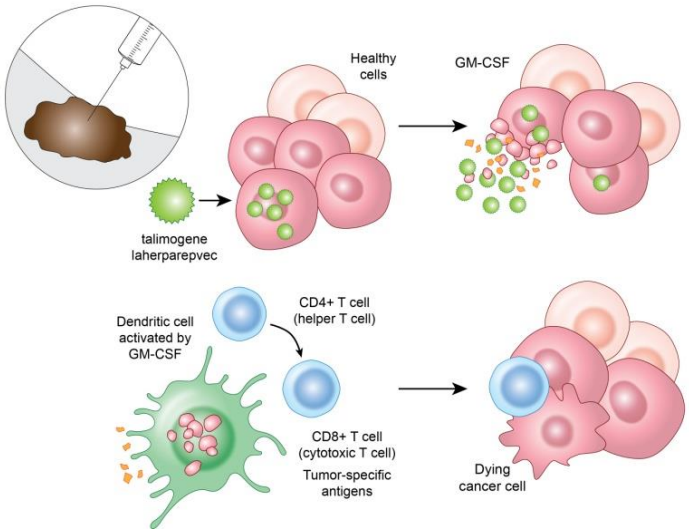
Phase III Trial of T-VEC vs GM-CSF PFS per Investigator



Melanoma



Andtbacks et al. ASCO 2013; LBA9008

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Checkpoint Antibodies

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BREAKTHROUGH OF THE YEAR 2013

CANCER IMMUNOTHERAPY

20 DECEMBER 2013 VOL 342 **SCIENCE** www.sciencemag.org

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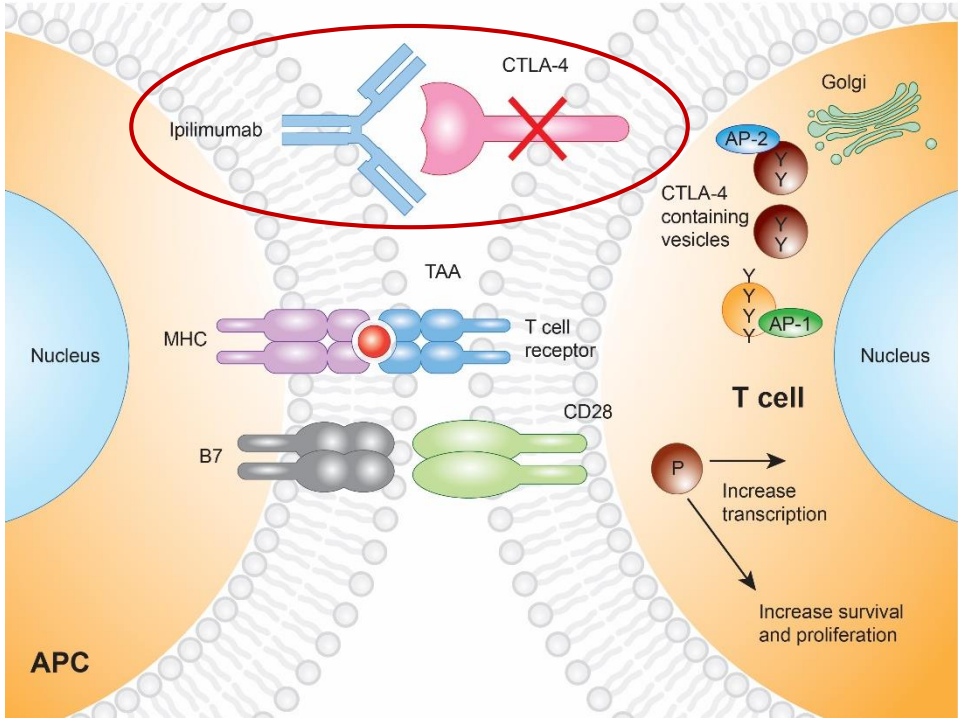
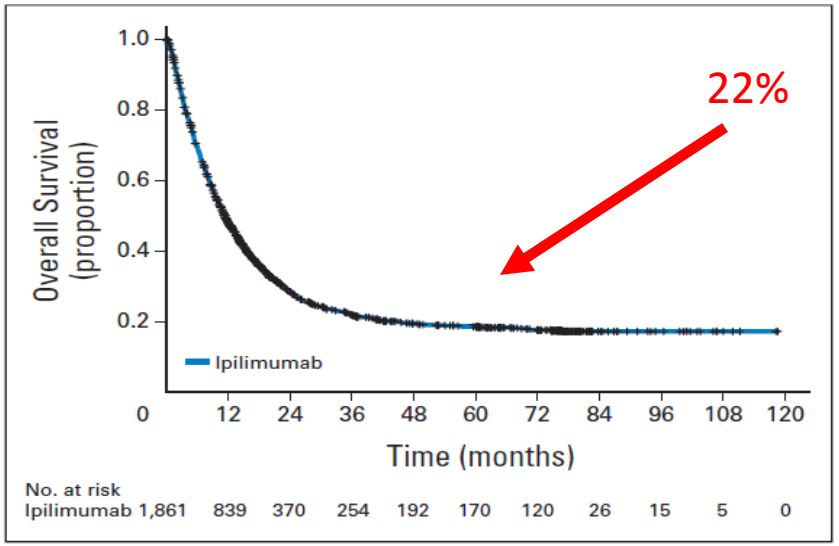
Ipilimumab & Immune Check-Point Blockade





Luke et al, Oncologist 2013
Schadendorf et al, J Clin Oncol 2015

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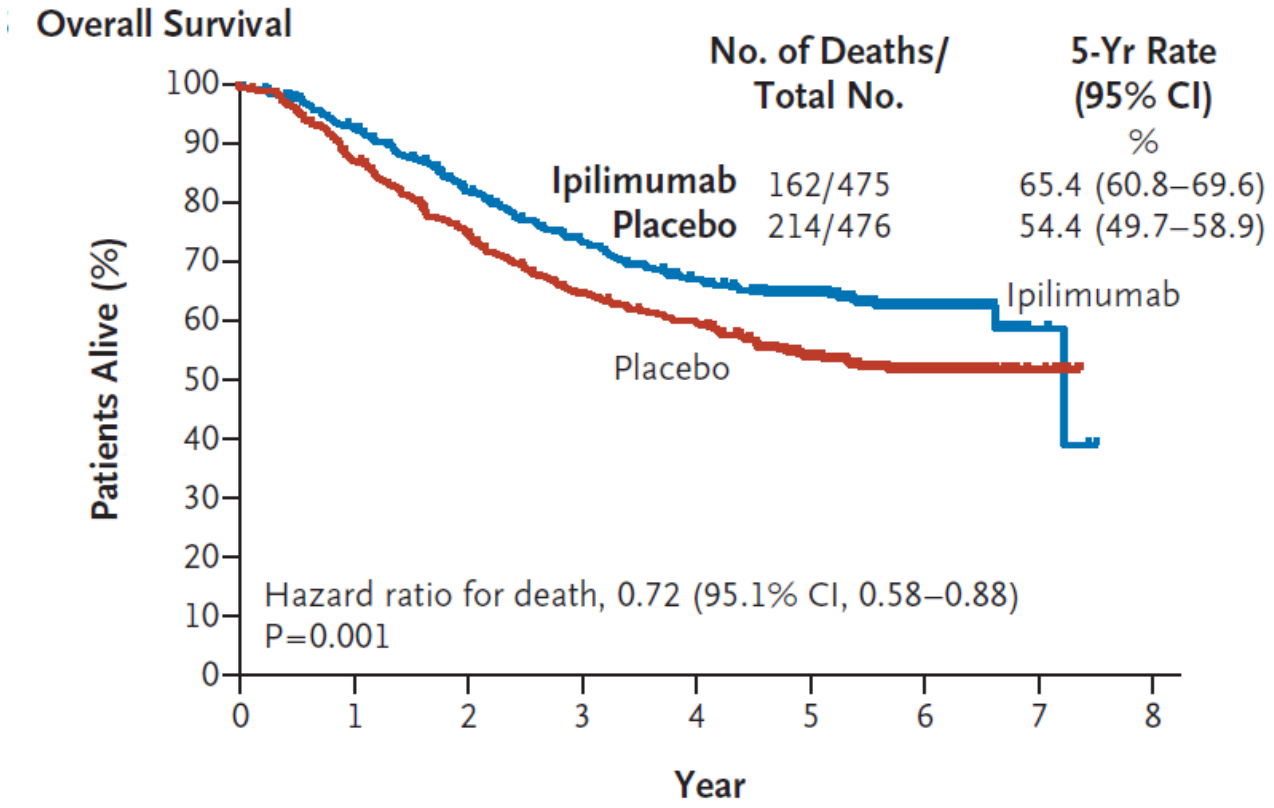
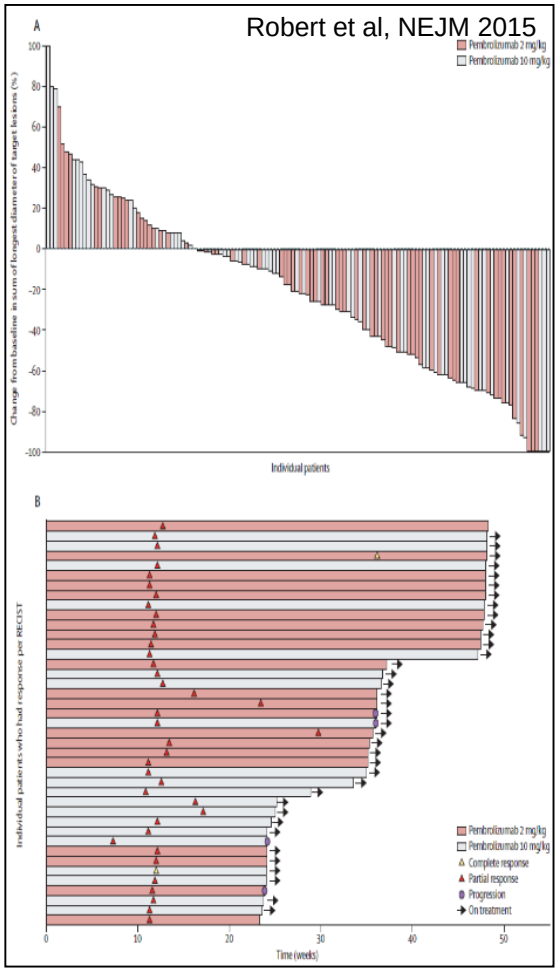
Adjuvant Ipilimumab in High-Risk Melanoma



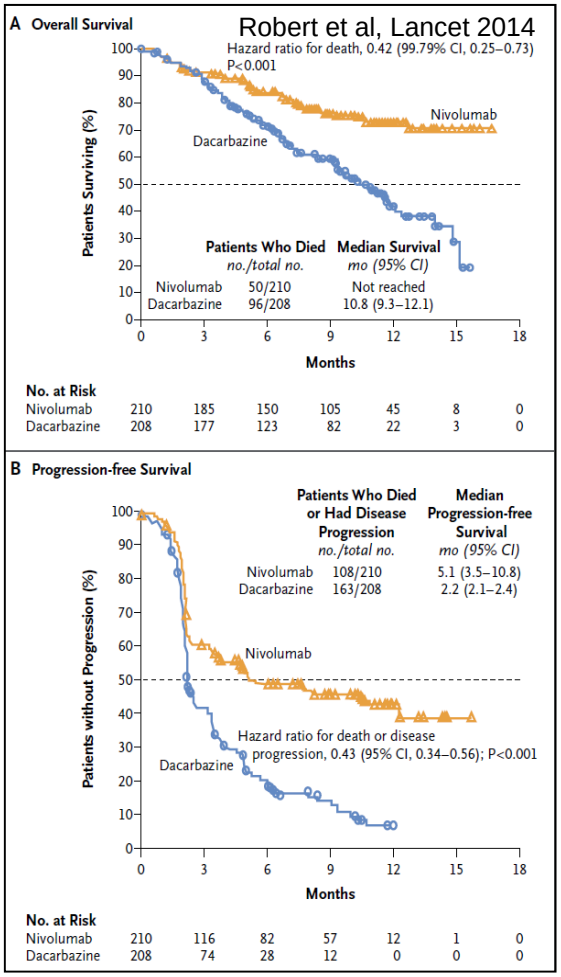
Eggermont *et al*. NEJM 2016

Anti-PD1 in Melanoma

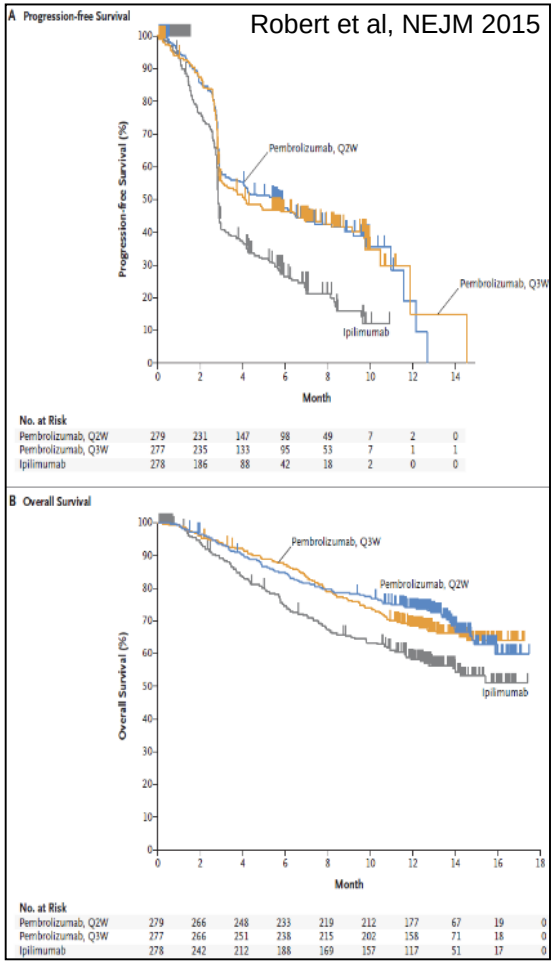
Anti-PD1 (pembrolizumab) *after* ipilimumab



Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma(BRAF WT)



Front-line anti-PD1 (pembrolizumab) vs. ipilimumab



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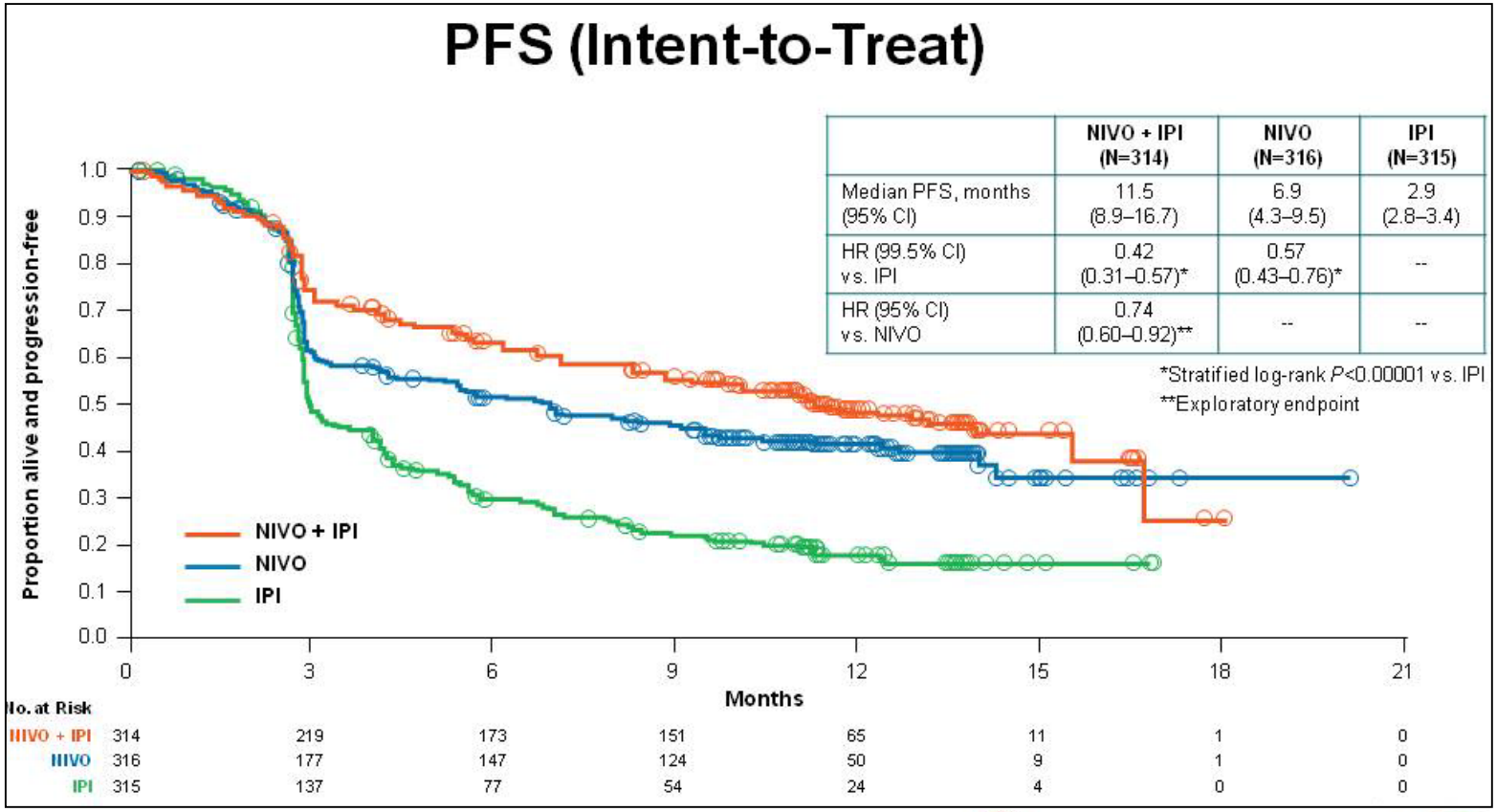
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

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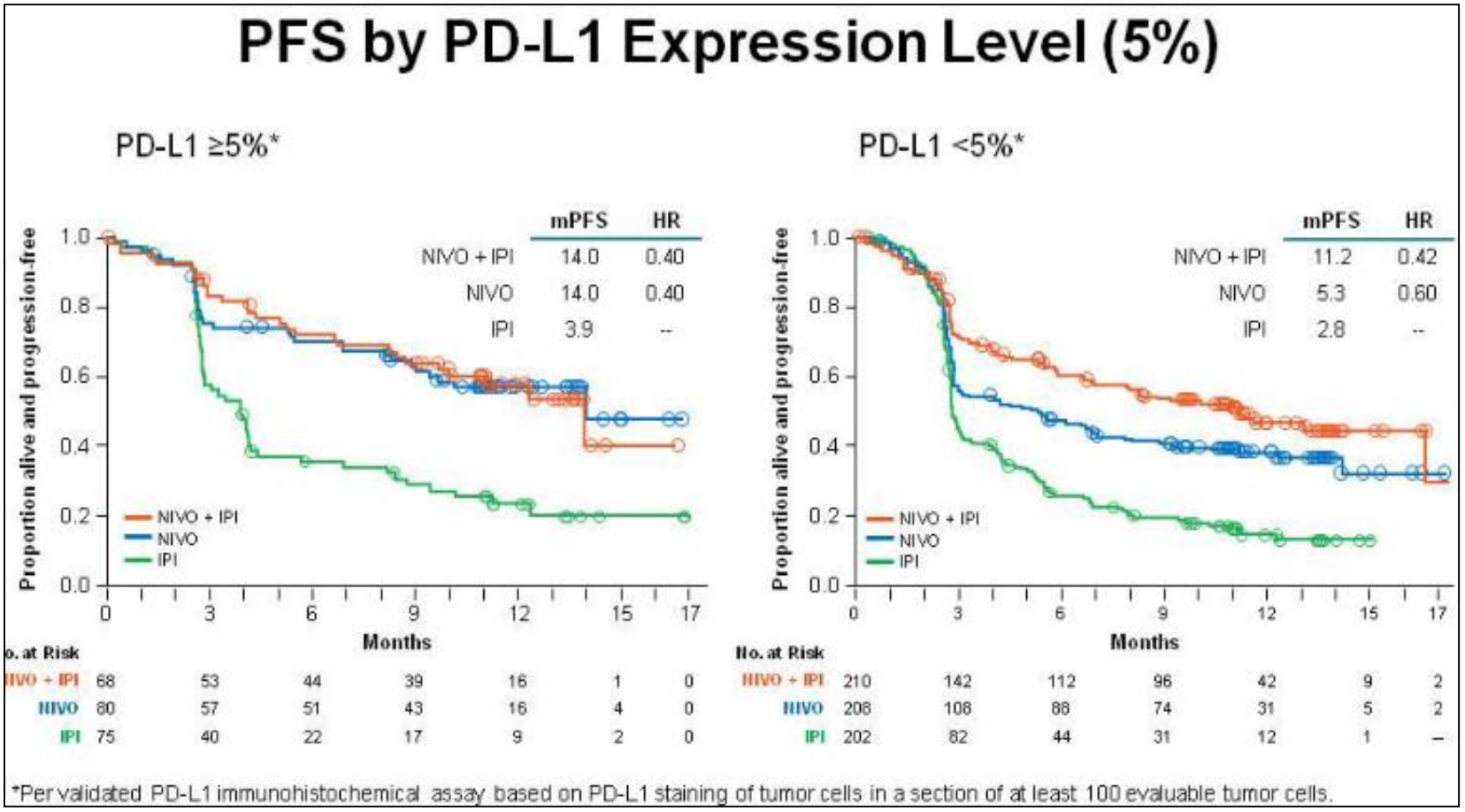
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

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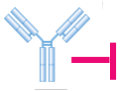
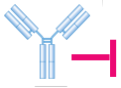
Ipilumamab:



Nivolumab:



Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma

Safety Summary

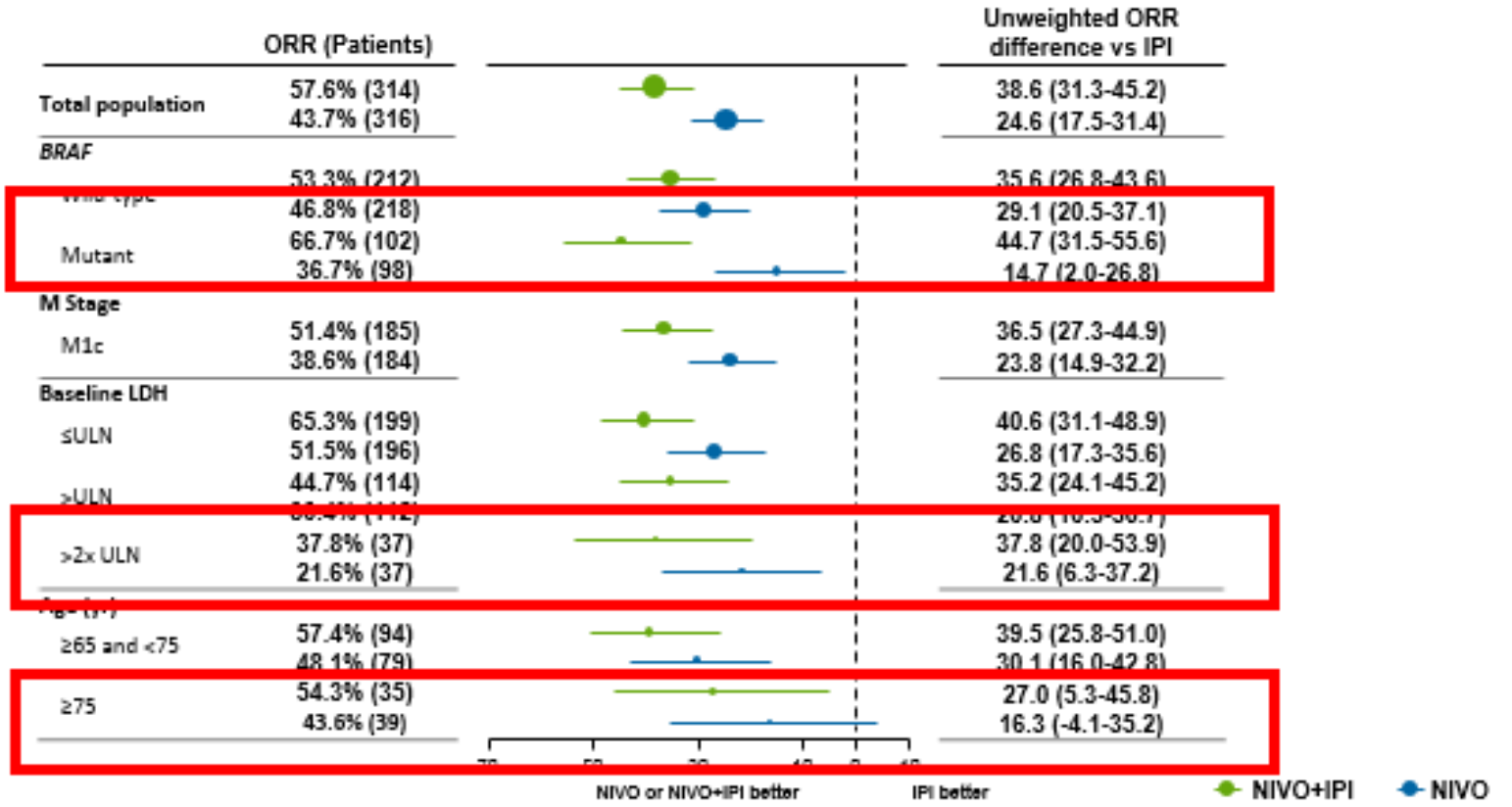
Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



Wolchok J et al, ASCO 2016

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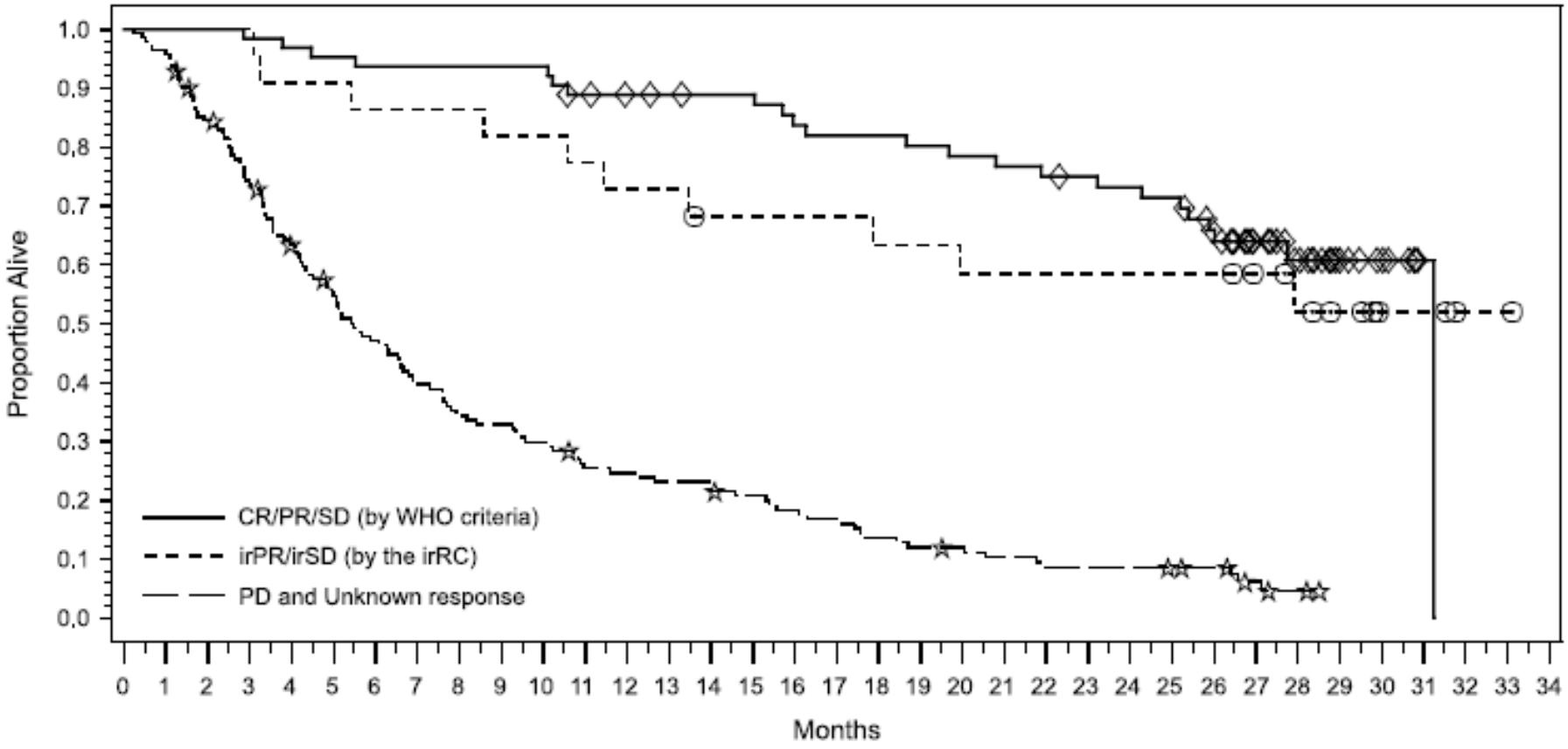
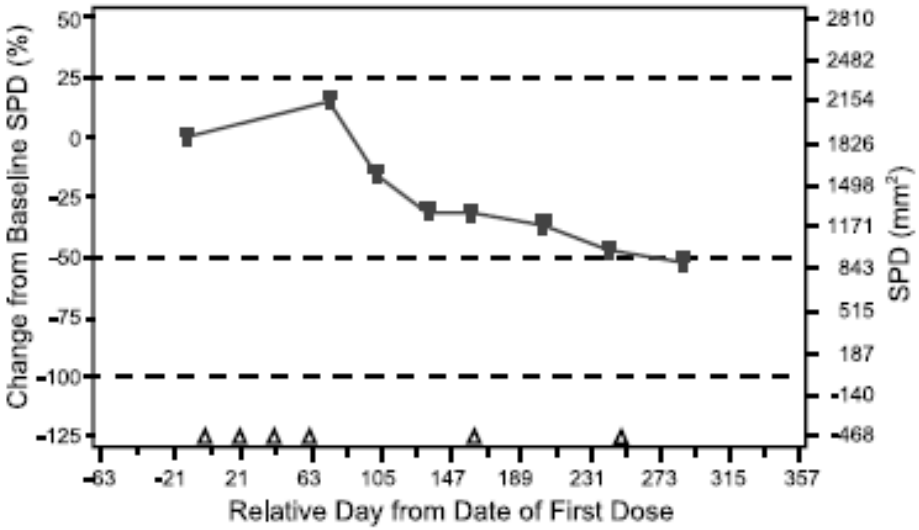
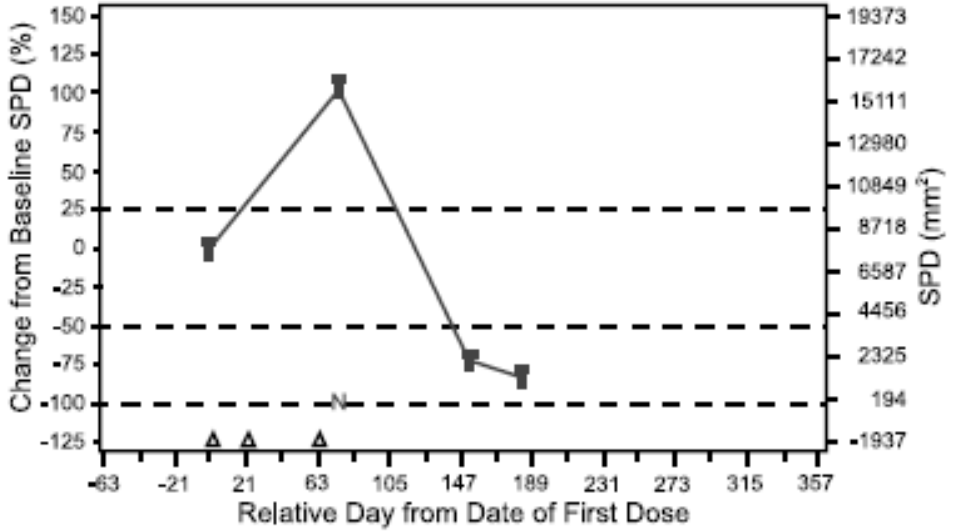
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2012

Immune Related Response Criteria





Wolchok et al. Clin Can Res 2012

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Case #1

60 y/o male patient

- H/o stage IIIC (T2aN3) melanoma with primary site on the back
- Initial surgery followed by adjuvant interferon
- Repeat surgery followed by XRT for initial regional recurrence
- Presentation with additional sites of disease in the subcutaneous tissue on the back; BRAF wild-type melanoma

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Case #1: Patient with recurrent disease following surgery and initial adjuvant therapy

- Systemic therapy
  - Pembrolizumab
  - Nivolumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Ipilimumab 3 mg/kg x 4
- Lesional therapy
  - Talimogene laherparepvec
  - Radiotherapy
  - Experimental intralesional treatment

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Best Therapies ⟶ Clinical Trials

- Tumor-infiltrating lymphocytes (TILs)
- Neoantigen vaccines
- Oncolytic virotherapy
- New/improved immune checkpoint blockers w/immunomodulators
  - of resistance (indoleamine dioxygenase inhibitors)
  - agonistic costimulatory antibodies (CD137, OX40)
  - hypofractionated or stereotactic radiotherapy
  - Intratumoral therapy

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Case 1 Management

- Treatment with pembrolizumab with repeat disease assessments every 3 months
- No significant treatment-associated toxicity
- Essentially stable disease without new sites of disease with 6 month imaging
- Plan for continued pembrolizumab treatment

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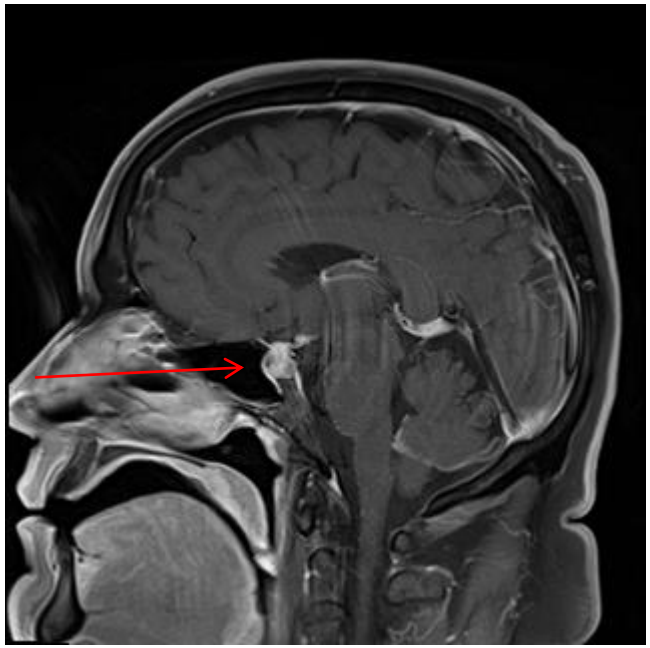
Case #2: Metastatic Melanoma BRAF mutant

49 y/o male patient

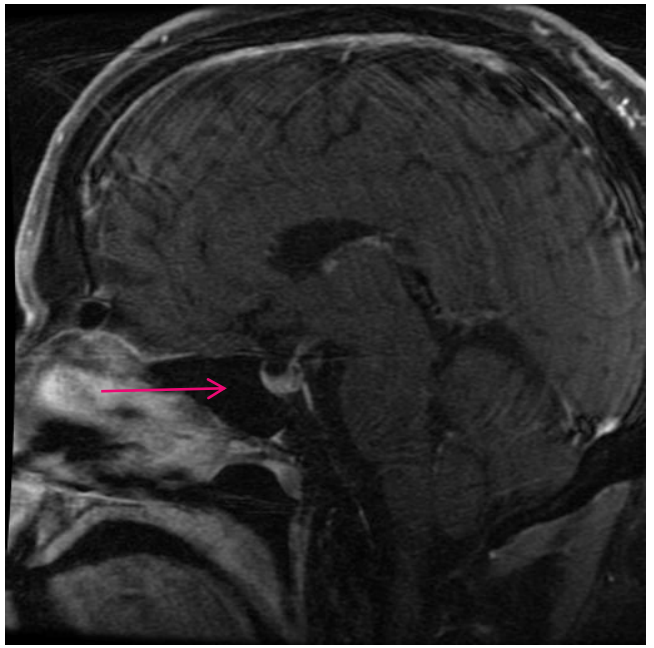
- Presented with biopsy confirmed mediastinal LN involvement; melanoma had $BRAF^{V600E}$ mutation
- Initial Therapy:
  - Ipilimumab and nivolumab
  - Tolerated therapy with minimal side effects for the first 2 cycles

Presented with significant headaches as well as nausea with vomiting 12 days after cycle #3 of ipilimumab and nivolumab

- Brain MRI with hypophysitis



2 weeks after cycle #3 of Ipi/Nivo



6 weeks after cycle #3 of Ipi/Nivo

Courtesy of Dr. Meghan Lubner

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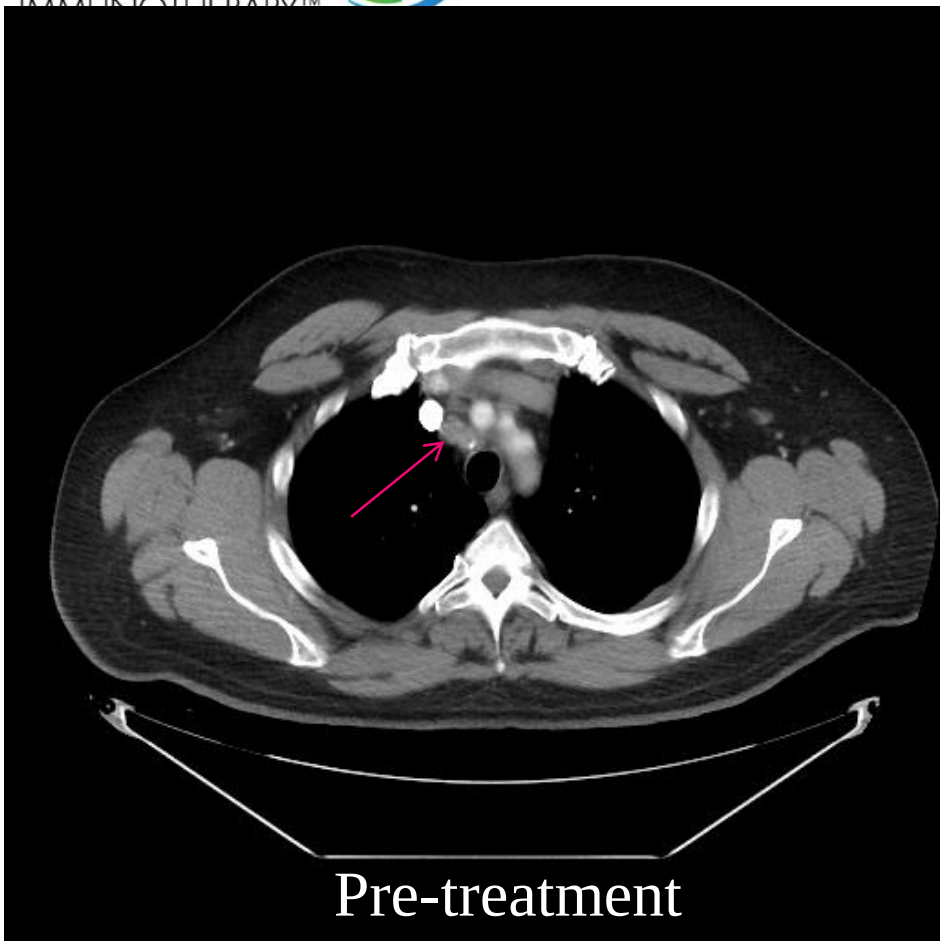
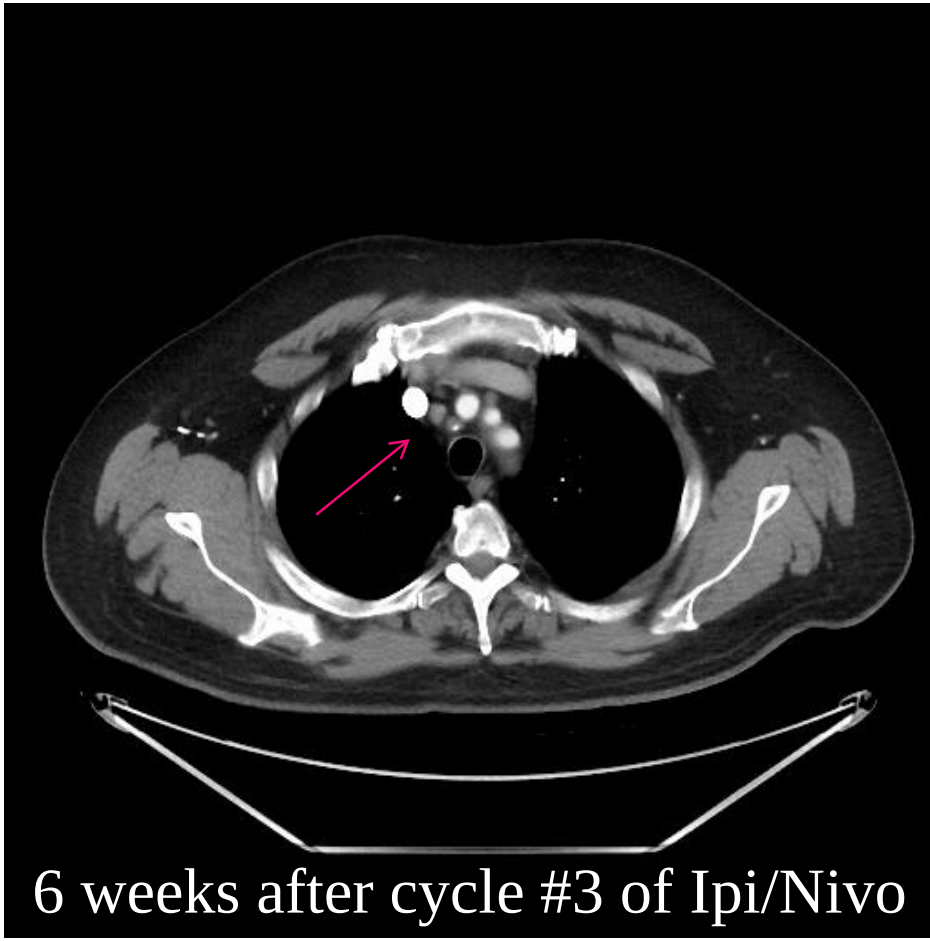
Management

- Comprehensive laboratory studies including cortisol, TSH, T3, T4, testosterone
- Methylprednisolone 1 mg/kg IV twice daily followed by gradual taper with oral prednisone





Courtesy of Dr. Meghan Lubner

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Clinical Status 20 months after cycle #3 Ipi/Nivo

- CT scans stable and without evidence for progression
- Remains on prednisone 5 mg in the AM and 2.5 mg in the PM

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On-Going Phase III Trials in Melanoma

- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi) + anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti PD(L)1

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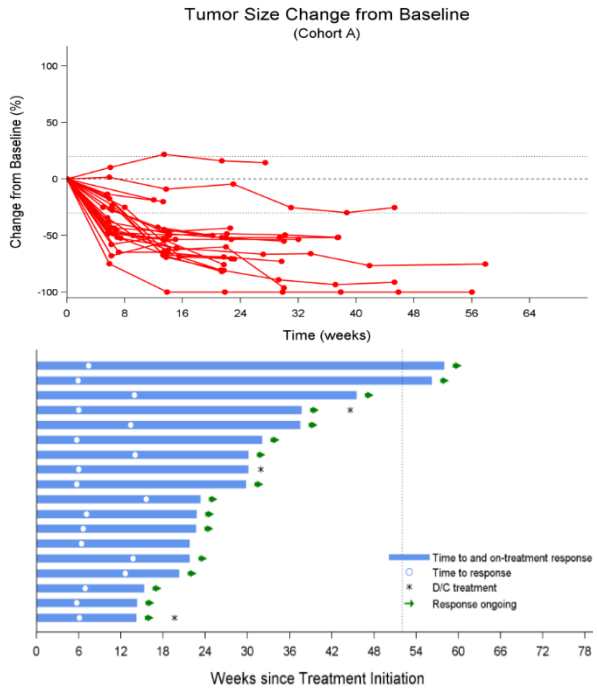
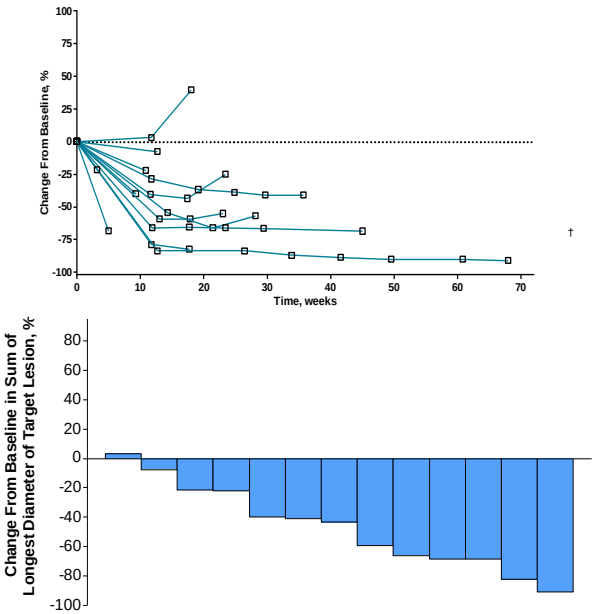
Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab



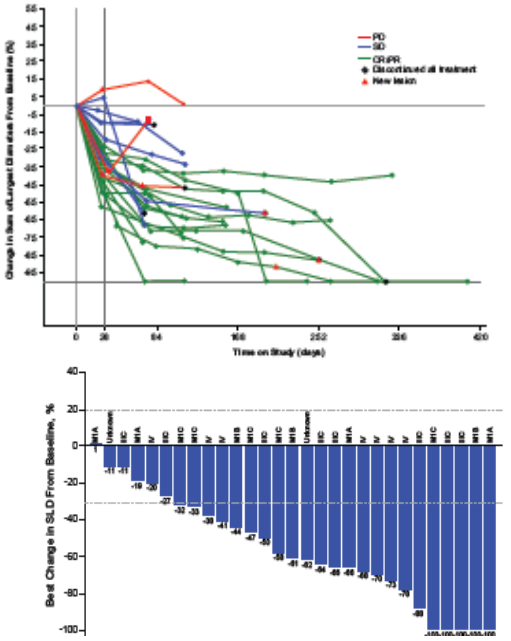
Ribas et al. J Clin Oncol (Meeting Abstracts) May 2015 vol. 33 no. 15_suppl 3003

Dabrafenib+Trametinib+ Pembrolizumab



Ribas et al. J Clin Oncol 34, 2016 (suppl; abstr 3014).

Vemurafenib+Cobimetinib+ Atezolizumab



Hwu et al. Annals of Oncology 27 (Supp 6); 2016: Abstract 1109PD.

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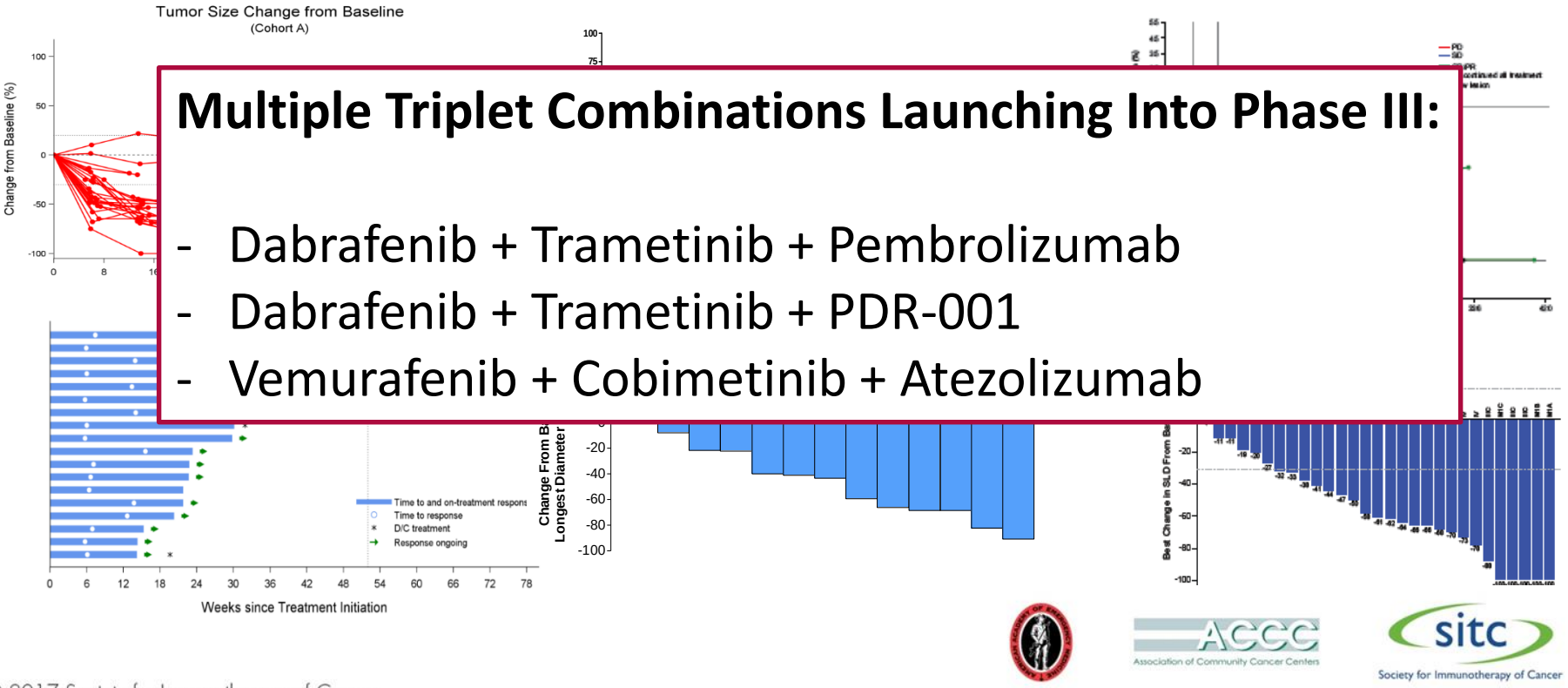
Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

Vemurafenib+Cobimetinib+ Atezolizumab



Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab

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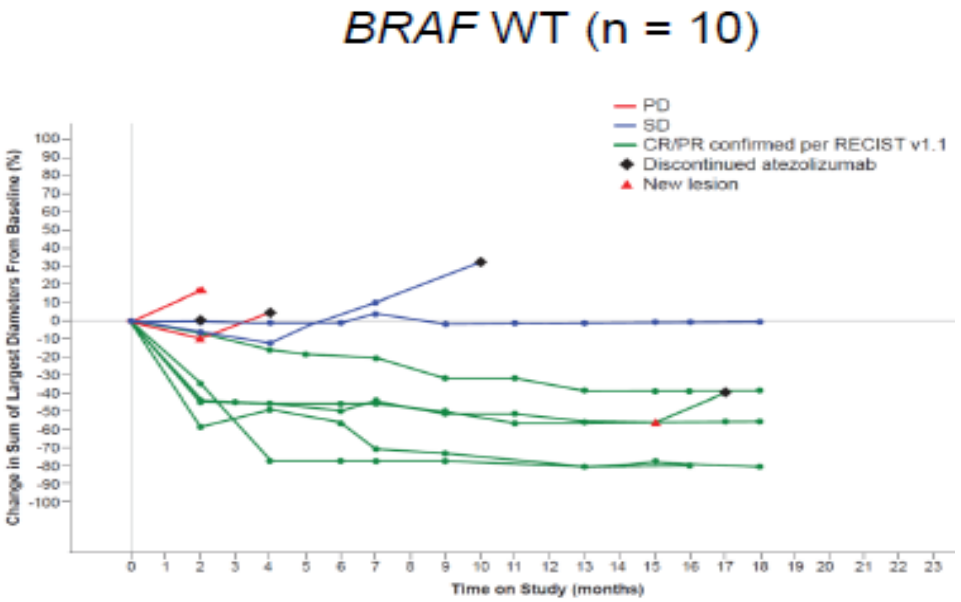
MEK inhibitor + PDL-1 for BRAFwt Melanoma Phase I Cobimetinib + Atezolizumab



	N = 22, n (%)
Median safety follow-up, mo (range)	14.0 mo (2.4-20.2)
All grade treatment-related AEs	22 (100%)
Grade 3-4 treatment-related AEs	13 (59%)
Grade 3-4 atezolizumab-related AEs	8 (36%)
Grade 3-4 cobimetinib-related AEs	10 (45%)
AEs leading to treatment dose modification/interruption	14 (64%)
Treatment-related SAEs[a]	4 (18%)
Treatment discontinuation[b]	3 (14%)
Cobimetinib discontinuation	3 (14%)
All treatment discontinuation	1 (5%)

Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

Atezolizumab: PD-L1

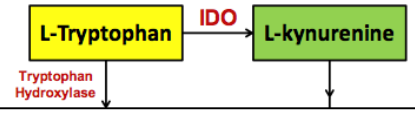
Pembrolizumab : PD-1

Infante *et al*. SMR 2016.

IDO inhibitor epacadostat + pembrolizumab

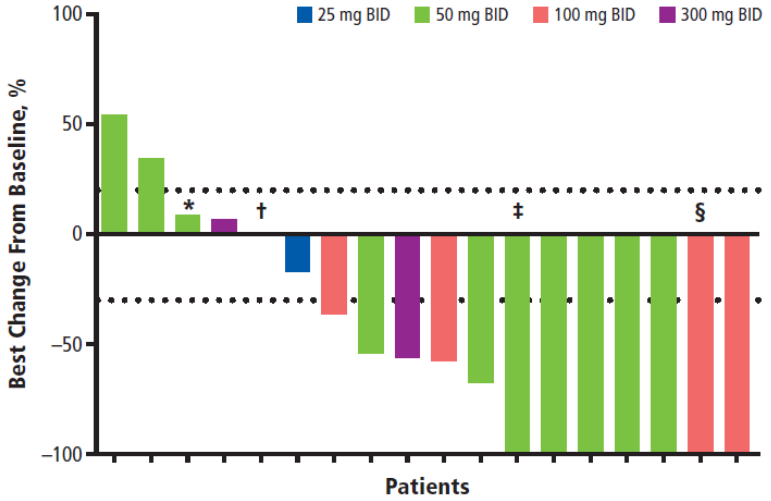
Indoleamine Dioxygenase-1 (IDO1)

- IDO1 is a heme-containing monomeric oxidoreductase that metabolizes tryptophan to kynurenine



Phase 1/2 Study of **Epacadostat** (INCB024360) + **Pembrolizumab** in Patients With Melanoma

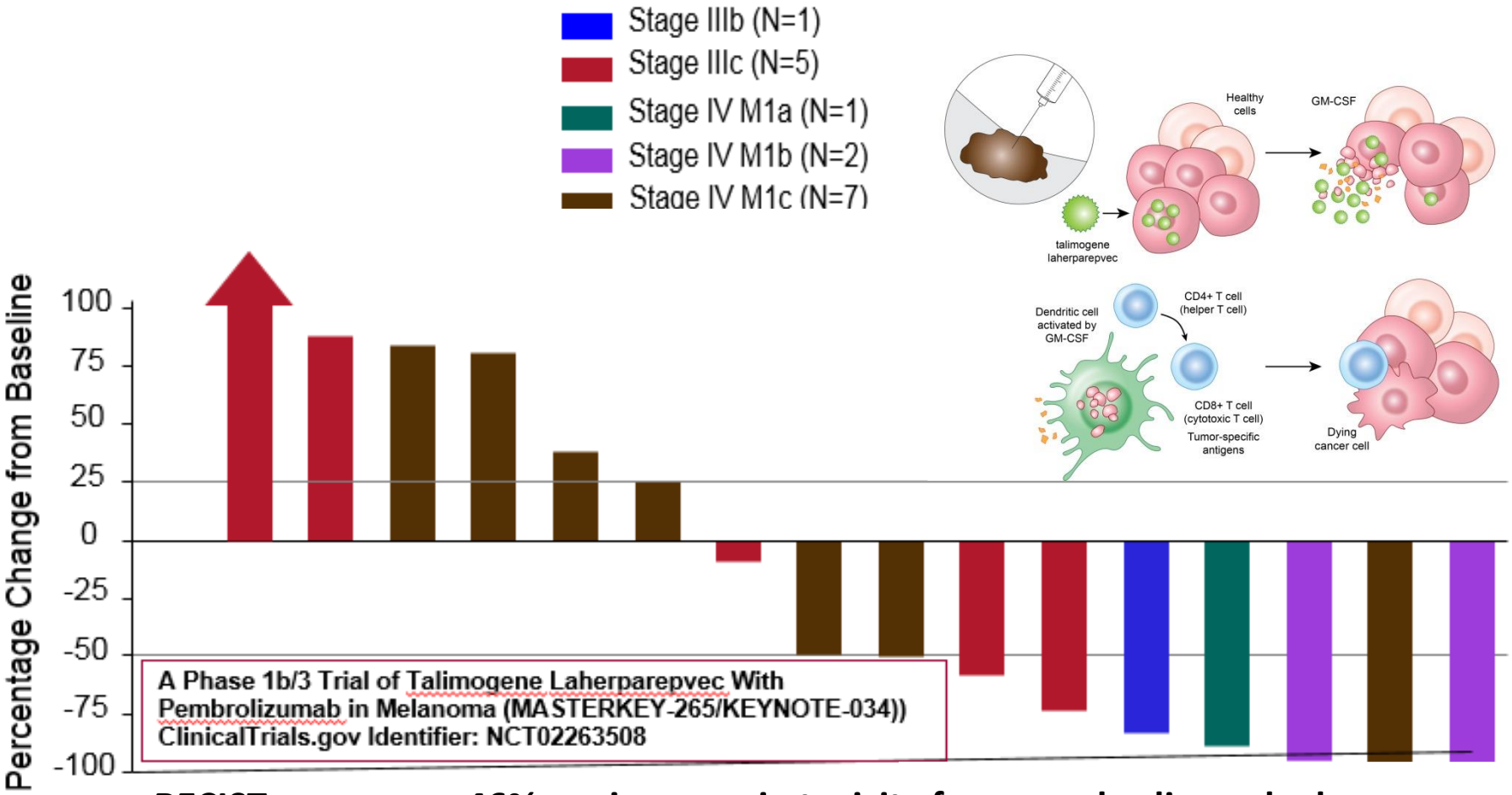
A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074



RECIST response = 58%, no increase in toxicity from pembrolizumab alone

Beatty et al. ASCO (2012) Abstract 2500^
Gangadhar *et al*. ESMO 2016

T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



RECIST response = 46%, no increase in toxicity from pembrolizumab alone

Long et al. SMR 2015

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Conclusions

- Immunotherapy is standard of care in melanoma
- Likely first and second line in most patients
- Understanding mechanisms of action important
- Manage side effects, understand long-term benefit
- Immunotherapy combinations are likely the future for melanoma and likely all cancers!