ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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City of Hope

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Disclosures

- Amgen Inc., Lion Biotechnologies, Inc., Pfizer, Consulting Fees
- I *will* be discussing non-FDA approved indications during my presentation.

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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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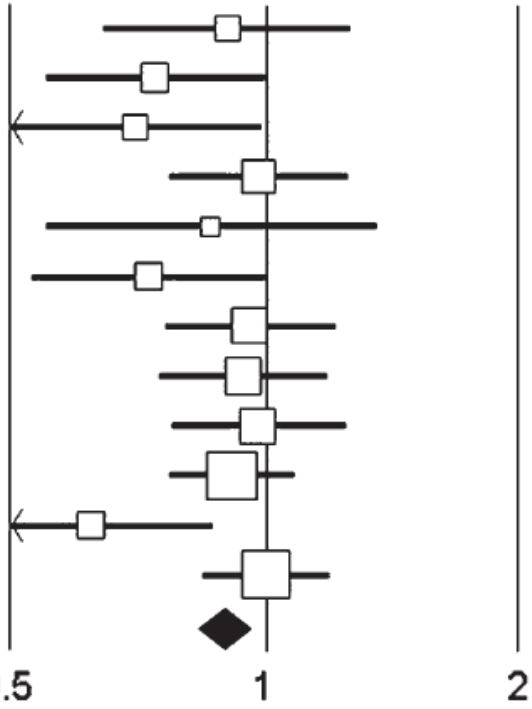
Adjuvant Treatment of High-Risk Melanoma

	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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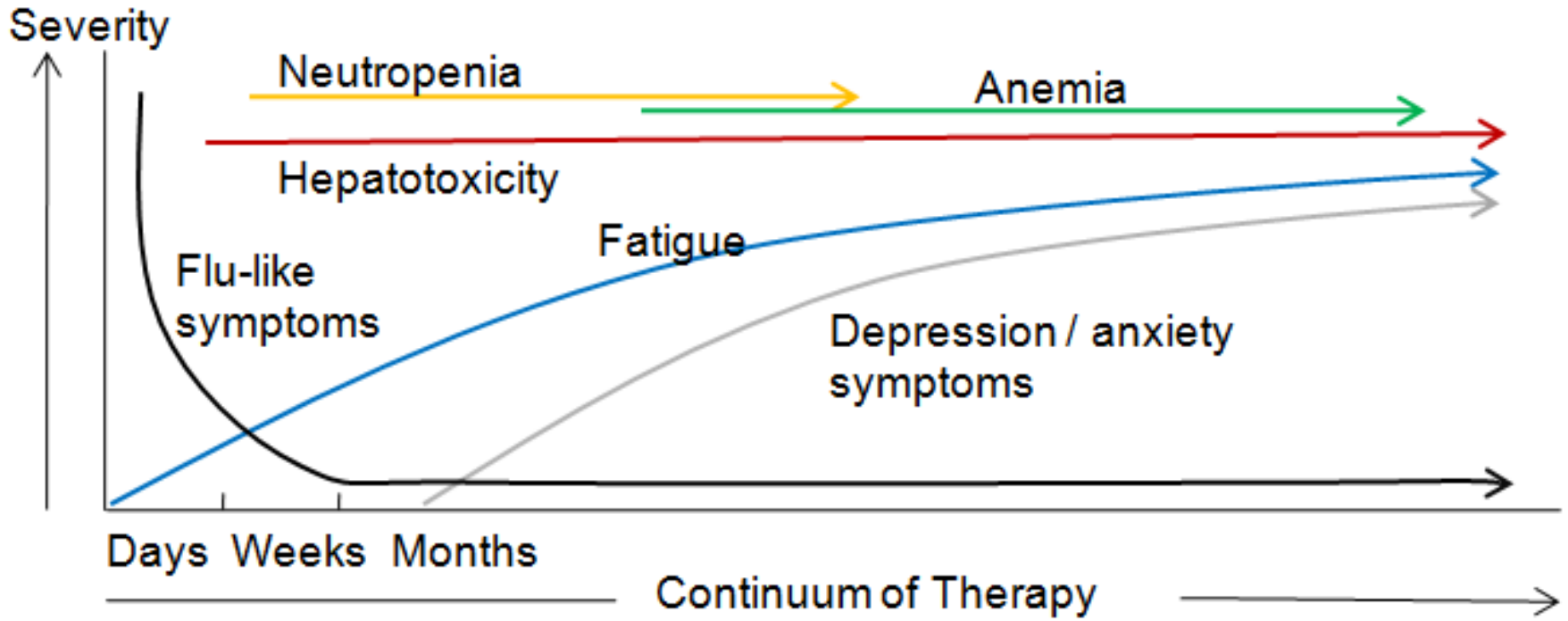
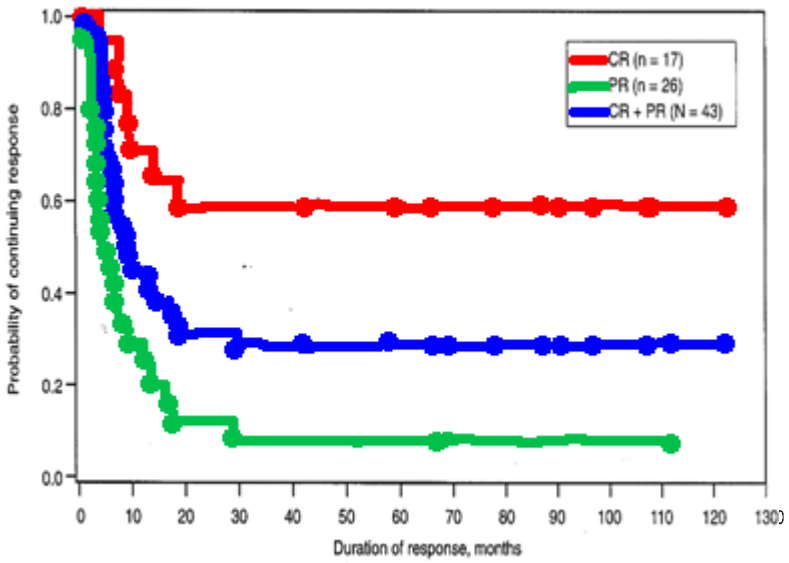
Toxicity of Adjuvant Interferon-α



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

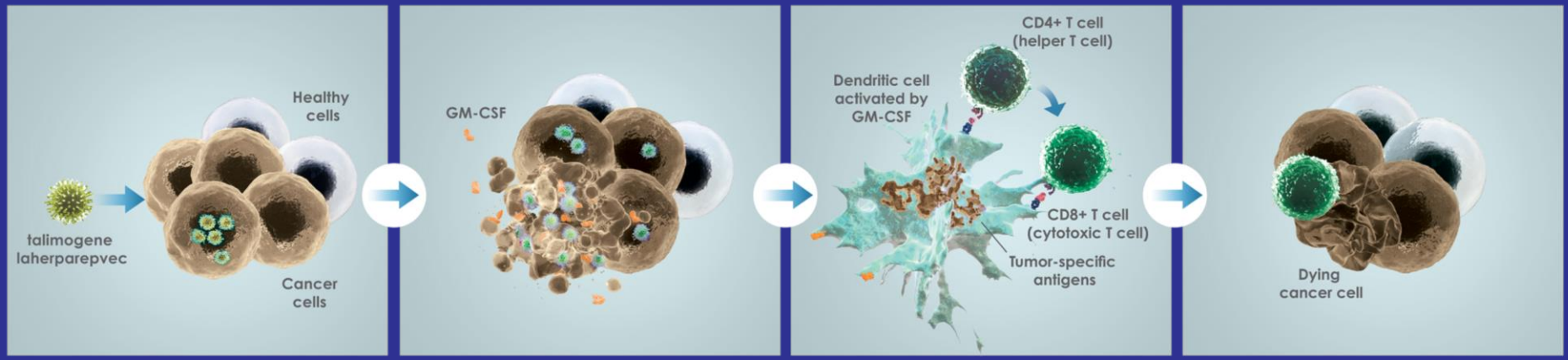


Atkins et al. J Clin Oncol. 1999

Atkins et al. J Clin Oncol. 1999

T-VEC: HSV-1-derived intratumoral therapy for local and systemic effects

Local Effect: Tumor Cell Lysis → **Systemic Effect: Tumor-Specific Immune Response**



Selective viral replication in tumor tissue

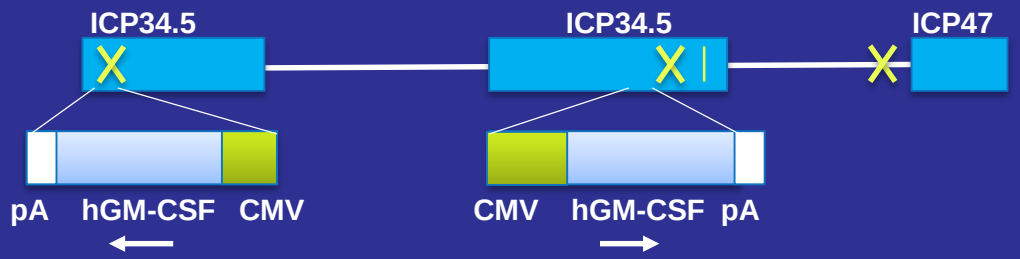
Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

T-VEC key genetic modifications:

JS1/ICP34.5-/ICP47-/hGM-CSF



Courtesy of Howard Kaufman

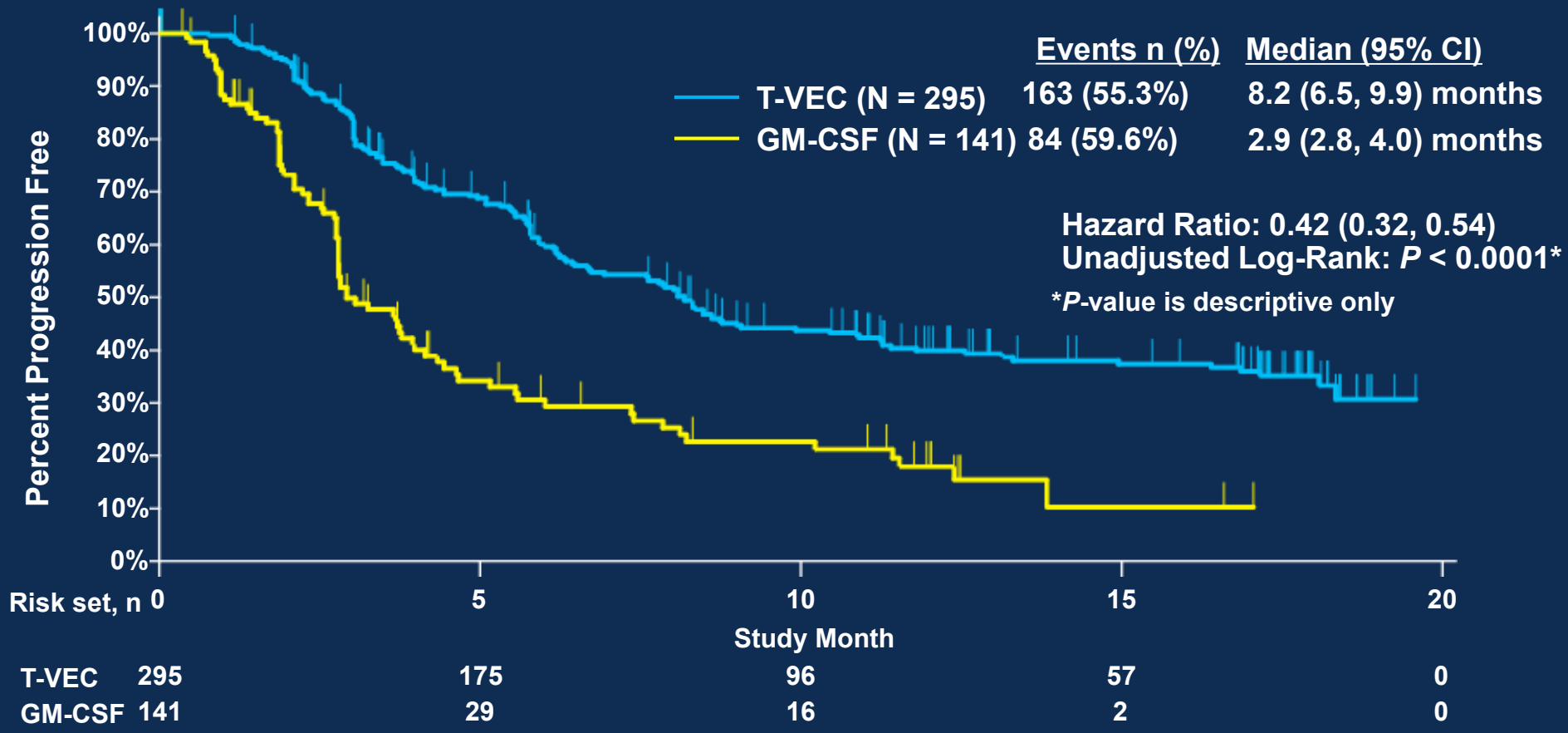
TVEC overall response rate

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	**Treatment Difference (T-VEC – GM-CSF)**
Overall Response Rate (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)	20.8% (14.4, 27.1) *P* < 0.0001[a] descriptive
CR	0.7%	10.8%	
PR	5.0%	15.6%	

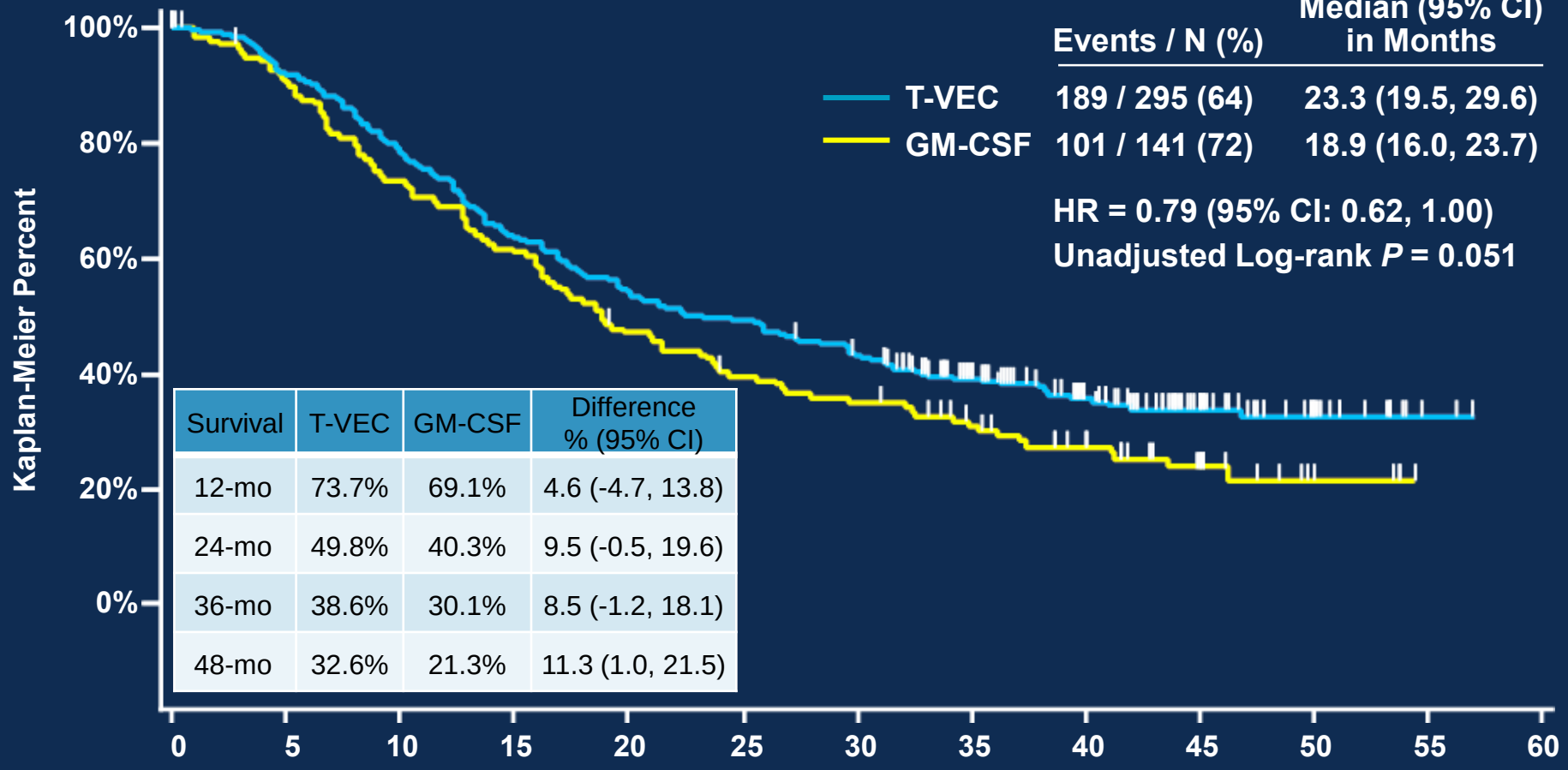
Durable response rate (primary endpoint)

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	**Treatment Difference (T-VEC – GM-CSF)**
Durable Response Rate	2.1%	16.3%	14.1% 95% CI: (8.2, 19.2) *P* < 0.0001[a]

Progression-free survival, TVEC vs GM-CSF



Overall Survival



	Events / N (%)	Median (95% CI) in Months
T-VEC	189 / 295 (64)	23.3 (19.5, 29.6)
GM-CSF	101 / 141 (72)	18.9 (16.0, 23.7)

HR = 0.79 (95% CI: 0.62, 1.00)
Unadjusted Log-rank *P* = 0.051

Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Patients at risk:

T-VEC	295	269	230	187	159	145	125	95	66	36	16	2	0
GM-CSF	141	124	100	83	63	52	46	36	27	15	5	0	0

Andtbacka R et al JCO 2015

PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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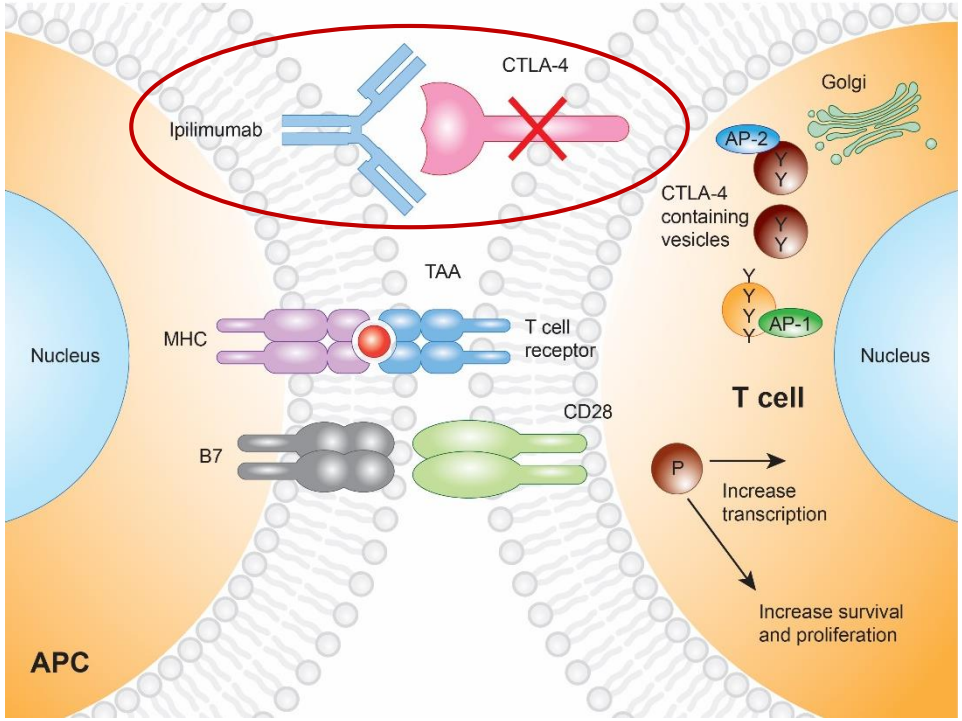
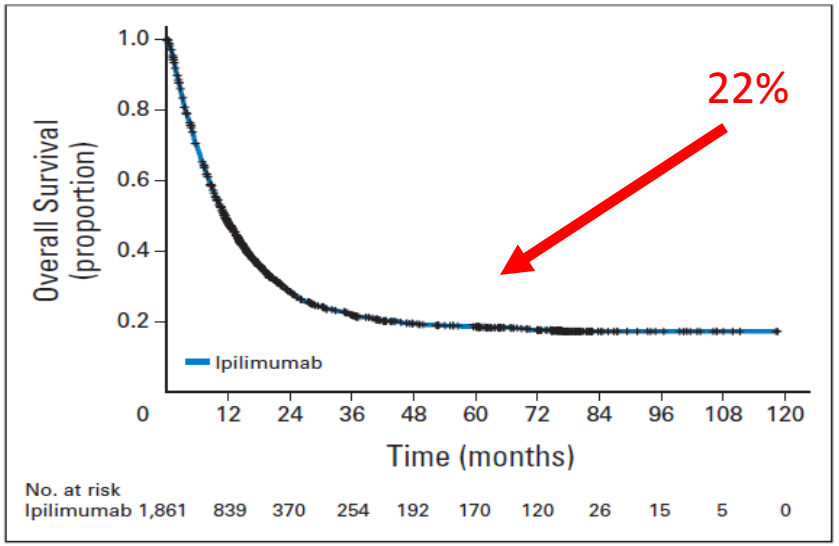
Ipilimumab & Immune Check-Point Blockade





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

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Case #1: stage III⟶stage IV-M1a

TL, male patient in 30s

- Therapeutic lymph node dissection of left inguinal node on 1/2017 revealed 3+ stage III melanoma of unknown primary origin
  - Randomized to pembrolizumab on SWOG-1404 adjuvant trial
  - 6 cycles: no significant irAEs
- Relapse in L neck and R back soft tissue

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Case #1: stage IV-M1a Oligometastatic M1a BRAFwt on adjuvant pembrolizumab

- Systemic therapy
  - Nivolumab
  - High-dose IL-2
  - Nivolumab plus ipilimumab
  - Targeted Rx based on next-generation sequencing
  - Ipilimumab 10 mg/kg x 4 then maintenance
  - Ipilimumab 3 mg/kg x 4
  - IFN-α (PEG- or unmodified)
- Lesional therapy
  - Talimogene laherparepvec
  - Radiotherapy
  - Intralesional IL-2
  - Intralesional GM-CSF

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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
- Molecularly-focused treatment paradigms—all immunomodulatory
  - Metabolic reprogramming
  - Next generation sequencing→molecular drivers and/or modifiers

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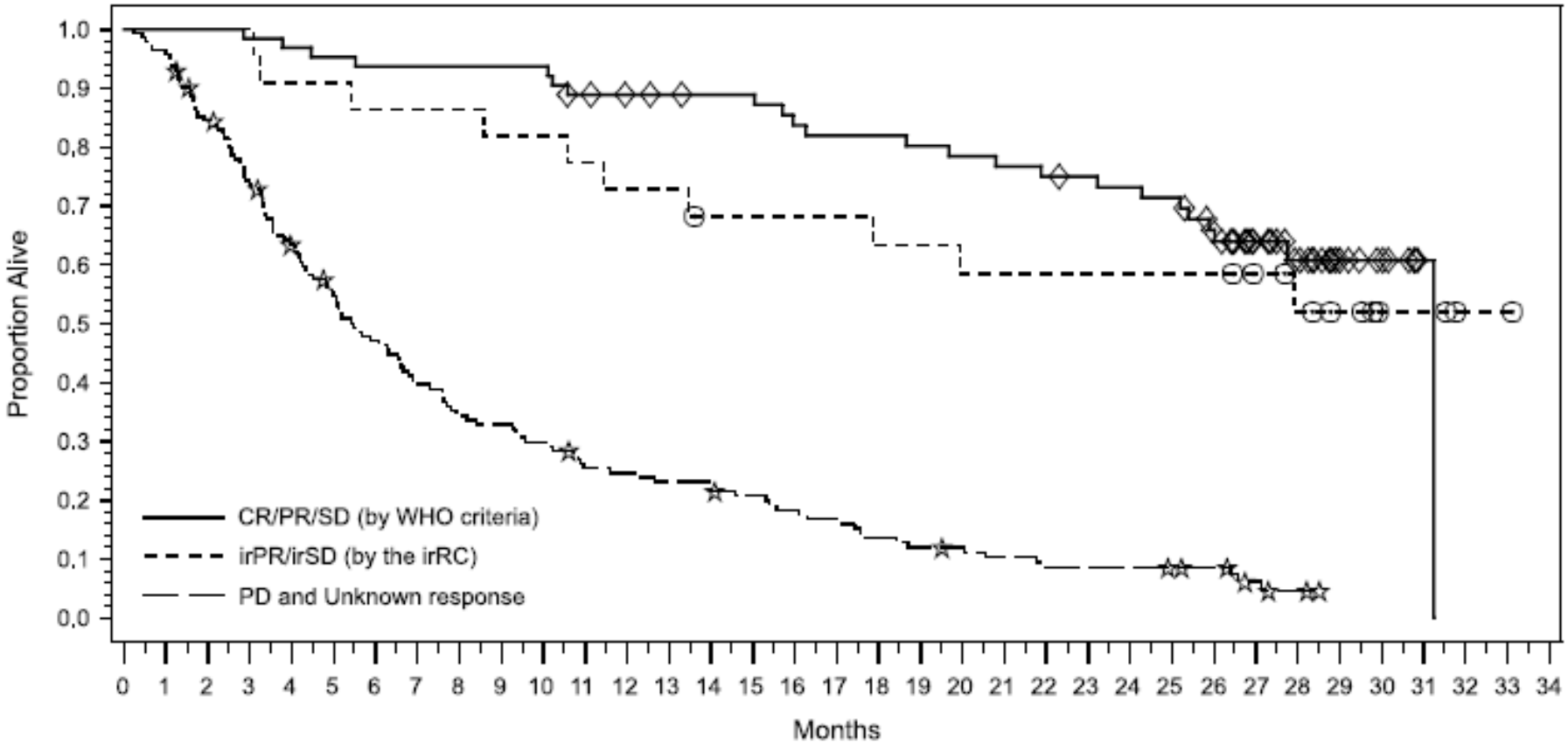
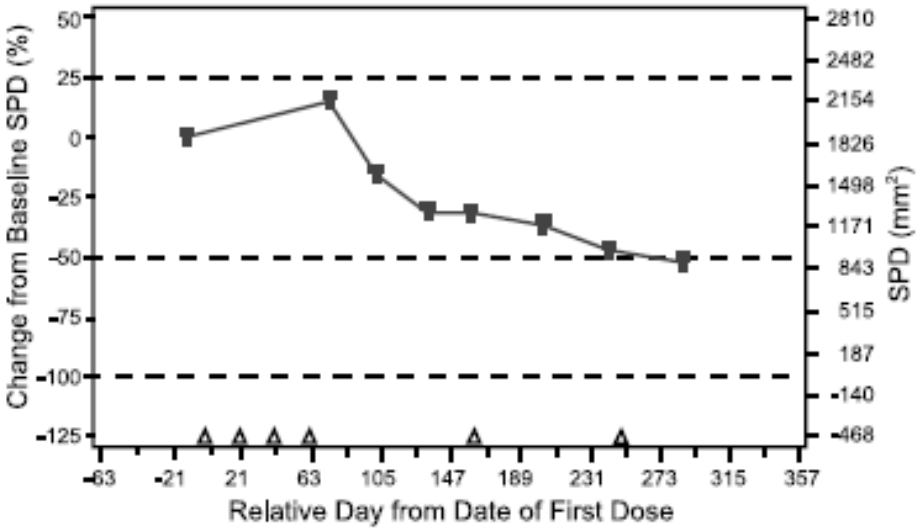
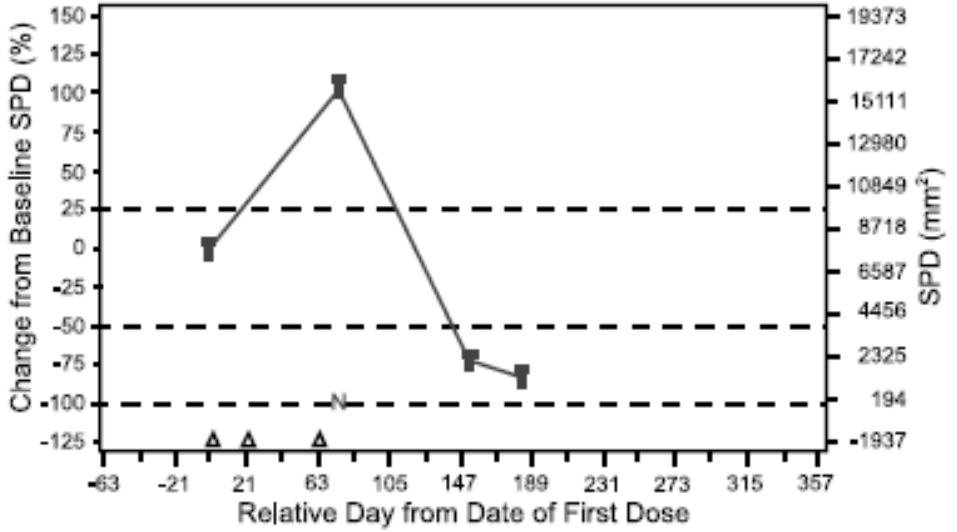
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2012

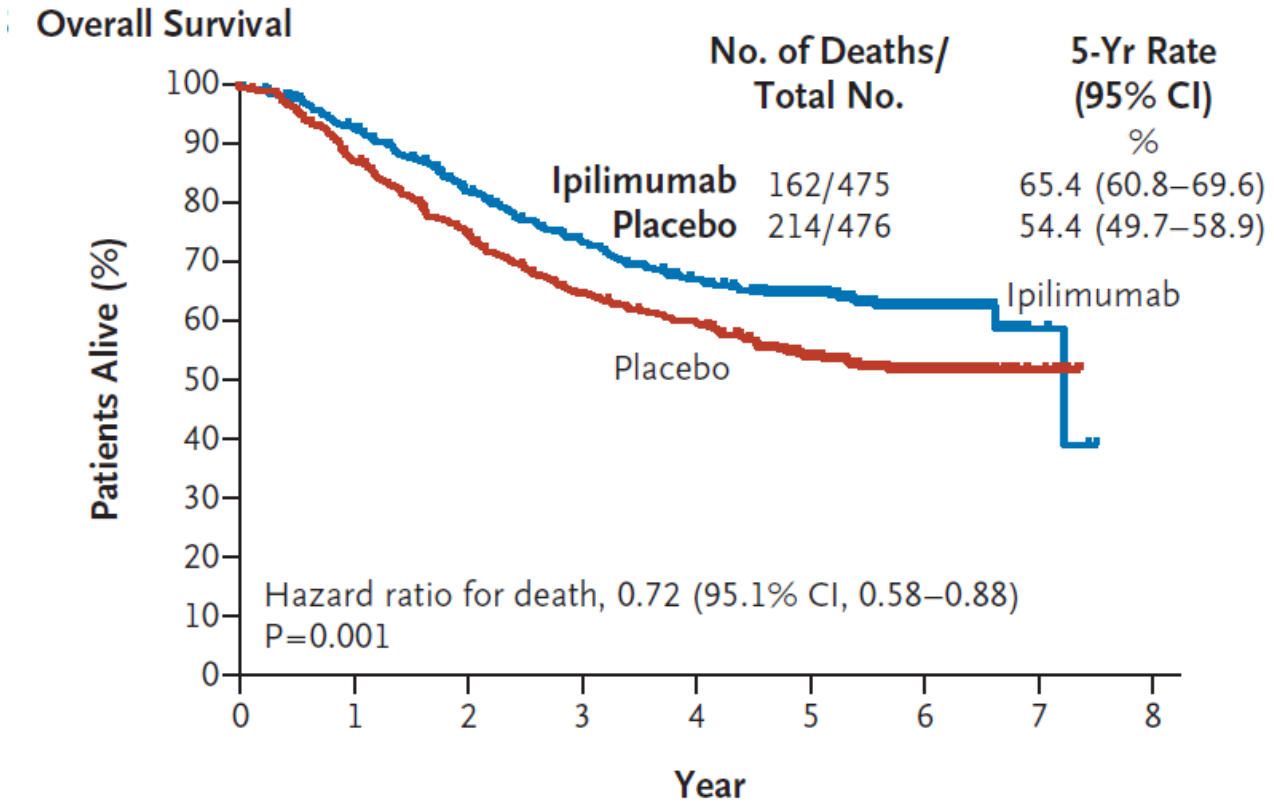
Immune Related Response Criteria





Wolchok et al. Clin Can Res 2012

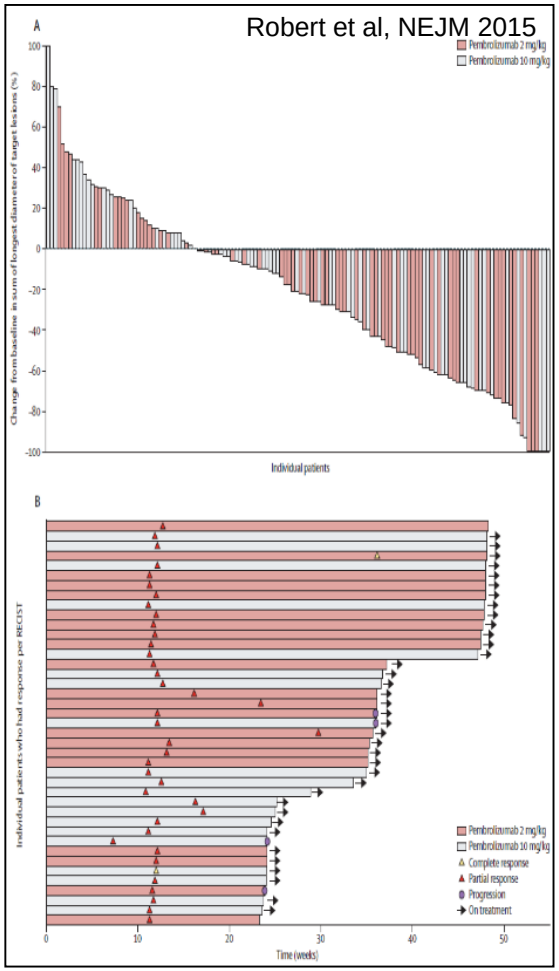
Adjuvant Ipilimumab in High-Risk Melanoma



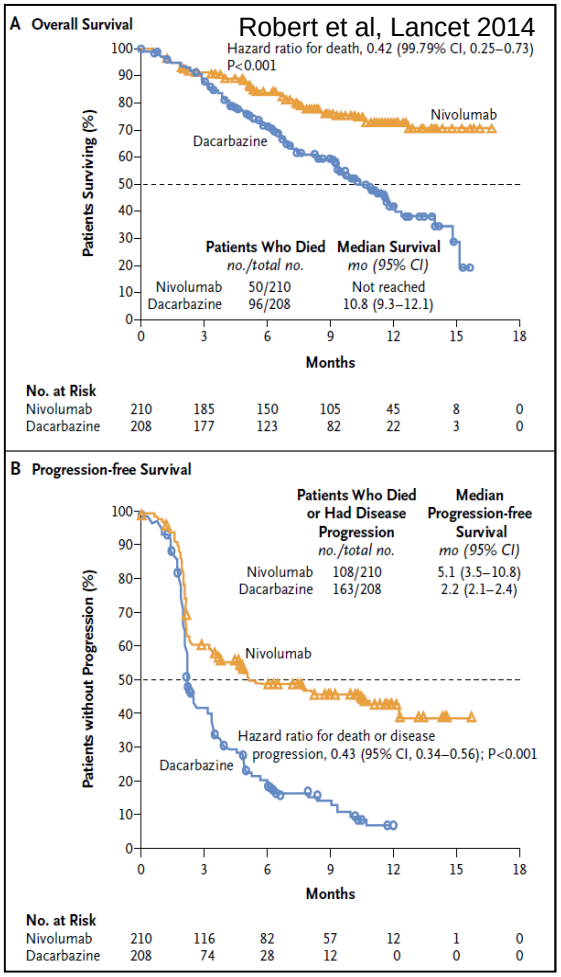
Eggermont *et al*. NEJM 2016

Anti-PD1 in Melanoma

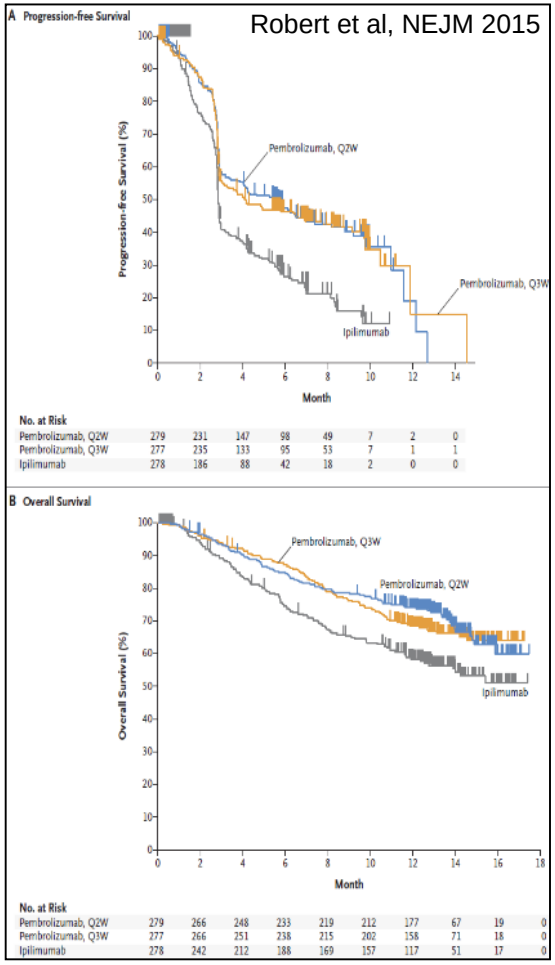
Anti-PD1 (pembrolizumab) *after* ipilimumab



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



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



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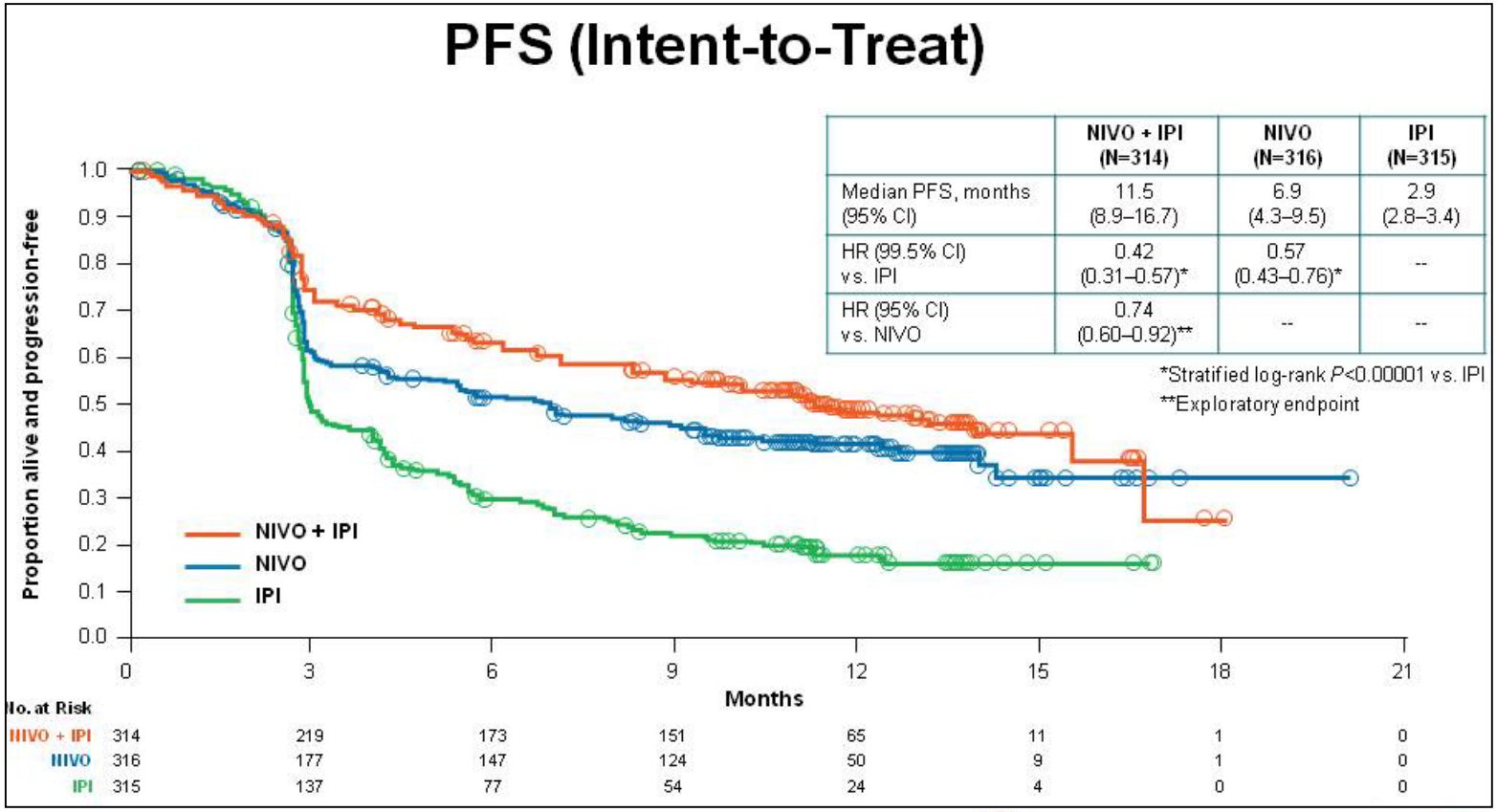
Ipilumamab: CTLA-4

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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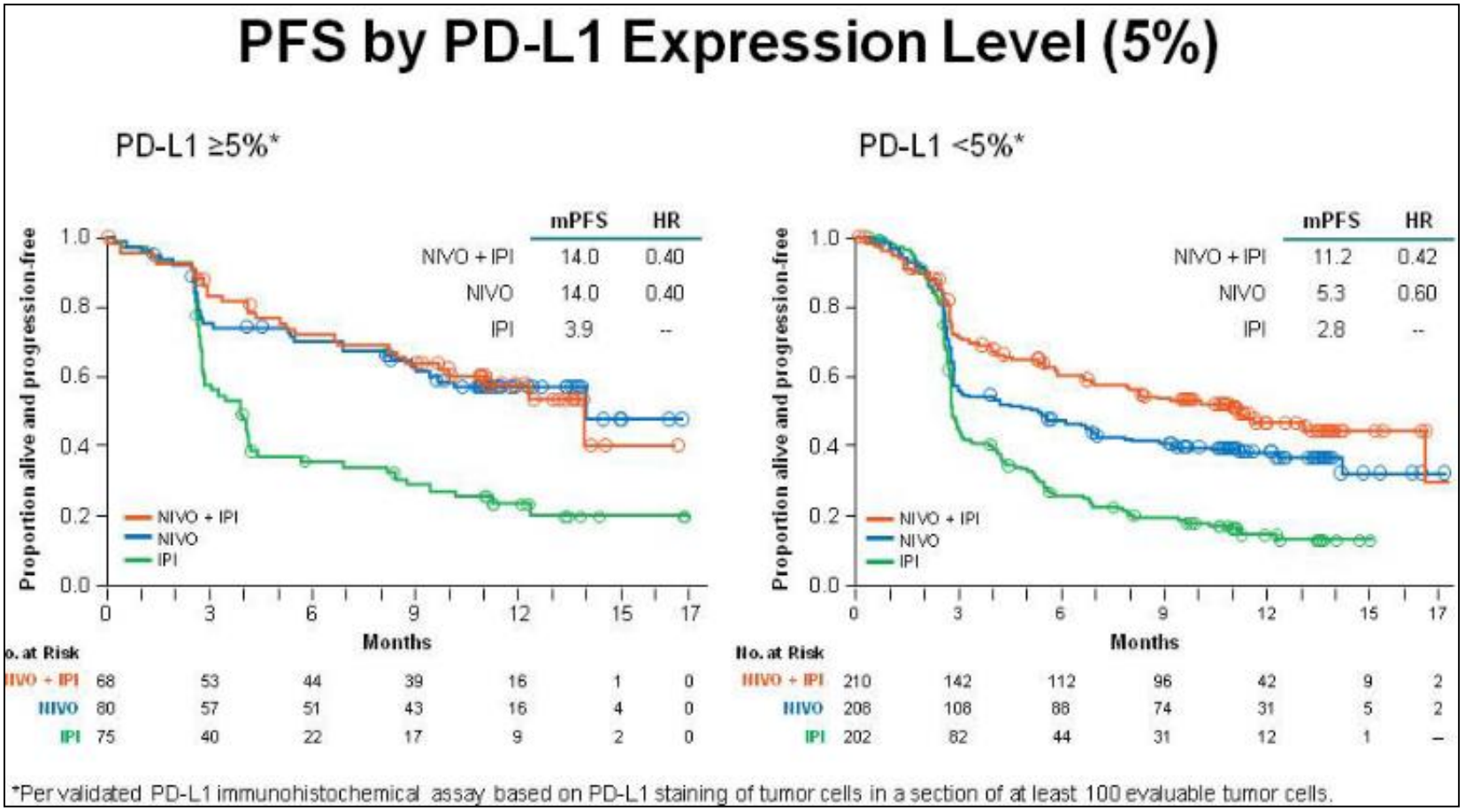
Ipilumamab: CTLA-4

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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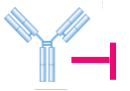
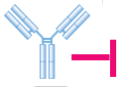
Ipilumamab:



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)

Case #2: same as #1, but BRAF^{V600}

Additional decision needed: MAPK inhibitor timing and choice

How I treated patient:

- Resected, sent tumor for research studies of tumor microenvironment
- Margins + at muscle—did not send for resection
- Ipilimumab at “adjuvant” dose of 10mg/kg with maintenance

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Case #2: metastatic melanoma BRAFm from unknown primary

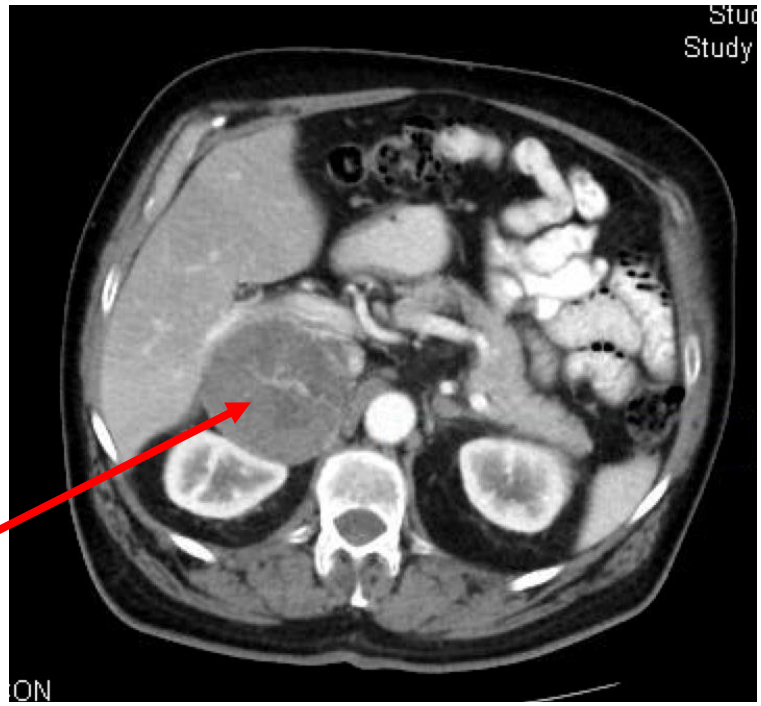
RN, male patient in 50s

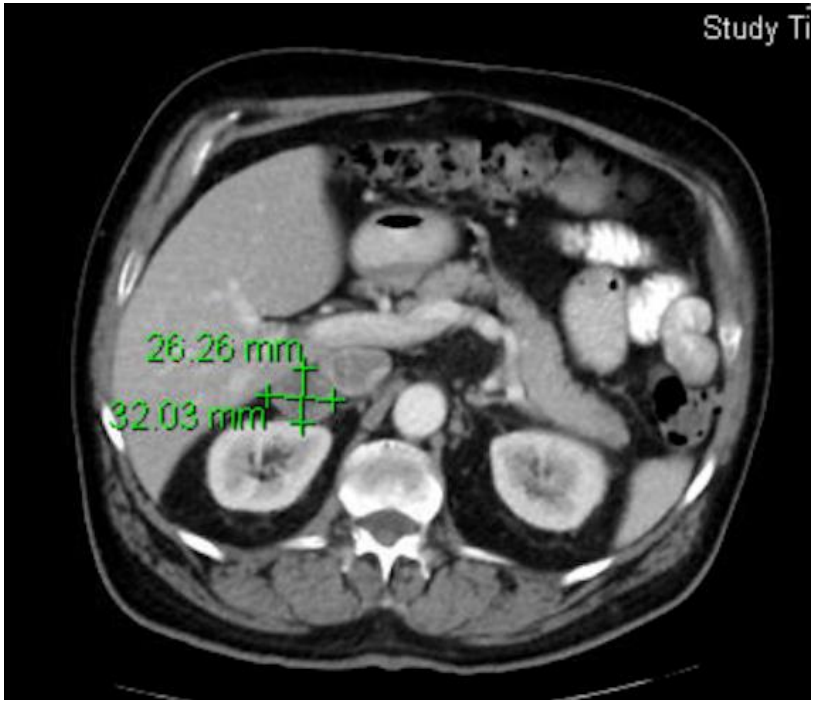
- Presented 8/2015 with pleuropulmonary disease symptoms and large R adrenal $BRAF^{V600E}$ metastasis
- Initial Therapy:
  - dabrafenib and trametinib
  - Near CR x 18 months
  - Tolerated therapy with minimal side effects—mainly peripheral edema

Progression in R adrenal but controlled in lung; new small asymptomatic brain metastasis

- Checkmate 209204
  - nivolumab plus ipilimumab for metastatic melanoma to brain

Therapeutic effect—representative images (also had small brain metastasis⟶ CR)





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Case #2: Questions raised

1. Was it appropriate to start with MAPKi? YES
2. Should he have received combination with immunotherapy NO
3. Is it best to switch to immunotherapy early, or at best response to MAPKi? UNKNOWN
4. Why did he have such a sustained response to MAPKi? Immunomodulation?
5. Is nivolumab plus ipilimumab the optimal immunotherapy in June 2017? PROBABLY
6. Should PD-L1 expression have been checked? Maybe…but many issues remain
7. How long to continue Rx? UNKNOWN/1 yr?

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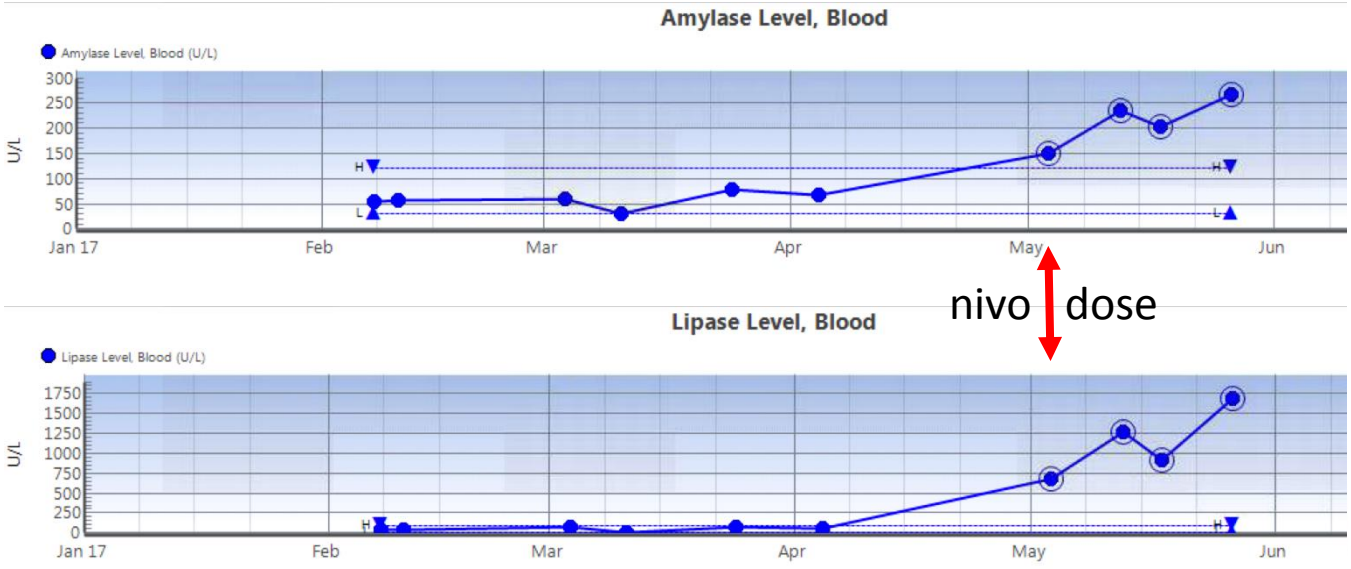
Toxicity management issues

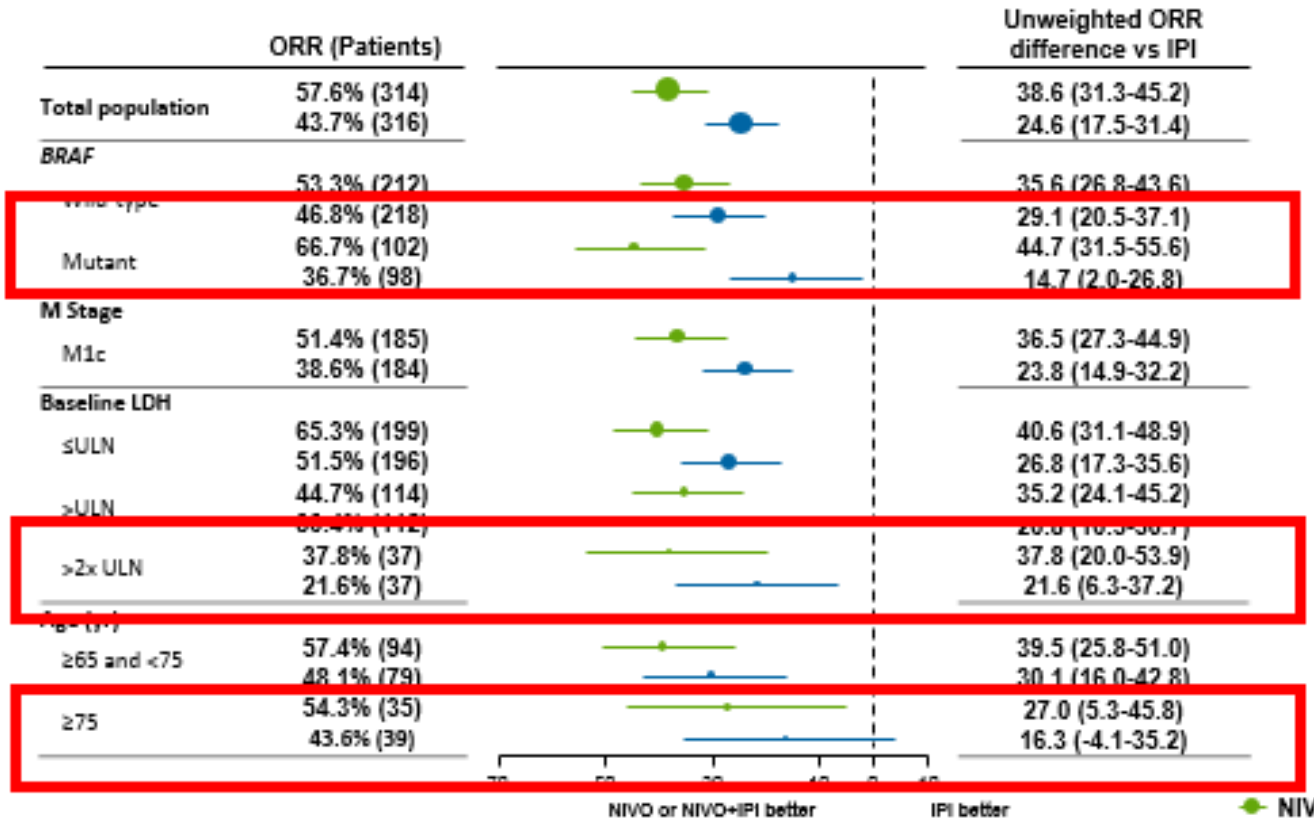
Diarrhea from ipilimumab/nivolumab combination responded to steroid; Ipilimumab dropped after 2 cycles, in part because pt was traveling to Poland (QoL)

Nivolumab dosed at 1 mg/kg in cycles 3 and 4—should it have been increased?

Pt developed chemical pancreatitis, initially without Sx, now with mild abdominal pain—enzymes rising despite skipping last dose nivolumab→steroid? [US not diagnostic, CT is negative, pt continues to work, eat, perform ADLs normally



Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



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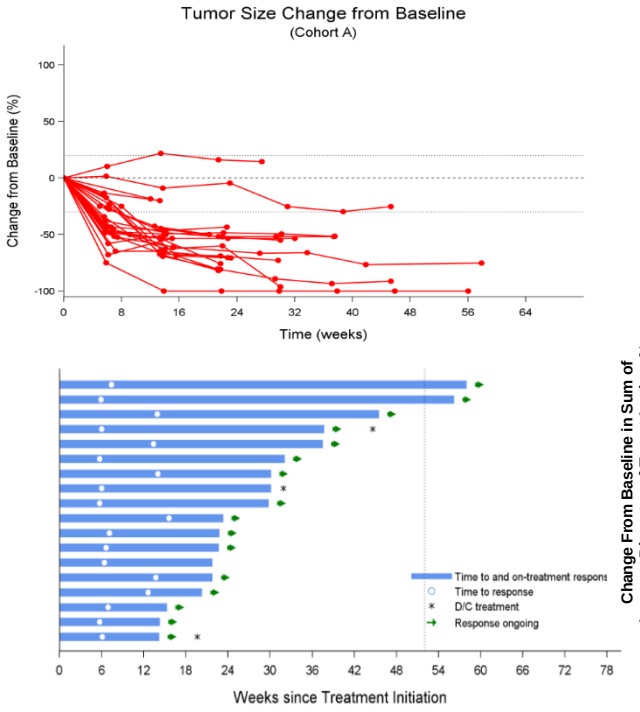
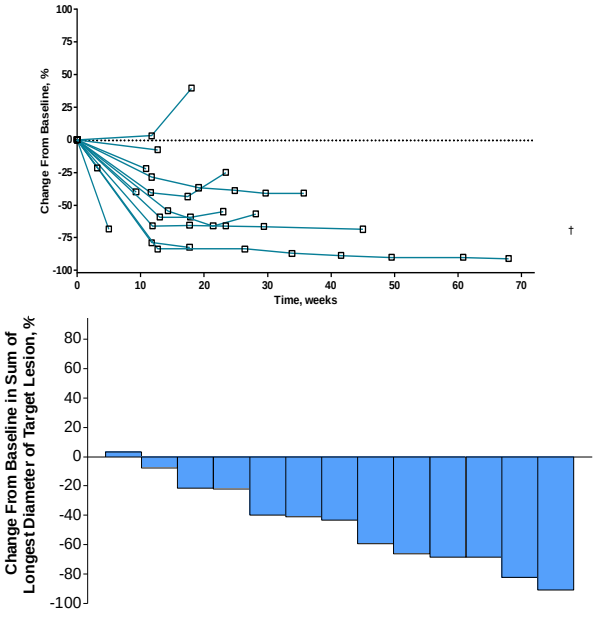
Target-Immuno Triplets: BRAF + MEK + PD1/L1

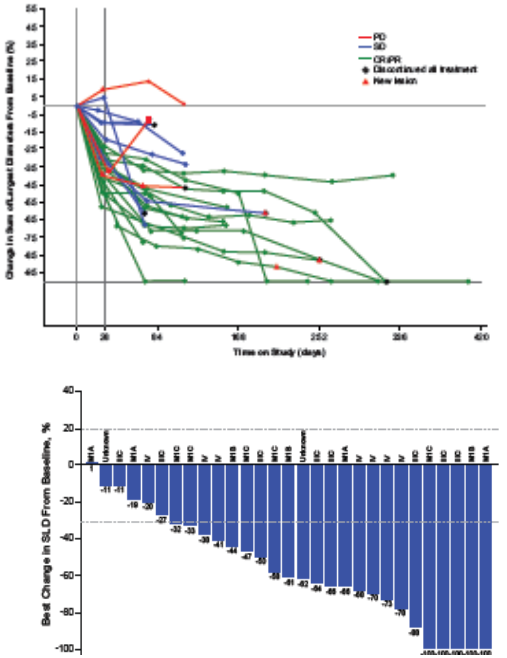
Dabrafenib+Trametinib+ Durvalumab



Dabrafenib+Trametinib+ Pembrolizumab



Vemurafenib+Cobimetinib+ Atezolizumab



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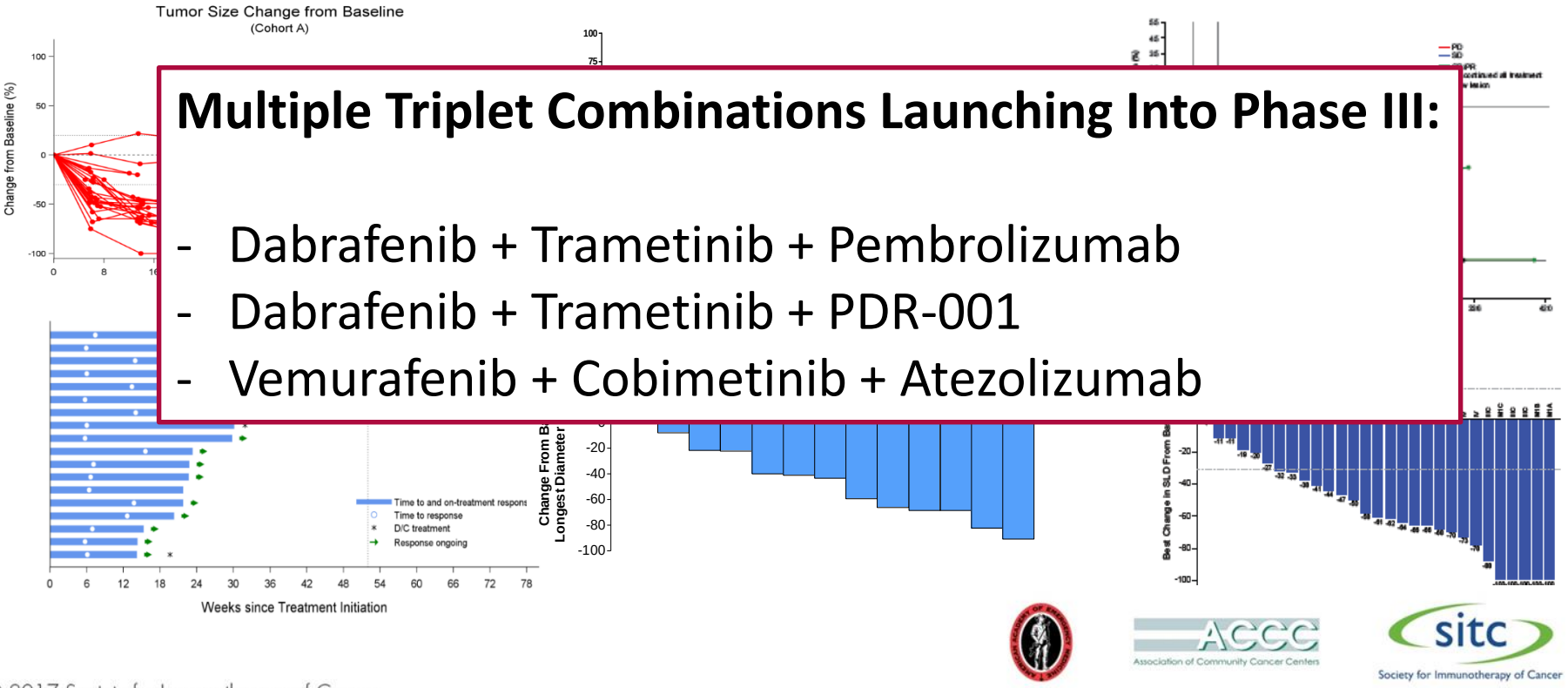
Target-Immuno Triplets: BRAF + MEK + PD1/L1

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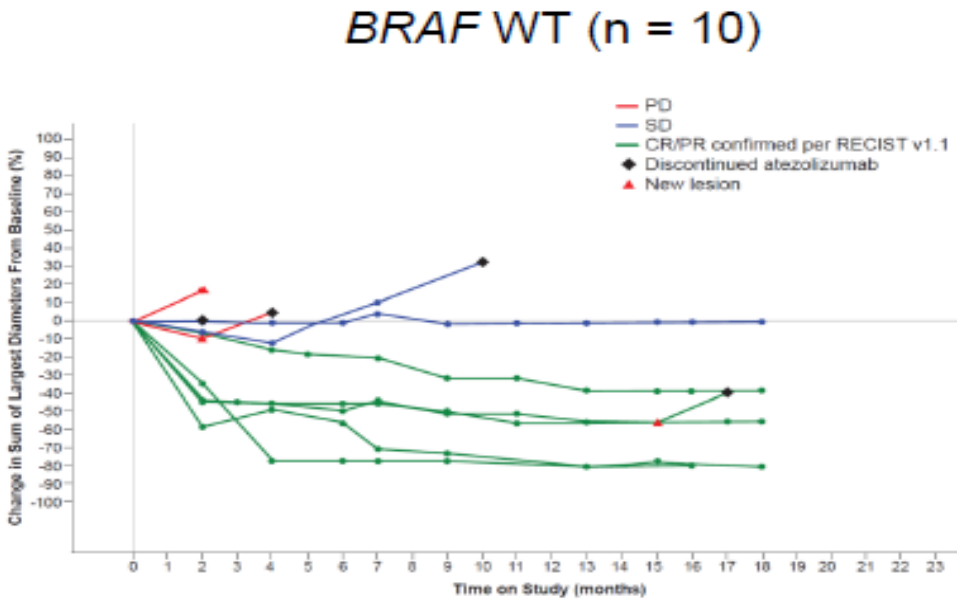
MEK inhibitor + PDL-1 for BRAFwt Melanoma Phase I Cobimetinib + Atezolizumab



	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

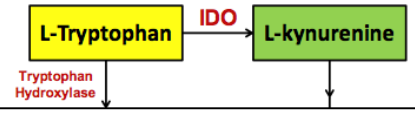
Atezolizumab: PD-L1

Pembrolizumab : PD-1

IDO inhibitor epacadostat + pembrolizumab

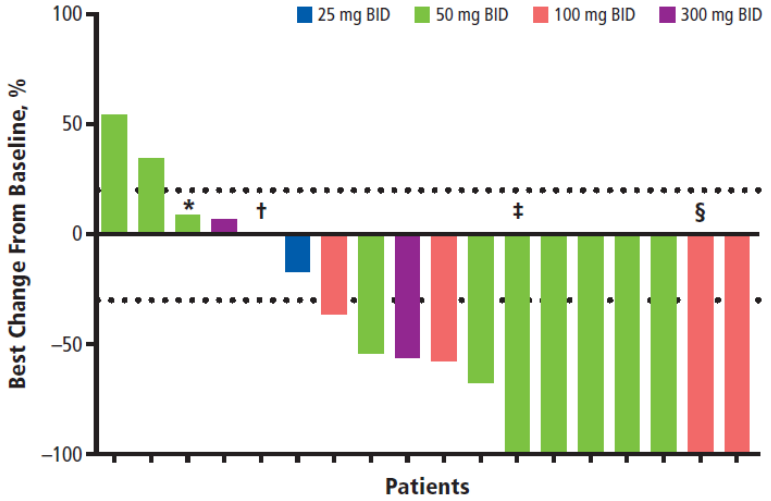
Indoleamine Dioxygenase-1 (IDO1)

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



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

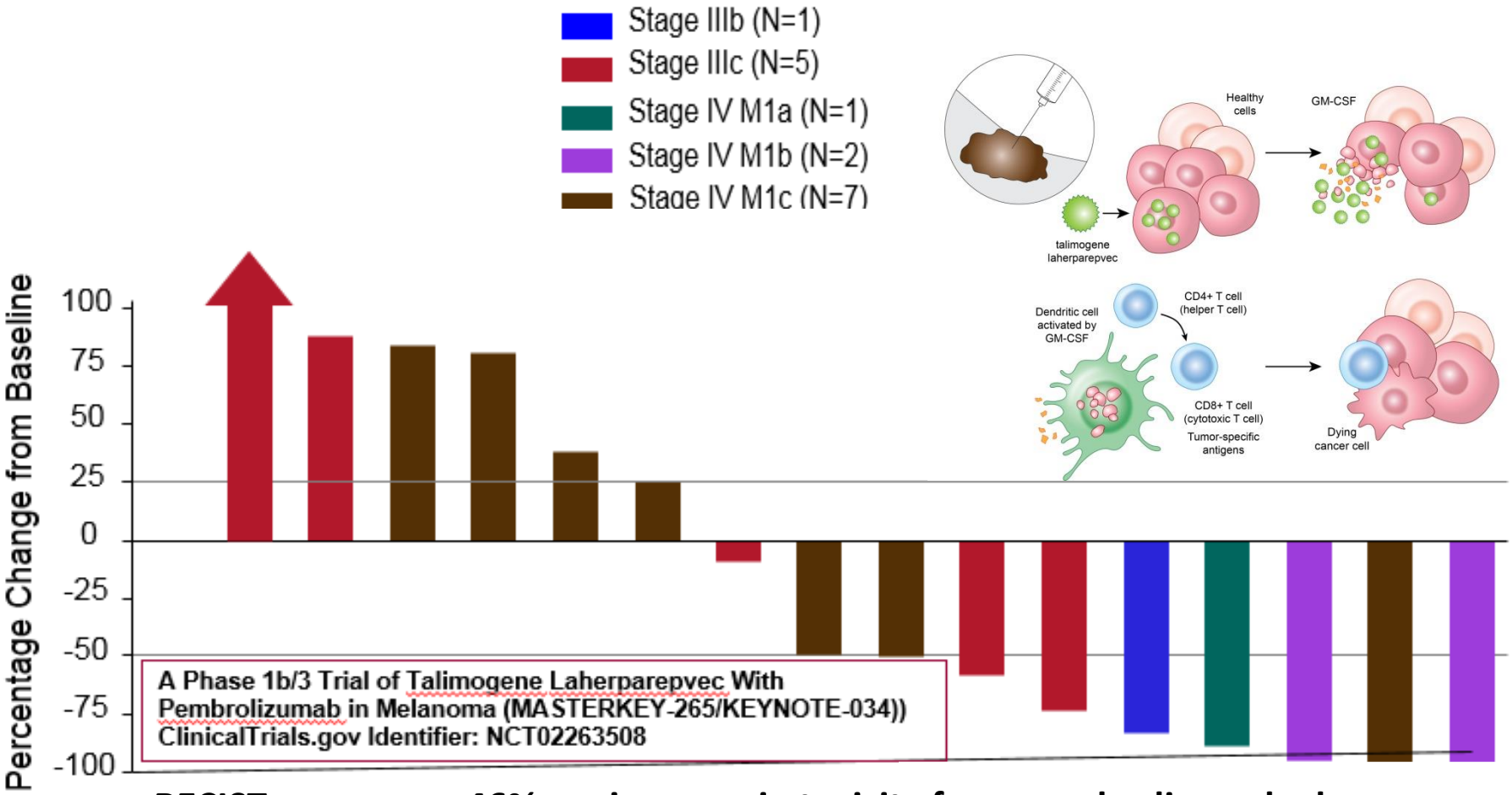
A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074



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

ADVANCES IN Cancer IMMUNOTHERAPY™

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!