ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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Dana Farber Cancer Institute

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Dana Farber Cancer Institute receives clinical trial support from Bristol Myers Squib, Merck, Genentech
- 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)

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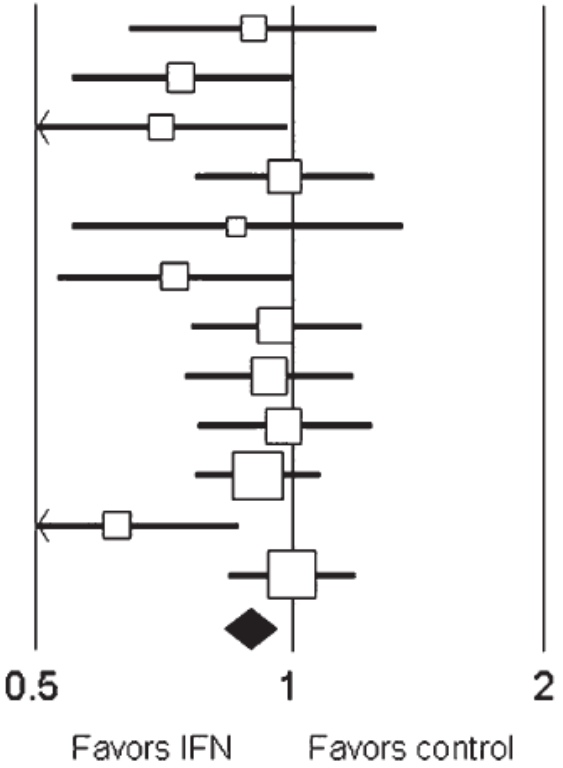
Adjuvant Treatment of High-Risk Melanoma

	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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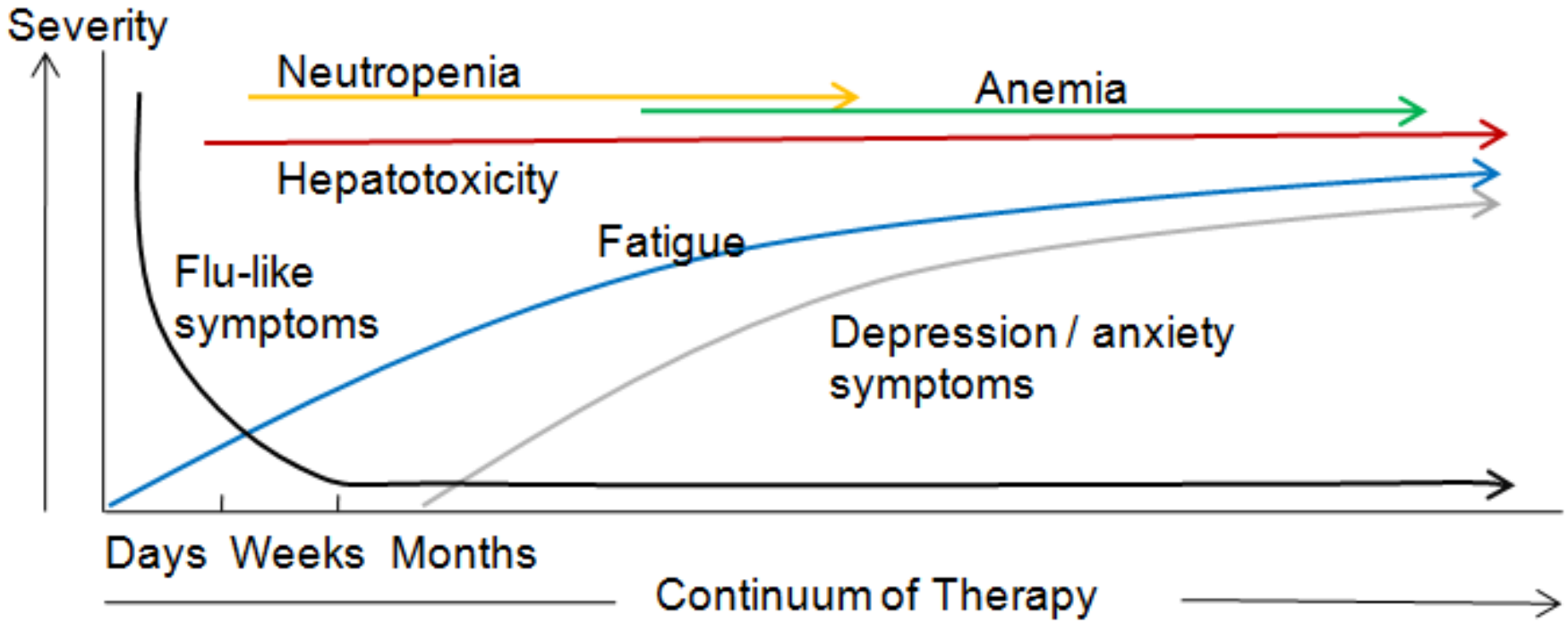
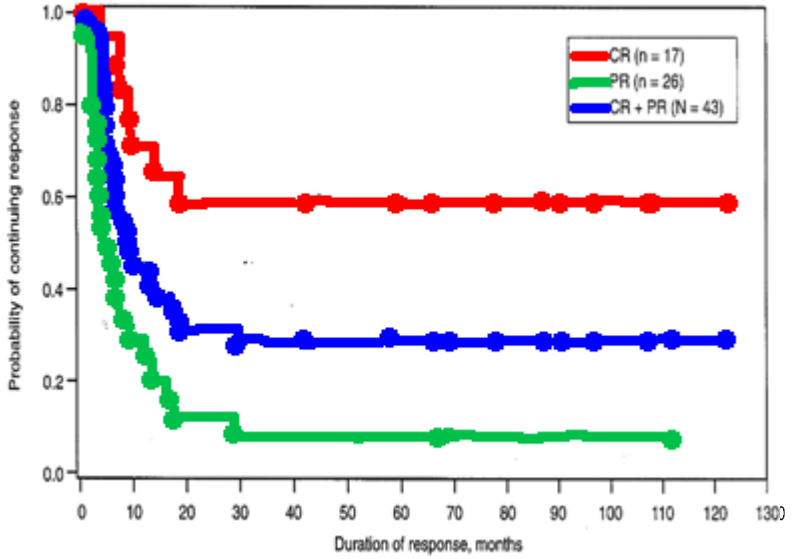
Toxicity of Adjuvant Interferon-α



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

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

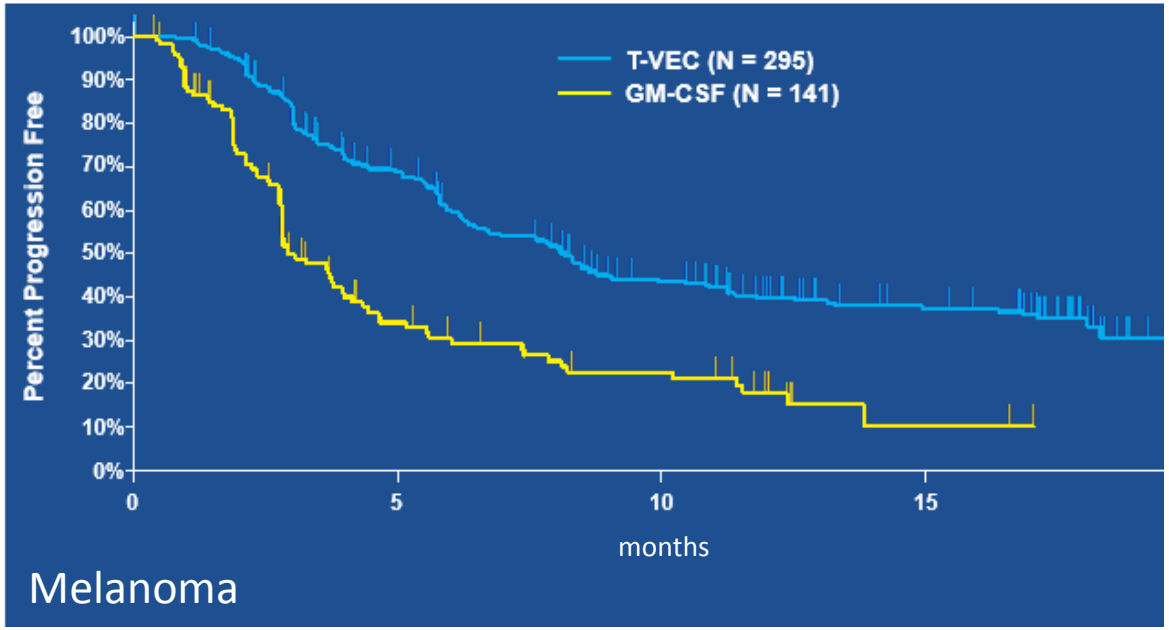
- HD IL-2 produces durable responses in 6%-10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (cured?)
- FDA approval for melanoma in 1998
- High toxicity

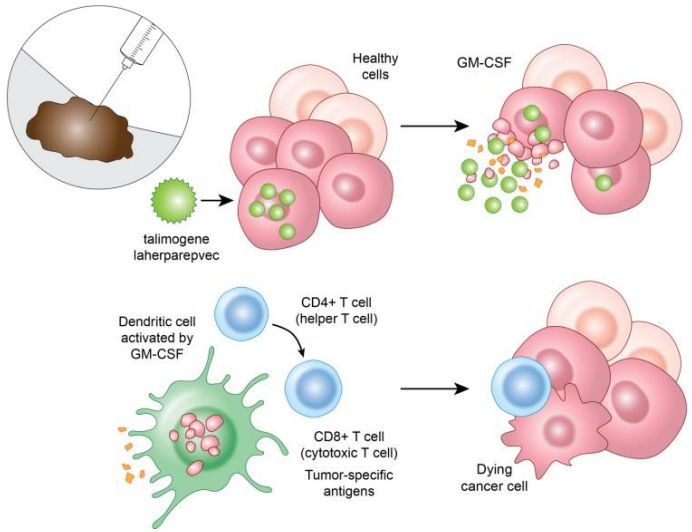


Atkins et al. J Clin Oncol. 1999

Atkins et al. J Clin Oncol. 1999

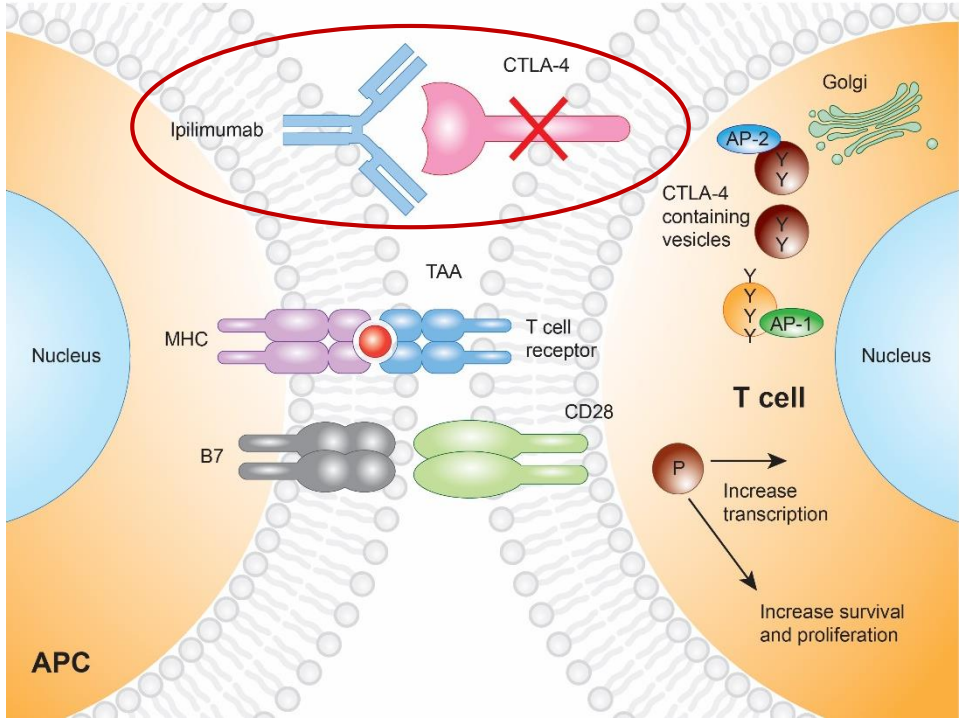
Phase III Trial of T-VEC vs GM-CSF PFS per Investigator

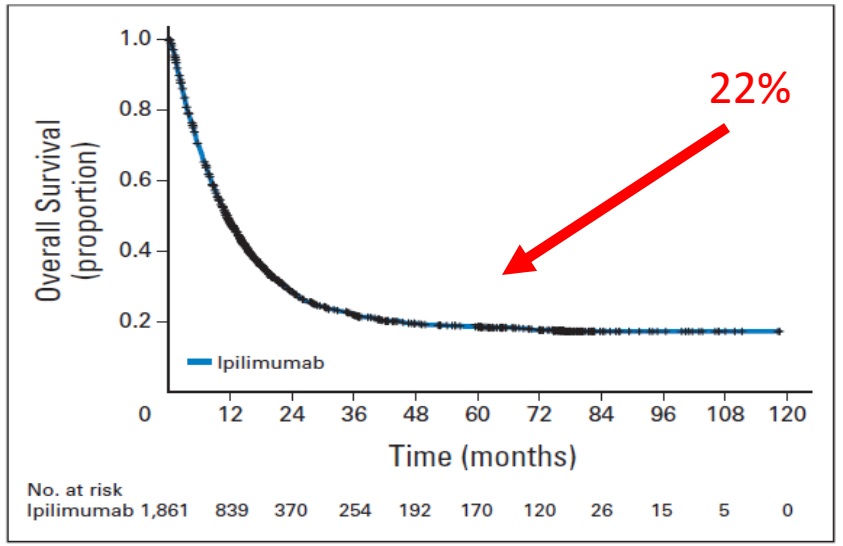




Andtbacks et al. ASCO 2013; LBA9008

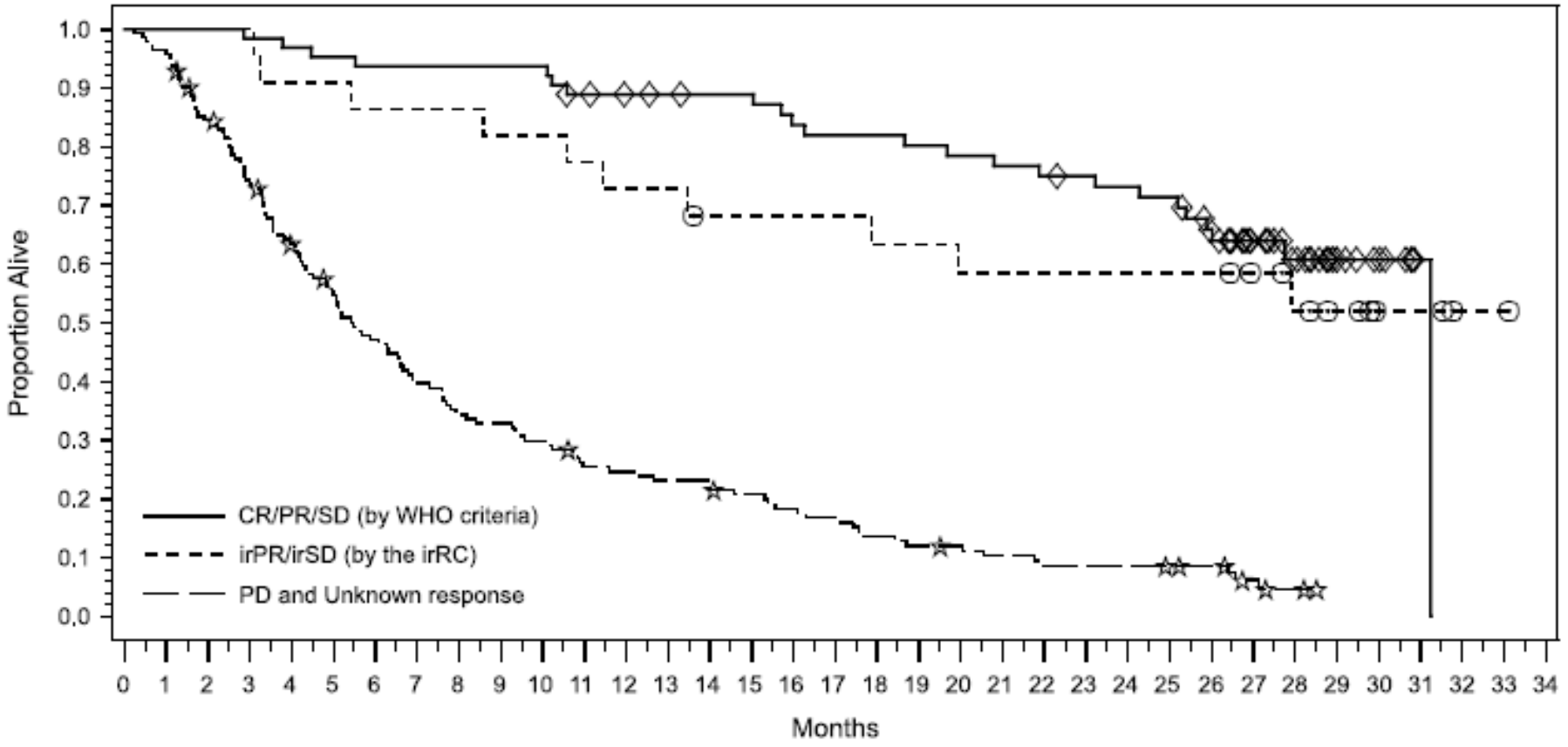
Ipilimumab & Immune Check-Point Blockade





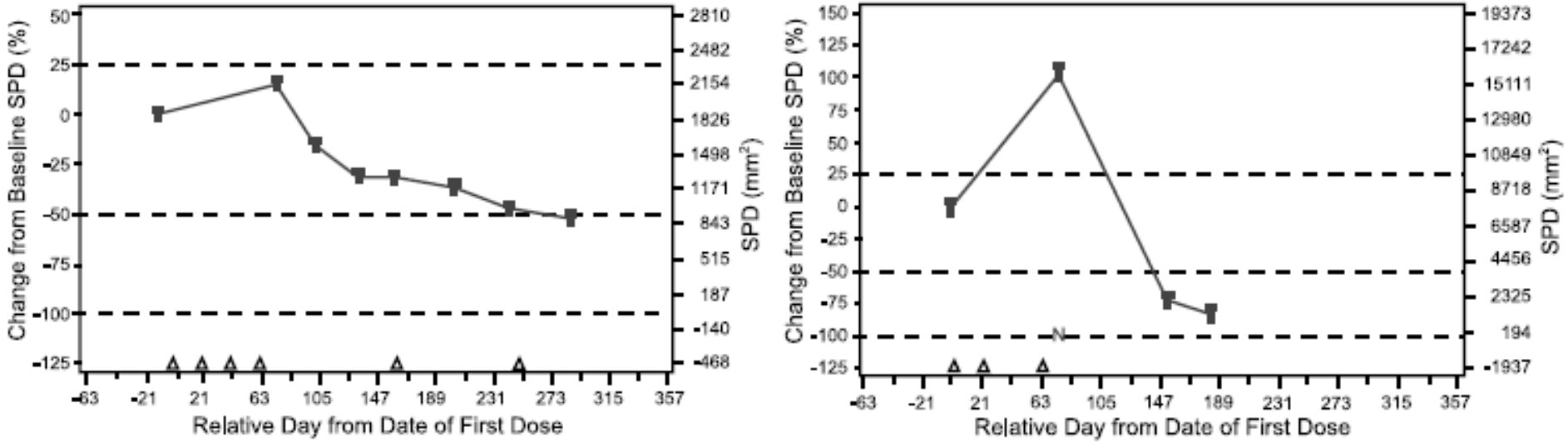
Luke et al, Oncologist 2013
Schadendorf et al, J Clin Oncol 2015

Immune Related Response Criteria



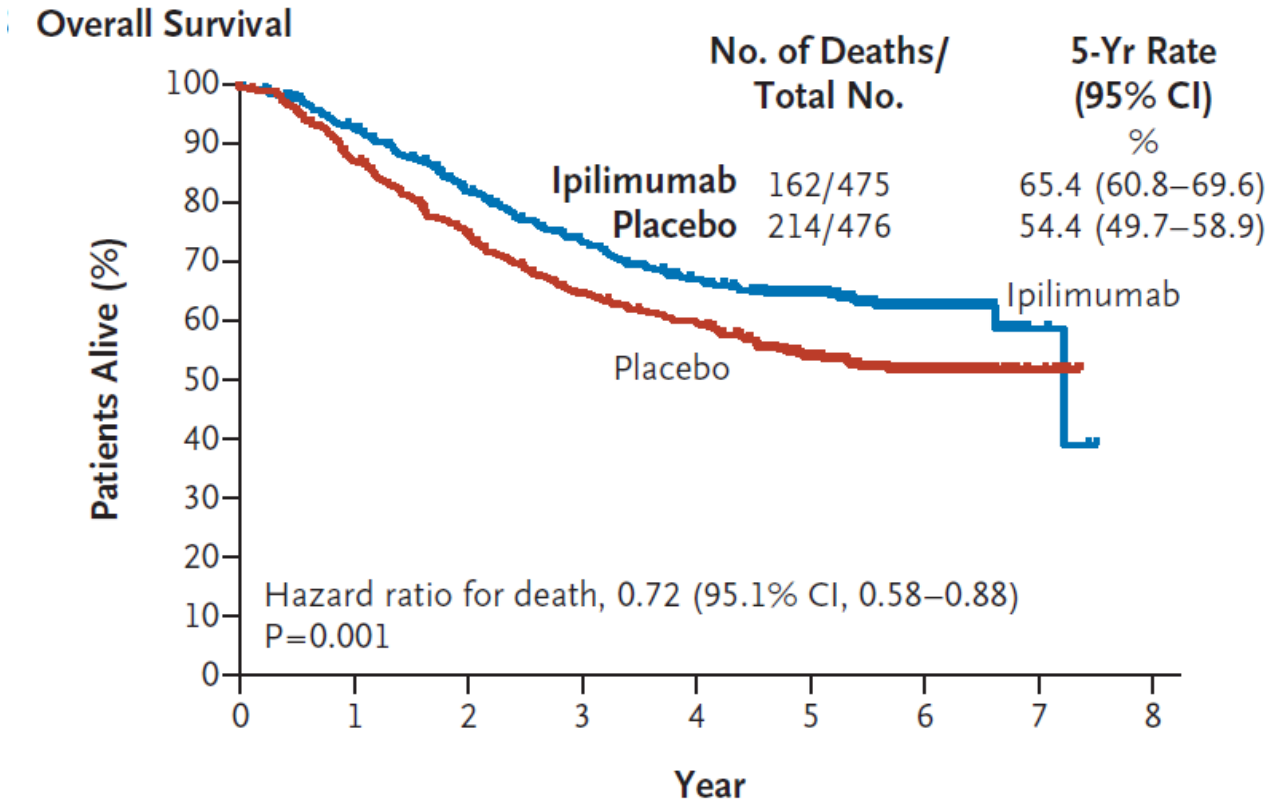
Wolchok et al. Clin Can Res 2009

Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009

Adjuvant Ipilimumab in High-Risk Melanoma



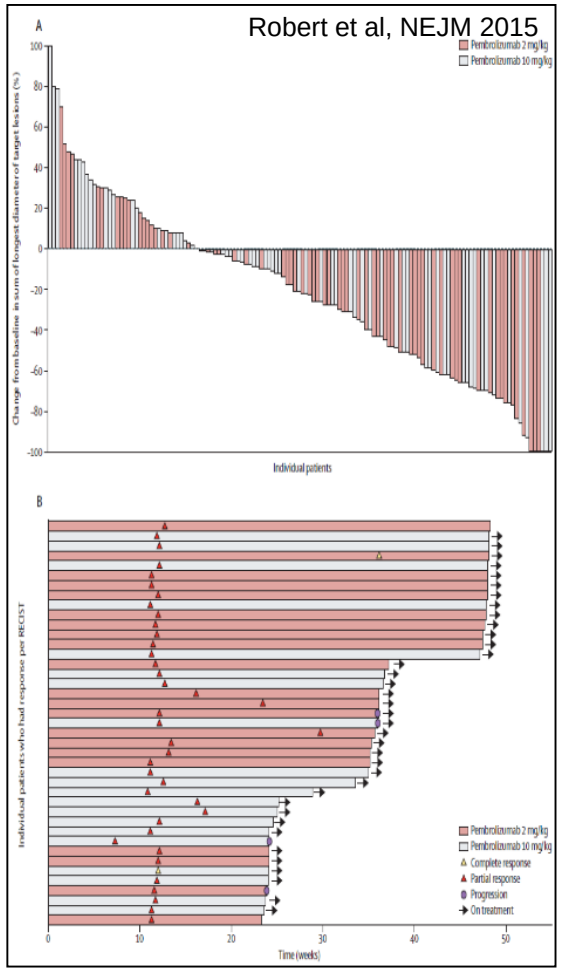
No. at Risk

Ipilimumab	475	431	369	325	290	199	62	4
Placebo	476	413	348	297	273	178	58	8

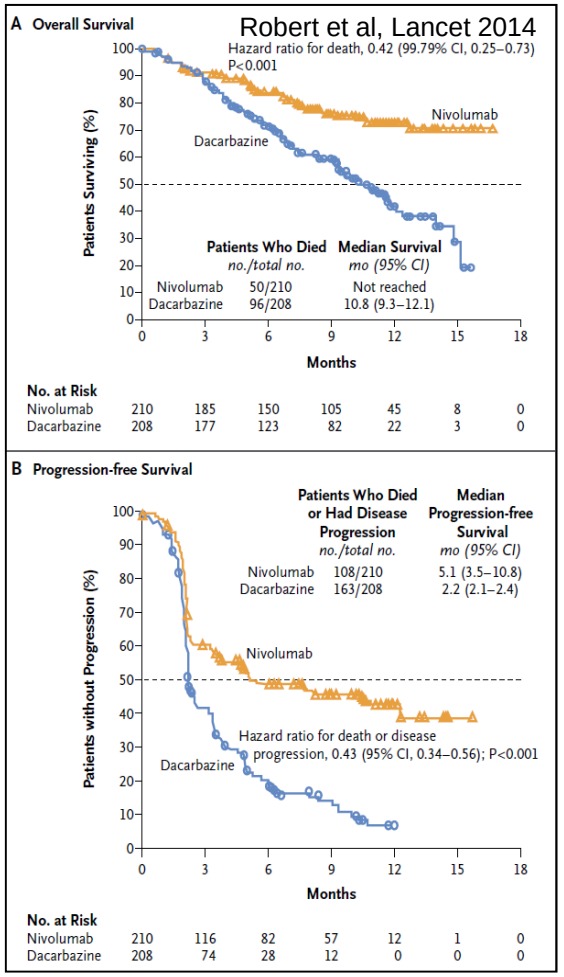
Eggermont *et al*. NEJM 2016

Anti-PD1 in Melanoma

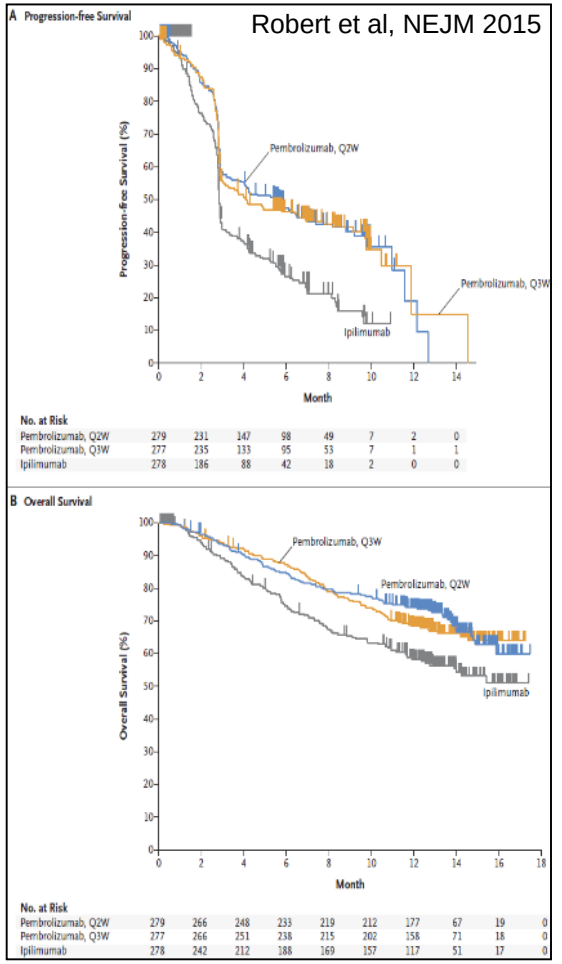
Anti-PD1 (pembrolizumab) *after* ipilimumab



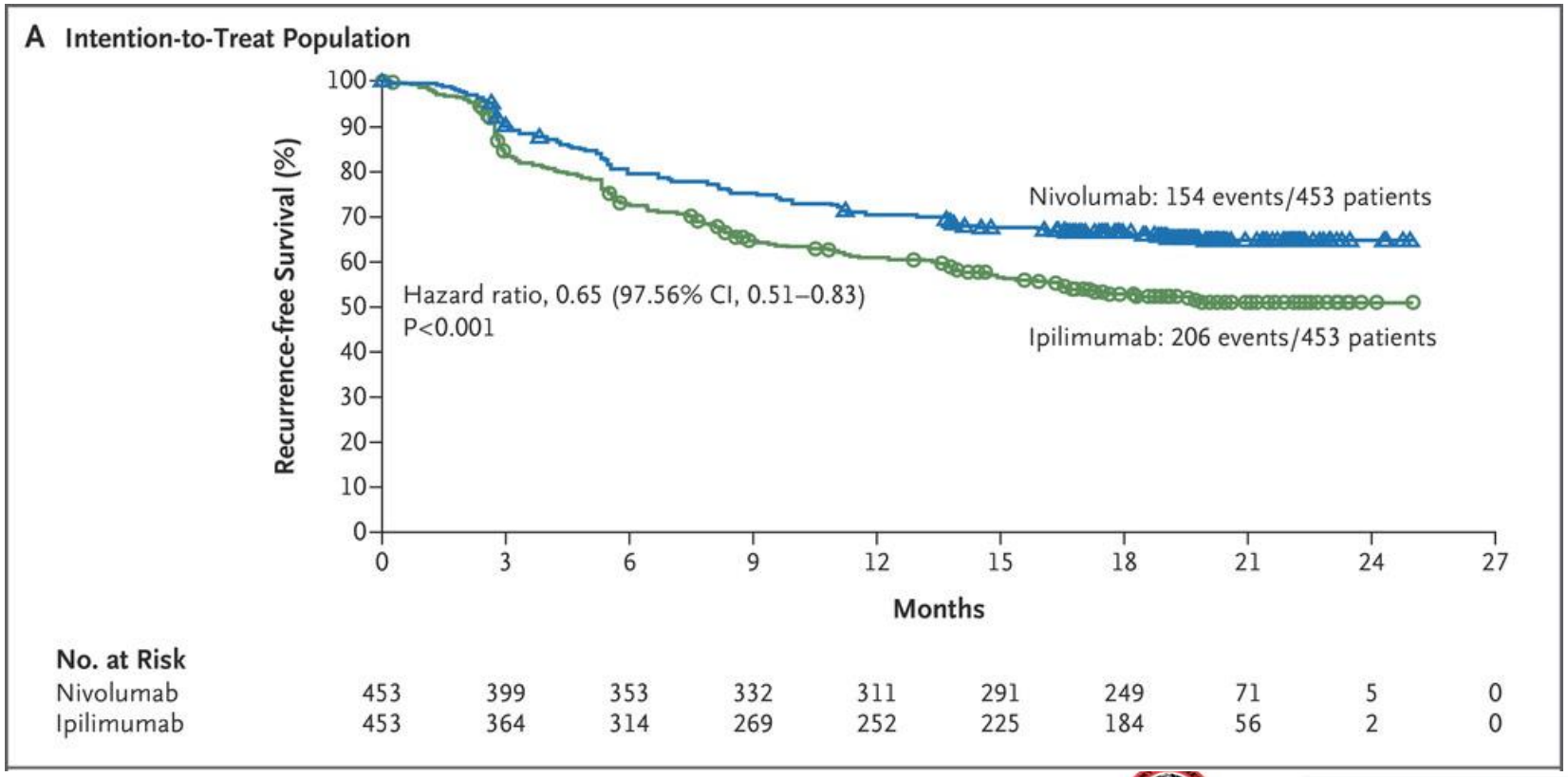
Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma(BRAF WT)



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



Adjuvant nivolumab in High-Risk Melanoma



Weber *et al*. NEJM 2017

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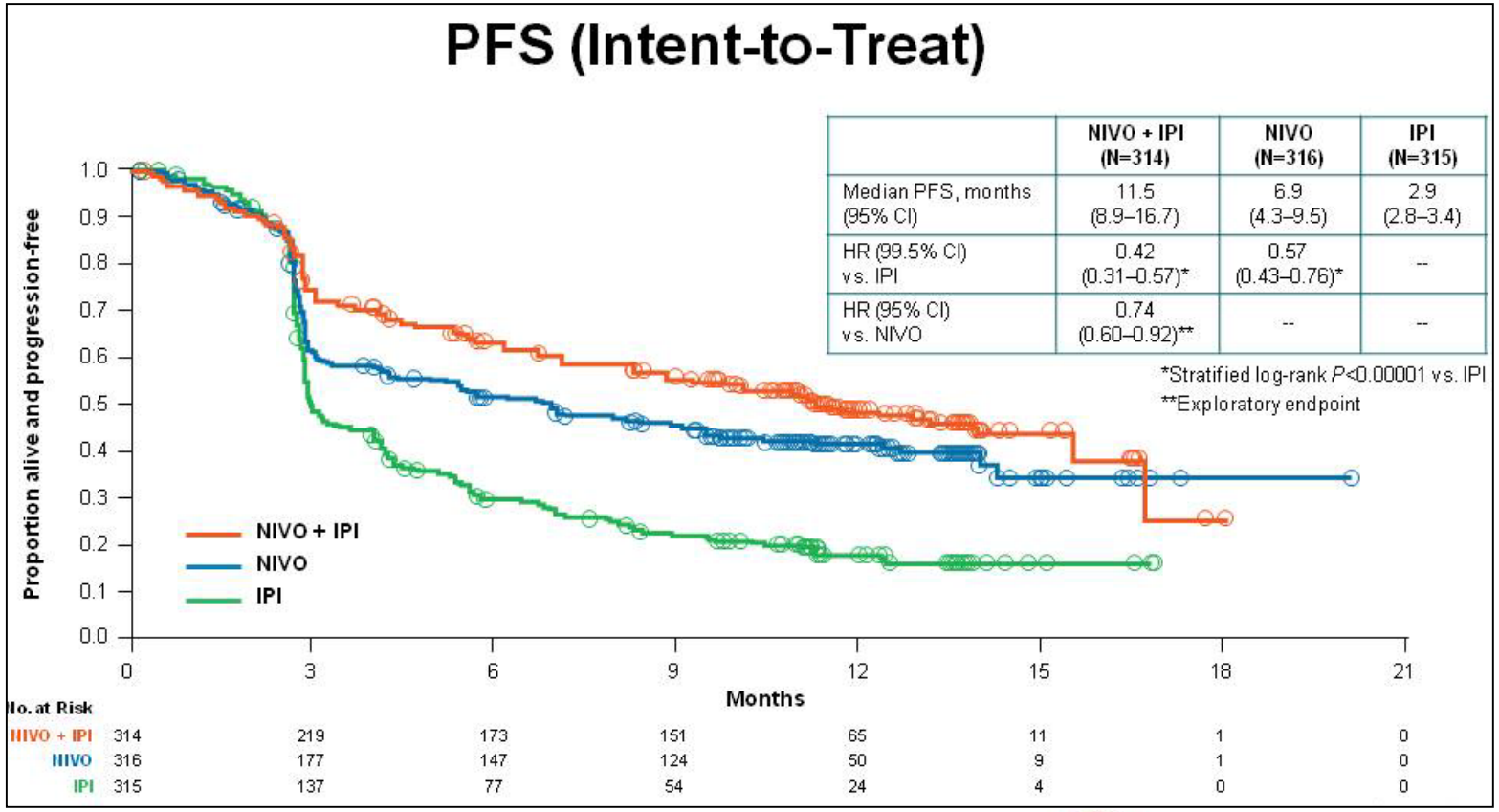
Ipilumamab: CTLA-4

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)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

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

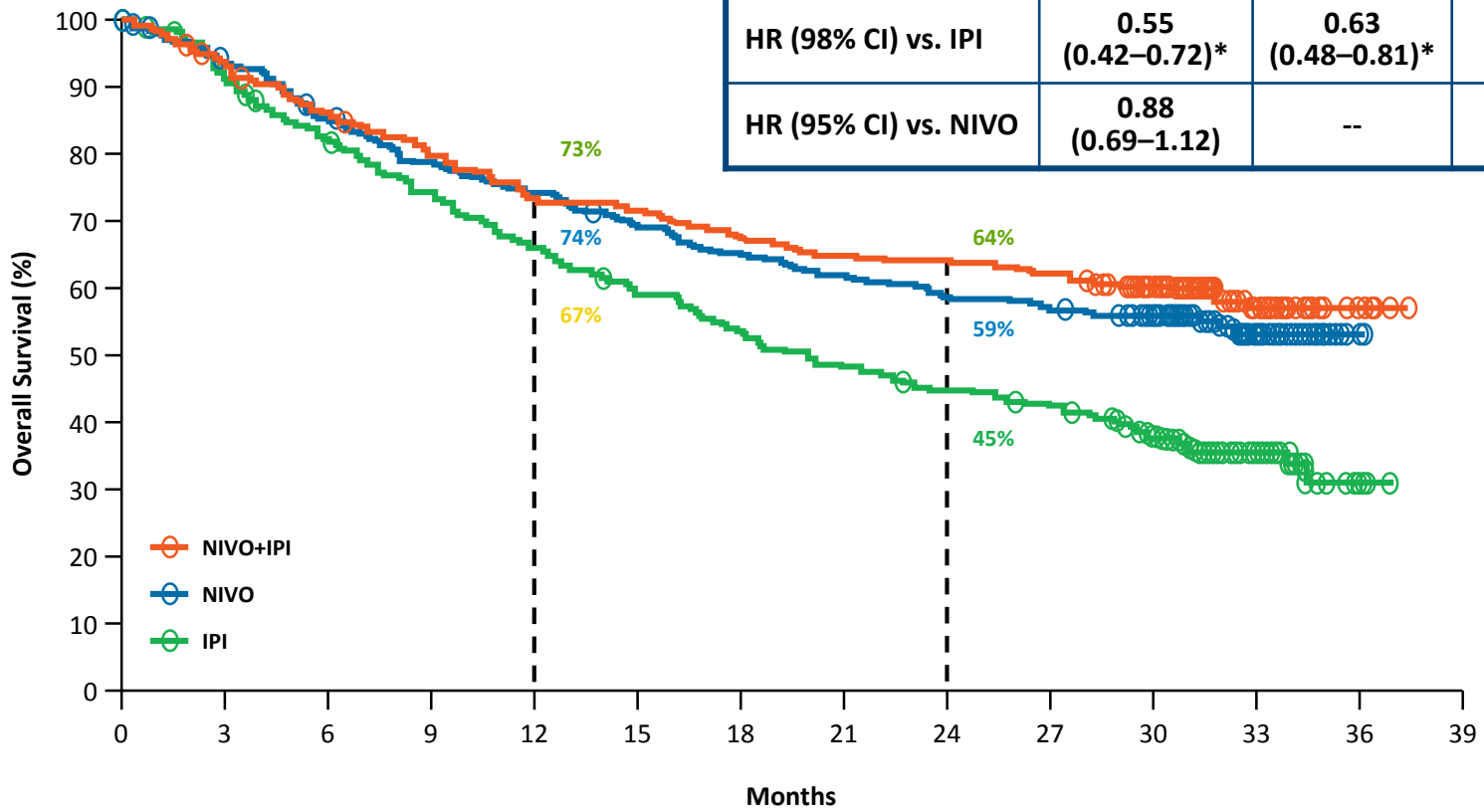
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*$P<0.0001$



Patients at risk:

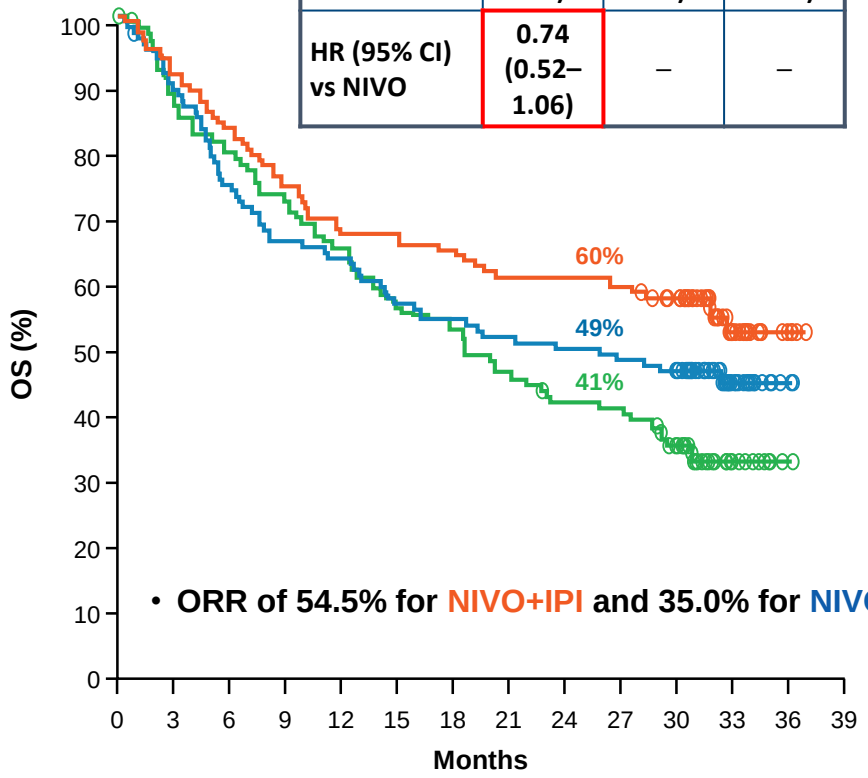
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept.13, 2016, minimum f/u of 28 months

Outcomes at a 1% Cutoff for PD-L1

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



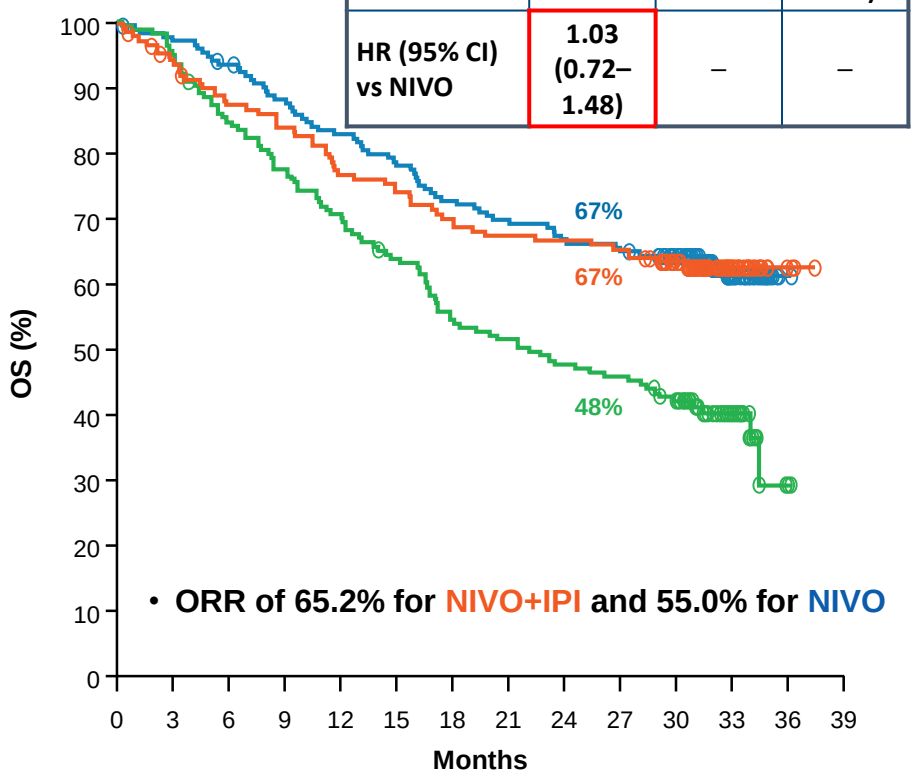
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–



- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	99	89	83	77	74	64	21	2	0

Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report[1]

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

- categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

1. Larkin J, et al. *NEJM* 2015;373:23–34.

Case #1: stage I⟶ III ⟶ IV

WR, male patient in 50s

- Initial T1b melanoma in 2015, subsequent right axillary LN enlargement followed by lymph node dissection in 2017 with 1 3.5 cm LN all other LN negative.
- Signed consent for SWOG-1404 adjuvant trial
- During initial screening he was found to have pulmonary metastasis, possible liver metastasis and left axillary adenopathy.

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Case #1: stage IV, BRAF wt, PD-L1 testing pending

- Systemic therapy
  - Single agent PD-1 inhibition with Nivolumab or Pembrolizumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Ipilimumab
  - Intralesional therapy on trial or with T-VEC
  - Clinical trial involving novel immunotherapy in combination with PD-1 inhibition

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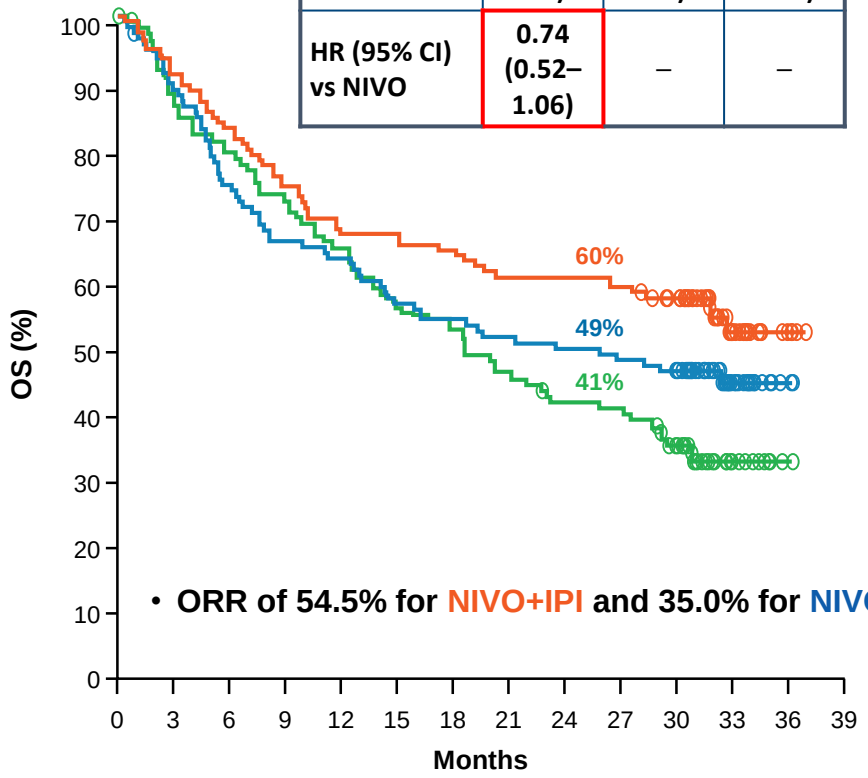
Clinical Trials

- Neoantigen vaccines in combination with PD-1 inhibition
- Injectable therapies with or without immune checkpoint blockade
  - TLR9 agonist
  - Oncolytic viruses
- Immune checkpoint blockade w/other immunomodulators
  - indoleamine dioxygenase inhibitors
  - agonistic costimulatory antibodies (CD137, OX40)
  - Other immune checkpoint inhibitors (Lag3, B7H3)
- Tumor-infiltrating lymphocytes (TILs)

Does PD-L1 staining influence the decision

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

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NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
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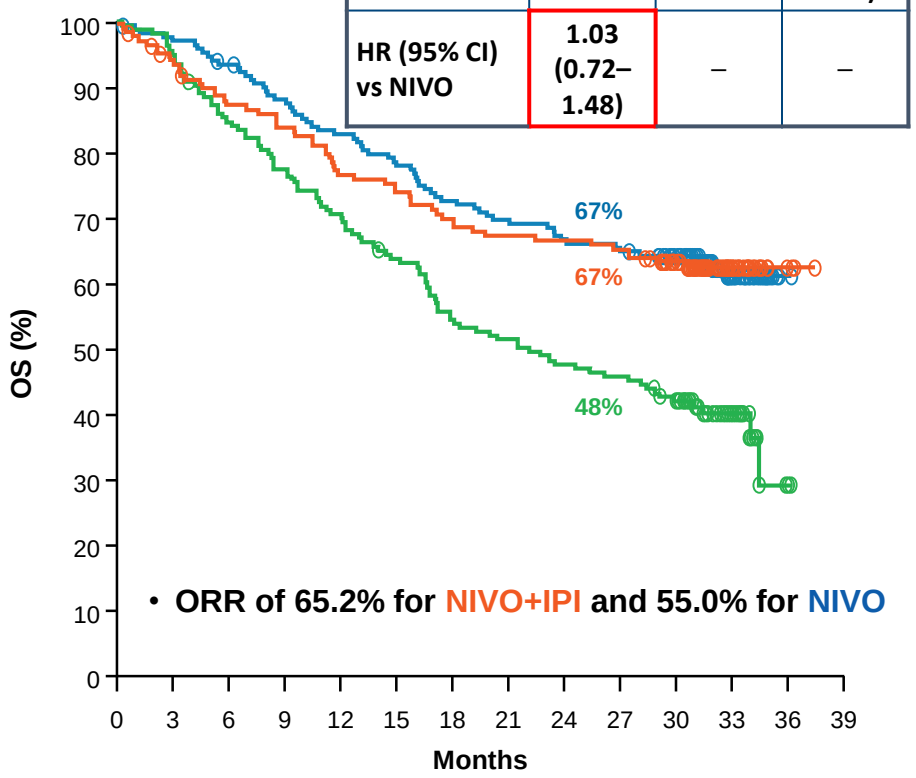

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Patients at risk:

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NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	10	89	83	77	74	64	21	2	0

Case #2: 50yo male metastatic disease, but $BRAF^{V600}$

WO, male patient in 40s

- Initially had IB melanoma of right ear in 2009, nodal recurrence 2016
- Treated with Interferon on adjuvant trial
- Recurrent distant disease in soft tissue and lung
- Asymptomatic

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Case #1: stage IV, BRAF wt, PD-L1 testing pending

- Systemic immunotherapy
  - Single agent PD-1 inhibition with Nivolumab or Pembrolizumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Ipilimumab
  - Intralesional therapy on trial or with T-VEC
  - Clinical trial involving novel immunotherapy in combination with PD-1 inhibition
- **Targeted therapy**
  - **BRAF/MEK inhibition**
  - **Clinical trial with BRAF/MEK inhibition with or without concurrent immunotherapy**

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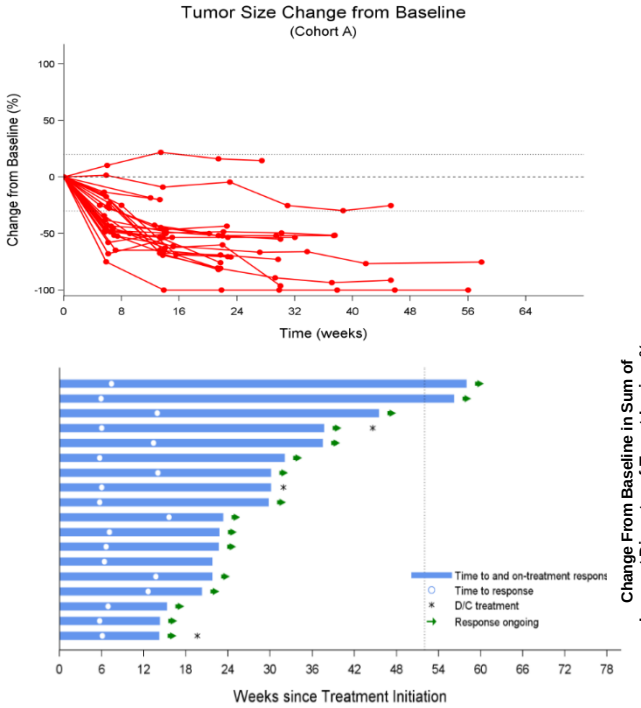
On-Going Phase III Trials in Melanoma

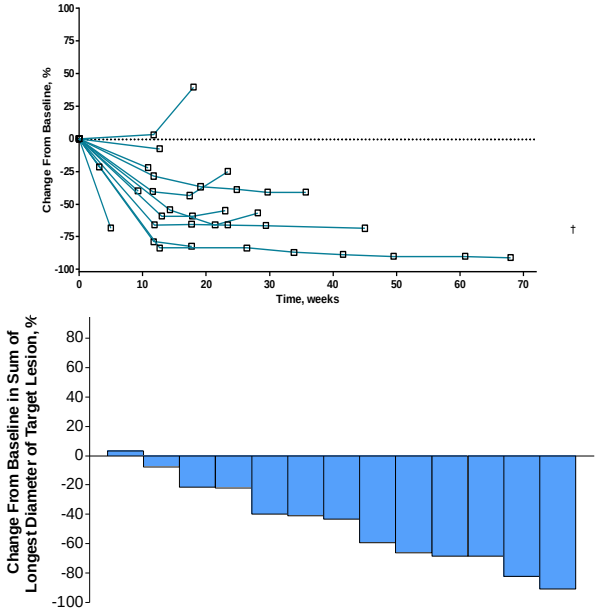
- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi) + anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti PD(L)1
- Adjuvant trials with nivolumab and pembrolizumab

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

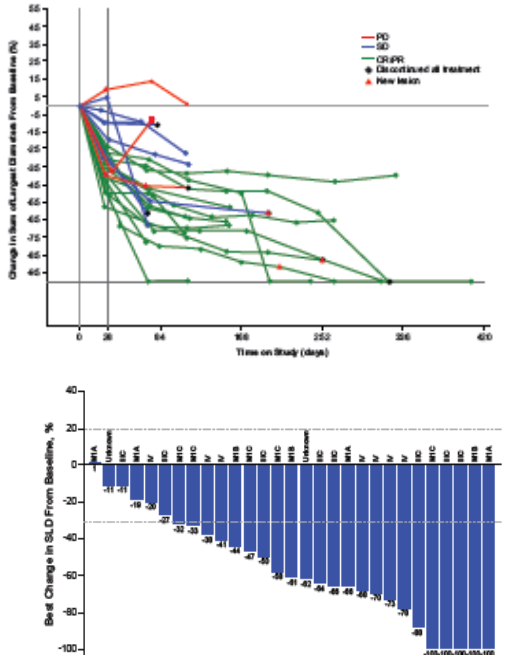
Dabrafenib+Trametinib+ Durvalumab



Dabrafenib+Trametinib+ Pembrolizumab



Vemurafenib+Cobimetinib+ Atezolizumab

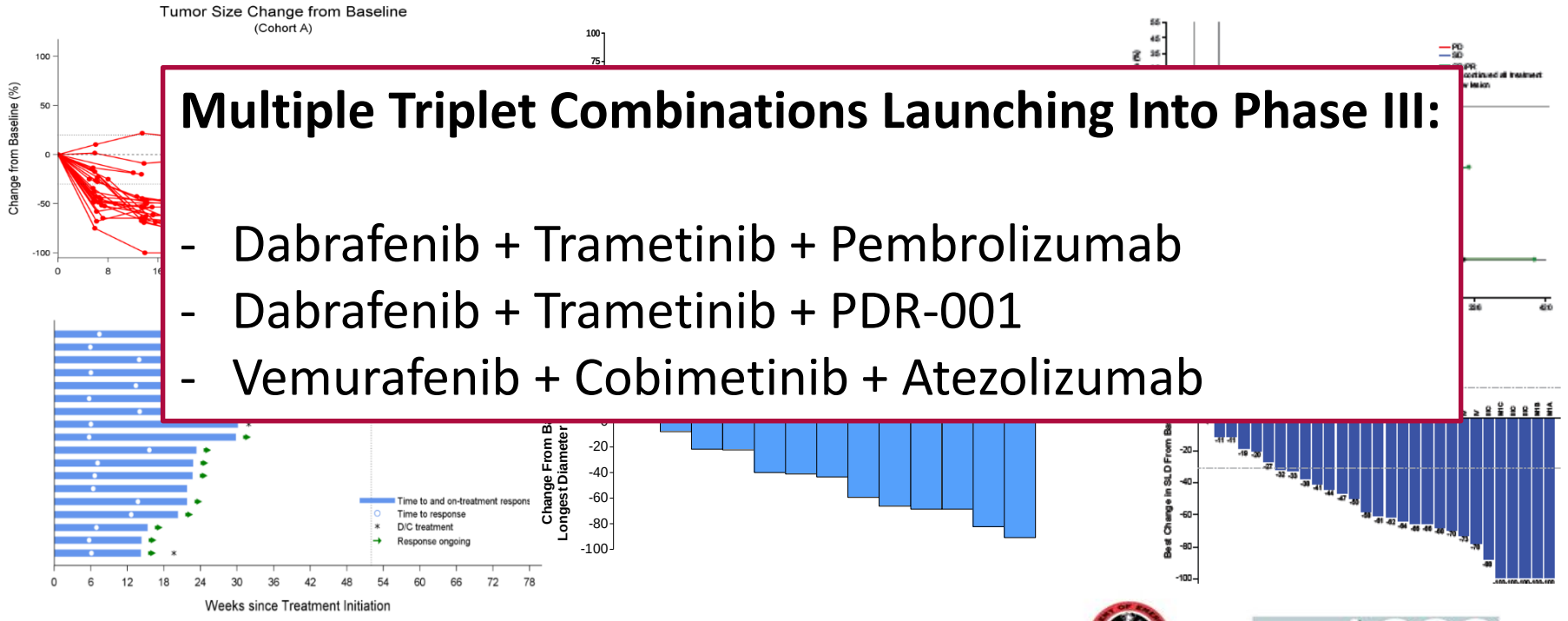


Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

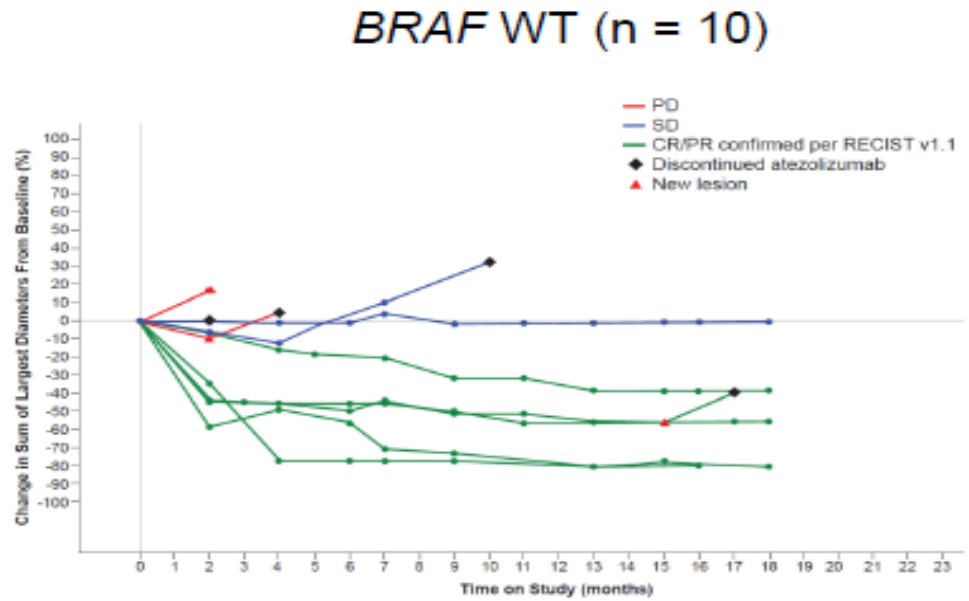
Vemurafenib+Cobimetinib+ Atezolizumab



Multiple Triplet Combinations Launching Into Phase III:

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

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%)

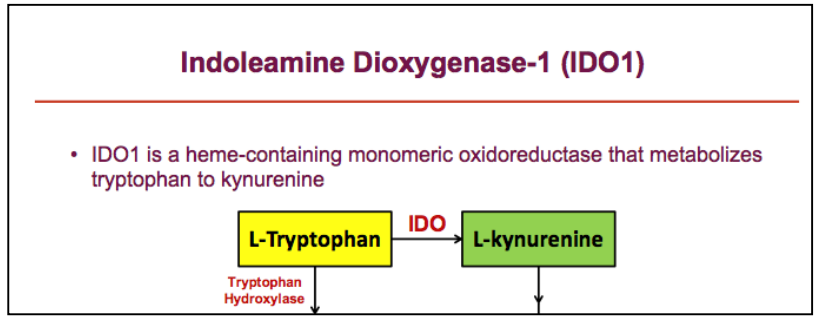
Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

Atezolizumab: PD-L1

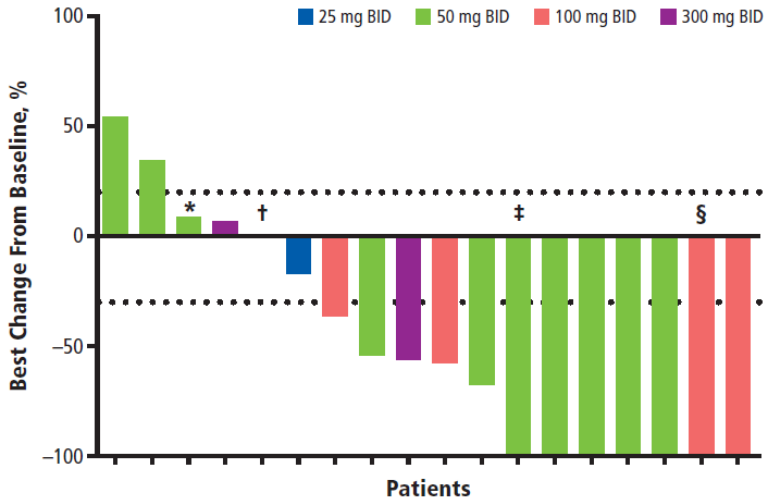
Pembrolizumab : PD-1

IDO inhibitor epacadostat + pembrolizumab



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

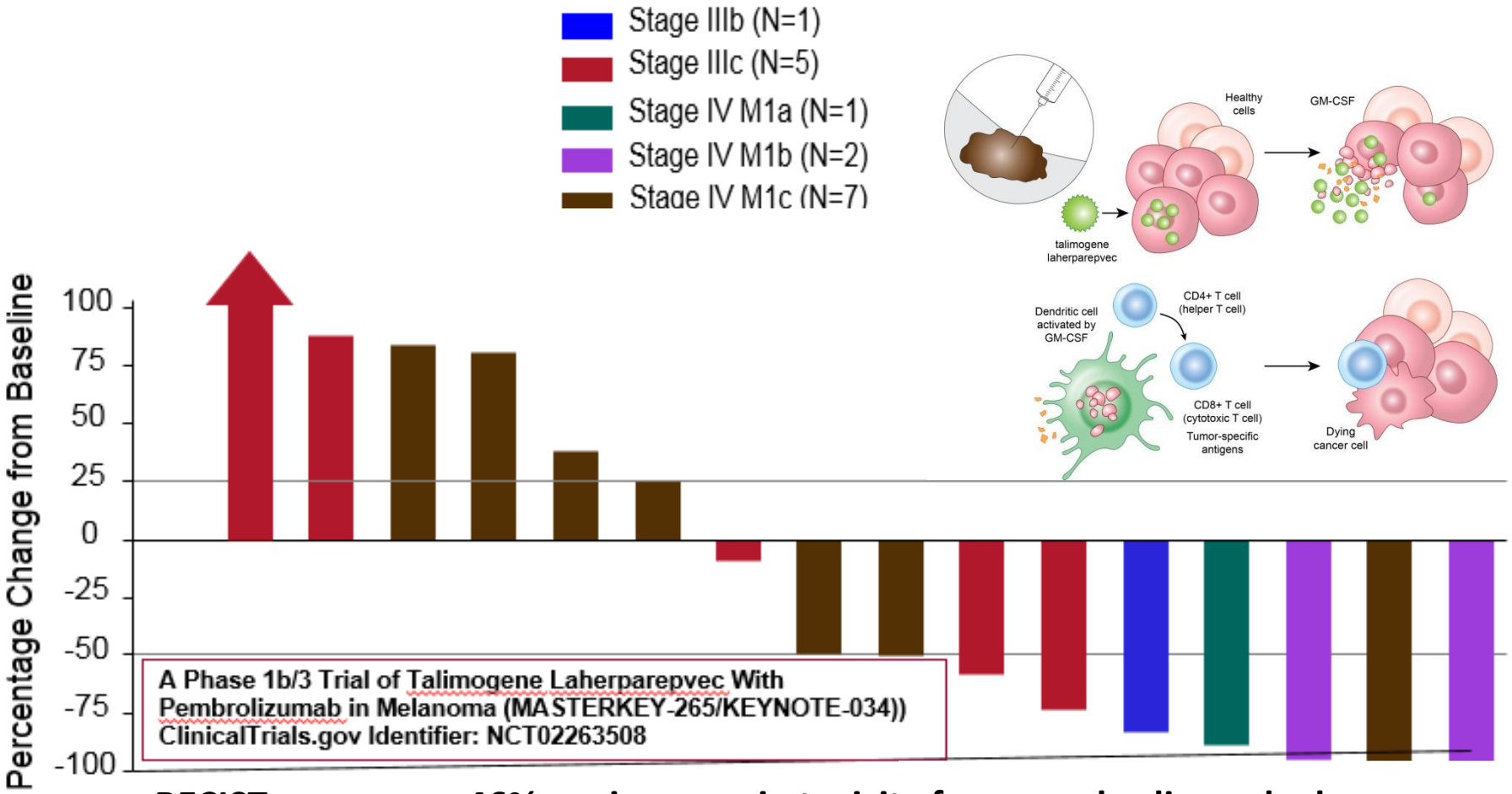
A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074



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
- Transitioning effective immunotherapy into the adjuvant setting effectively and safely a must!
- Immunotherapy combinations are likely the future for melanoma and likely all cancers!