ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

David H. Lawson , MD

Winship Cancer Institute of Emory University

Atlanta, GA

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- No disclosures

  No relevant financial relationships to disclose

- I will be discussing non-FDA approved indications during my presentation.

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IMMUNOTHERAPY IN ADJUVANT SETTING

- Alpha interferon/pegylated interferon are still options but virtually no indications to use them in the front-line setting
- Ipilimumab at 10 mg/kg dose (perhaps 3mg/kg dose is equivalent, data not yet available)
- Nivolumab at 3mg/kg superior to ipilimumab in IIIB and C and stage IV, now FDA approved. Discussable whether 240 mg flat dose should be used instead

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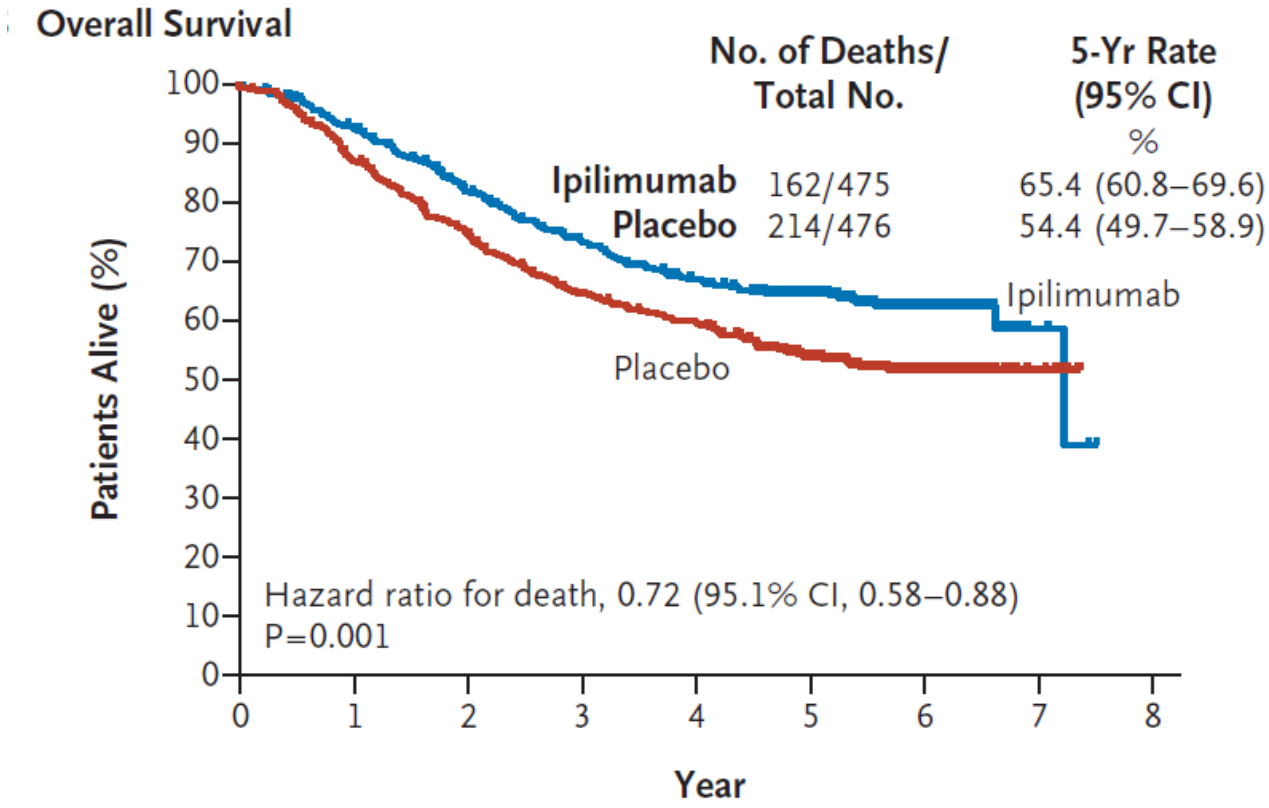
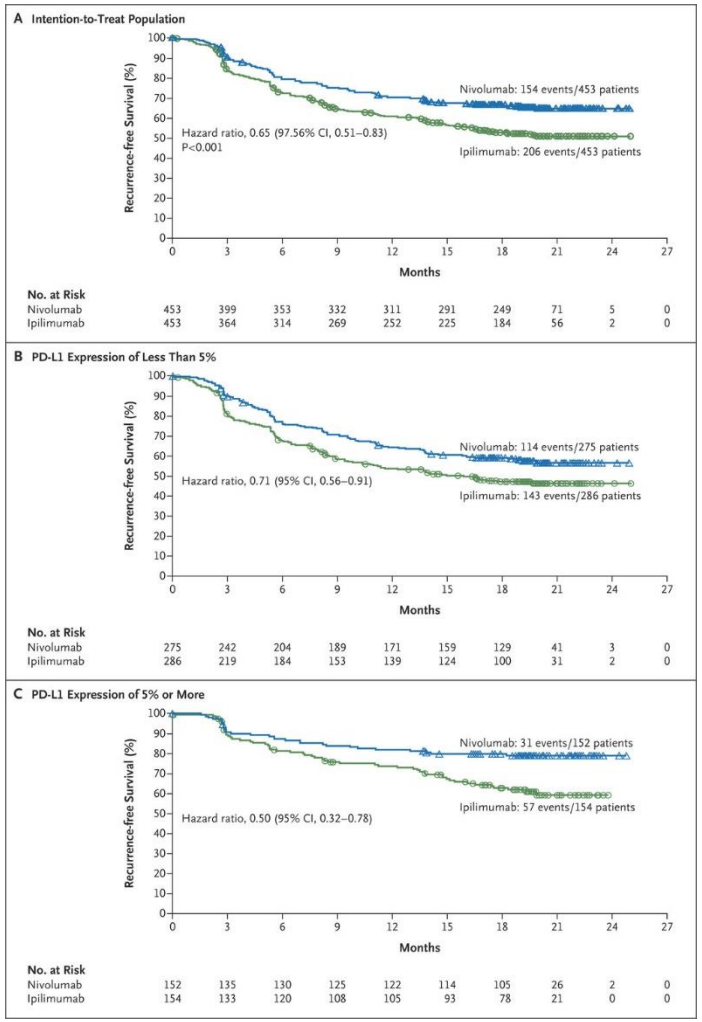
Adjuvant Ipilimumab in High-Risk Melanoma



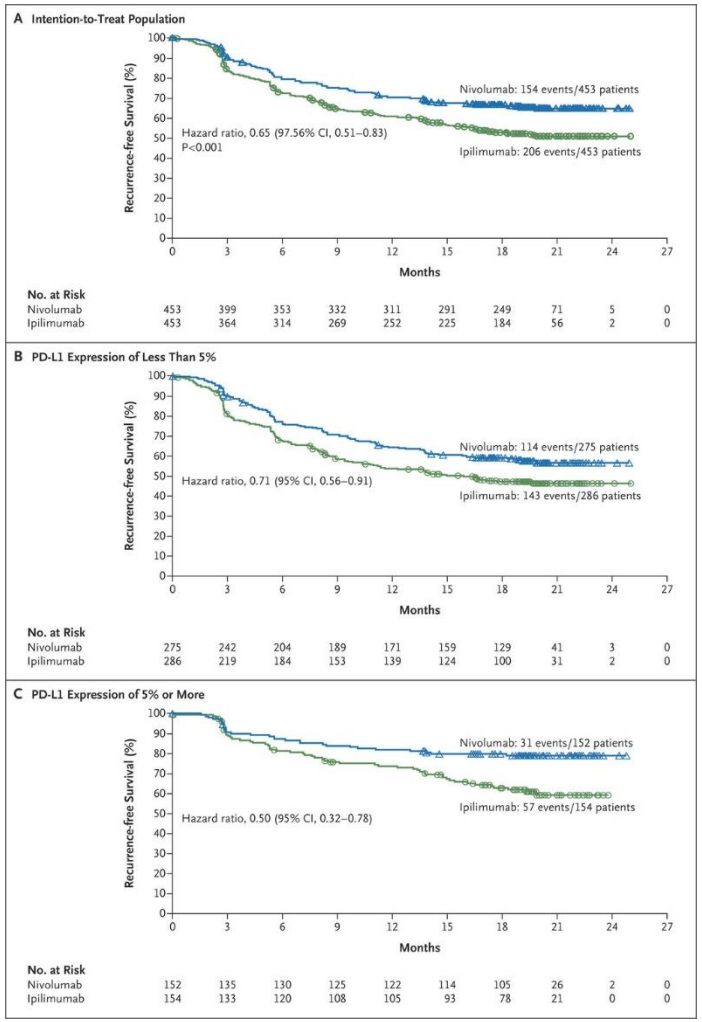
No. at Risk

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

Eggermont *et al*. NEJM 2016



Weber J et al. N Engl J Med 2017;377:1824-1835.



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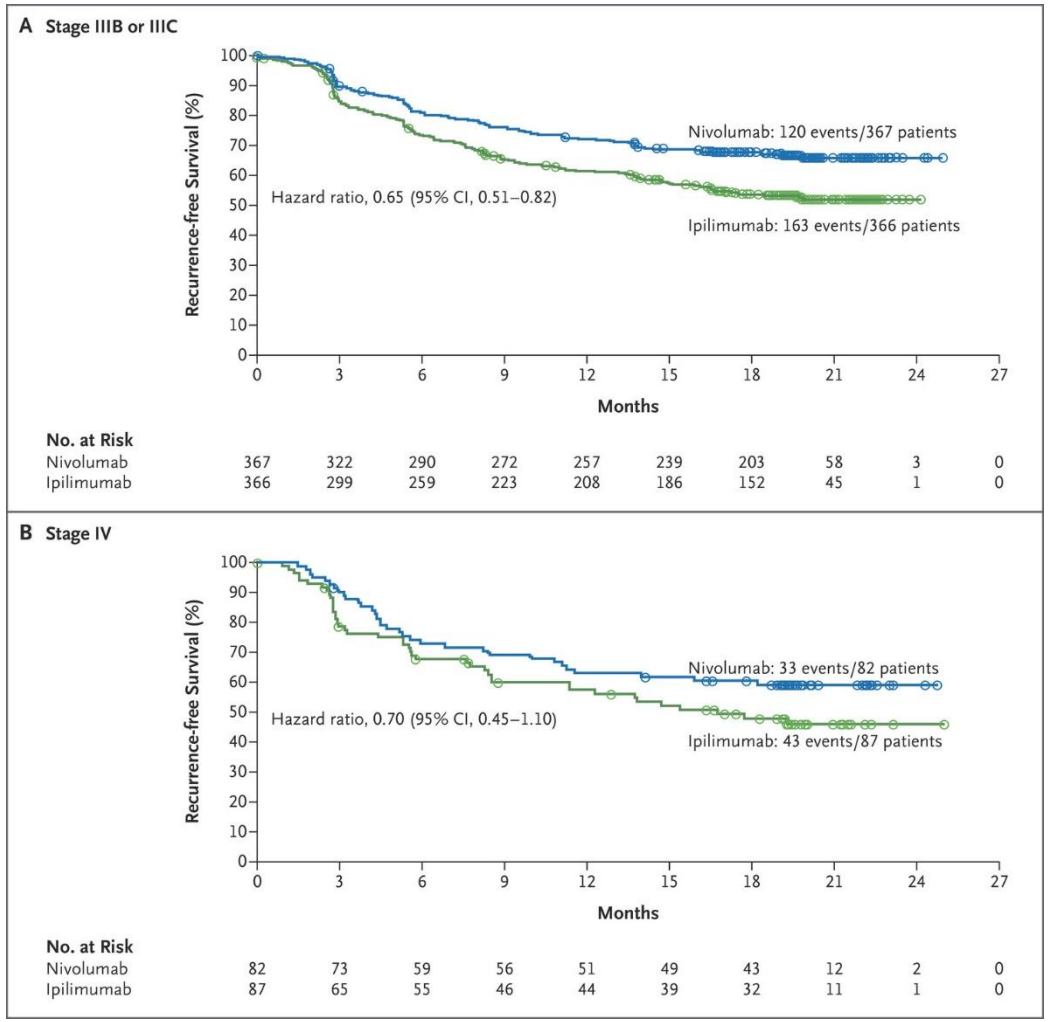

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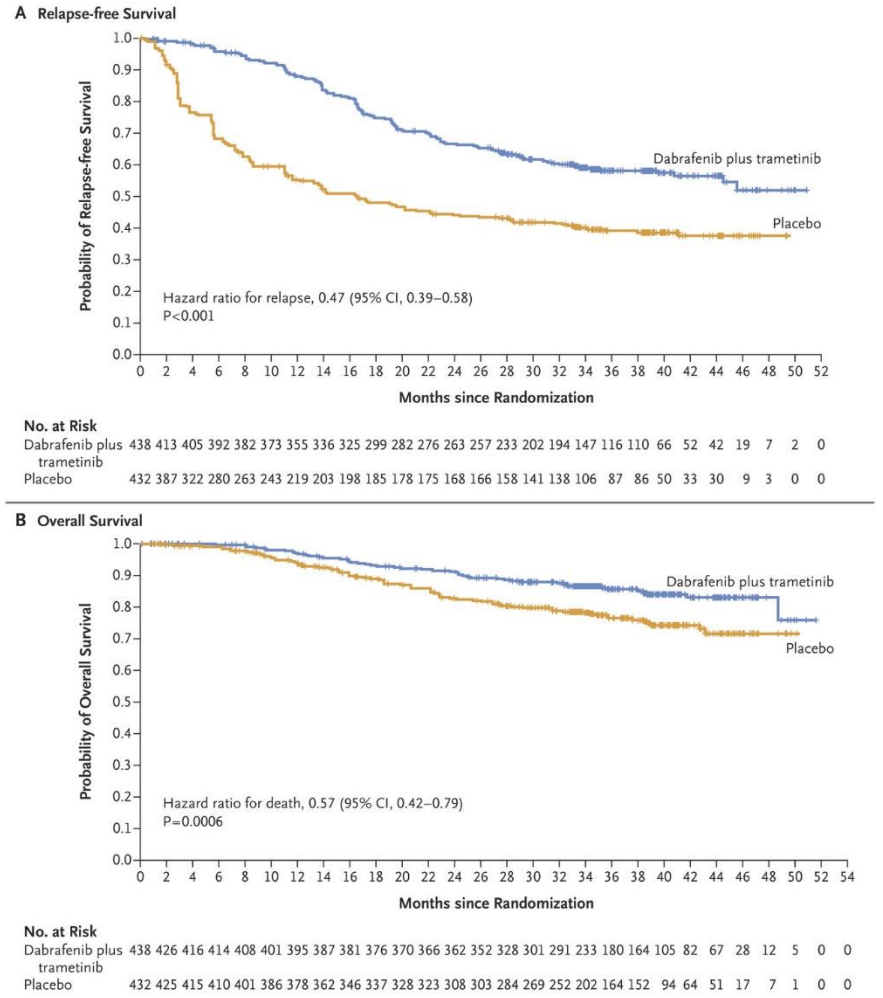

Long GV et al. N Engl J Med 2017;377:1813-1823.

Table 3. Adverse Events (Safety Population).*

Adverse Event	Dabrafenib plus Trametinib (N=435)		Placebo (N=432)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (<1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (<1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhea	144 (33)	4 (1)	65 (15)	1 (<1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (<1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Elevated alanine aminotransferase	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza-like illness	67 (15)	2 (<1)	29 (7)	0
Elevated aspartate aminotransferase	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in limb	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)
Peripheral edema	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0
Adverse event leading to dose interruption	289 (66)	NA	65 (15)	NA
Adverse event leading to dose reduction	167 (38)	NA	11 (3)	NA
Adverse event leading to discontinuation of study regimen	114 (26)	NA	12 (3)	NA

* Listed are adverse events that were reported in more than 10% of the patients who received combination therapy with dabrafenib plus trametinib. NA denotes not applicable.

Long GV et al. N Engl J Med 2017;377:1813-1823.

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ADJUVANT THERAPY CONCLUSIONS

- Nivolumab 3mg/kg or 240 mg flat dose is first choice for adjuvant therapy of IIIB/C and IV melanoma. Caveat: Survival data still pending. Extend to IIIA?
- Ipilimumab 10mg/kg (perhaps 3mg/kg) likely second line, but ECOG comparison with IFN pending
- High dose interferon likely 3d line now
- Targeted therapy vs immunotherapy for BRAF mutated patients, especially V600E, is an open question

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TREATMENT OF UNRESECTABLE MELANOMA

- Definition of unresectable beyond single metastasis is fluid, especially since targeted therapies are capable of achieving long term survival in many patients
- Anti-PD1 agents are the core.
- Combinations may be better
- Special situations include cutaneous mets only and CNS mets

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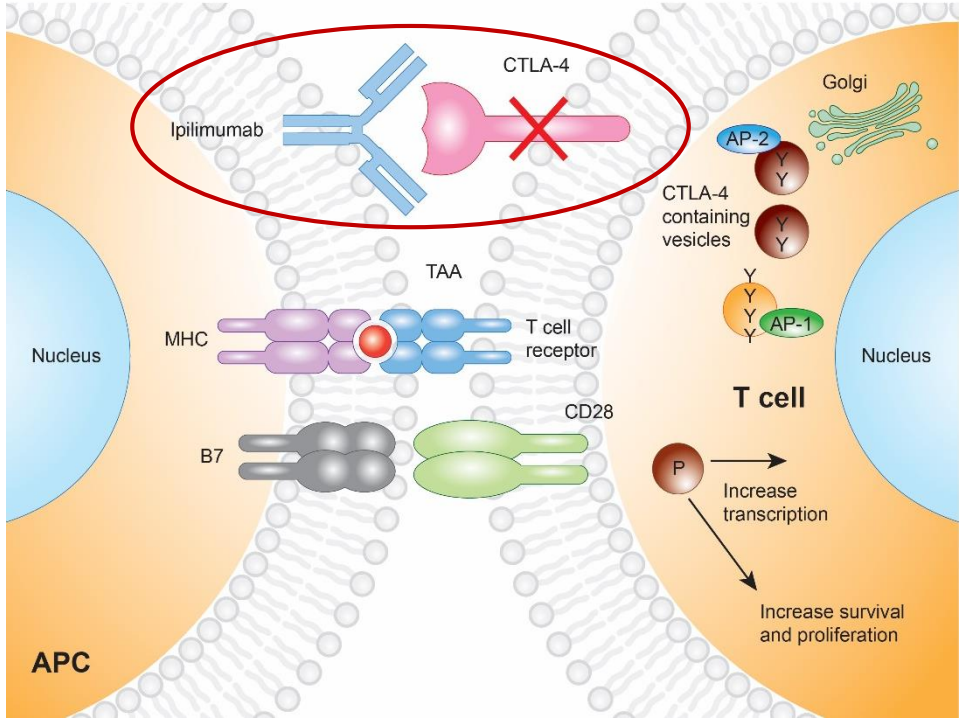
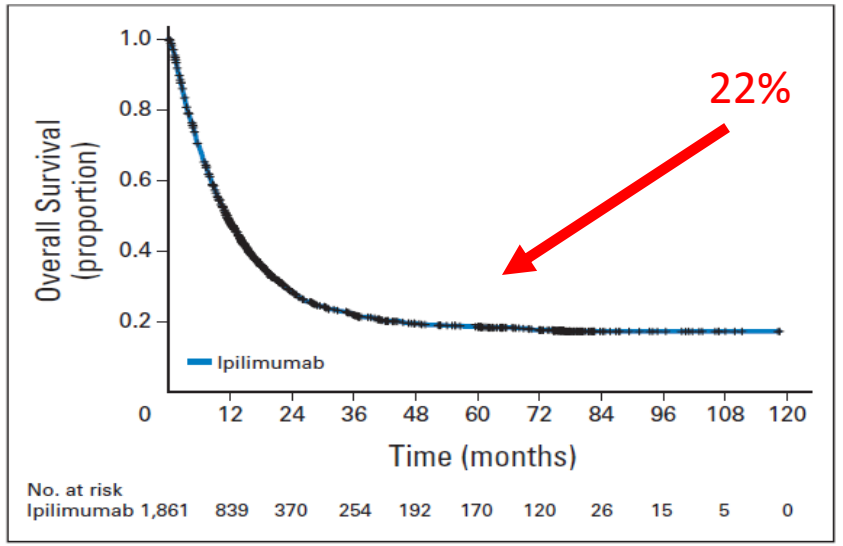
Ipilimumab & Immune Check-Point Blockade

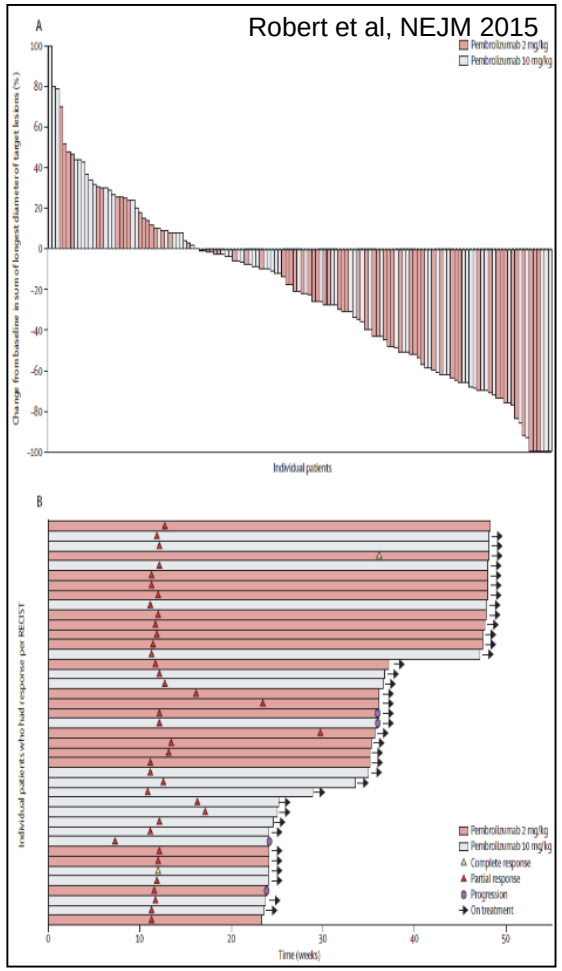




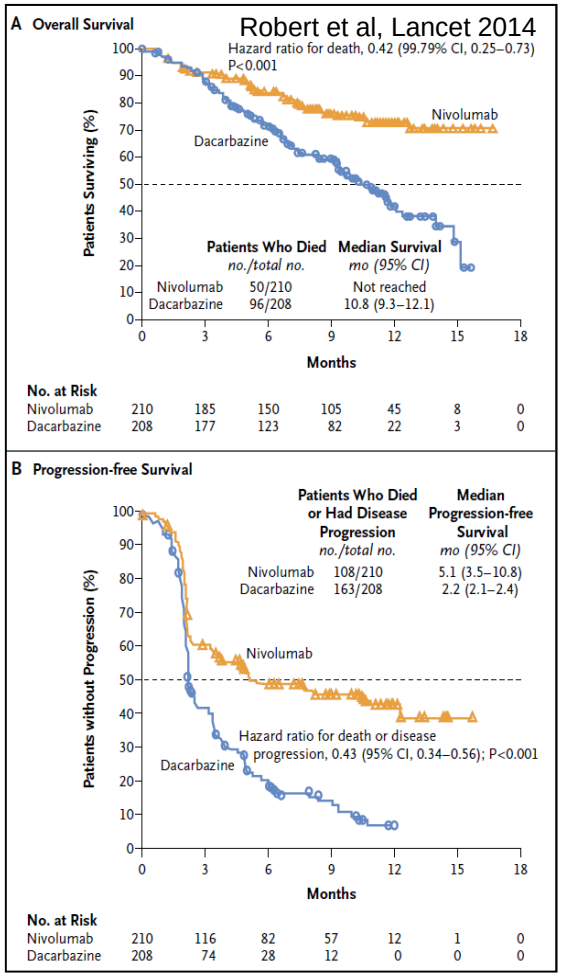
Luke et al, Oncologist 2013
Schadendorf et al, J Clin Oncol 2015

Anti-PD1 in Melanoma

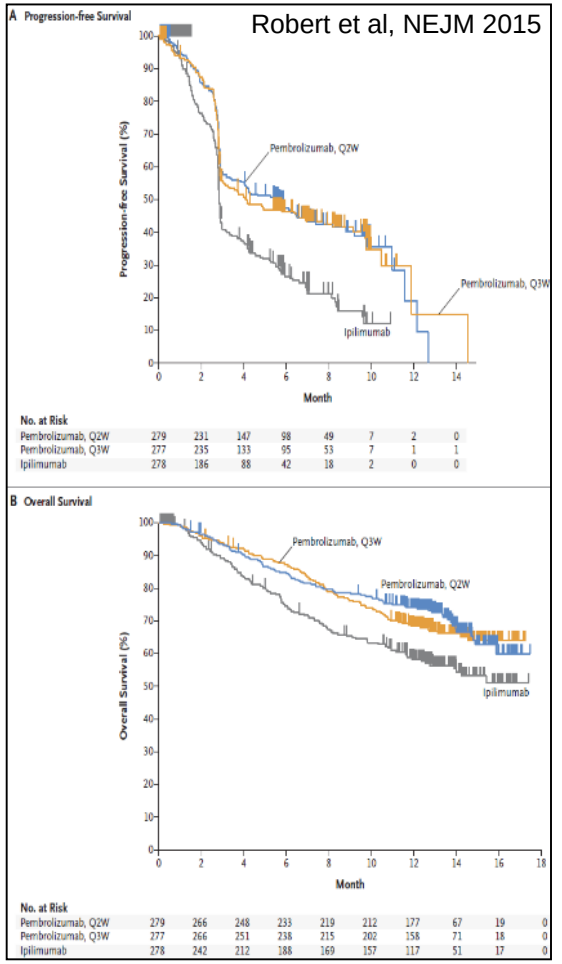
Anti-PD1 (pembrolizumab) *after* ipilimumab



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



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



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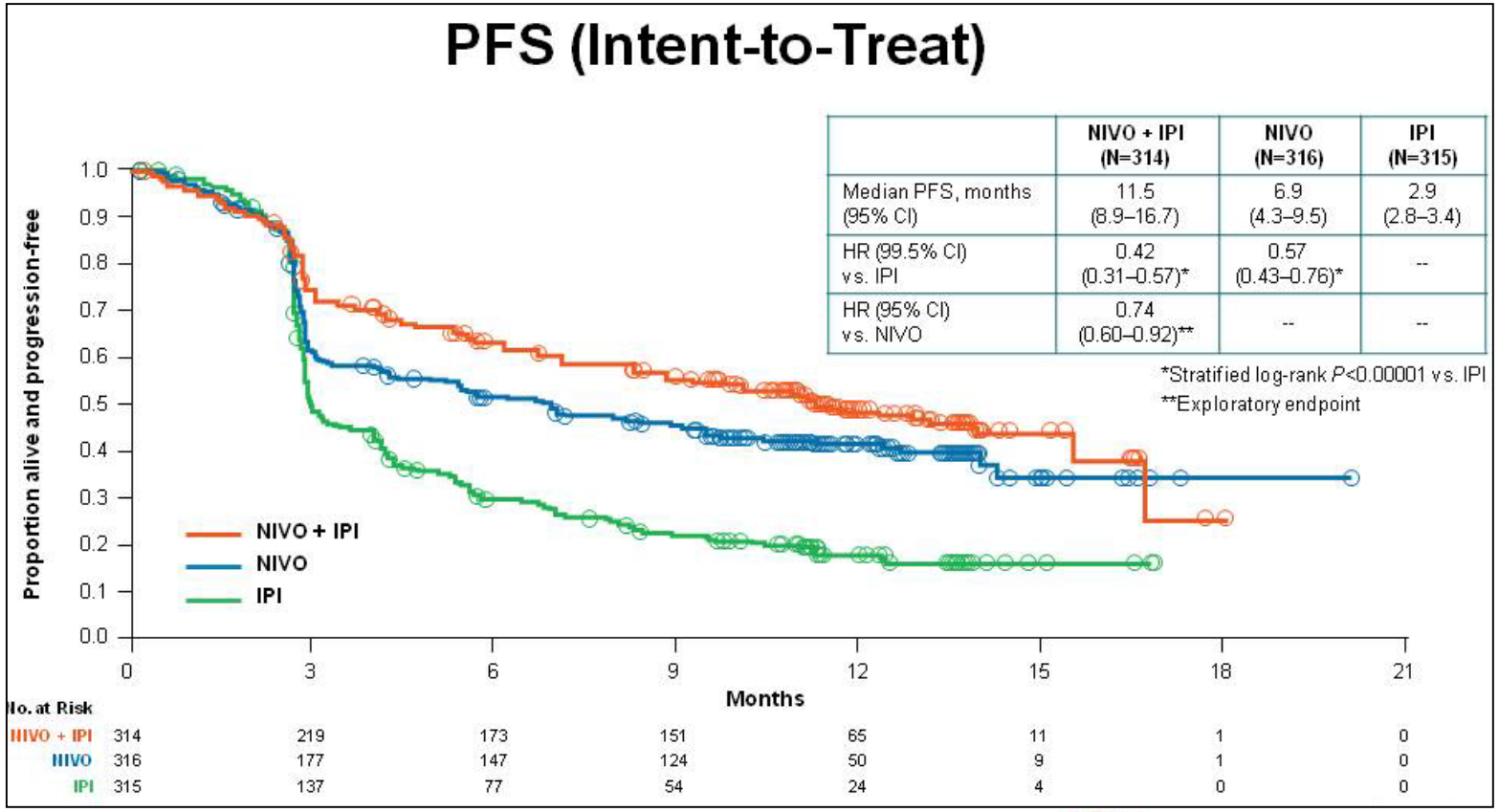
Ipilumamab: CTLA-4

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)**	--	--

*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)

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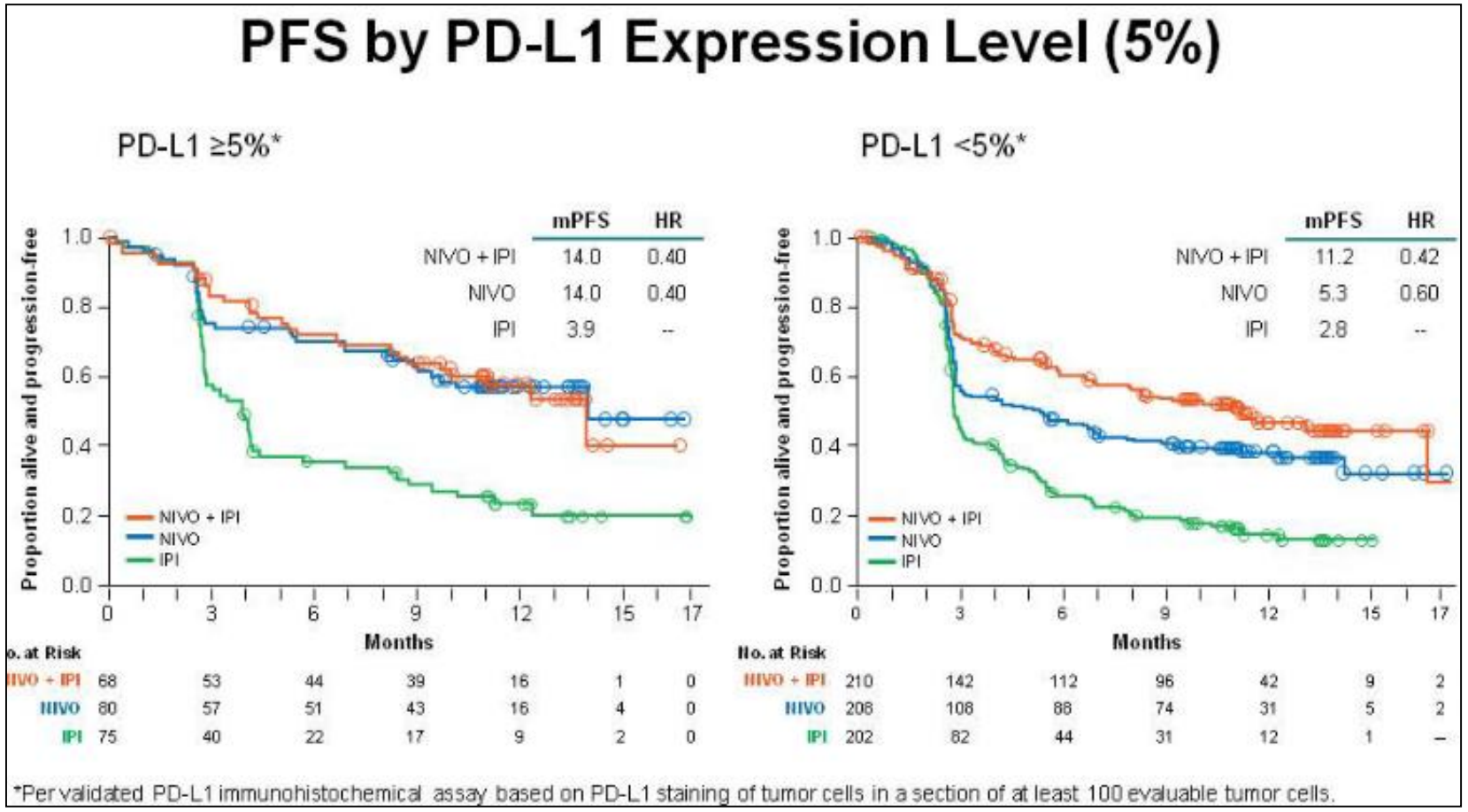

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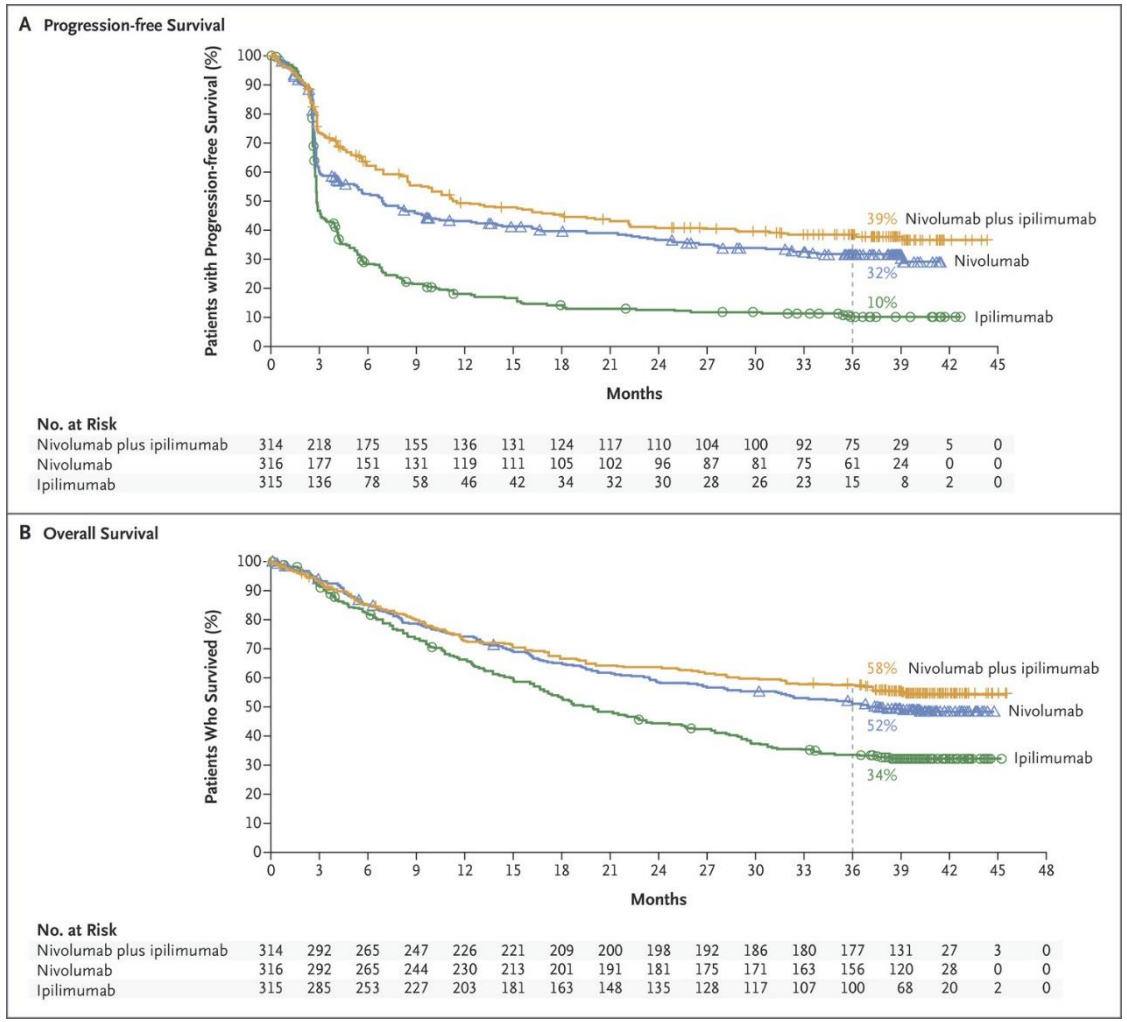
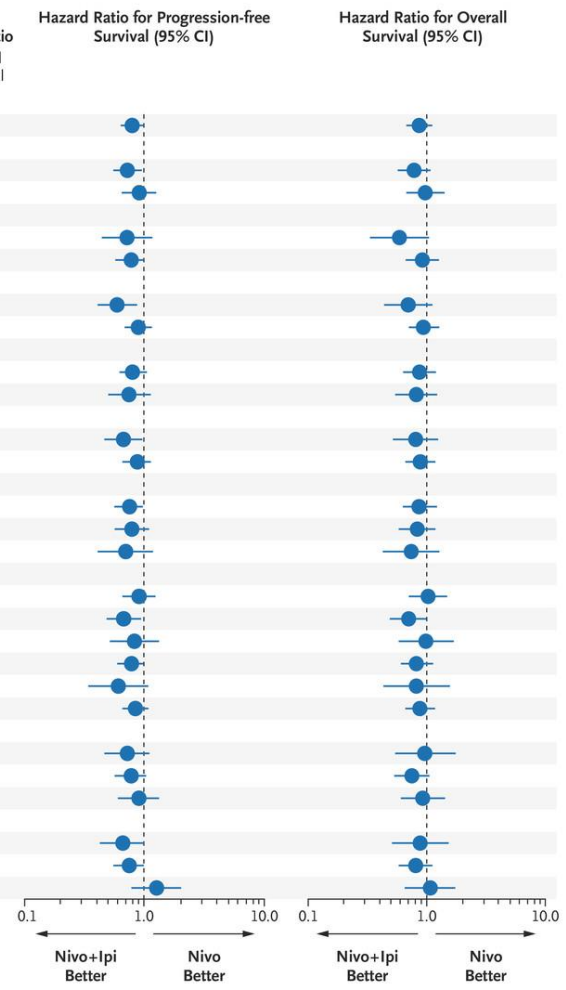


Wolchok JD et al. N Engl J Med 2017;377:1345-1356.

Subgroup	No. of Patients		3-Yr Progression-free Survival Rate		3-Yr Overall Survival Rate		Unadjusted Hazard Ratio	
	Nivo+Ipi	Nivo	Nivo+Ipi	Nivo	Nivo+Ipi	Nivo	Progression-free Survival	Overall Survival
			%		%			
All patients	314	316	39	32	58	52	0.79	0.85
Age								
<65 yr	185	198	39	31	61	51	0.73	0.78
≥65 yr	129	118	37	34	54	52	0.90	0.96
Geographic region								
United States	64	68	45	31	70	57	0.71	0.59
Europe	177	170	34	28	53	49	0.77	0.91
BRAF mutation								
Yes	102	98	40	22	68	56	0.59	0.69
No	212	218	38	36	53	50	0.89	0.94
ECOG performance-status score								
0	230	237	39	33	64	58	0.80	0.85
1	83	79	37	27	43	32	0.75	0.81
Metastasis stage								
M0, M1a, or M1b	129	132	50	39	72	64	0.67	0.79
M1c	185	184	31	27	48	42	0.87	0.88
LDH level								
≤ULN	199	197	45	37	66	61	0.75	0.86
>ULN	114	112	28	21	44	34	0.79	0.83
>2×ULN	37	37	17	11	31	14	0.69	0.73
PD-L1 expression level								
≥1%	155	171	43	39	62	60	0.90	1.02
<1%	123	117	35	26	54	42	0.67	0.70
≥5%	68	80	49	41	65	61	0.83	0.99
<5%	210	208	36	31	56	50	0.78	0.82
≥10%	46	59	58	39	67	58	0.61	0.82
<10%	232	229	35	32	57	51	0.84	0.87
Tumor burden								
≤31 mm	78	85	45	38	72	69	0.72	0.96
>31 mm and ≤97 mm	154	150	38	30	59	48	0.76	0.74
>97 mm	82	80	33	29	41	39	0.89	0.92
No. of lesion sites								
1	89	80	47	37	70	65	0.65	0.88
2 or 3	166	176	38	28	57	48	0.74	0.80
>3	59	59	27	36	42	44	1.25	1.06



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Ipilumamab: CTLA-4

Nivolumab: PD-1

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)

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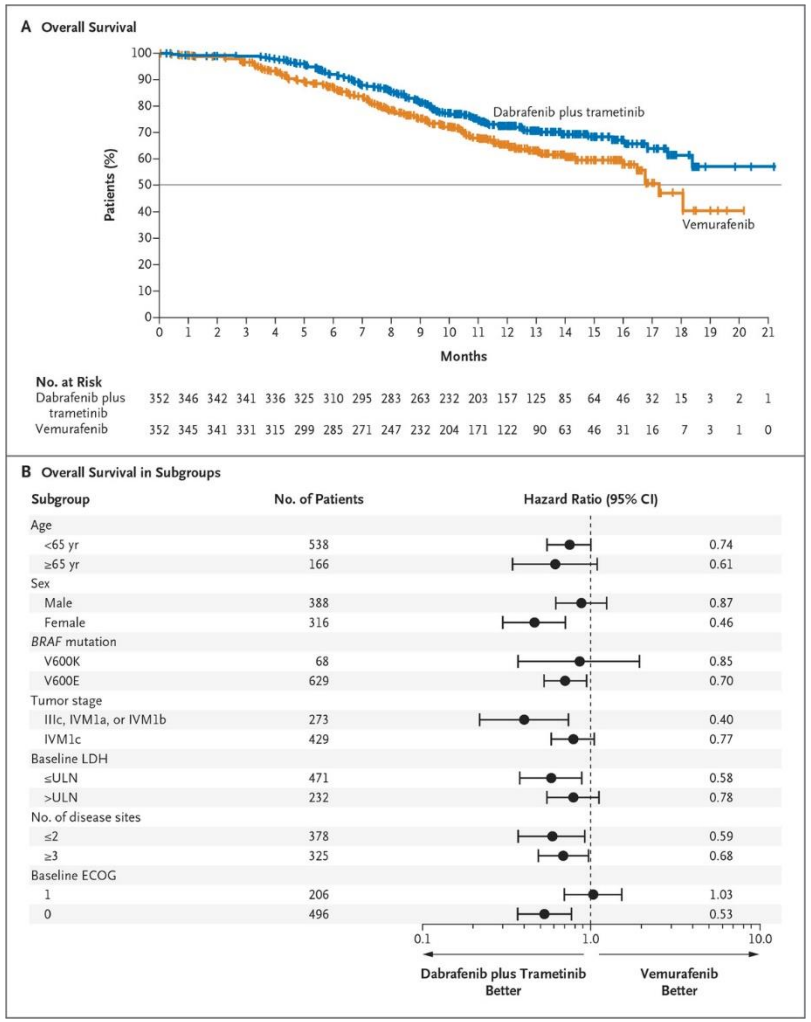

Robert C et al. N Engl J Med 2015;372:30-39.

Table 2. Investigator-Assessed Best Response (Intention-to-Treat Population).*

Response	Dabrafenib plus Trametinib (N=351)	Vemurafenib (N=350)
Type of response — no. (%)		
Complete	47 (13)	27 (8)
Partial	179 (51)	153 (44)
Stable disease	92 (26)	106 (30)
Progressive disease	22 (6)	38 (11)
Not evaluated	11 (3)	26 (7)
Objective response rate		
No. of patients with response (%)†	226 (64)	180 (51)
95% CI	59.1–69.4	46.1–56.8
Duration of response (95% CI) — mo	13.8 (11.0–NR)	7.5 (7.3–9.3)

* Data are missing for one patient in the combination-therapy group and two patients in the vemurafenib group because these patients did not have measurable disease at baseline. NR denotes not reached.
† Included in the objective response are complete and partial responses. P<0.001 for the between-group difference of 13% (95% CI, 6 to 20).

Robert C et al. N Engl J Med 2015;372:30-39.

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First line treatment of advanced melanoma

- Anti-PD1 drugs are the core
- Whether ipilimumab significantly adds to nivolumab not totally clear
- Enrollment of patients in trials of a PD-1 drug plus another is reasonable even in the first line setting
- Whether immunotherapy is superior to targeted therapy in BRAF mutated patients is not known. EA6134 will help answer that question and accrual to that study is encouraged

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Special Situations

Cutaneous Only Metastases

CNS Metastases

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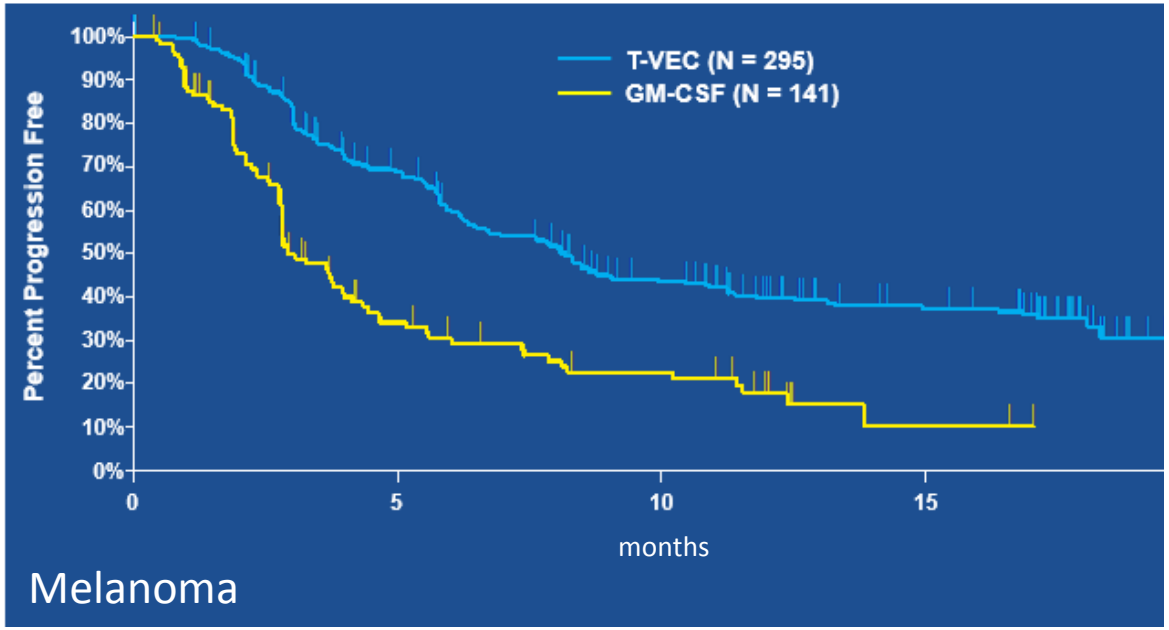
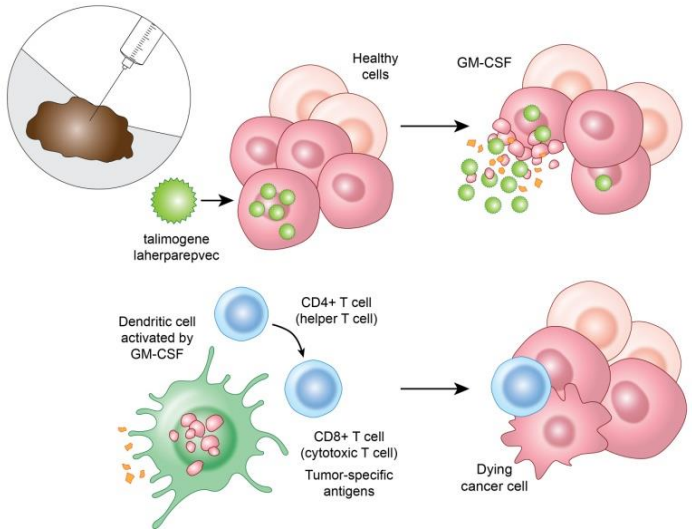
Phase III Trial of T-VEC vs GM-CSF PFS per Investigator





Andtbacks et al. ASCO 2013; LBA9008

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CNS metastases

- Abst 9057 ASCO 2017 Tawbi et al Checkmate 204
- Ipi3 plus Nivo1 phase 2
- 1 or more brain mets 0.5-3cm no symptoms no steroids
- Intracranial response rate 42%, 14% CR, duration not given in abstract
- Similar results from smaller Australian studies
- There is single agent activity for ipi and for PD-1 drugs as well

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Targeted Therapy for CNS Mets

- Abst 9506 Davies et all ASCO 2017 Combi-MB
- Dabrafenib and trametinib
- 125 patients
- 58% RR but PFS only 5.6mos

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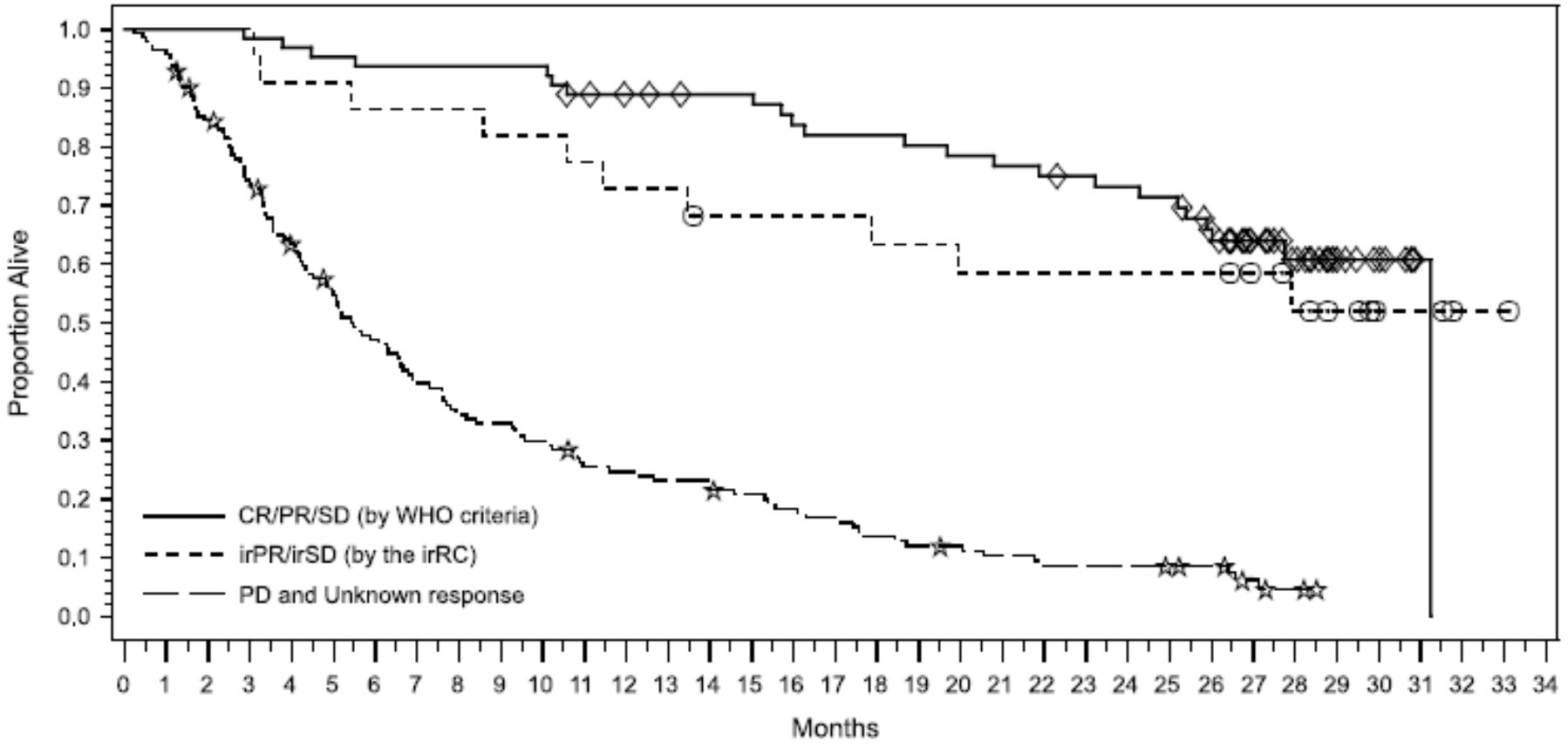
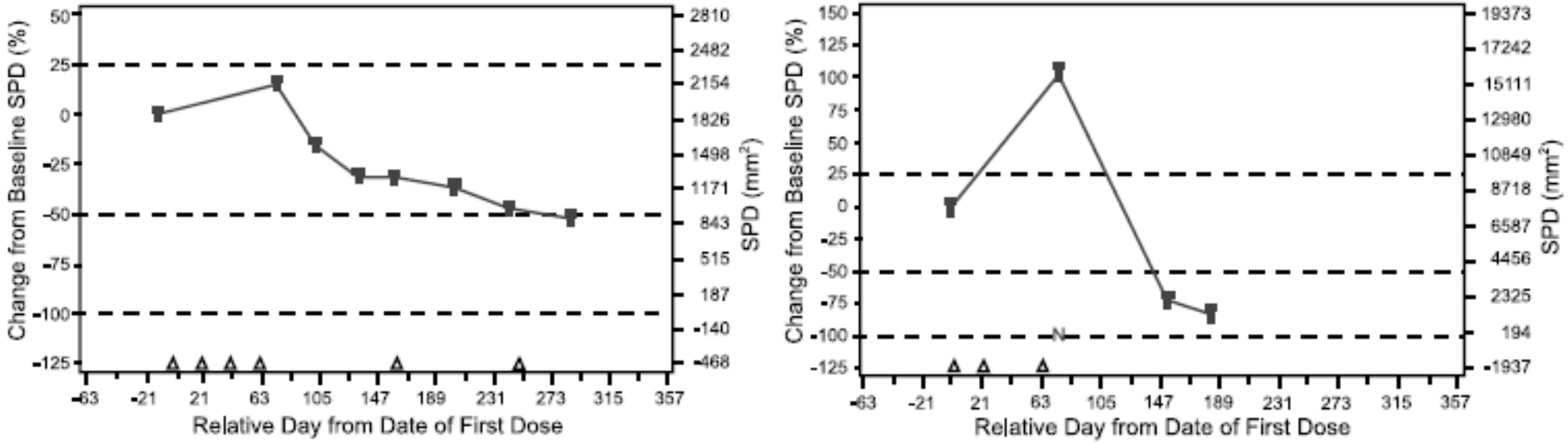
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009

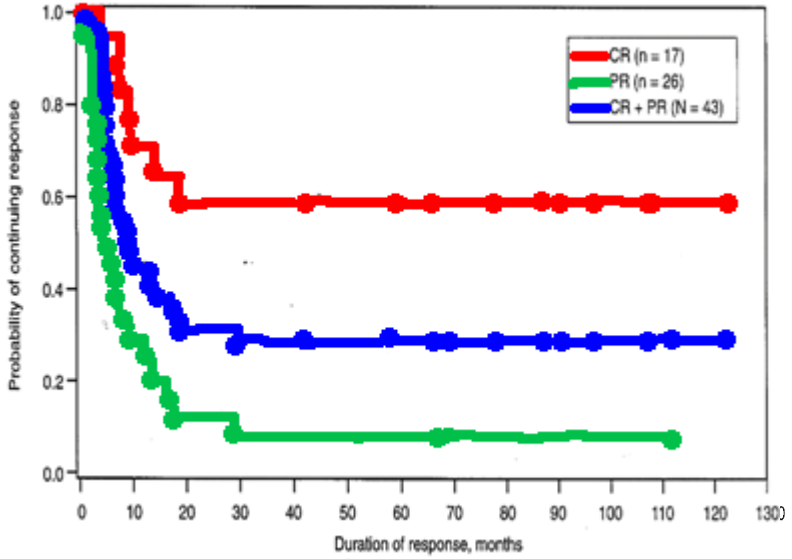
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009

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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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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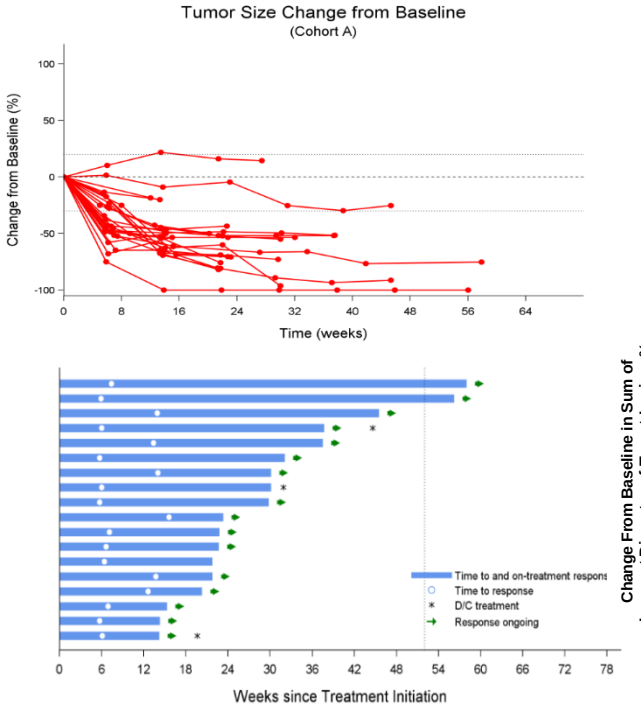
On-Going Phase III Trials in Melanoma

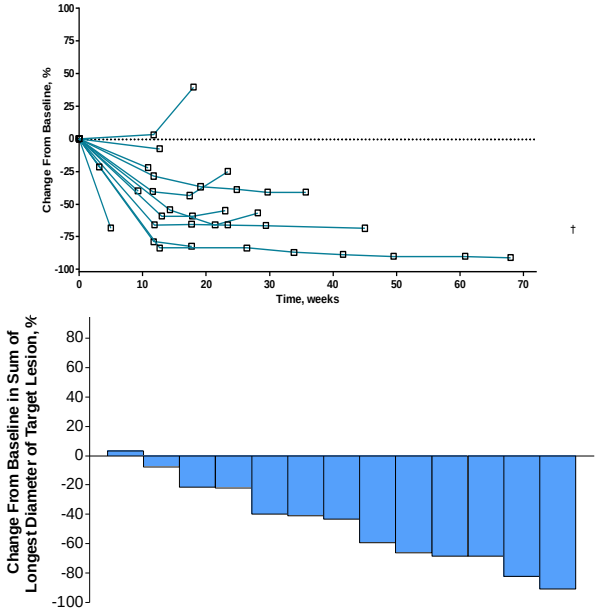
- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi) + anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti PD(L)1
- Pegylated IL2 plus pembroliumab

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

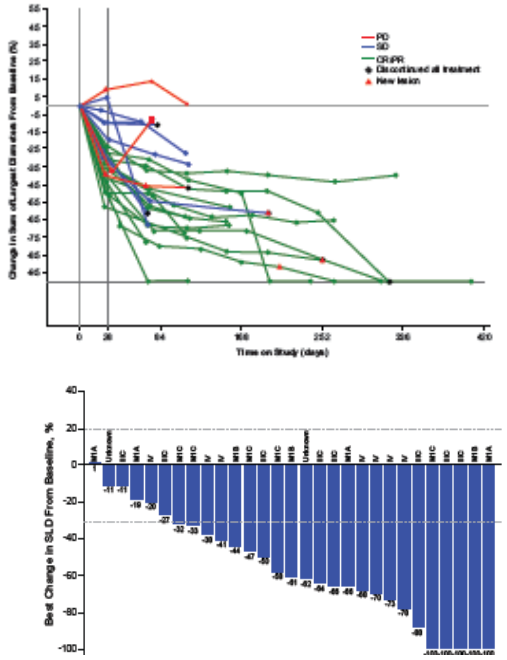
Dabrafenib+Trametinib+ Durvalumab



Dabrafenib+Trametinib+ Pembrolizumab



Vemurafenib+Cobimetinib+ Atezolizumab

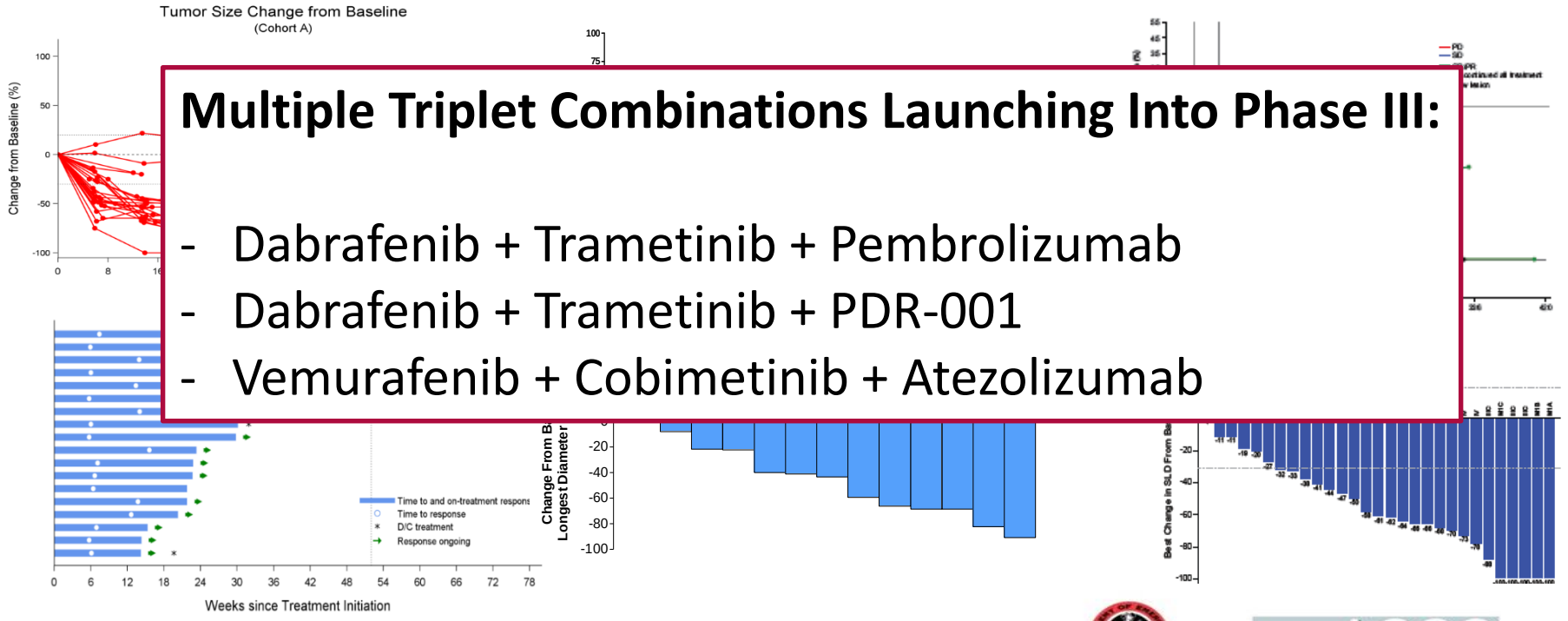


Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

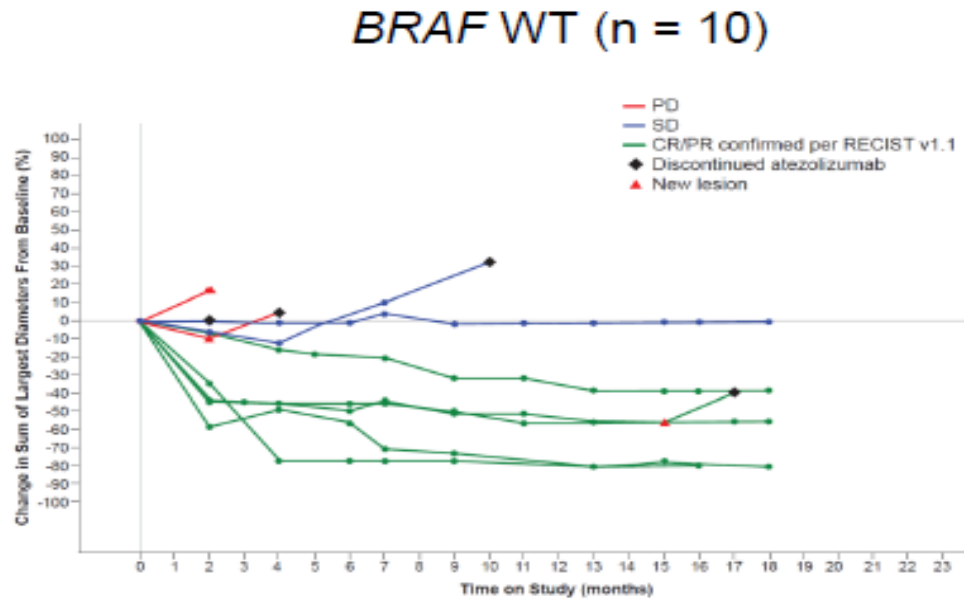
Vemurafenib+Cobimetinib+ Atezolizumab



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%)

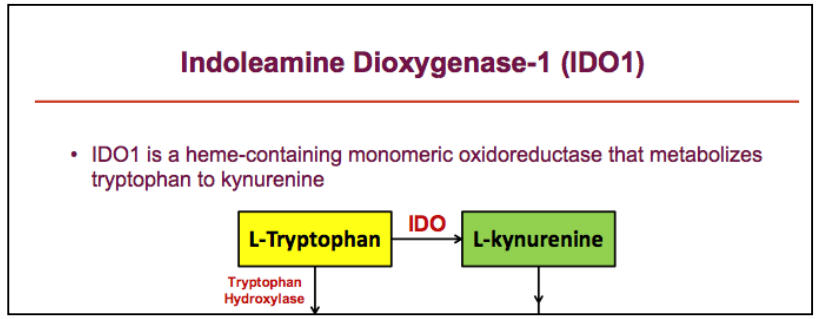
Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

Atezolizumab: PD-L1

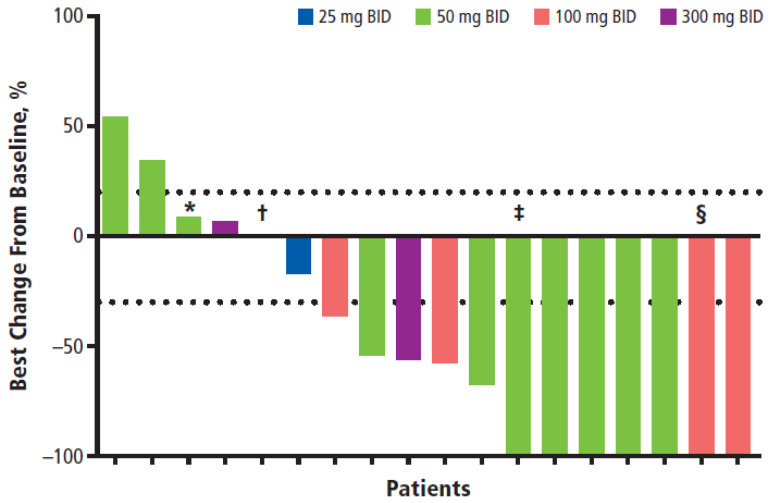
Pembrolizumab : PD-1

IDO inhibitor epacadostat + pembrolizumab



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

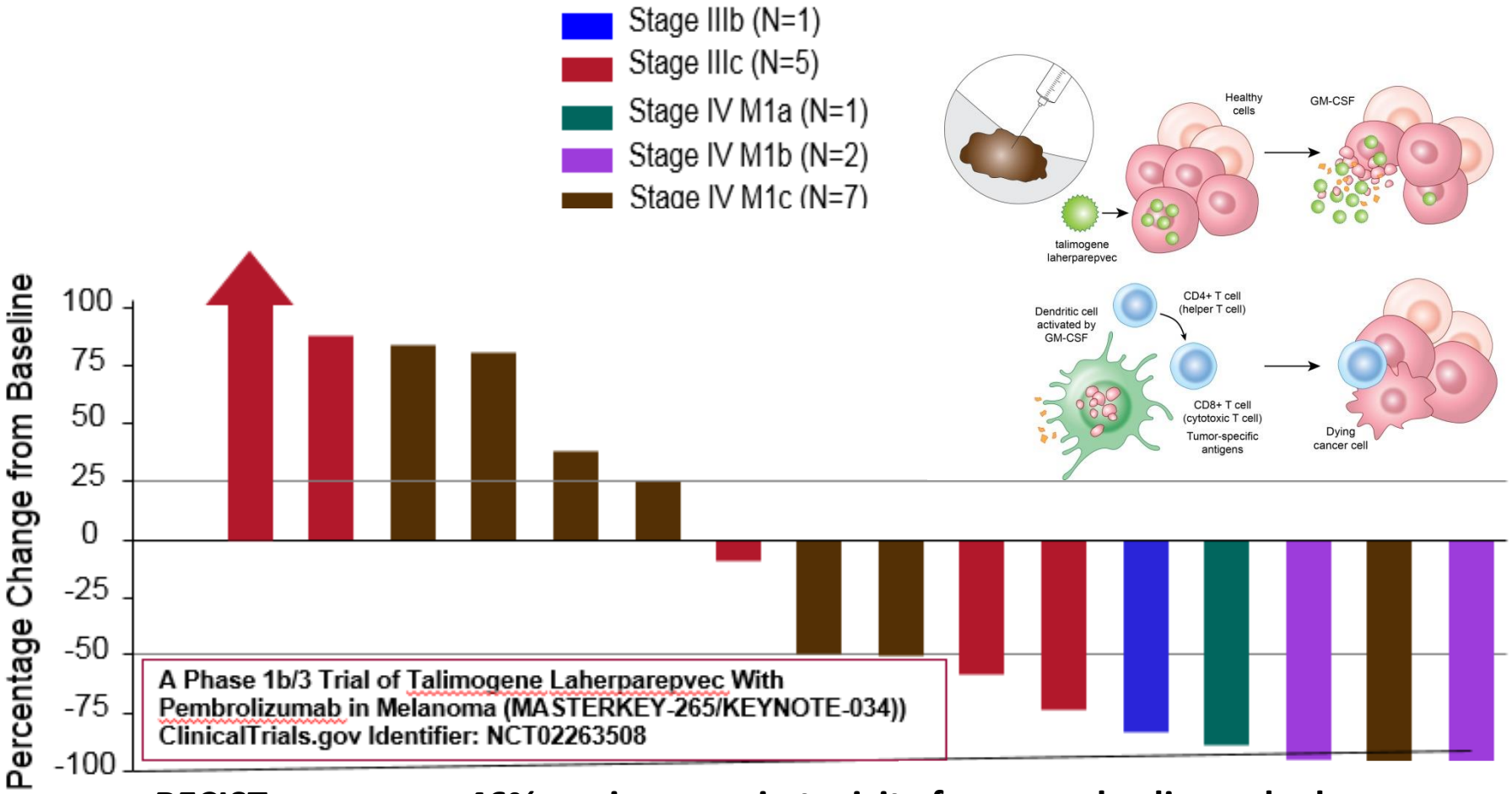
A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074



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

ADVANCES IN Cancer IMMUNOTHERAPY™

THE TREATMENT OF CHOICE FOR MELANOMA PATIENTS IS STILL A CLINICAL TRIAL!

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer