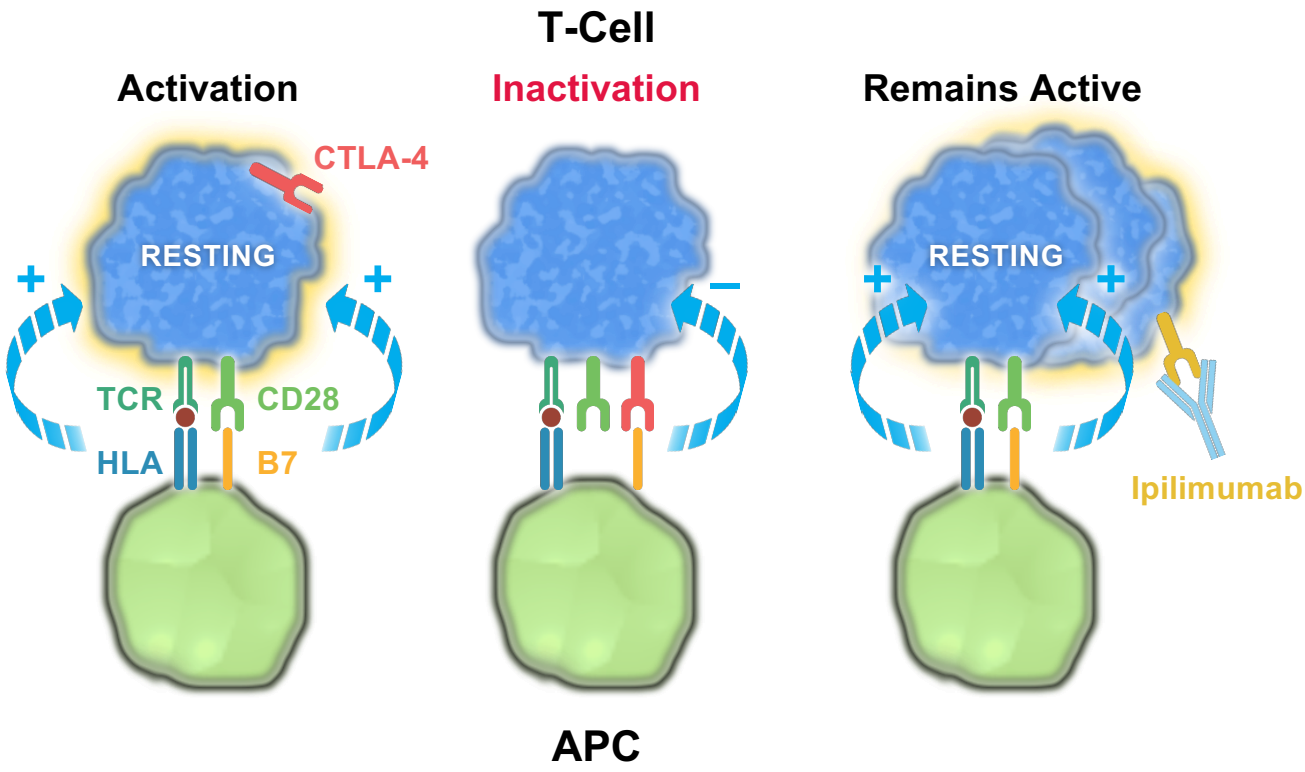
NASDC
NCI Awardee Skills Development Consortium

Oncology Drug Development 101: Implications for Immunotherapy Trials

Jedd Wolchok, MD, PhD
Lloyd J. Old/Virginia and Daniel K. Ludwig Chair in Clinical Investigation
Chief, Immuno-Oncology Service, Memorial Sloan Kettering Cancer Center
Director, Parker Institute for Cancer Immunotherapy at MSK
Associate Director, Ludwig Center for Cancer Immunotherapy

Memorial Sloan Kettering Cancer Center

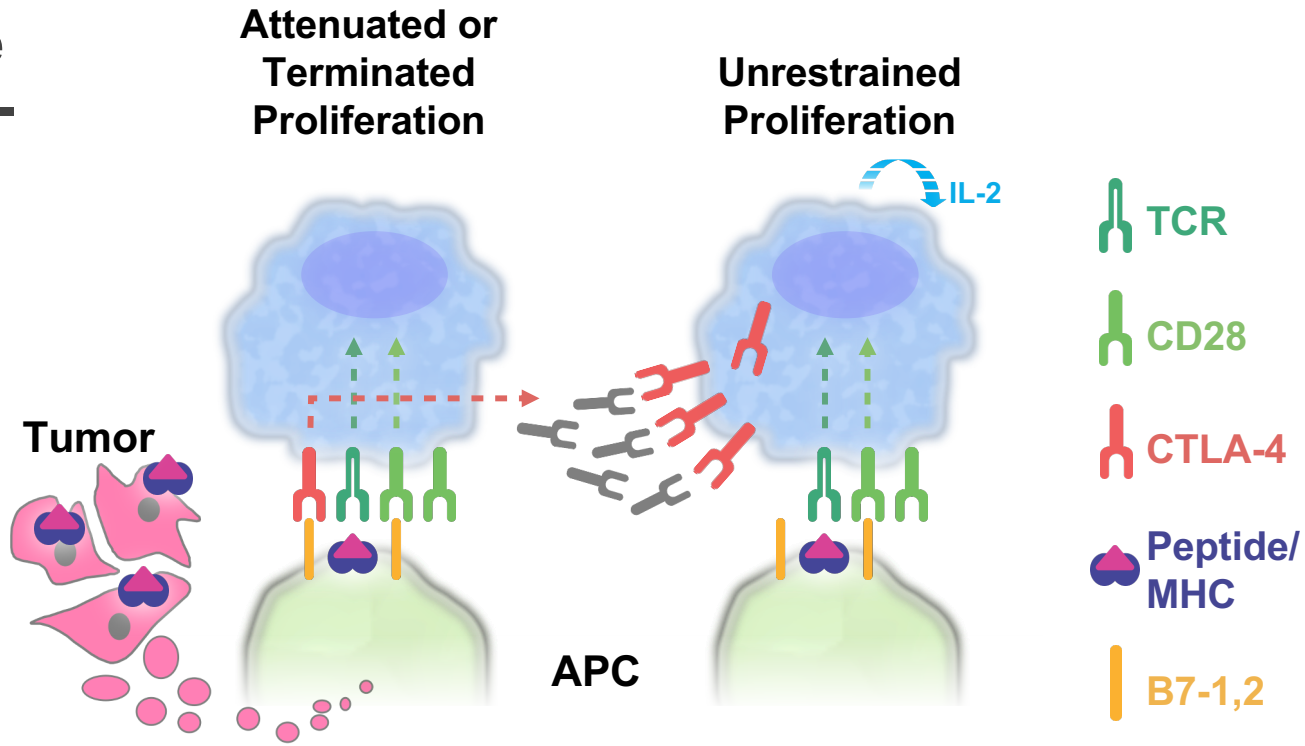
Ipilimumab, a CTLA-4 Blocking Monoclonal Antibody, Augments T-Cell Activation



Korman, Peggs and Allison: Adv. In Immunol. 2006;90:297-339

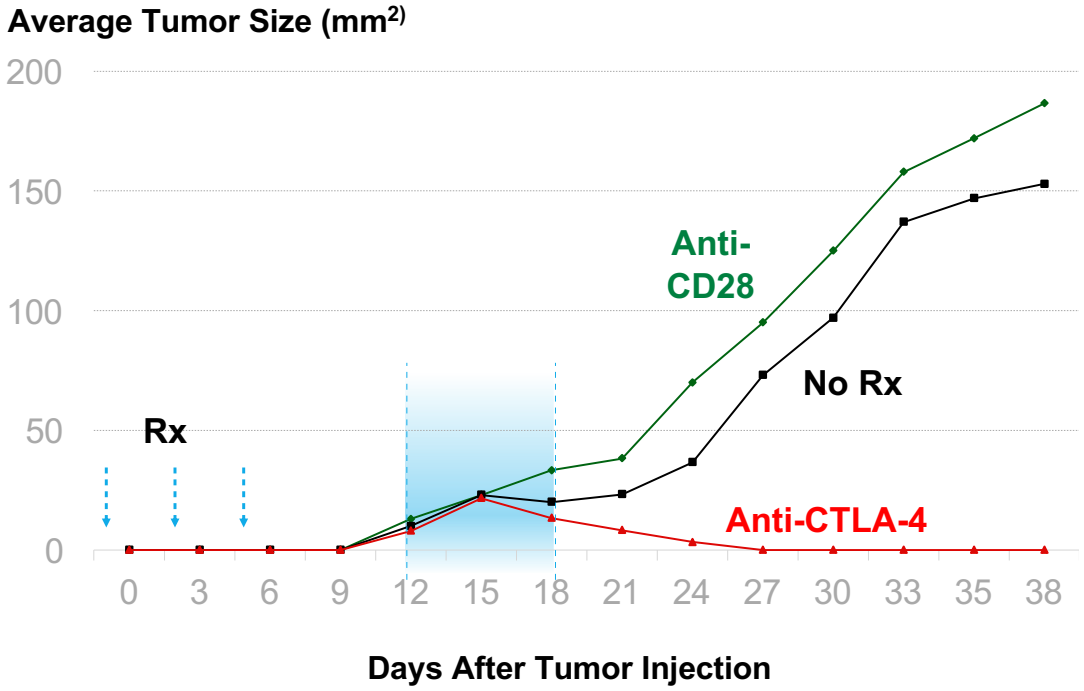
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Necrotic Death Vaccines
Chemotherapy Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies



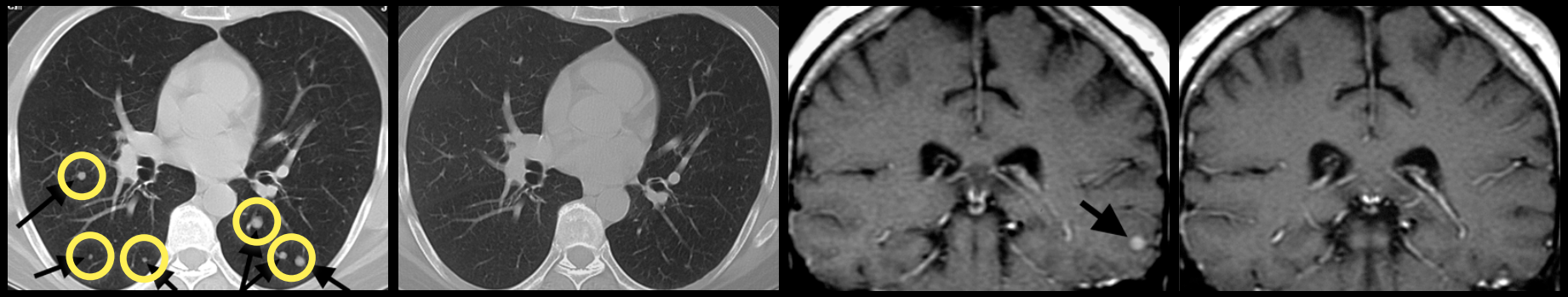
Korman, Peggs and Allison: Adv. In Immunol. 2006;90:297-339

Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

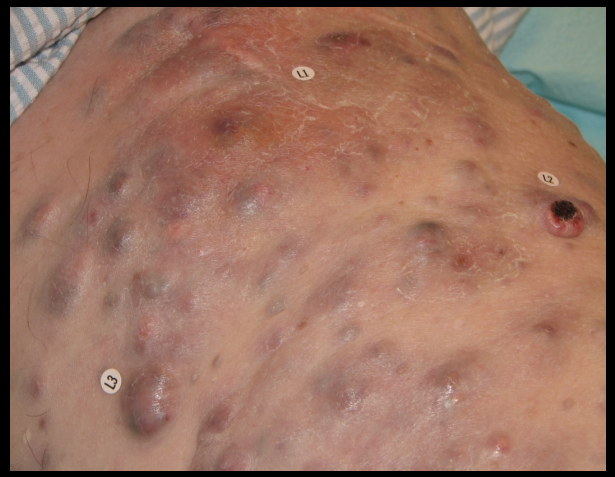


Clinical Response in Melanoma: NCI

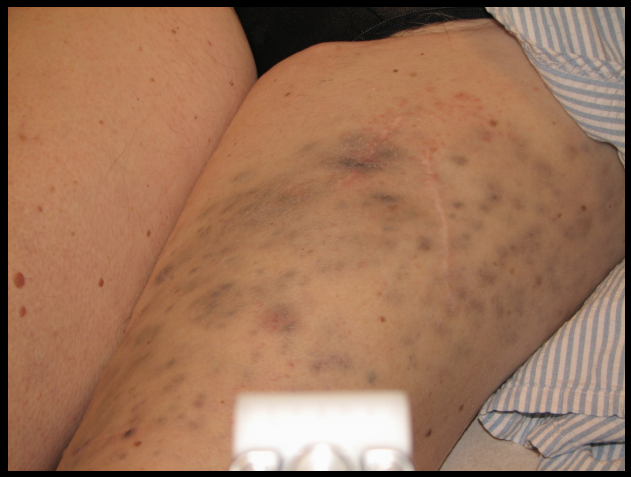
Experienced complete resolution of 2 subcutaneous nodules,
31 lung metastases and 0.5 cm brain metastasis.



Clinical Response in Melanoma:

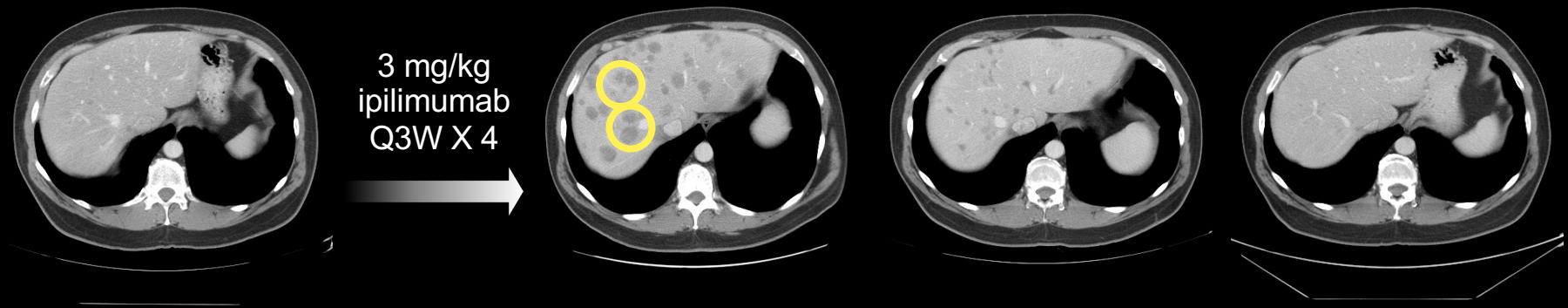


Nov 28, 2006



Jan 9, 2007

Ipilimumab Pattern of Response After the Appearance and Subsequent Disappearance of New Lesions



Pre-Treatment | **Week 12: Progression** | **Week 20: Regression** | **Week 36: Still Regressing**

Source: 2008 ASCO Abstract #3020 Wolchok.

Four Patterns of Response to Ipilimumab Therapy were Observed

2 conventional:

- Response in baseline lesions
- 'Stable disease' with slow, steady decline in total tumor volume

2 novel:

- Response after initial increase in total tumor volume
- Response in index plus new lesions at or after the appearance of new lesions

Proportion of Response to Ipilimumab

Patients randomized to 10 mg/kg ipilimumab monotherapy:
CA184-008 and -022
n = 227

mWHO PD at Week 12
n = 123

Unknown
(No follow-up scan)
n = 41

mWHO Disease control in baseline lesions
n = 63

Followed beyond mWHO PD
n = 57

Response in baseline lesions
n = 2
ongoing

"Stable disease" with a slow, steady decline in total tumor volume
n = 8 **
6 ongoing
1 decline with intermittent progression

Response after initial increase in total tumor volume
n = 1
ongoing

Response of index plus new lesions after the appearance of new lesions
n = 3
1 ongoing

Response in baseline lesions
n = 18 *
12 ongoing *
1 response with intermittent progression

* Including 1 patient with confirmation of response in roll-over study CA184-025

mWHO SD in baseline lesions
n = 45
25 ongoing

"Stable disease" with a slow, steady decline in total tumor volume
n = 18
15 ongoing
1 decline with intermittent progression

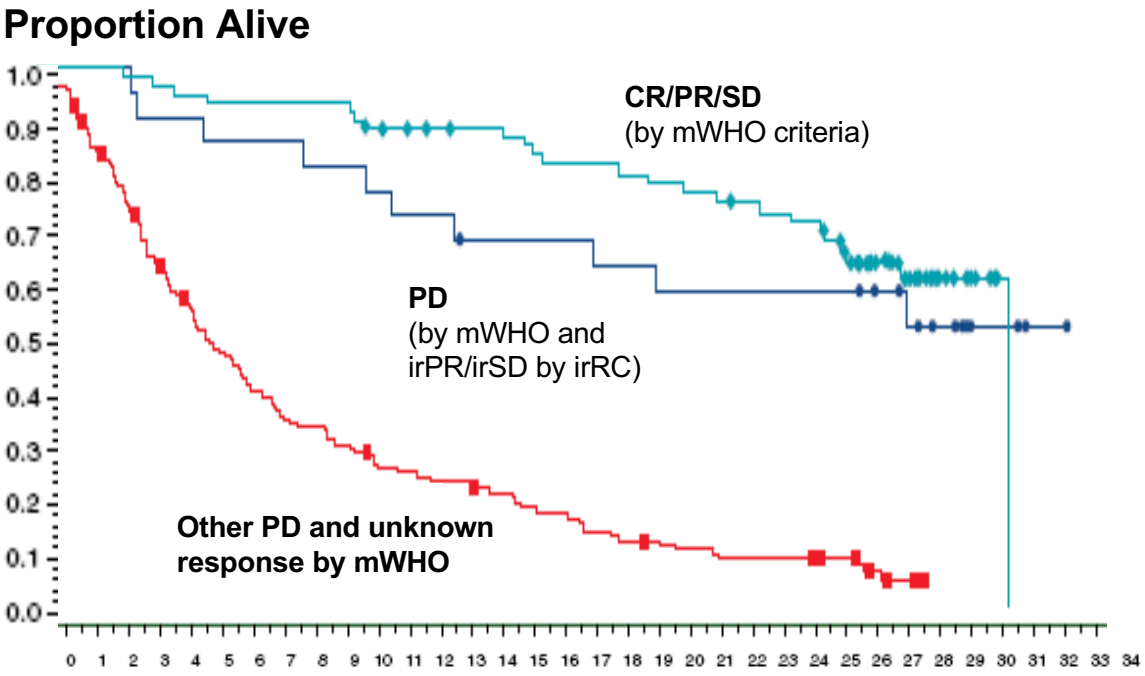
14 patients with evidence of clinical activity
(13 after mWHO PD +
1 w/o follow-up beyond mWHO PD)

**** 2 of these patients demonstrated SD compared to baseline after initial increase in total tumor volume (both ongoing). One of these had 24% reduction from peak and 2% increase from baseline at the last evaluable tumor assessment.**

Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died. Slow steady decline is defined as a > 25% reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.

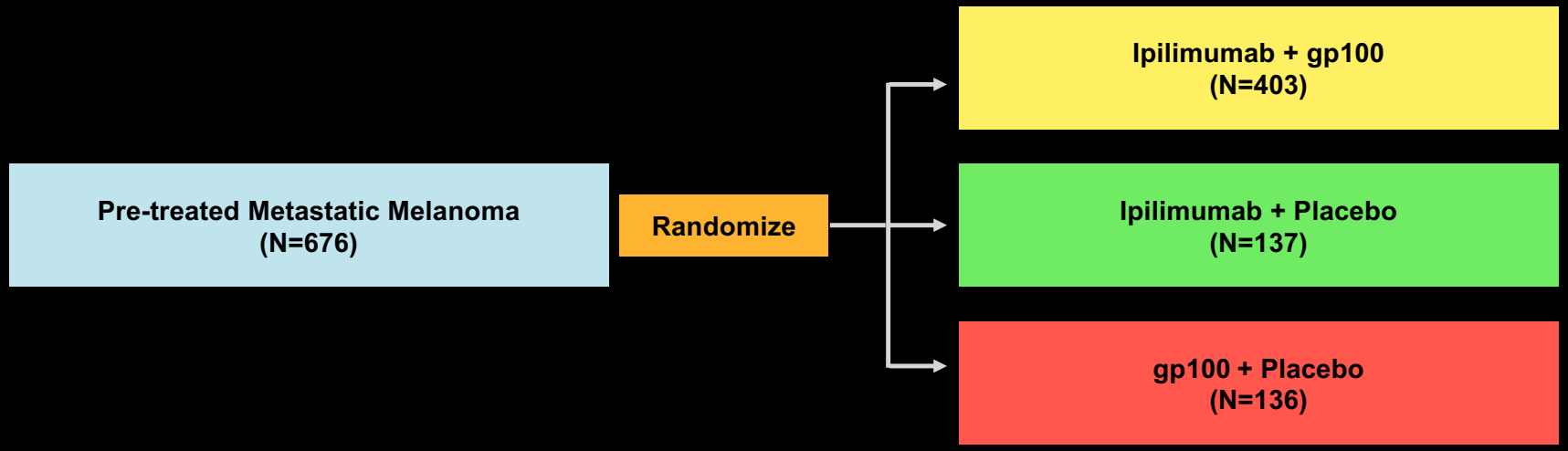
irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)



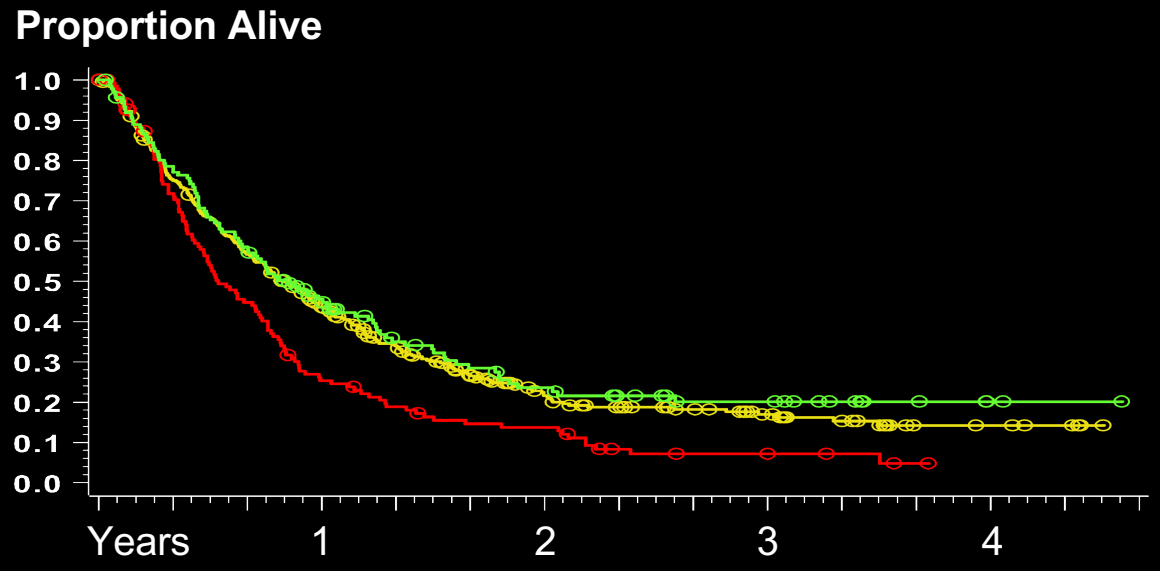
Wolchok et al, *Clin Cancer Res*, 2009

MDX010-20: Study Design



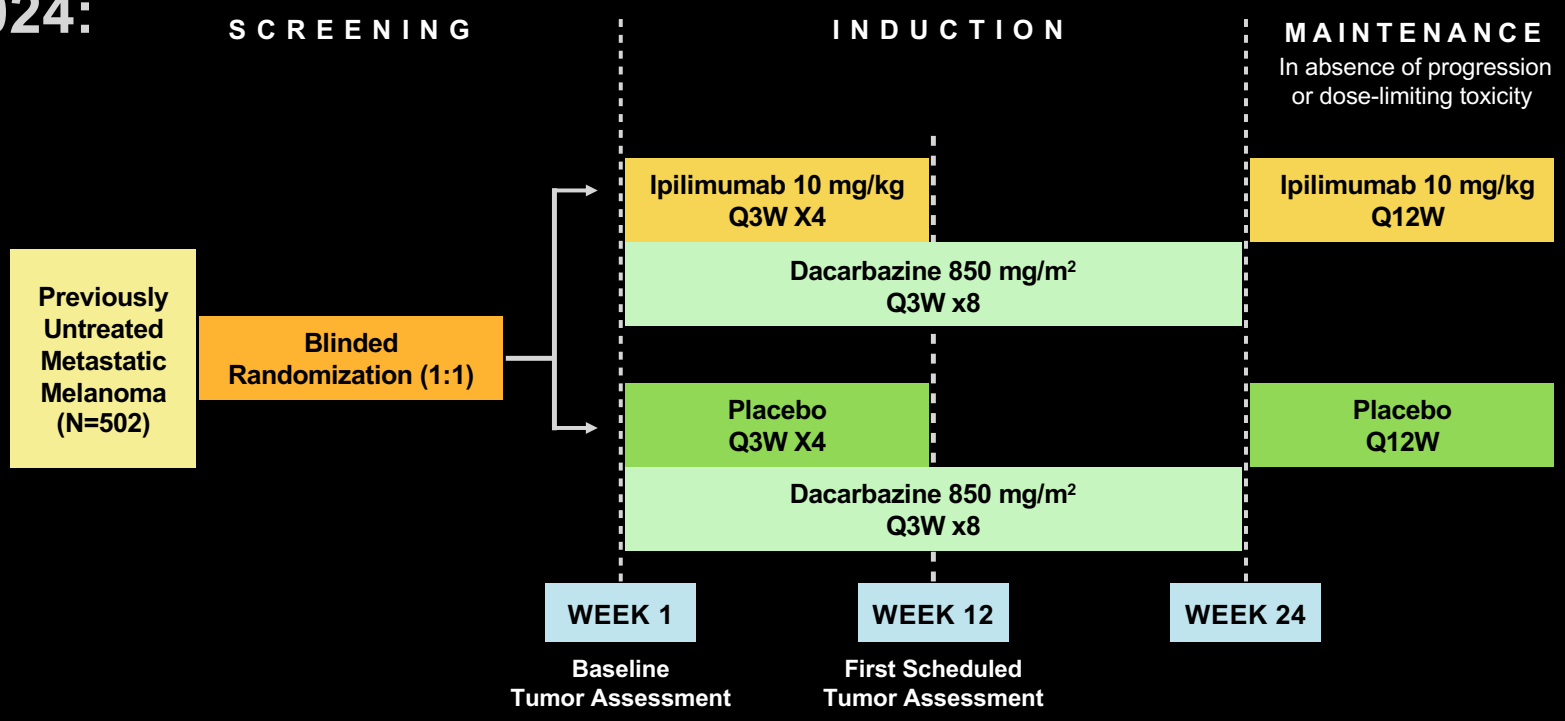
Kaplan-Meier Analysis of Survival

- Ipi + gp100 (A)
- Ipi alone (B)
- gp100 alone (C)



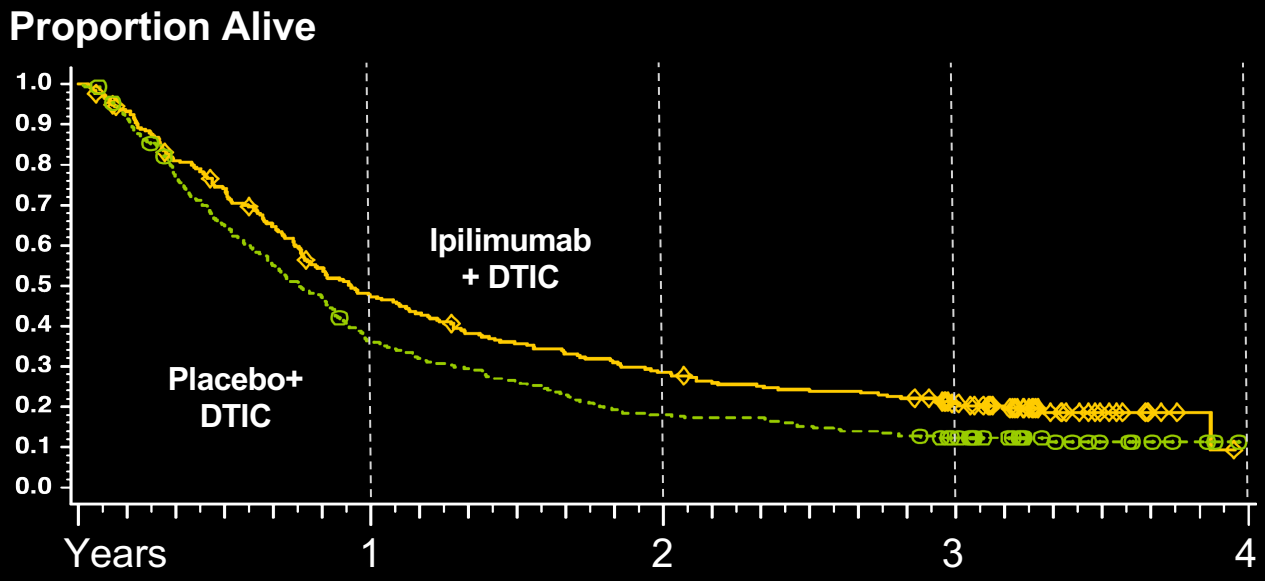
Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=13
1 year	44%	46%	25%
2 year	22%	24%	14%

Study 024: Design



Study 024: Overall Survival

*3-year survival was a post-hoc analysis



Estimated Survival Rate	1 Year	2 Years	3 Years
Ipilimumab + DTIC • n=250	47.3	28.5	20.8
Placebo + DTIC• n=252	36.3	17.9	12.2

Study 024: Select Adverse Events

*1 (0.4%) hypophysitis in a patient on maintenance was reported on Day 364

Select adverse events are shown, regardless of attribution

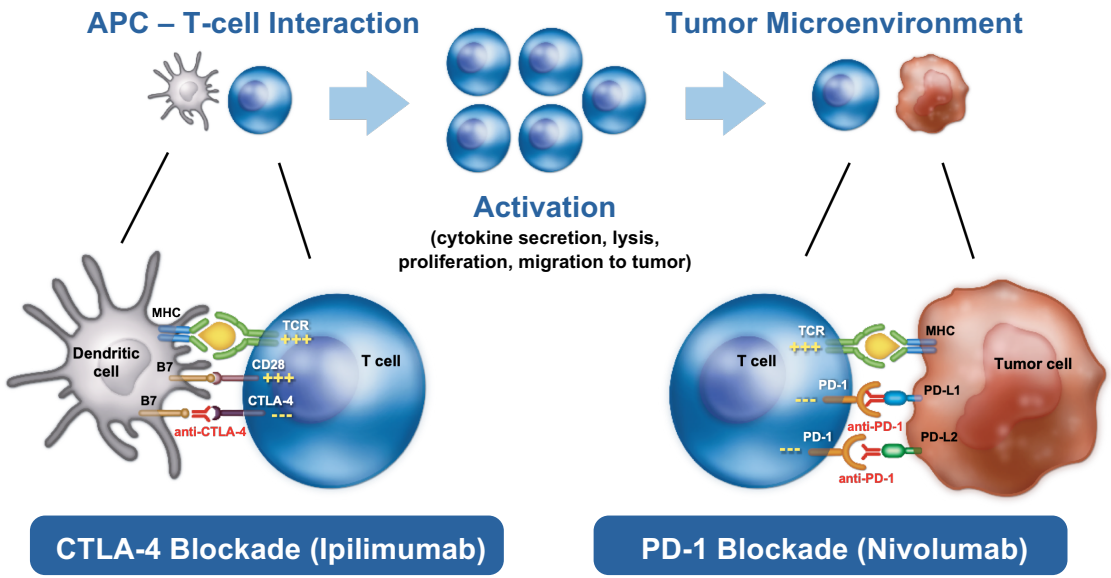
	Ipilimumab + DTIC n=247		Placebo + DTIC n=251	
	PERCENT OF PATIENTS			
	Total	Grade 3-4	Total	Grade 3-4
Hepatic				
Increased ALT	33.2	21.9	5.6	0.8
Increased AST	29.1	18.2	5.6	1.2
Endocrine				
Hypothyroidism	1.6	0	0.4	0
Thyroiditis	0.8	0	0	0
Hyperthyroidism	0.4	0	0.4	0
Hypophysitis*	0	0	0	0

Biologic Rationale for Combined PD-1 and CTLA-4 Blockade

Ipilimumab (IPI) monotherapy in melanoma improves OS (~20% of treated patients alive ≥3 years)[1]

Phase III studies of nivolumab (NIVO) monotherapy in advanced melanoma:[2,3]

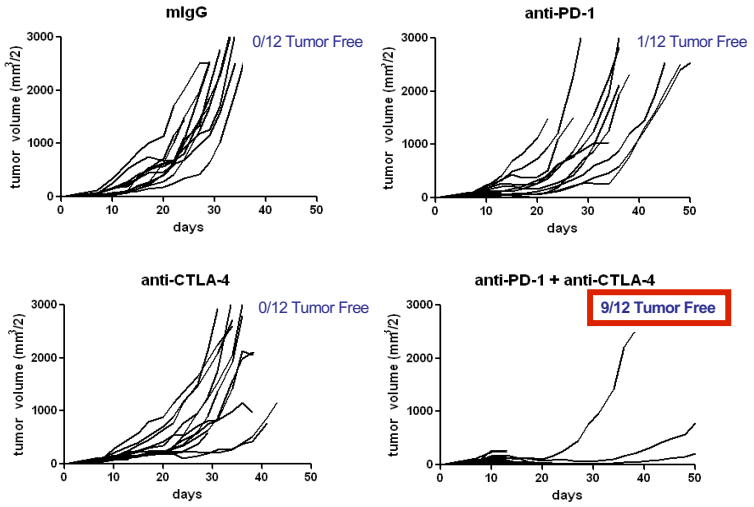
- –1-year OS rate of 73% and ORR of 40% in untreated melanoma (BRAF wild-type)
- –ORR of 32% after progression on IPI, or IPI and a BRAF inhibitor if BRAF mutation-positive



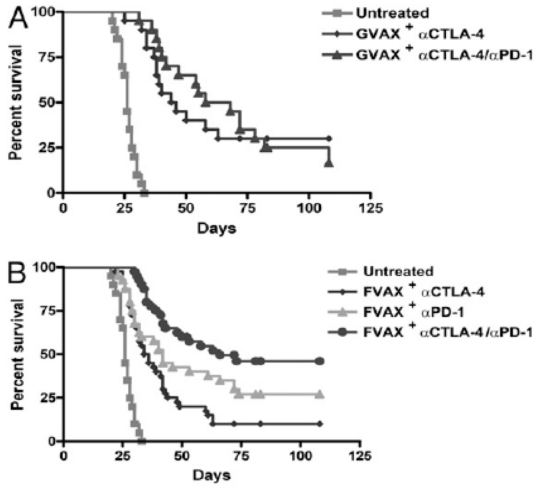
1. Schadendorf et al. J Clin Oncol 2015 Feb 9 [Epub ahead of print]; 2. Robert et al. N Engl J Med 2015;372:320-330; 3. Weber et al. Lancet Oncol 2015;16:375-384.

Antitumor Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only[1,2]



B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]



1. Korman et al. J Immunol 2007;178:48.37. 2. Selby et al. ASCO 2013, abs 3061. 3. Curran et al. Proc Natl Acad Sci USA 2010;107:4275-4280.

Clinical Experience With NIVO Plus IPI Combination

Phase I study of NIVO plus IPI in advanced melanoma[1,2]

- ORR up to 53% (CR rate of 18%)
- 2-year OS rate up to 88%

Phase II study of NIVO plus IPI in untreated melanoma[3]

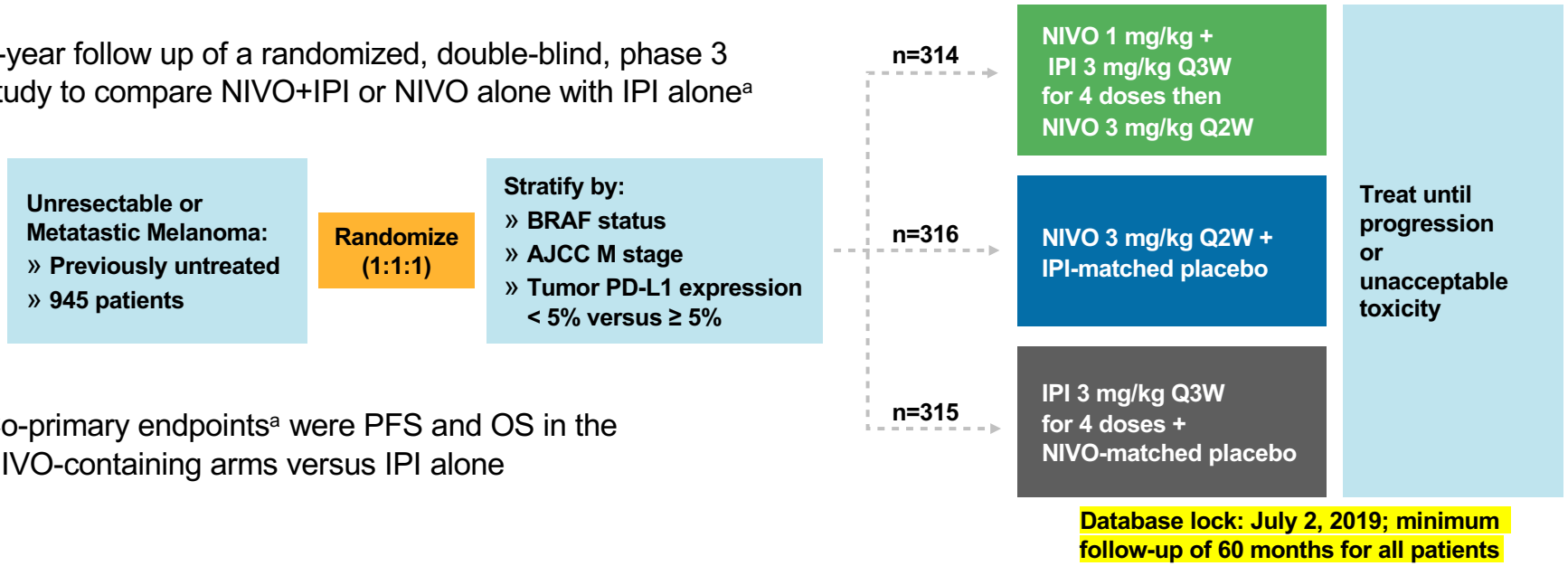
- ORR of 59% with the combination vs. 11% for IPI alone; CR rate of 22% with the combination
- Treatment-related grade 3–4 adverse events (AEs): 54% for the combination vs. 24% for IPI

Response rates were similar regardless of PD-L1 expression[1-3]

1. Wolchok et al. *N Engl J Med* 2013;369:122-33;
2. Oral presentation by Dr. Mario Sznol at the ASCO 2014 Annual Meeting;
3. Postow et al. *N Engl J Med* 2015;372:2006-17.

CheckMate 067: Study Design

5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone with IPI alone[a]

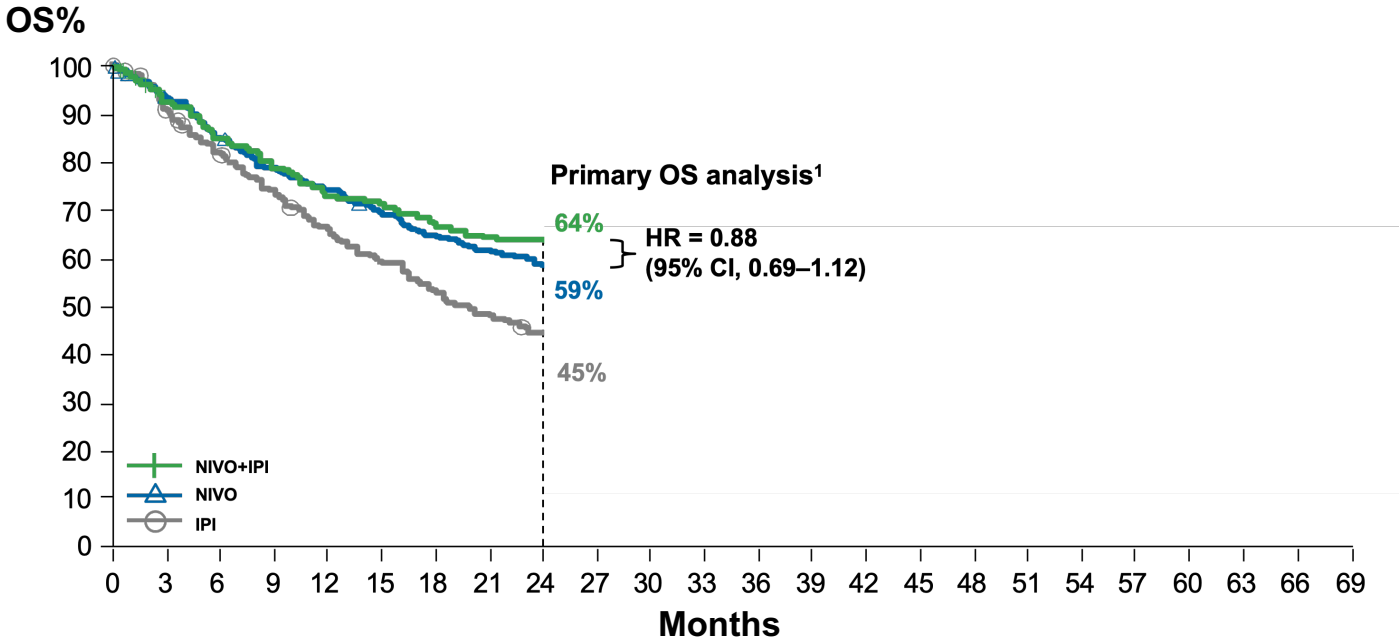


Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

Database lock: July 2, 2019; minimum follow-up of 60 months for all patients

NCT01844505 • [a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Overall Survival



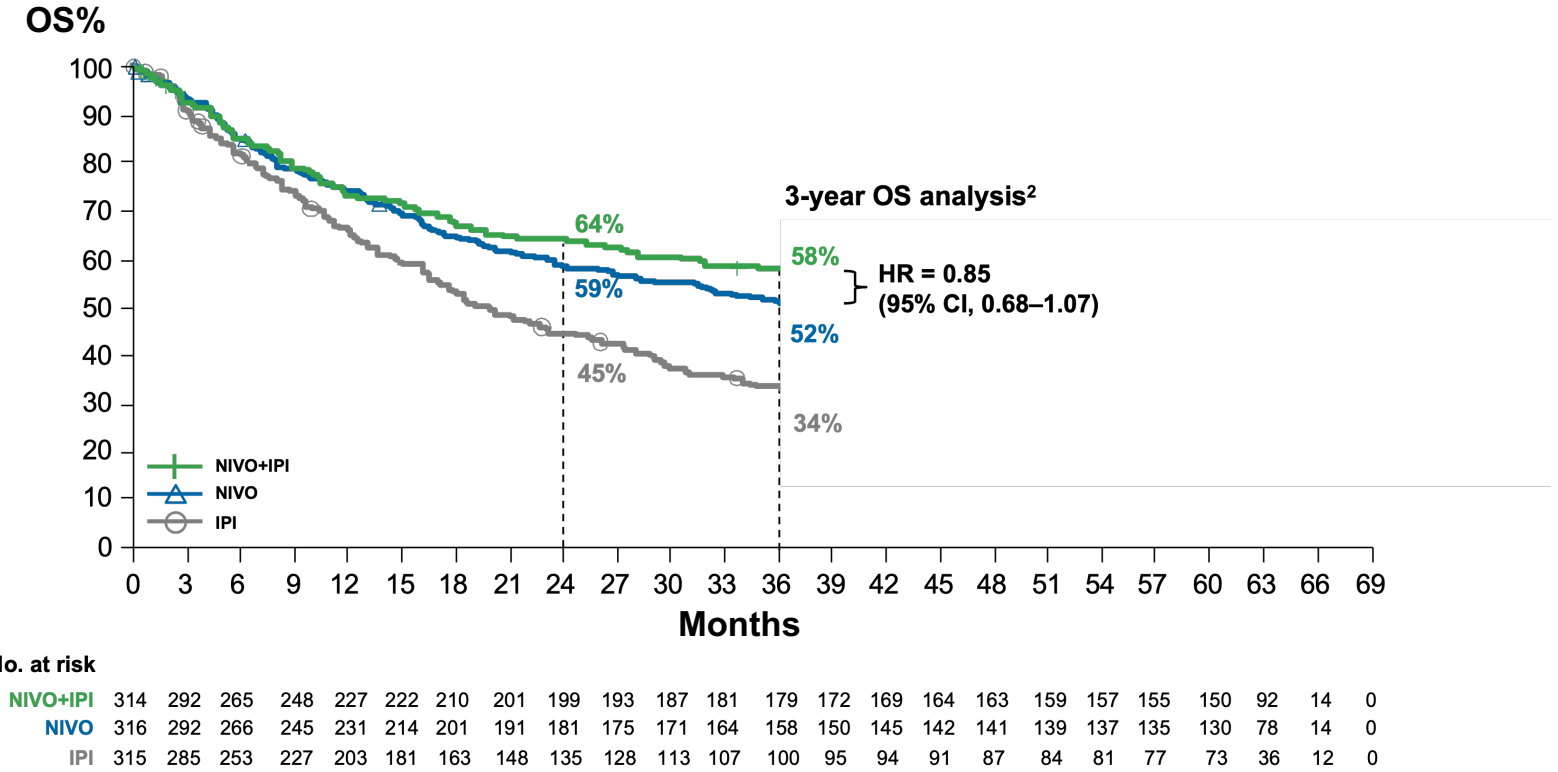
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis.

1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075;

Overall Survival



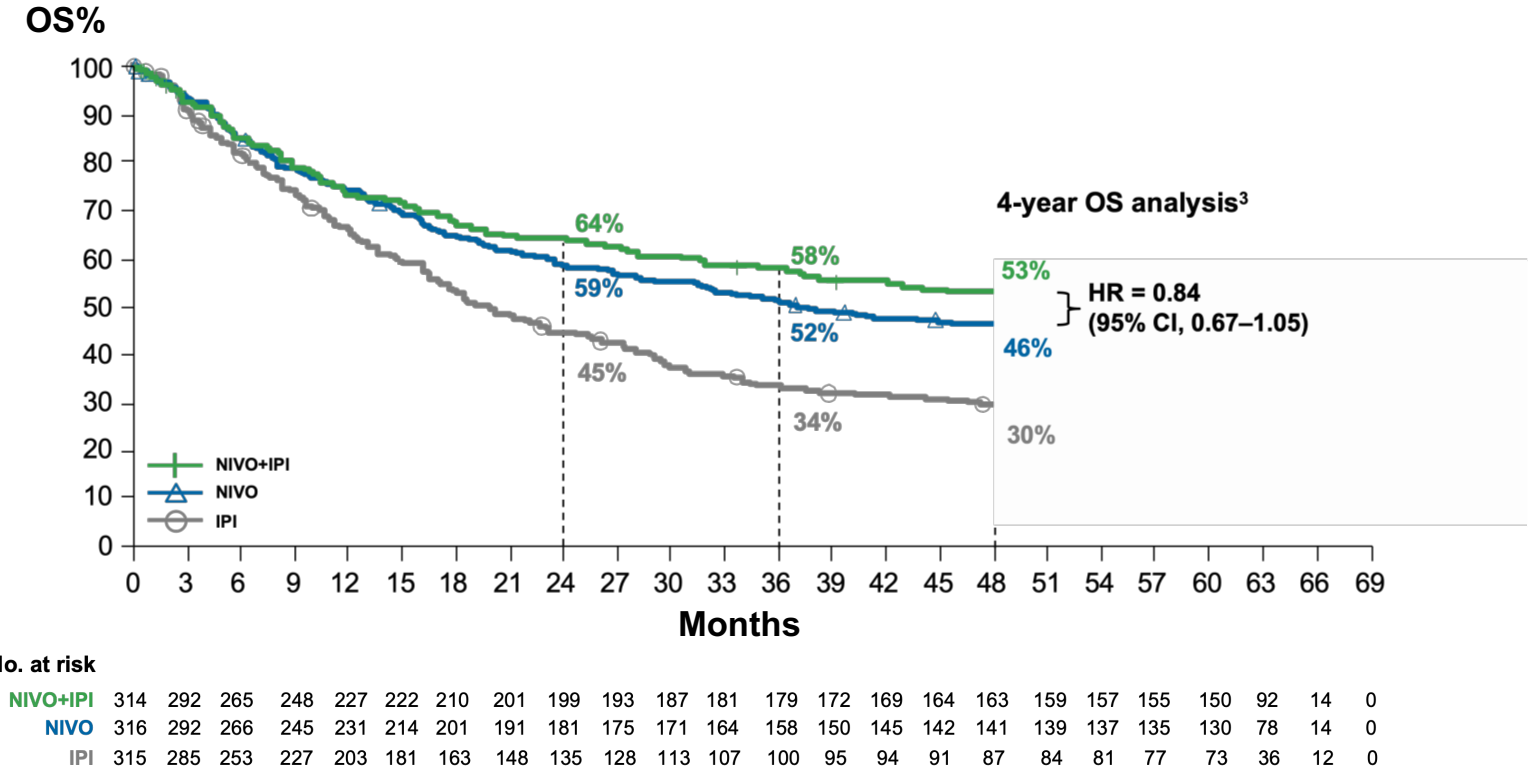
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis.

1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075;
2. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356;

Overall Survival



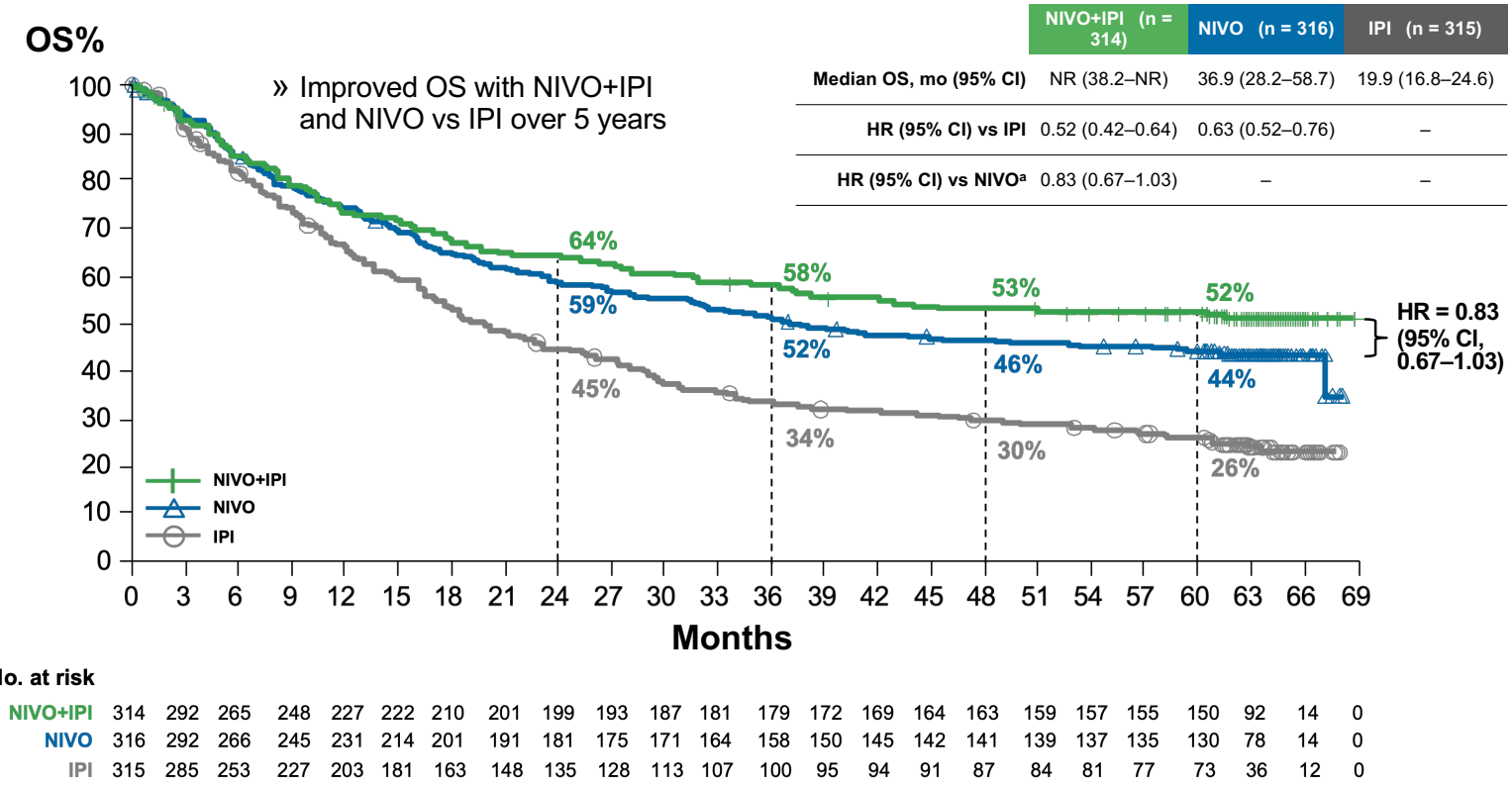
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis.

1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075;
2. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356;
3. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492.

Overall Survival



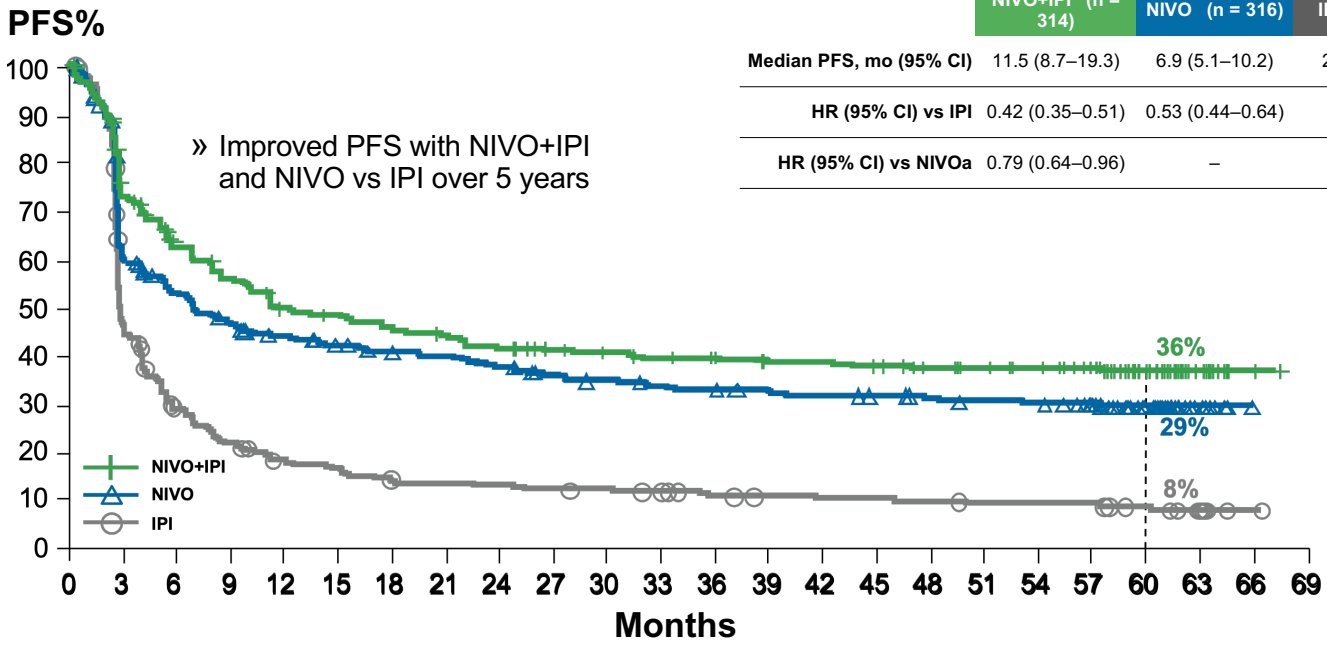
No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis.

1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075;
2. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356;
3. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492.

Progression-Free Survival



	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVOa	0.79 (0.64–0.96)	–	–

No. at risk

NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

[a]Descriptive analysis.

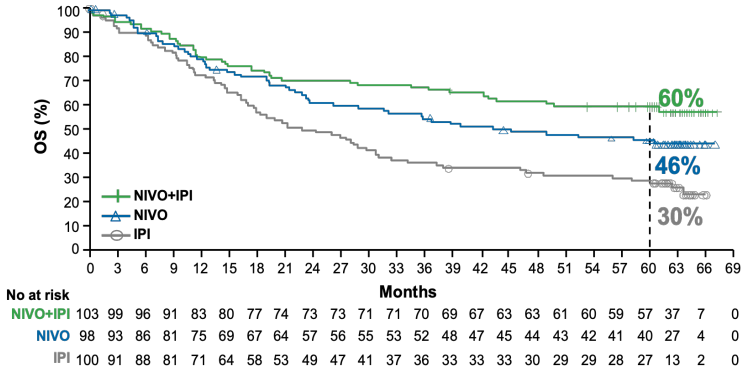
OS in Patients With BRAF-Mutant and Wild-Type Tumors

» Improved OS and PFS with NIVO+IPI and NIVO vs IPI regardless of BRAF mutation status

[a]Descriptive analysis.

BRAF Mutant

	NIVO+IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median, mo (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs IPI	0.44 (0.30–0.64)	0.63 (0.44–0.90)	–
HR (95% CI) vs NIVOa	0.70 (0.46–1.05)	–	–



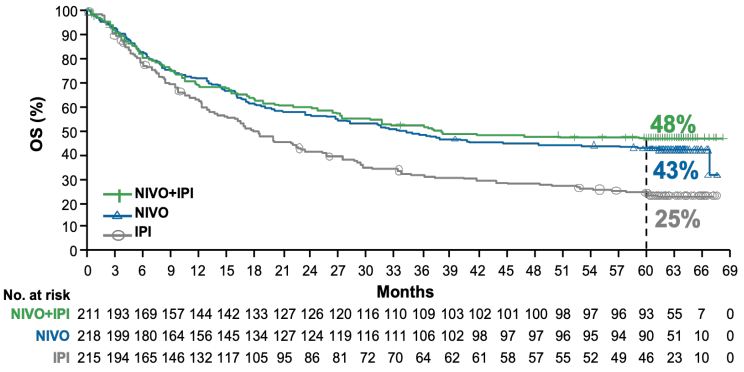
No at risk

NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	59	57	37	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	41	40	27	4	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	13	2	0

5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

BRAF Wild-Type

	NIVO+IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1–59.2)	18.5 (14.1–22.7)
HR (95% CI) vs IPI	0.57 (0.45–0.73)	0.64 (0.50–0.81)	–
HR (95% CI) vs NIVOa	0.89 (0.69–1.15)	–	–



No. at risk

NIVO+IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	97	96	93	55	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	94	90	51	10	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	46	23	10	0

5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NRa**	**NR (50.4–NR)**	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]

- 19%, 21%, and 22% for NIVO+IPI
- 16%, 18%, and 19% for NIVO
- 5%, 5%, and 6% for IPI

[a]Although a median was reported at the previous analysis, that estimate was immature and greater than the minimum study follow-up. ITT, intention to treat.

1. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356; 2. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492.

Safety Summary

» No new safety signals were observed with the additional follow-up

» No additional deaths due to study drug toxicity were reported since the prior analysis[a]

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 AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

» Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]

› Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.