Combination Immunotherapies for Metastatic Melanoma: What Agents and When?

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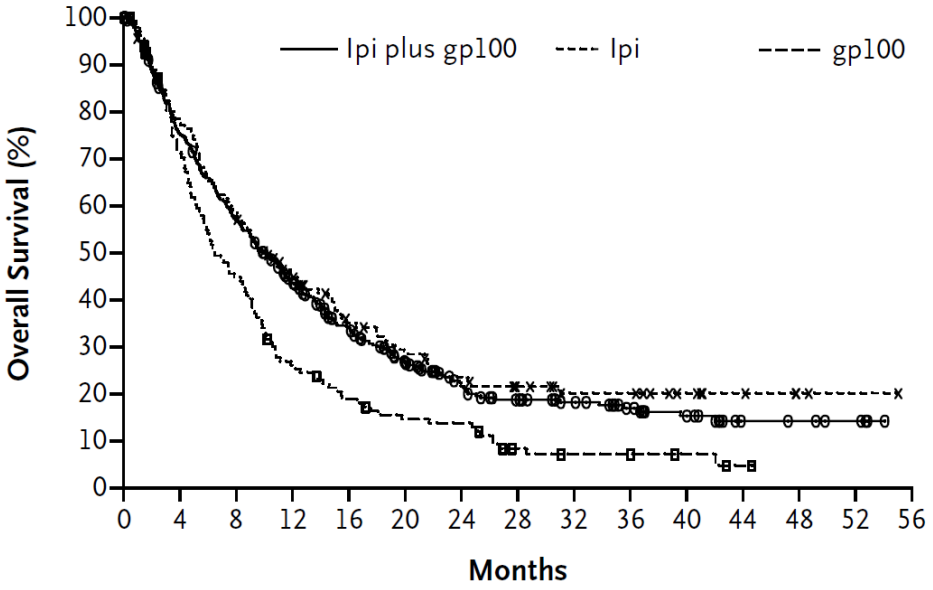
SITC: Advances in Cancer Immunotherapy Meeting 2014

Disclosures

- Consultant and steering committee member for Genentech/Roche
- Consultant for Bristol-Myers Squibb

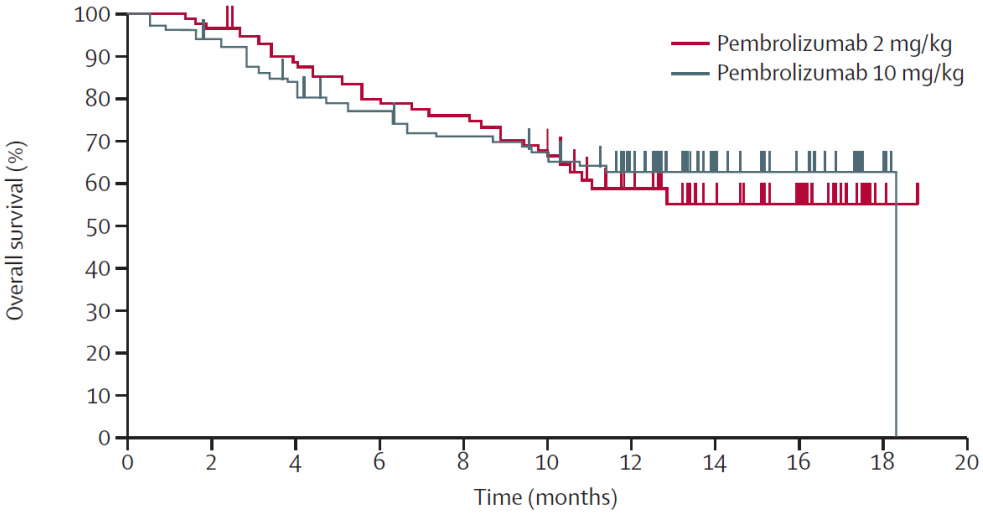
Why combination immunotherapies?

Ipilimumab



Hodi FS *et al*
N Eng J Med 2011

Pembrolizumab



Robert C *et al*
Lancet 2014

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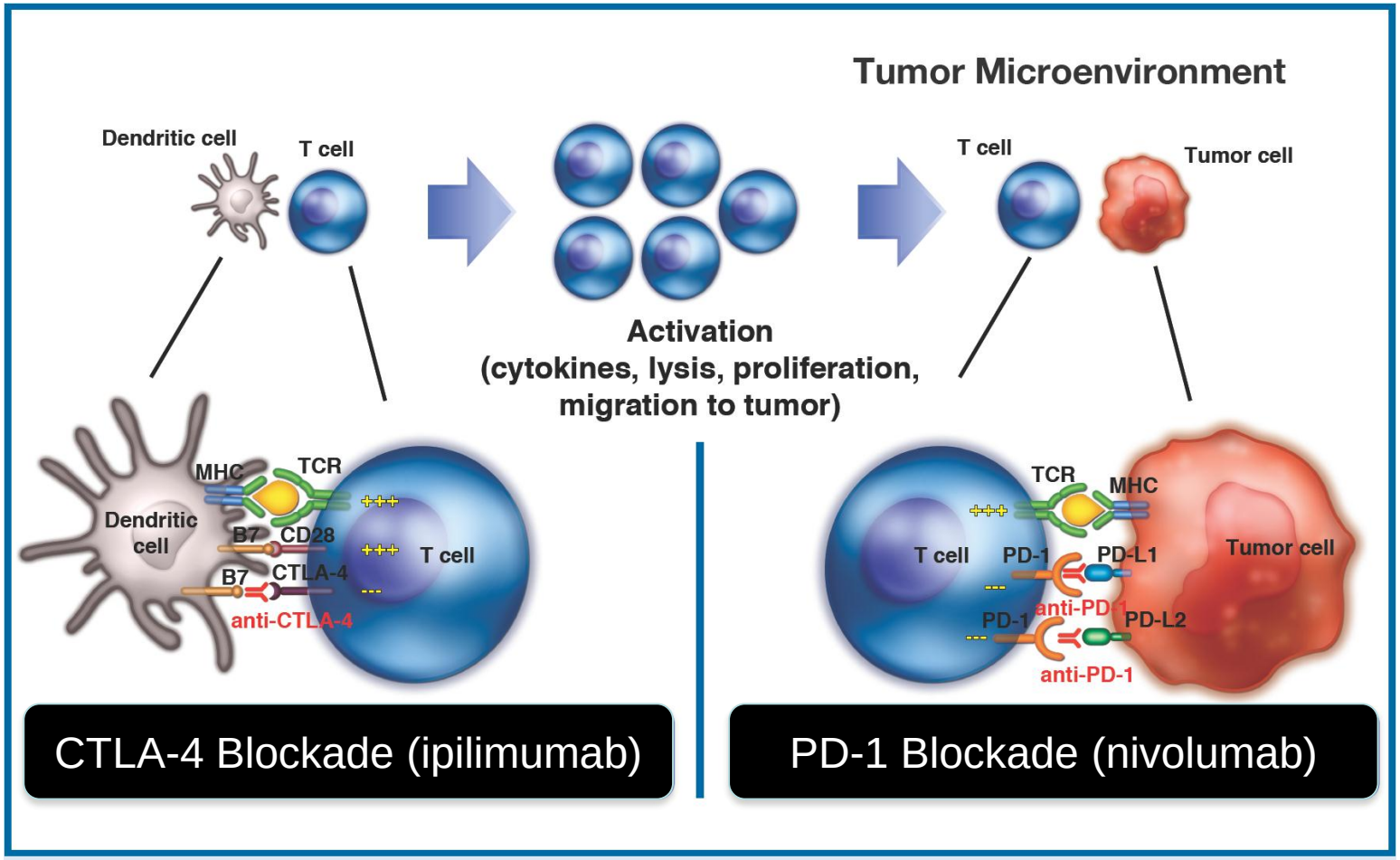
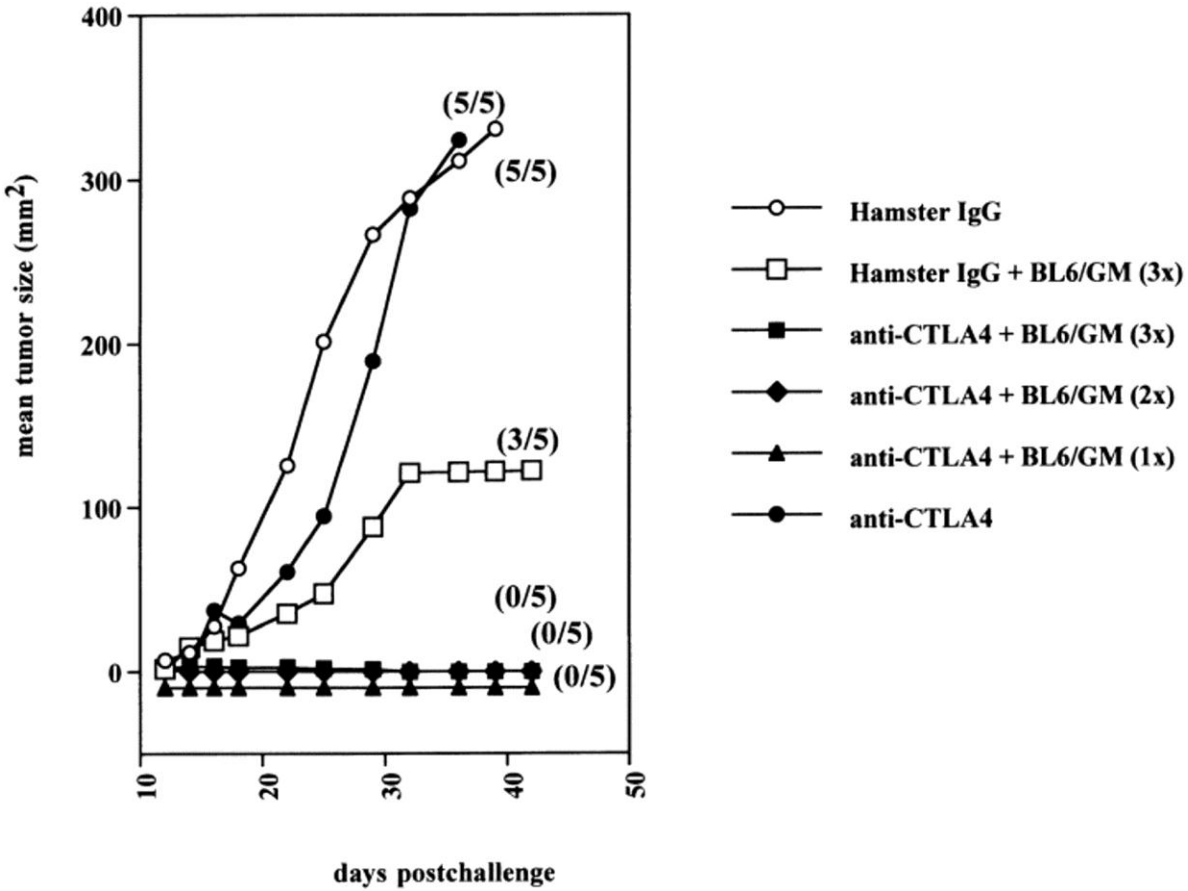
Potential Synergism of Checkpoint Inhibitors



Adapted from Kluger H, SMR 2014

Checkpoint plus Cytokine therapies?

"A single dose of GM-CSF–producing vaccine cooperates with CTLA-4 blockade to induce 100% cure of B16-BL6"



van Elsas A *et al,* J Exp Med 1999

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Most promising clinical strategies so far in metastatic melanoma

Combined checkpoint inhibition

- Ipilimumab plus Nivolumab

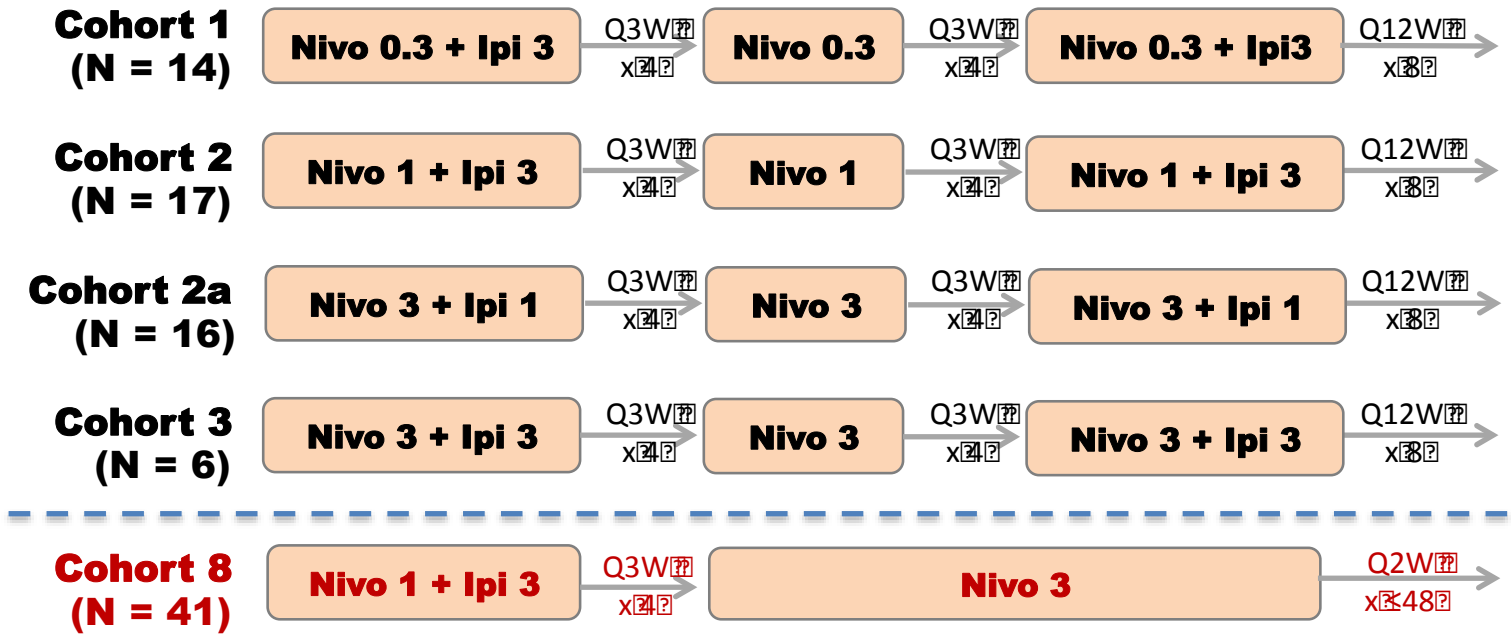
Combined checkpoint inhibition and cytokine therapy

- Ipilimumab plus GM-CSF
- Ipilimumab plus pegylated-interferon
- Ipilimumab plus bevacizumab

Other combined strategies

- Ipilimumab plus IDO1 inhibitor

Phase 1 CA209-004 Concurrent Cohorts



Provided by Harriet Kluger
Presented SMR 2014

All dose units are mg/kg.

Results from Cohorts 6 and 7 (sequenced treatment cohorts – ipilimumab followed by nivolumab) were reported previously (Kluger et al. ESMO 2014)
Ipi = ipilimumab; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q12W = every 12 weeks

Baseline Characteristics

	Cohort 1–3 (N = 53)*	Cohort 8 (N = 41)*
Median age, years (range)	57 (22–79)	55 (22–80)
Male, n (%)	60	44
ECOG performance status, n (%)		
0	83	66
1	15	29
Not reported	2	5
Lactate dehydrogenase level, n (%)		
≤Upper limit of the normal range	62	61
>Upper limit of the normal range	38	39
Systemic cancer therapy, n (%)		
Immunotherapy	19	29
BRAF inhibitor	4	7
Number of prior systemic cancer therapies, n (%)		
0	60	49
1	28	27
≥2	11	24

*All treated patients
JUNE 2014 data analysis.
ECOG = Eastern Cooperative Oncology Group.

Provided by Harriet Kluger
Presented SMR 2014

Activity Summary

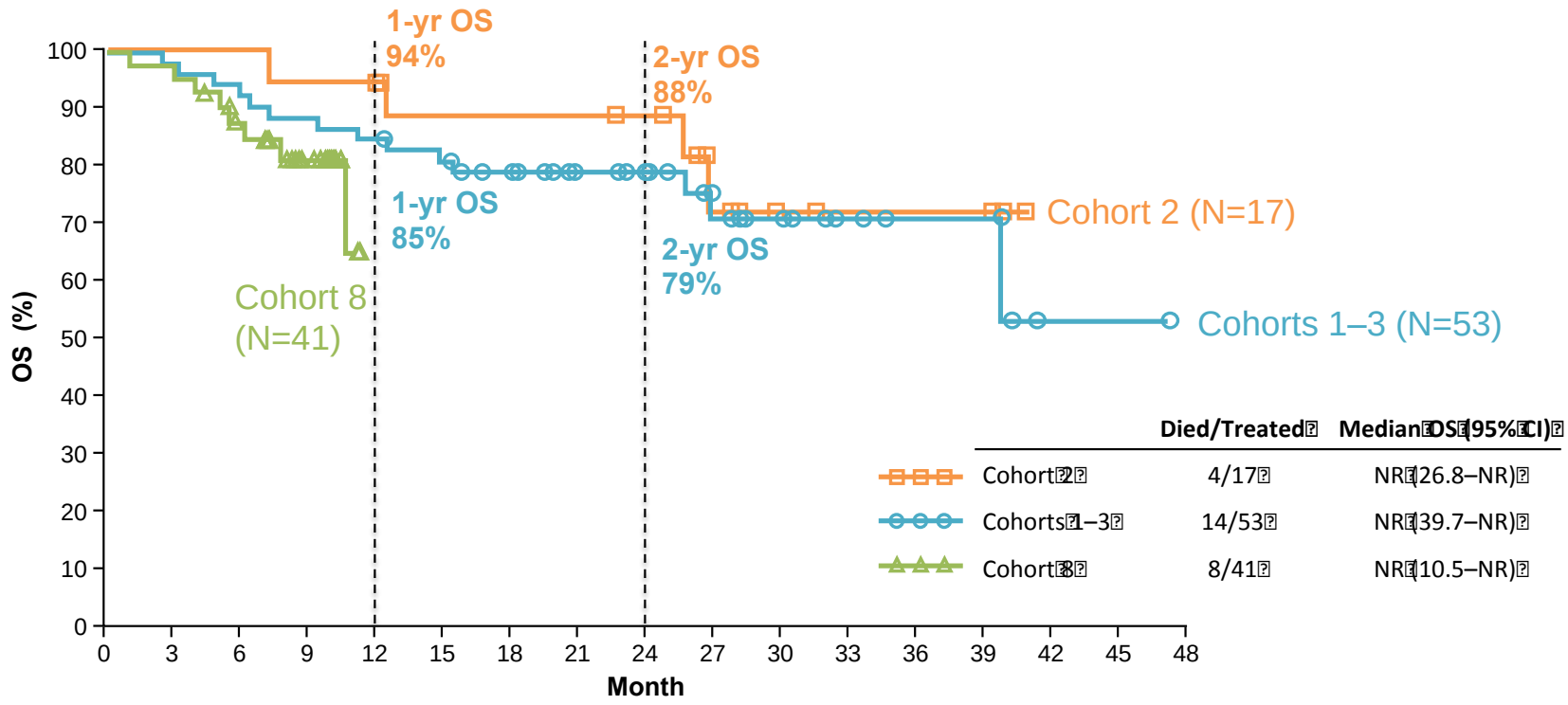
Cohort(s)	Nivo (mg/kg) + Ipi (mg/kg)	N[b]	ORR,[a] %	CR, %	Aggregate Clinical Activity Rate, %	≥80% Tumor Burden Reduction at 36 Weeks,[c] %
1–3		**53**	**42**	**17**	**72**	**42**
1	0.3 + 3	14	21	14	57	36
2	1 + 3	17	47	18	65	53
2a	3 + 1	16	50	25	88	31
3	3 + 3	6	50	0	83	50
8[d]	**1 + 3**	**41**	**44**	**7**	**56**	**29**
All Concurrent Cohorts		**94**	**43**	**13**	**65**	**36**

[a]Per modified World Health Organization (mWHO) criteria, [CR+PR]/Nx100. [b]Number of response-evaluable patients. [c]Best overall response.
[d]Cohort 8 using the phase 3 trial dose schedule, started November 2013.

Provided by Harriet Kluger
Presented SMR 2014

JUNE 2014 data analysis

Overall Survival



Patients at Risk

Cohort 2 (Nivo 1 + Ipi 3)	17	17	17	16	16	14	14	14	13	7	4	3	3	3	0	0	0
Cohorts 1–3	53	52	49	47	45	42	37	30	25	16	11	7	5	5	1	1	0
Cohorts 8 (Nivo 1 + Ipi 3)	41	40	31	16	0	0	0	0	0	0	0	0	0	0	0	0	0

- **Cohort 8 uses the same dosing schedule that is being tested in the phase 3 trial (CA209-067)**

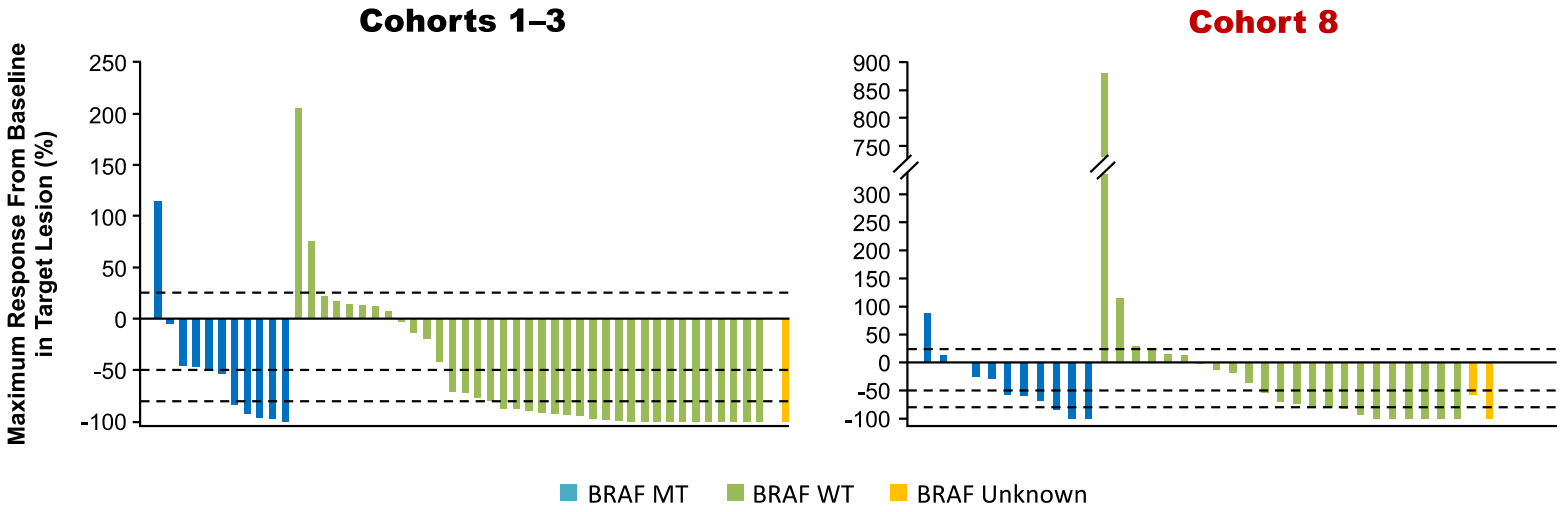
JUNE 2014 data analysis.

Provided by Harriet Kluger
Presented SMR 2014

ORR and Tumor Burden Change by BRAF Mutation Status

Cohort(s) [N*]	Evaluable Sample, N	ORR, n/N (%)	
		BRAF WT	BRAF MT
1–3 [53]	51	18/39 (**46**)	3/12 (**25**)
8 [41]	39	10/27 (**37**)	6/12 (**50**)

*Number of patients treated. MT=mutant (BRAFT V600 mutation positive); WT=wild-type (BRAF V600 mutation negative).



JUNE 2014 data analysis.

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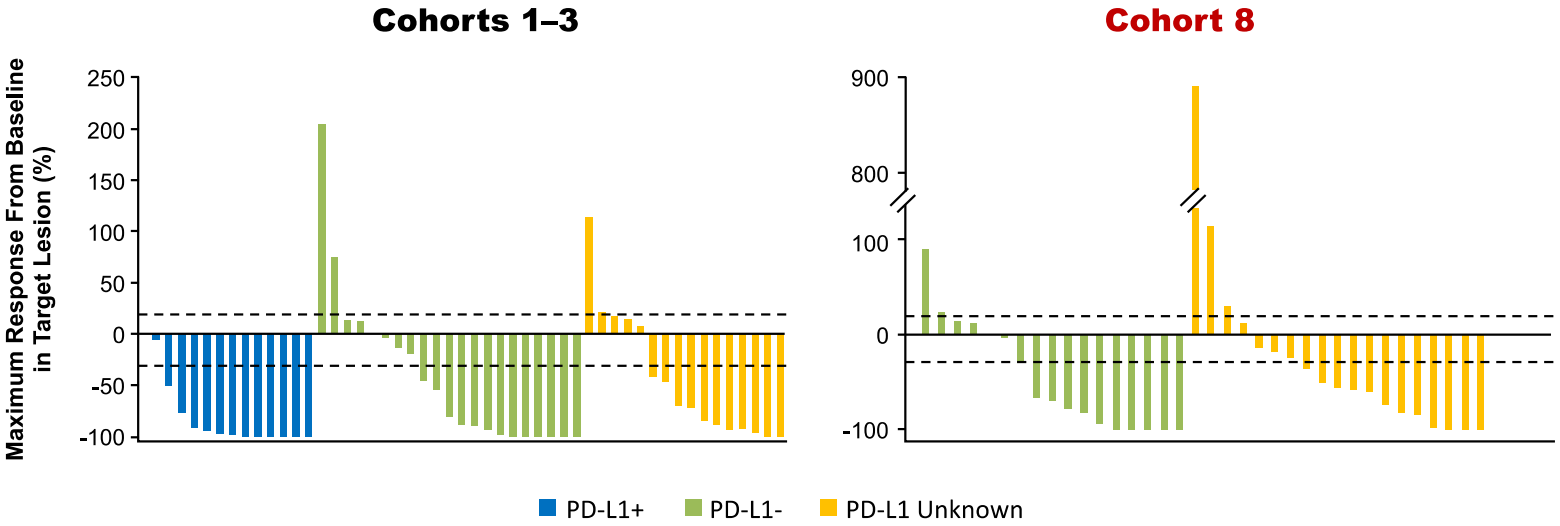
ORR and Tumor Burden Change by PD-L1 Status

Cohort(s) [N*]	Evaluable Sample, N	ORR, n/N (%)	
		PD-L1 Positive†	PD-L1 Negative†
1–3 [53]	37	8/14 (**57**)	8/23 (**35**)
8 [41]	21	0/0‡	8/21 (**38**)

*Number of patients treated. †5% cut-off, tumor cell surface staining. ‡None of the 21 evaluable patient samples was test positive for PD-L1 by 5% tumor cell surface staining cutoff



JUNE 2014 data analysis.

Provided by Harriet Kluger
Presented SMR 2014

Treatment-Related AEs Reported in ≥ 15% of Patients*

Patients with an event, %	Cohort 1–3 (N=53)			Cohort 8 (N=41)		
	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5
All drug-related	**97**	**63**	**0**	**98**	**66**	**2†**
Rash	62	4	0	66	10	0
Pruritus	57	0	0	46	0	0
Fatigue	43	2	0	46	0	0
Diarrhea	42	4	0	34	12	0
Nausea	23	2	0	24	2	0
Lipase increased	26	19	0	17	10	0
AST increased	25	13	0	12	7	0
Pyrexia	23	0	0	22	0	0
ALT increased	23	11	0	12	12	0
Amylase increased	21	6	0	12	7	0
Vitiligo	15	0	0	7	0	0
Abdominal pain	9	0	0	20	2	0
Arthralgia	9	0	0	20	0	0

*Listing adverse events reported in ≥ 15% of patients in cohorts 1–3 or in cohort 8, sorted by any grade frequency in cohort 1–3;
†One patient died due to grade 5 multi-organ failure related to study treatment in cohort 8; another patient died due to reason reported as 'unknown'
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

JUNE 2014 data analysis.

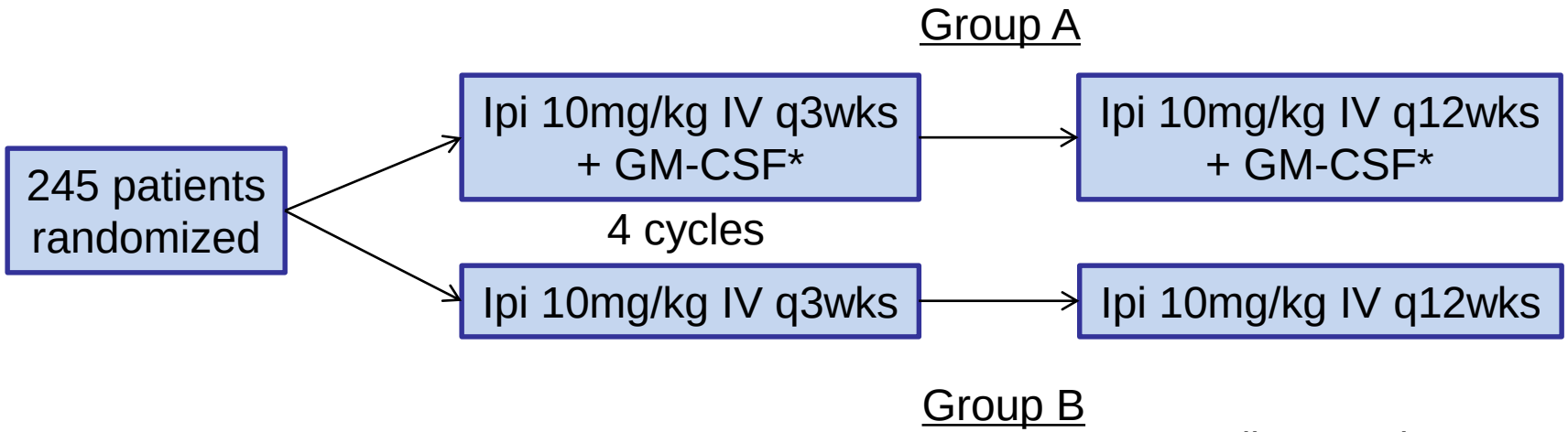
Provided by Harriet Kluger
Presented SMR 2014

Research

Original Investigation

Ipilimumab Plus Sargramostim vs Ipilimumab Alone for Treatment of Metastatic Melanoma
A Randomized Clinical Trial

F. Stephen Hodi, MD; Sandra Lee, ScD; David F. McDermott, MD; Uma N. Rao, MD; Lisa H. Butterfield, PhD; Ahmad A. Tarhini, MD, PhD; Philip Leming, MD; Igor Puzanov, MD; Donghoon Shin, SM; John M. Kirkwood, MD



*250 ug SC daily days1-14 qcycle

Hodi FS *et al*, JAMA 2014

Table 1.
Baseline Characteristics

Characteristic	No. (%)	
	Ipilimumab Plus Sargramostim (n = 123)	Ipilimumab Only (n = 122)
Age, median (range), y	61 (25-86)	64 (21-89)
Sex		
Men	85 (69.1)	78 (63.9)
Women	38 (30.9)	44 (36.1)
Race		
White	122 (99.2)	119 (97.6)
Black	0	1 (.8)
Unknown	1 (0.8)	2 (1.6)
ECOG performance status[a]		
0	68 (56.2)	78 (64.5)
1	53 (43.8)	43 (35.5)
Metastatic stage		
Unresectable III	29 (23.6)	31 (25.4)
M1a/M1b	33 (26.8)	31 (25.4)
M1c	61 (49.6)	60 (49.2)
Serum lactate dehydrogenase		
Normal	69 (58)	68 (57.6)
Elevated	50 (42)	50 (42.4)
Prior therapy		
None	67 (54.5)	68 ((55.8)
Interferon	18 (14.6)	17 (13.9)
One investigational or systemic therapy	38 (30.9)	37 (30.3)

Hodi FS *et al*, JAMA 2014

Safety

Table 3. Treatment-Related Grades 3-5 Toxicity With Incidence Rate of More Than 3% in at Least 1 Group[a]

	No. (%) of Patients With Grades 3-5 Toxicity, No. (%)	
	Ipilimumab Plus Sargramostim (n = 118)	Ipilimumab Only (n = 120)
Toxicity		
Diarrhea	15 (12.7)	16 (13.3)
Rash maculopapular	11 (9.3)	11 (9.2)
Colitis	7 (5.9)	10 (8.3)
Fatigue	7 (5.9)	4 (3.3)
Alanine aminotransferase increased	6 (5.1)	7 (5.8)
Aspartate aminotransferase increased	5 (4.2)	9 (7.5)
Lipase increased	5 (4.2)	6 (5.0)
Dehydration	5 (4.2)	5 (4.2)
Hyponatremia	5 (4.2)	3 (2.5)
Pruritus	3 (2.5)	7 (5.8)
Endocrine disorders (other)	3 (2.5)	5 (4.2)
Nausea	3 (2.5)	4 (3.3)
Colonic perforation	2 (1.7)	7 (5.8)
Generalized muscle weakness	2 (1.7)	4 (3.3)
Abdominal pain	1 (0.8)	4 (3.3)
Autoimmune disorder	0	4 (3.3)
Blood bilirubin increased	0	4 (3.3)
Any toxicity (worst degree)	53 (44.9)	70 (58.3)

Hodi FS *et al*, JAMA 2014

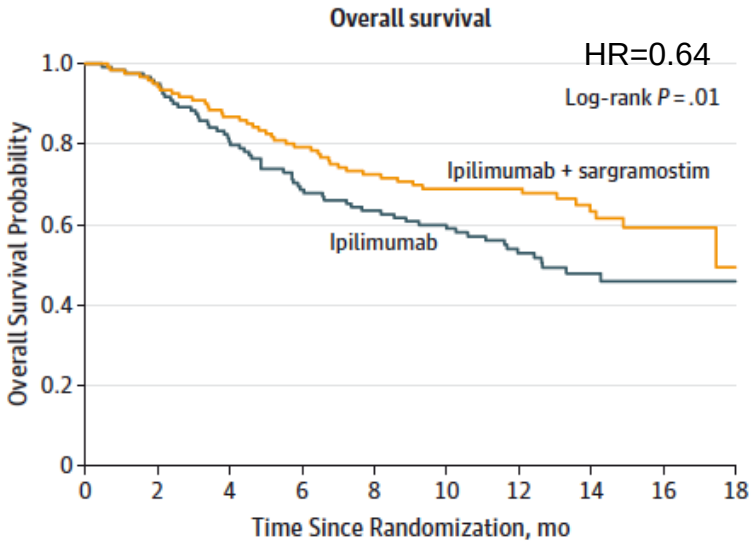
Efficacy Summary

	Ipilimumab Plus Sargramostim (n = 123)	Ipilimumab Only (n = 122)	*P* Value[a]
Overall survival			
No. of deaths	44	60	
Median survival time (95% CI), mo	17.5 (14.9-Not reached)	12.7 (10.0-Not reached)	.01[b]
1-y Survival rate (95% CI), %[c]	68.9 (60.6-85.5)	52.9 (43.6-62.2)	
Mortality HR (1-sided 90% repeated CI)	0.64 (Not applicable-0.90)	1 [Reference]	.01[d]
Progression-free survival			
No. of events (progression or death)	90	93	
Median survival time (95% CI), mo	3.1 (2.9-4.6)	3.1 (2.9-4.0)	.37[b]
6-mo Survival rate (95% CI), %[c]	34.0 (25.3-42.8)	29.6 (21.1-38.1)	
Difference between groups HR (95% CI)	0.87 (0.64-1.18)	[Reference]	.37[d]
Clinical response, No. (%)			
Complete response	2 (1.6)	0	
Partial response	17 (13.8)	18 (14.8)	
Stable disease	26 (21.1)	23 (18.9)	
Progressive disease	55 (44.7)	52 (42.6)	
Unevaluable	20 (16.3)	23 (18.9)	
Unknown	3 (2.4)	6 (4.9)	
Overall response rate			
No./total	19/123	18/122	
% (95% CI)	15.5 (9.6-23.1)	14.8 (9.0-22.3)	.88[e]

Hodi FS *et al*, JAMA 2014

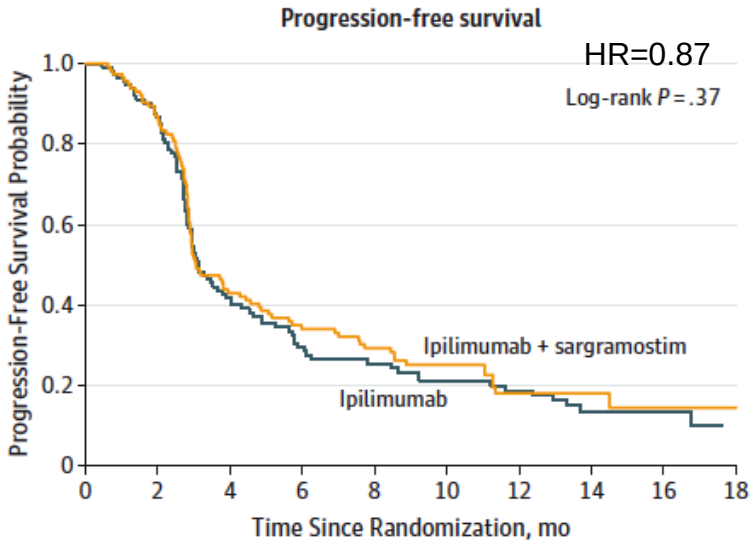
Survival

Figure 2. Kaplan-Meier Estimates for Overall Survival and Progression-Free Survival



No. at risk

Ipilimumab + sargramostim	123	115	104	94	84	75	63	39	11
Ipilimumab	122	114	94	80	72	64	49	28	14



No. at risk

Ipilimumab + sargramostim	123	99	49	36	31	22	10	7	4
Ipilimumab	122	97	46	29	25	19	15	8	5

Hodi FS *et al*, JAMA 2014

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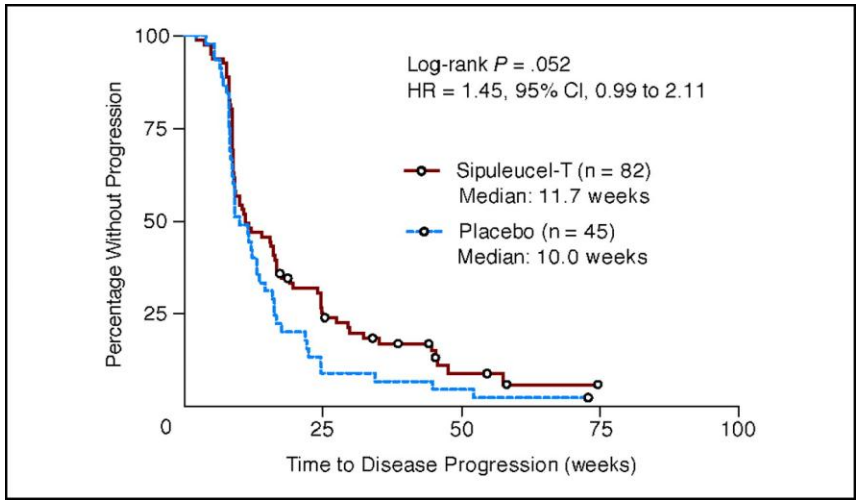
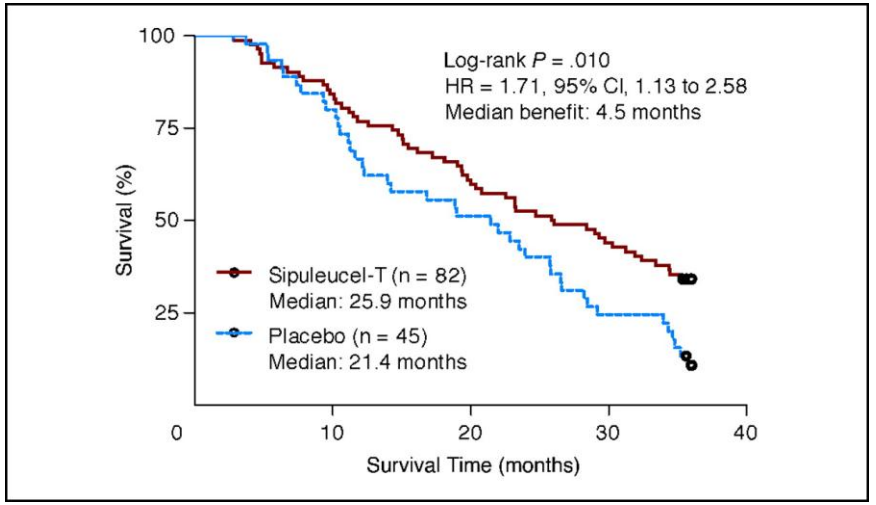
Sipuleucel-T*
in advanced prostate cancer

TTP



OS



* a dendritic cell vaccine from PBMCs stimulated *ex vivo* with recombinant PAP fused to GM-CSF

Small EJ *et al*, J Clin Oncol 2006

Ipilimumab plus PEG-IFN

Patient characteristics N=31	
Median age	61 years
Male	58%
Primary site Cutaneous Acral Unknown	 23 2 6

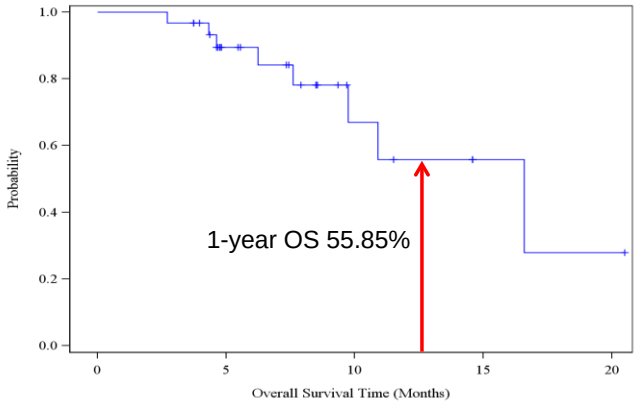
Clinical Activity	
Best ORR	47%
6-month PFS	56%
12-month OS	56%
Median OS	16.6 months

Kudchadkar R *et al*, ASCO 2014

Table 1. All drug related grade 3/4 toxicities

Toxicity	No. of patients (n)	
	Gr 3	Gr 4
Hypothyroidism	1	0
Nausea/Vomiting	4	0
Rash	4	0
Pruritis	3	0
Dehydration	1	0
Neutropenia	2	0
Panhypopituitarism	1	0
Colitis	1	0
Pneumonitis	0	1
Diarrhea	2	0
Hyponatremia	1	0

Figure 1. KM curve for OS



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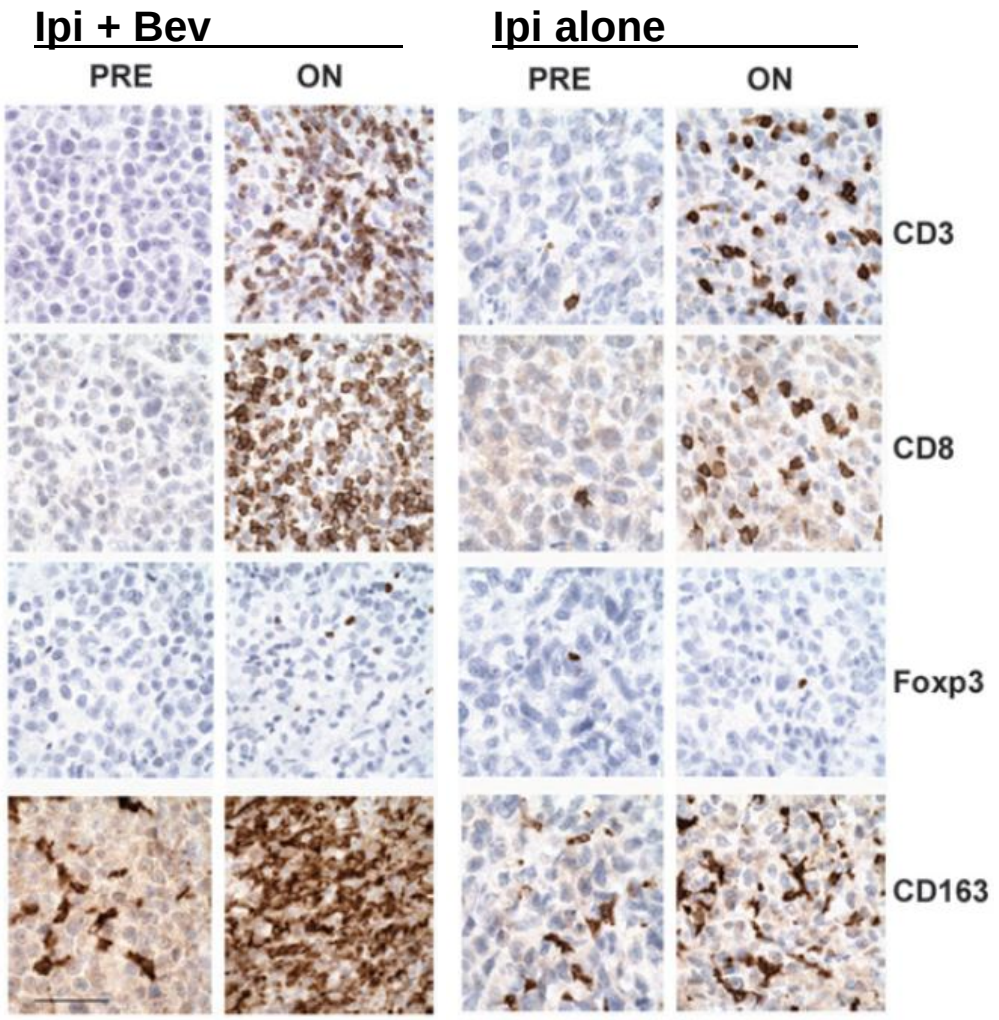
Ipilimumab plus Bevacizumab

Hodi FS *et al*, Cancer Immunol Res 2014

	Cohort (N)	Ipi	Bev
	1 (5)	10mg/kg	7.5mg/kg
MTD	2 (17)	10mg/kg	15mg/kg
	3 (12)	3mg/kg	7.5mg/kg
	4 (12)	3mg/kg	15mg/kg

Clinical Activity	
Week 12 ORR	10.9%
Best ORR	19.6%
6-month TTP	63%
Median TTP	9 months
12-month OS	79%
Median OS	25.1 months



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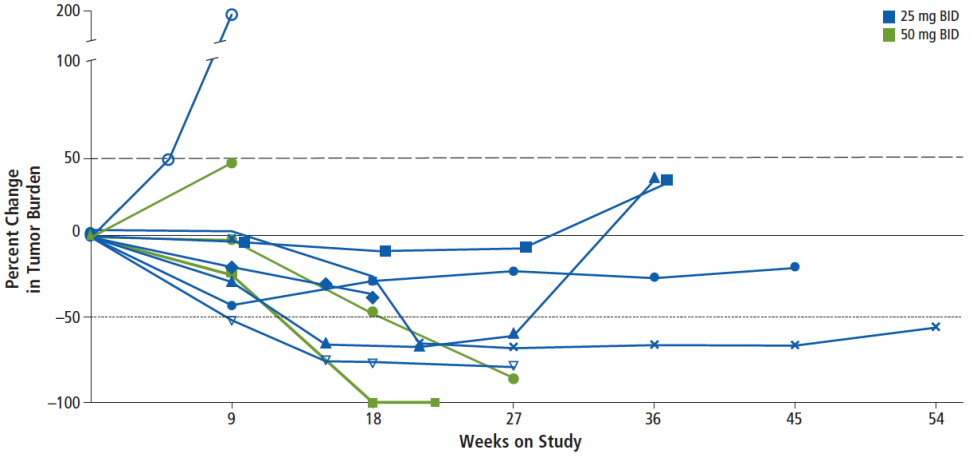
Ipilimumab plus IDO1 inhibition

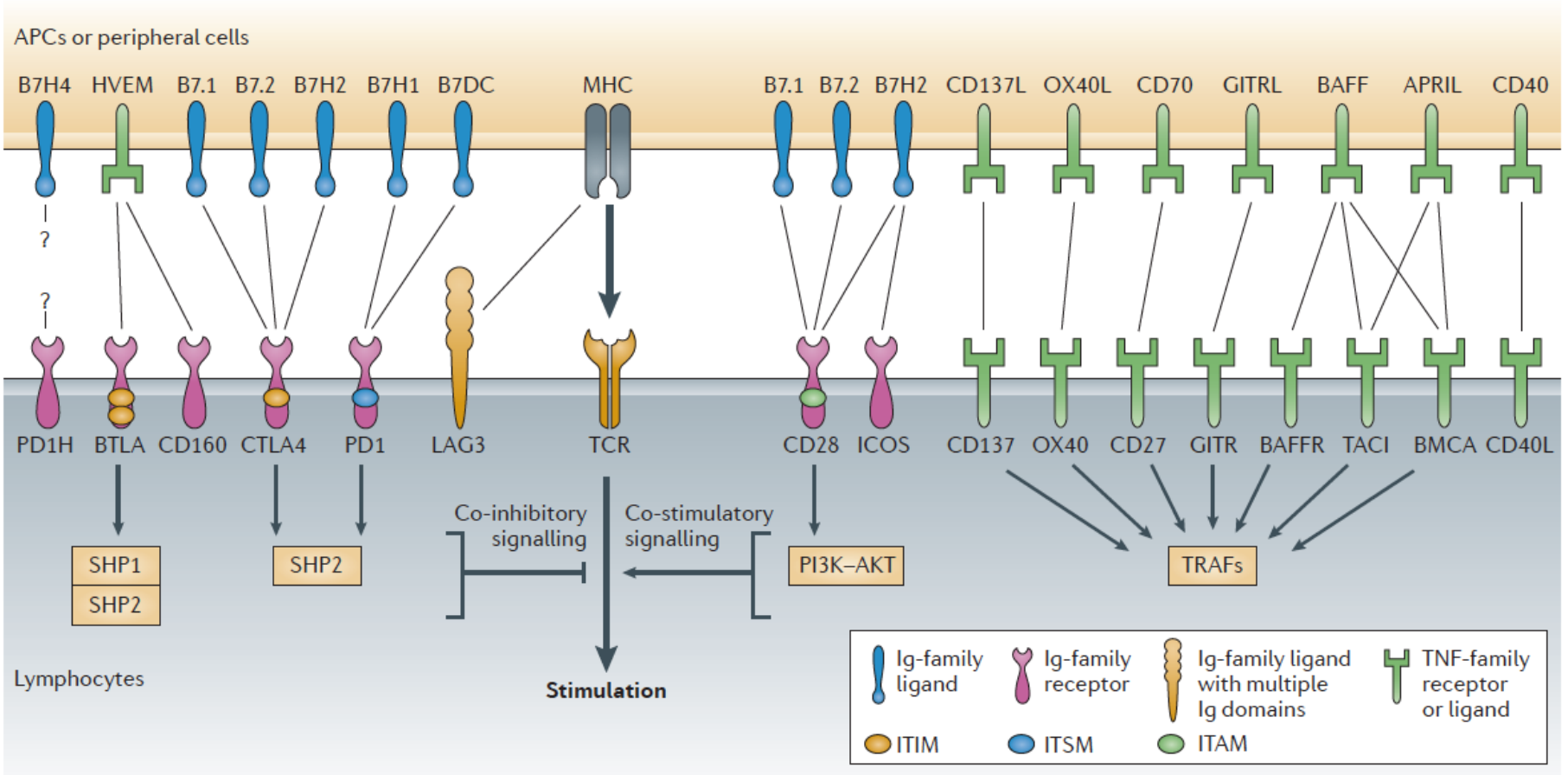
Cohort (N)	Ipi	INCB024360
1 (7)	3mg/kg	300mg BID
2 (8)	3mg/kg	25mg BID
3 (9)	3mg/kg	50mg BID

	Immunotherapy-Naive			Prior Immunotherapy
n (%)	25 mg BID (n=8)	50 mg BID (n=4)	Total (n=12)	50 mg BID (n=5)
ORR (CR + PR)	3 (37.5)	2 (50.0)	5 (41.7)	0
CR	0	1 (25.0)	1 (8.3)	0
PR	3 (37.5)	1 (25.0)	4 (33.3)	0
SD	3 (37.5)	1 (25.0)	4 (33.3)	2 (40.0)
PD	1 (12.5)	0	1 (8.3)	3 (60.0)
Not evaluable	1 (12.5)	1 (25.0)	2 (16.7)	0
Disease control*	6 (75.0)	3 (75.0)	9 (75.0)	2 (40.0)



Gibney GT *et al*, ASCO 2014

New Strategies



Yao S *et al*, Nat Rev Drug Disc 2013

Select ongoing combined immunotherapy trials in melanoma

Combined check-point inhibitors	Check-point inhibitor plus cytokine	Check-point inhibitor plus immune modulator
Ipilimumab plus Nivolumab 067 (NCT01844505)	Ipilimumab plus HD IL-2 (NCT01856023)	Ipilimumab plus Panobinostat (NCT02032810)
Sequential Nivolumab and Ipilimumab 064 (NCT01783938)	Ipilimumab plus HD IFN (NCT01708941)	Ipilimumab plus GR-MD-02 (NCT02117362)
Nivolumab plus anti-LAG-3 (NCT01968109)	Ipilimumab plus TVEC (NCT01740297)	Nivolumab plus lirilumab (NCT01714739)
Pembrolizumab plus Ipilimumab (NCT02089685)	Pembrolizumab plus PEG-IFN (NCT02089685)	Pembrolizumab plus INCB024360 (NCT02178722)

Lessons and Take Home Messages

- Combined immunotherapy strategies can potentially increase anti-tumor activity and survival in metastatic melanoma patients
- Increased immune-related adverse events generally occur when immunotherapies are combined.
- Ongoing randomized trials will define whether combination immunotherapies become the next standard in metastatic melanoma.
- Potential for biomarker-driven, patient-tailored immunotherapies.