Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Melanoma

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Advances in Cancer Immunotherapy™ - Washington, DC
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Disclosures

- Steering Committee: *Genentech/Roche*
- Consultation: *Genentech/Roche, Novartis, and Bristol-Myers Squibb*

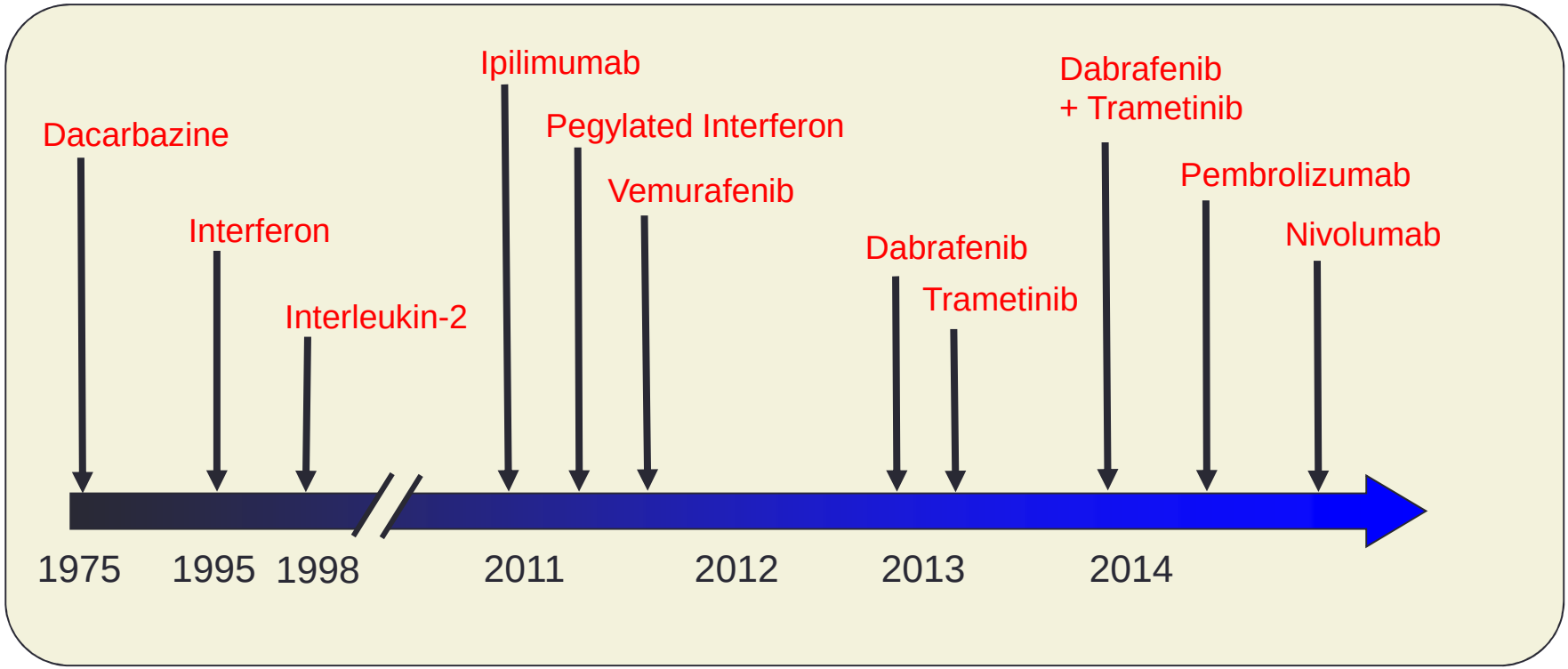
Objectives

Objective 1: To develop a better understanding of the evolution of immunotherapies from cytokines to checkpoint blockade.

Objective 2: To learn about the clinical benefit of targeted checkpoint immunotherapies in melanoma

Objective 3: To learn about the future directions of immunotherapy combination strategies in melanoma.

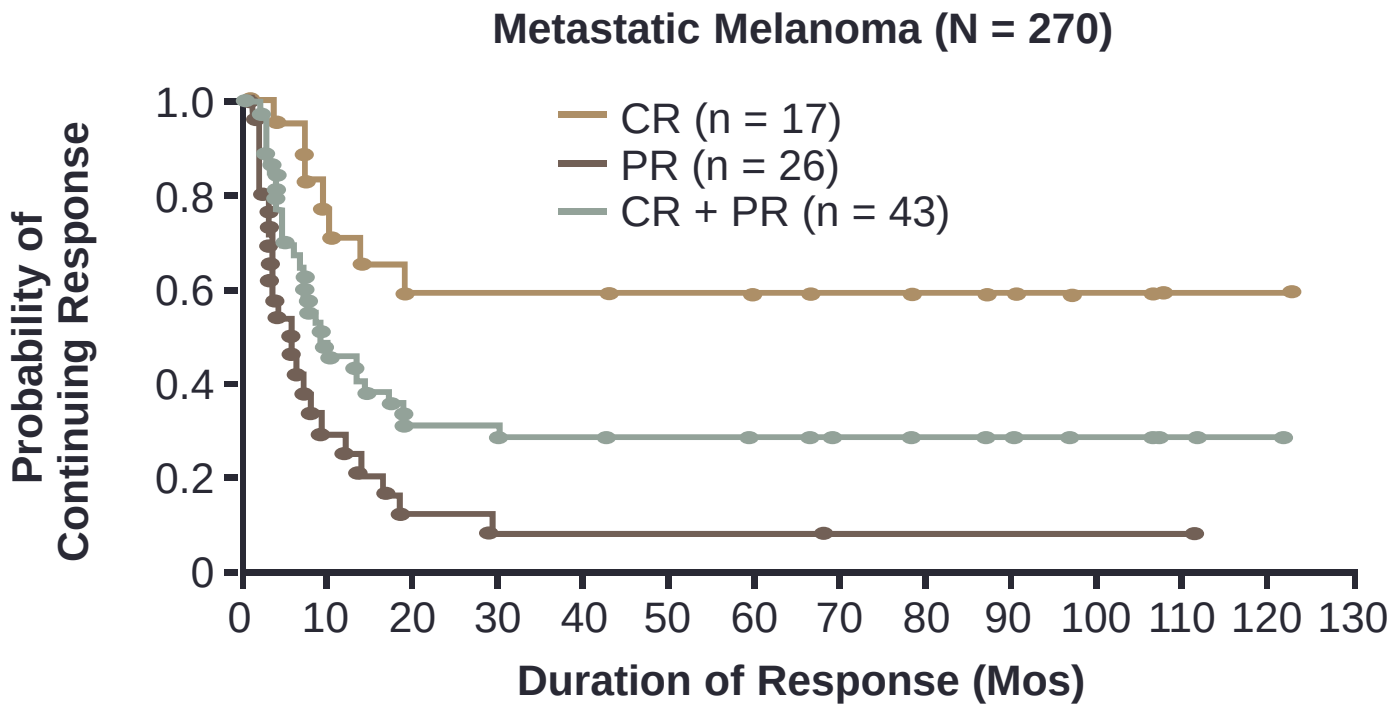
Approved therapies in Melanoma in 2015



Gibney GT and Atkins MB, Clin Adv Hematol Oncol, 2015

High-Dose IL-2 Therapy: Durable Responses Seen

- High-dose IL-2 produces durable responses in 16-17% of pts with advanced melanoma
- Few relapses in pts responding for over 2.5 yrs (likely cured)



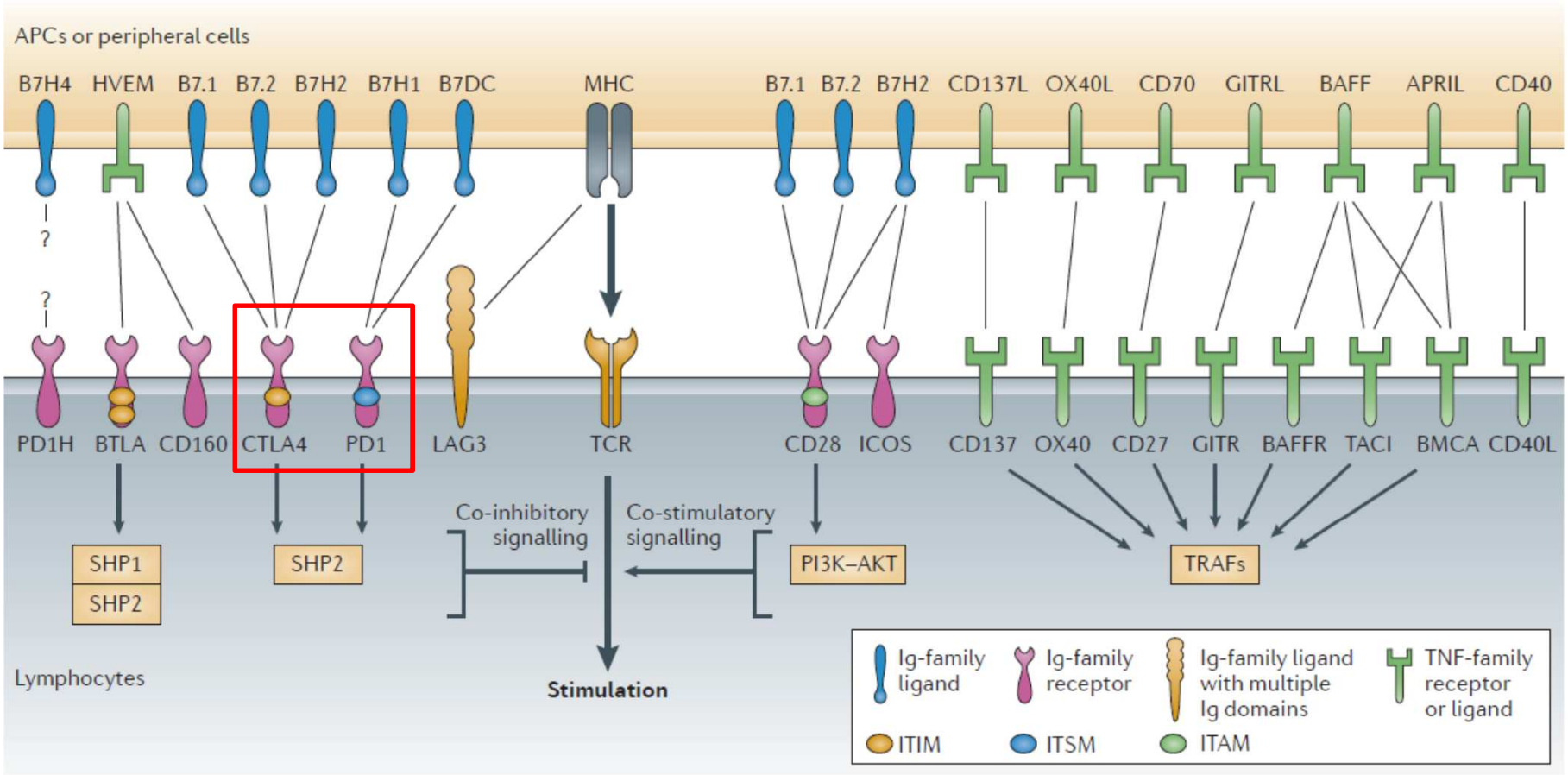
Atkins MB, et al, J Clin Oncol, 1999
Rosenberg SA, et al, JAMA, 1994

High-Dose IL-2 Therapy in Melanoma and RCC

- High-dose IL-2 benefits patients, but:
  - Toxic
  - Complex; must be delivered as an inpatient regimen
- Use remains limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy have produced modest advances
- **Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer strategies are needed**

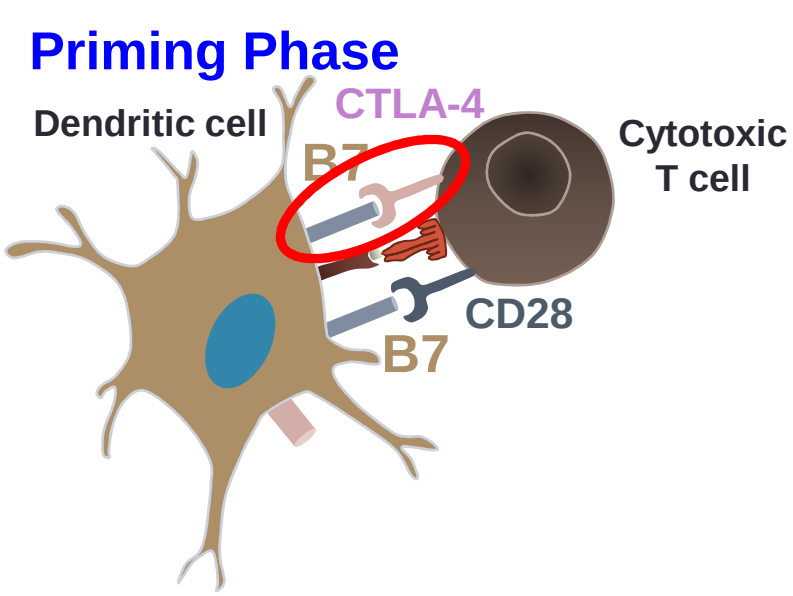
Immune Checkpoints

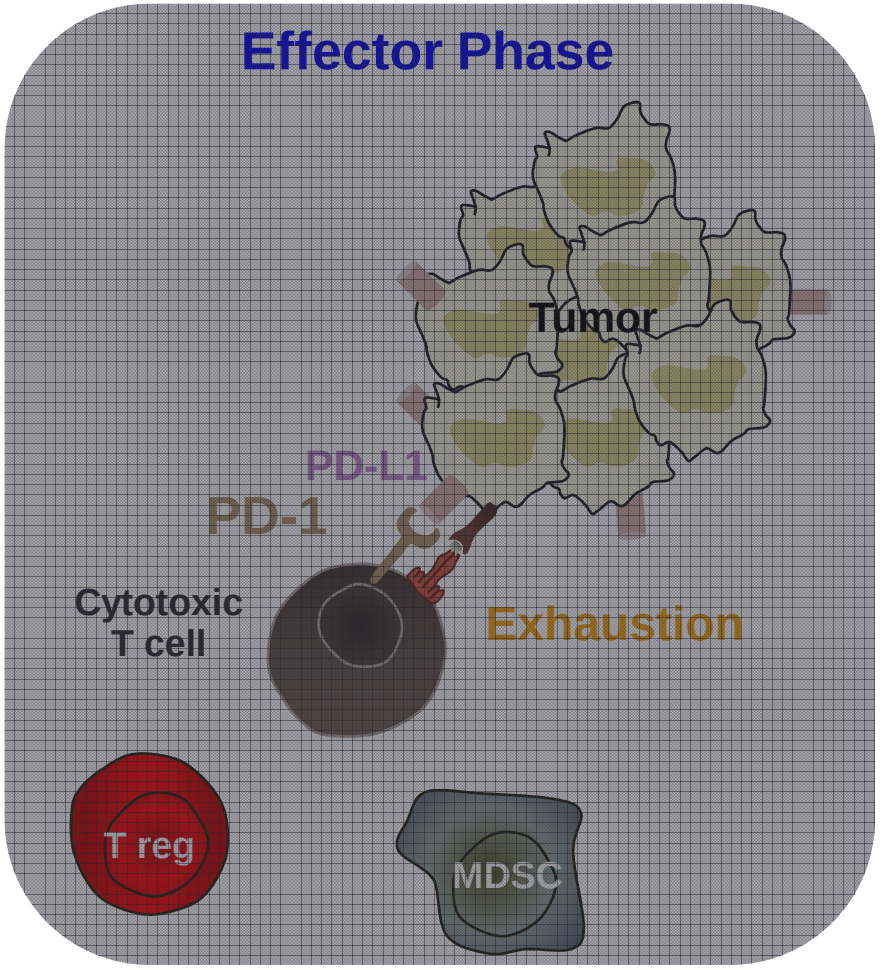
Accelerator versus Brake



Yao S, et al, Nat Rev Drug Discov, 2013

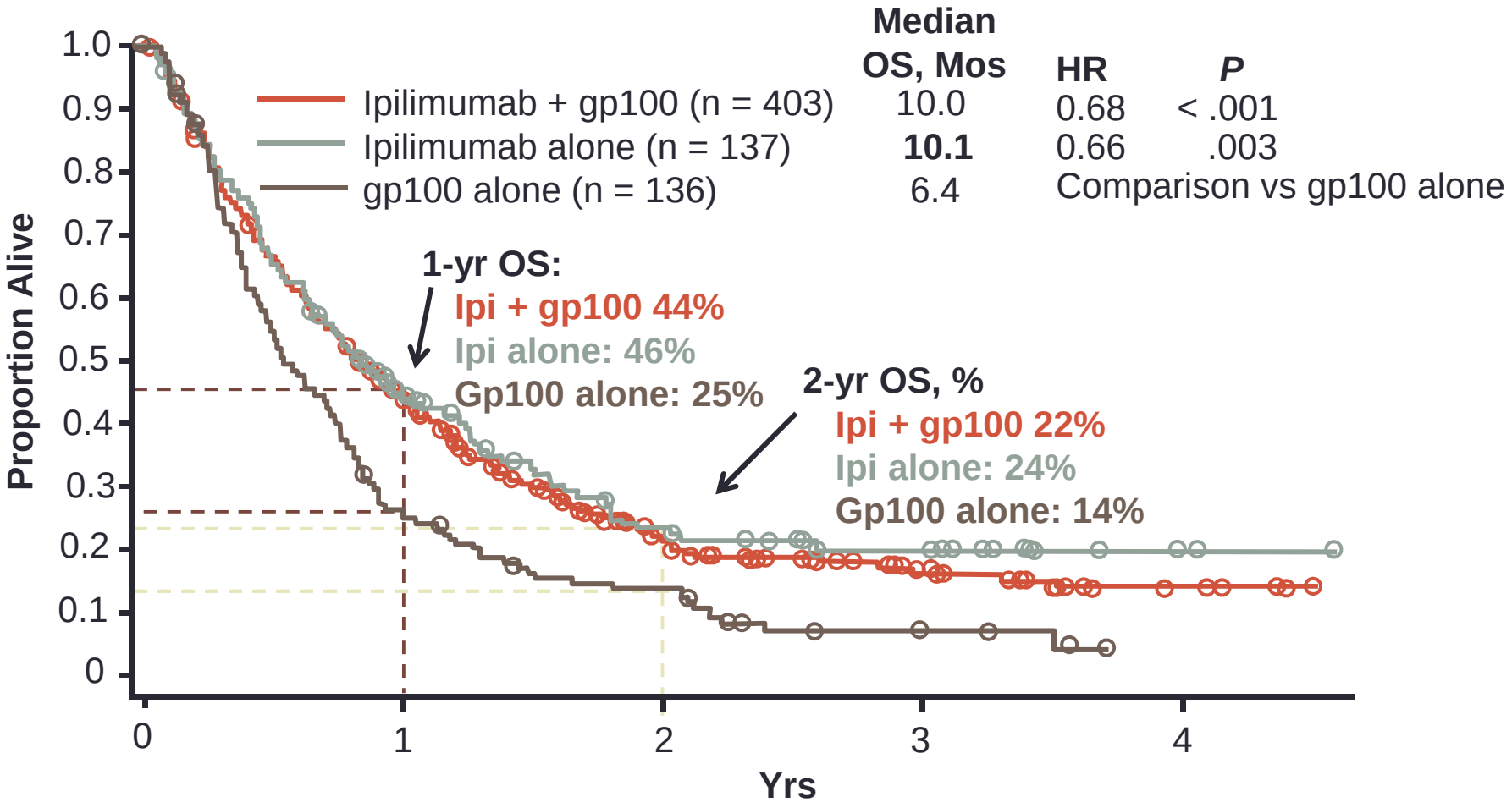
Dampening the Immune System in Cancer





Ribas A, et al, N Engl J Med, 2012.
Spranger S, et al, J Immunother Cancer, 2013.

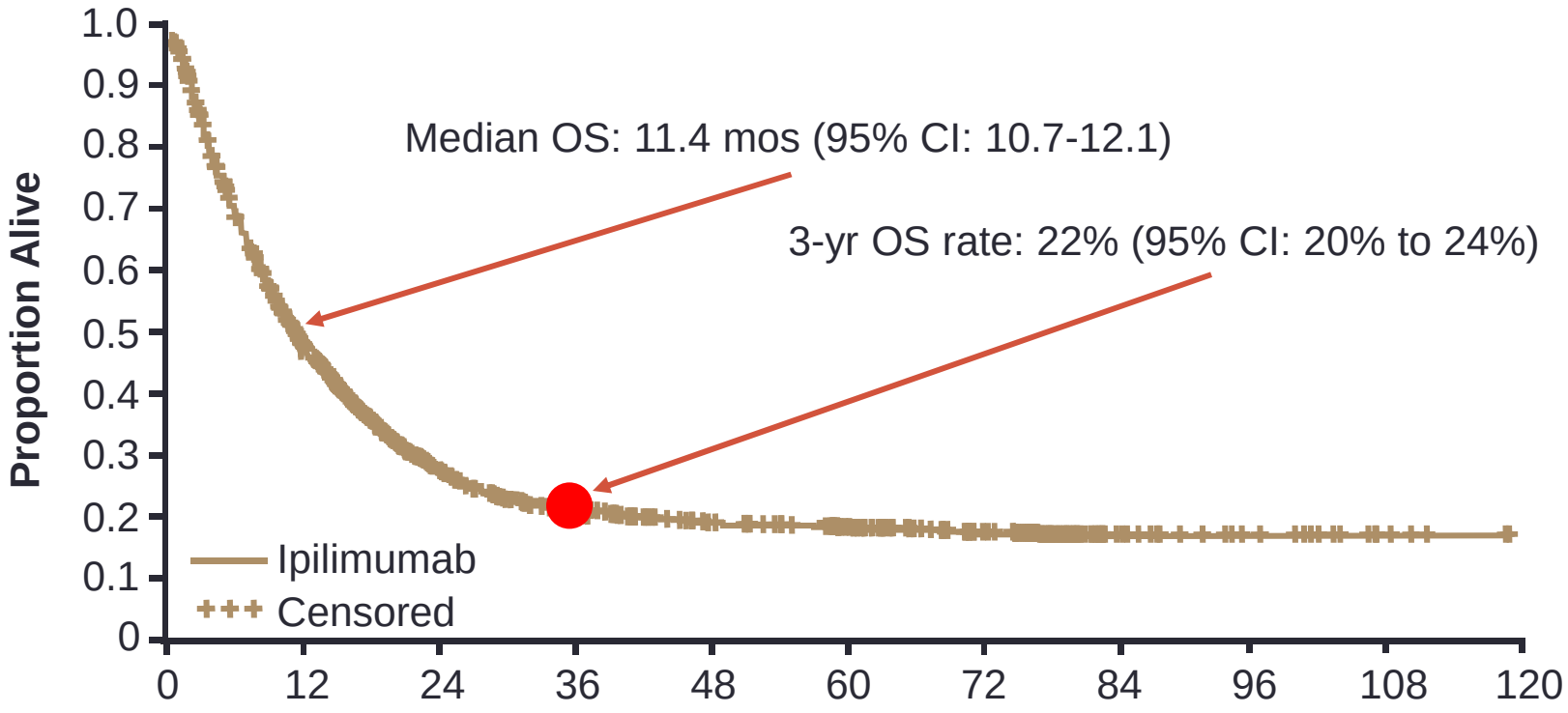
Ipilimumab, gp100, or Both: OS in Advanced Melanoma



Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Hodi FS, et al, N Engl J Med, 2010

Pooled data from 12 studies of Ipilimumab Show OS Plateau at 3 Years



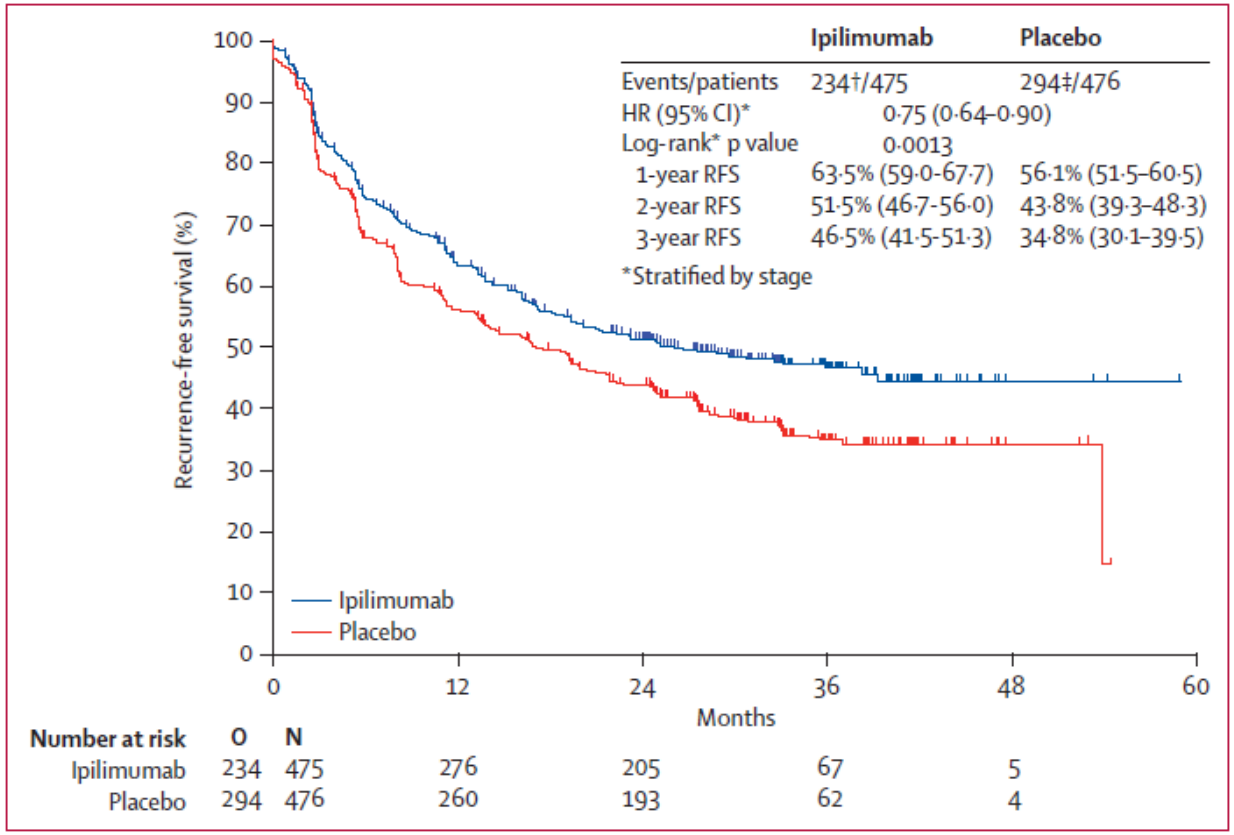
Pts at Risk, n

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Hodi FS, et al, 2013 European Cancer Congress, Abstract LBA 24
Schadendorf D, et al, J Clin Oncol, 2015

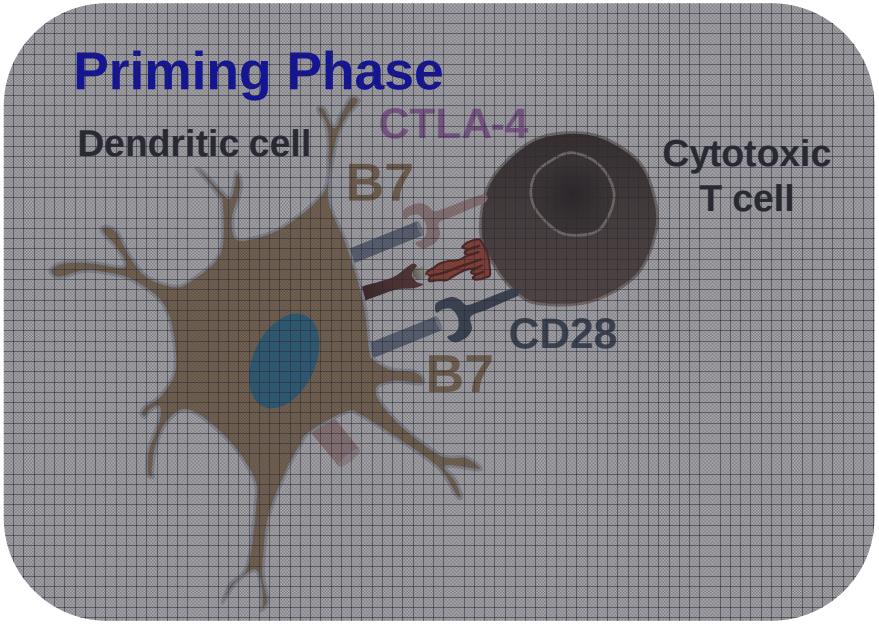
Adjuvant Ipilimumab for resected stage III melanoma

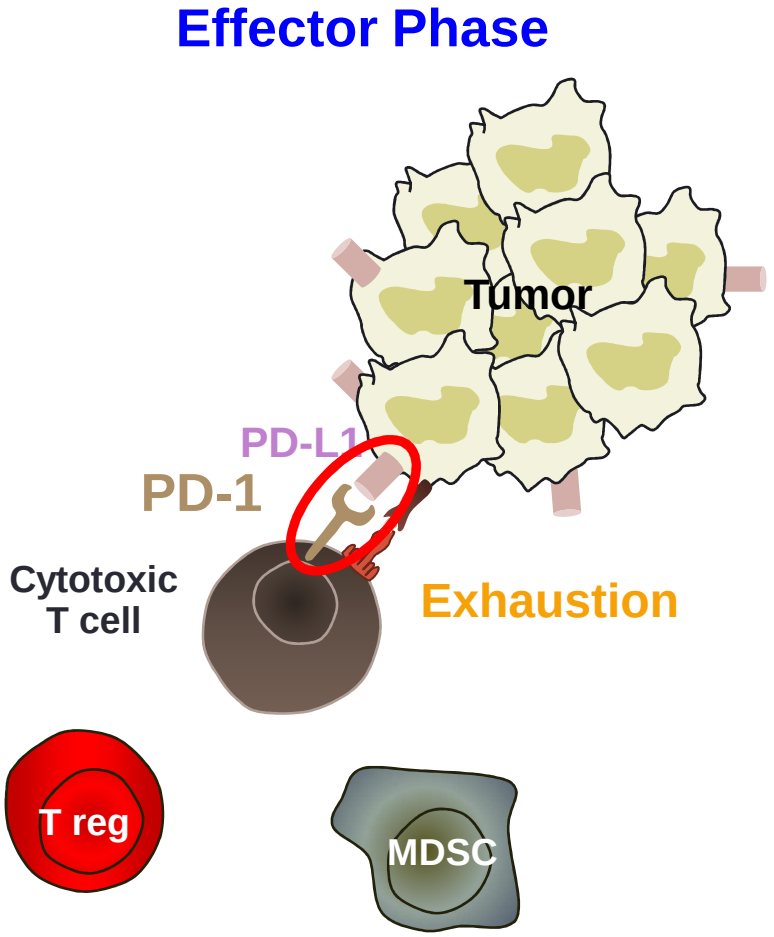
- EORTC 18071: Ipilimumab 10mg/kg vs placebo, 951 pts
- mRFS was 26.1 months vs 17.1 months



Eggermont AMM, et al, Lancet Oncol, 2015

Dampening the Immune System in Cancer





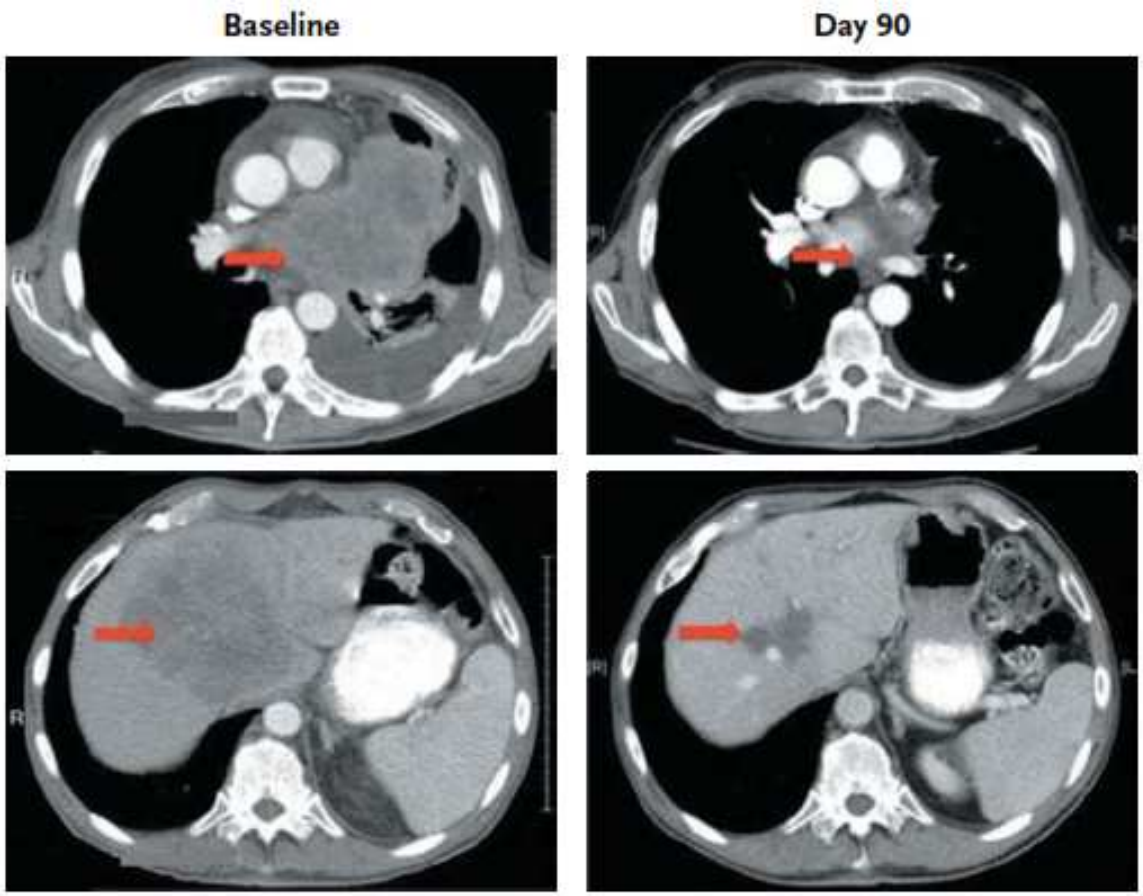
Ribas A, et al, N Engl J Med, 2012.
Spranger S, et al, J Immunother Cancer, 2013.

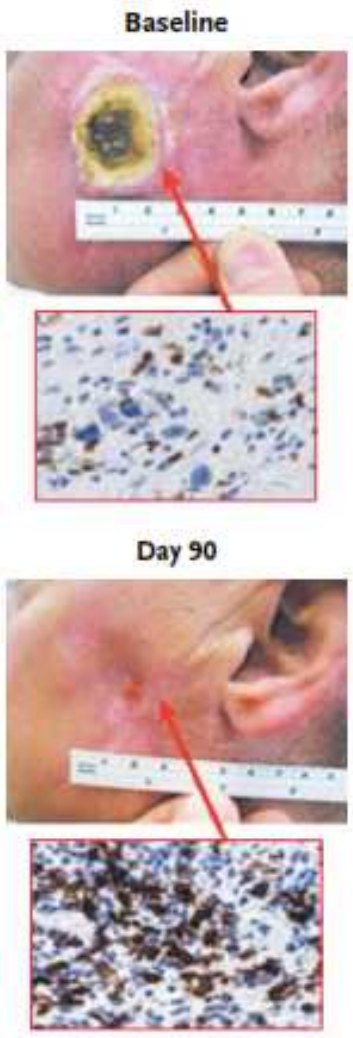
Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Development stage
PD-1	Nivolumab* (BMS-936558)	Fully human IgG4	Phase III multiple tumors melanoma, RCC, NSCLC, HNSCC
	Pembrolizumab* (MK-3475)	Humanized IgG4	Phase I-II multiple tumors Phase III NSCLC/melanoma
	Pidilizumab (CT-011)	Humanized IgG1	Phase II multiple tumors
PD-L1	MEDI-4736*	Engineered human IgG1	Phase I-II multiple tumors Phase III NSCLC
	MPDL-3280A*	Engineered human IgG1	Phase I-II multiple tumors Phase III NSCLC
	Avelumab (MSB0010718C)	Fully human IgG1	Phase I-II solid tumors

Responses with anti-PD1 therapy

(example pembrolizumab in metastatic melanoma patient)

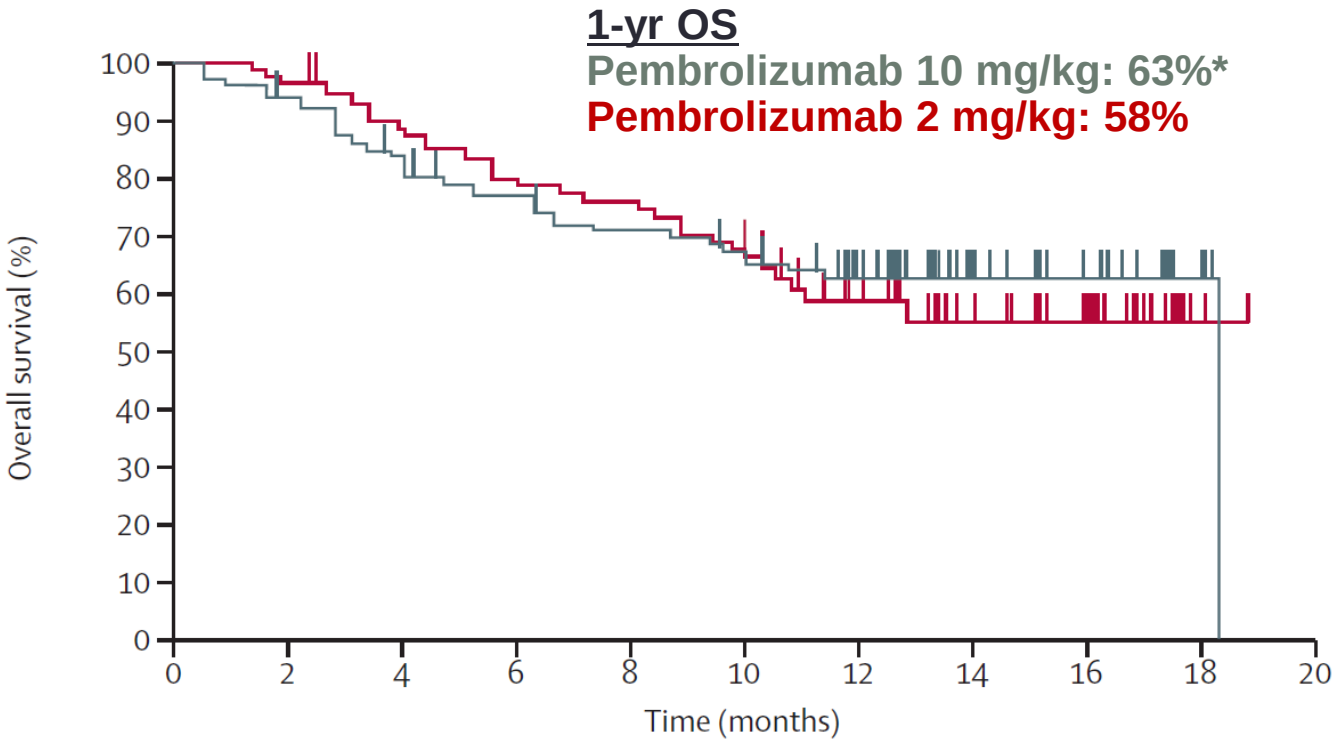




Hamid O, et al, N Engl J Med, 2013

Phase I Trial of Pembrolizumab (Keynote 001)

- Included 173 pts with advanced melanoma with progression after ipilimumab
- ORR 26%
  (68%* & 73% with tumor reduction)
- mPFS 14 wks* & 22 wks



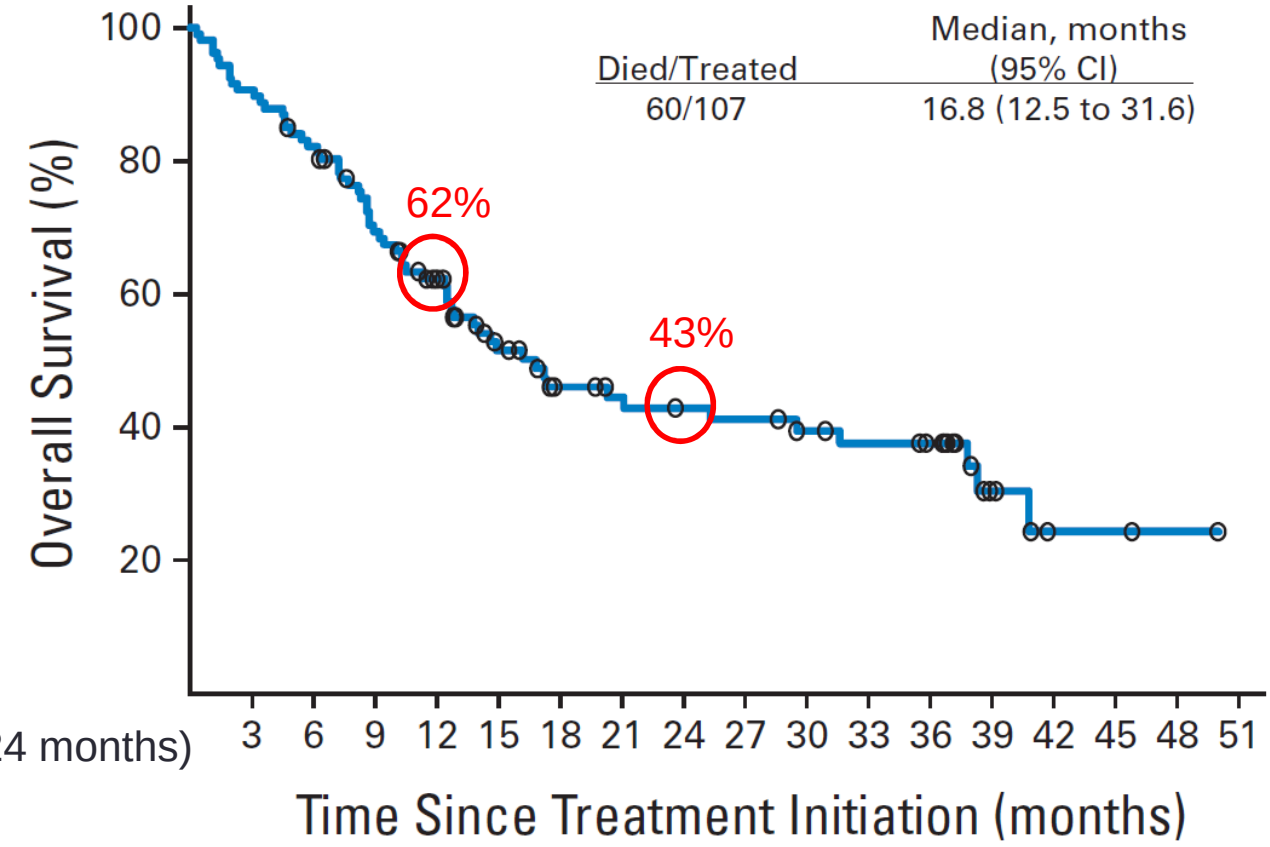
**Pembro 10mg/kg*

Robert C, et al, Lancet 2014

Phase I Trial: Nivolumab Leads to High Rate of Long-term OS

- Included 107 pts with advanced melanoma (majority with 2-6 prior treatments)
- median follow-up 22 months
- ORR 31%
- mPFS 3.7 months

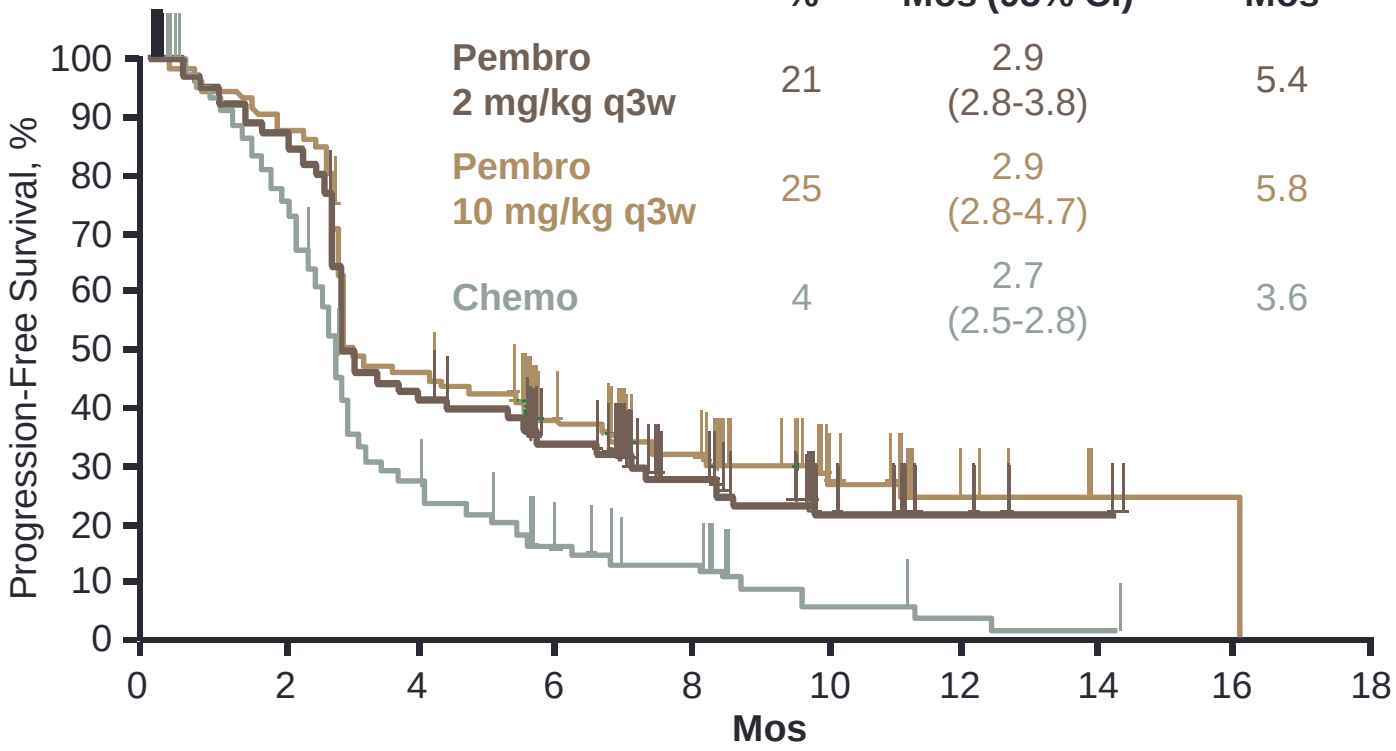
(mPFS of responders = 24 months)



Topalian SL, et al, J Clin Oncol 2014

KEYNOTE-002: Pembrolizumab vs Chemotherapy in Ipi-Refractory Melanoma

- An international, randomized phase II study in pts with advanced melanoma with PD within 24 wks after ≥ 2 Ipi doses



Arm	ORR, %	Median PFS, Mos (95% CI)	Mean PFS, Mos	PFS HR (95% CI)	PFS *P* value
Pembro 2 mg/kg q3w	21	2.9 (2.8-3.8)	5.4	0.57 (0.45-0.73)	< .0001
Pembro 10 mg/kg q3w	25	2.9 (2.8-4.7)	5.8	0.50 (0.39-0.64)	< .0001
Chemo	4	2.7 (2.5-2.8)	3.6		

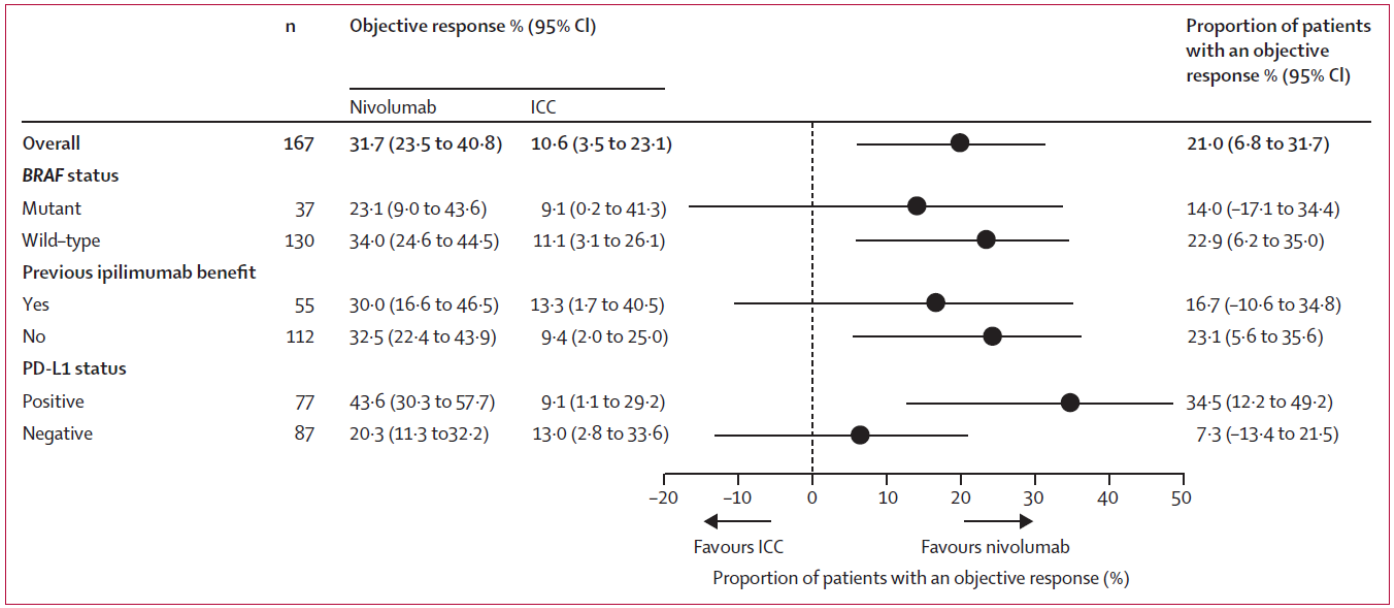
Pembro vs Chemo

Ribas A, SMR 2014: November 16, 2014

Checkmate-037: Phase III Trial of Nivolumab vs Chemotherapy in IPI-Refractory Melanoma Patients

Treatment	N	CR + PR, n	ORR,* % (95% CI)
Nivolumab	120	38 (4 CR)	32 (24-41)
Chemotherapy	47	5 (0 CR)	11 (4-23)

*Confirmed response.
†Independent radiology review committee based on RECIST 1.1.



Weber JS, et al, Lancet Oncol, 2015

Does PD-L1 Expression predict for response with anti-PD-1/PD-L1 therapy?

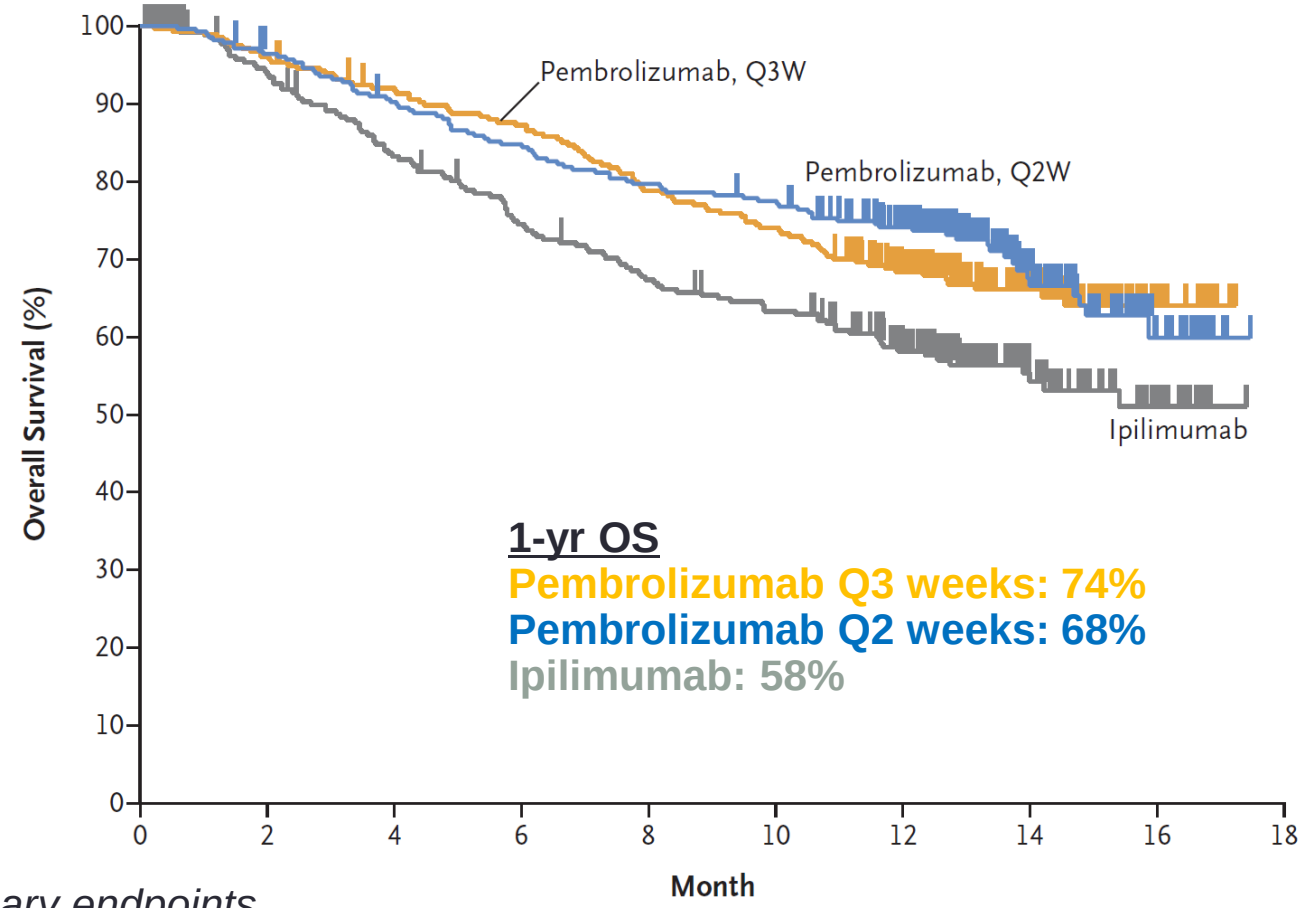
Objective Response rates	Solid tumors Topalian NEJM 2012	Melanoma Weber JCO 2013	Melanoma Grosso ASCO 2013	Melanoma Daud AACR 2014	NSCLC Gandh AACR 2014	Head+Neck Selwert ASCO 2014 *	Melanoma Ribas ASCO 2014	Solid tumors Herbst ASCO 2013	Melanoma Hamid ASCO 2013	NSCLC Soria ECC 2013	Bladder Powles ASCO 2014
n=	42	44	34	113	129	55	411	94	30	53	65
unselected	**21%**	**32%**	**29%**	**40%**	**19%**	**18%**	**40%**	**21%**	**29%**	**23%**	**26%**
PD-L1 +	**36%**	**67%**	**44%**	**49%**	**37%**	**46%**	**49%**	**36%**	**27%**	**46%**	**43%**
PD-L1 -	**0%**	**19%**	**17%**	**13%**	**11%**	**11%**	**13**	**13%**	**20%**	**15%**	**11%**
Treatment:	anti-PD-1 Antibody							anti-PD-L1 Antibody			
Assay:	Membranous pattern on tumor cells							Immune infiltrate			

Mahoney and Atkins, Oncology, 2014

Does anti-PD-1 therapy provide more clinical benefit than ipilimumab? YES.

Phase 3 study of Pembro 10mg/kg Q2wks or Q3wks versus Ipi 3mg/kg

- ORR 33% and 34%* vs 12%
- PFS HR 0.58
- OS HR 0.63* - 0.69



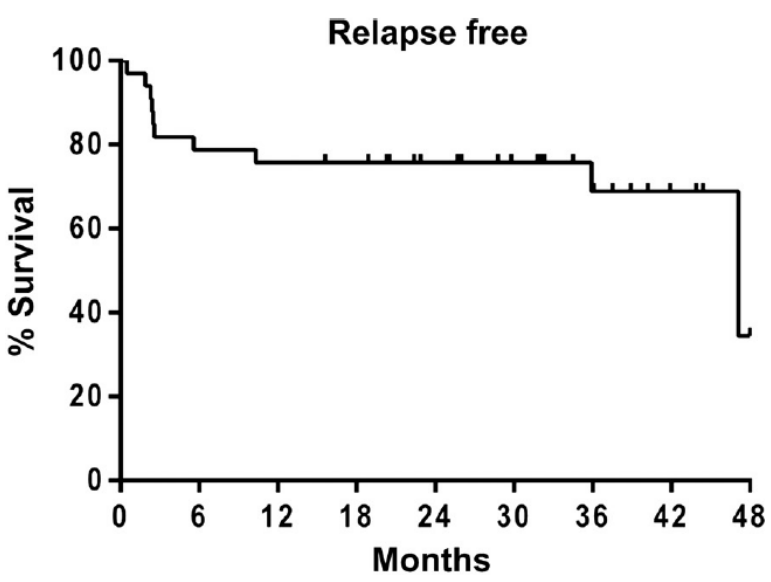
**Pembro Q2W*

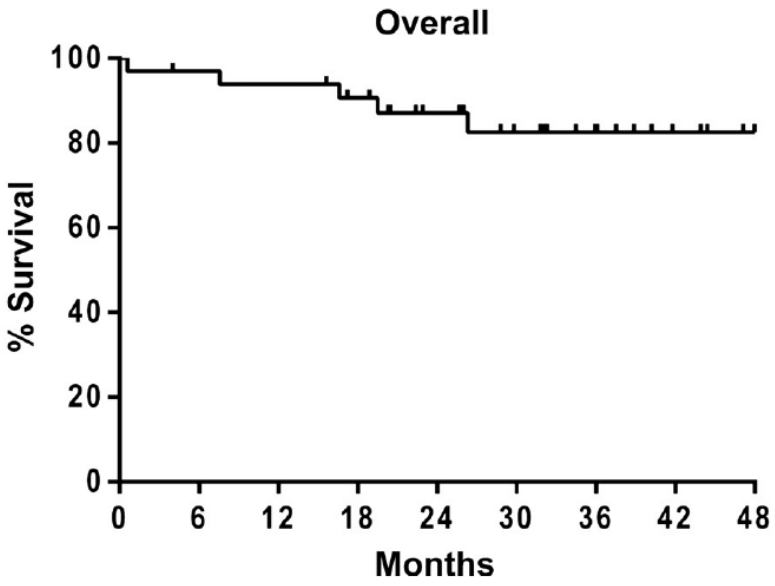
PFS and OS were co-primary endpoints

Robert C, et al, N Engl J Med 2015

Can anti-PD-1 therapy be used as an adjuvant therapy? Probably.

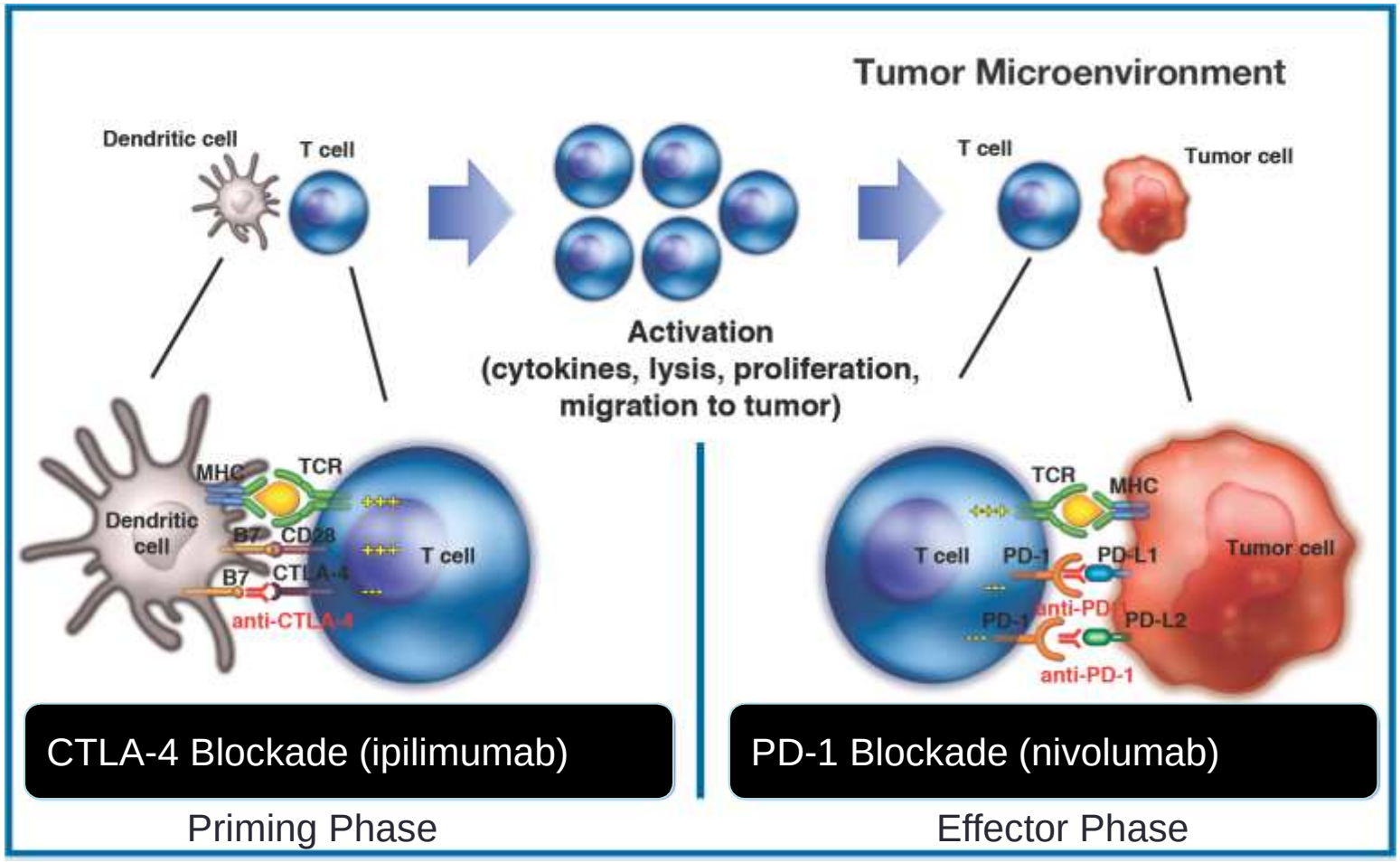
- Phase I study of nivolumab + vaccine: 33 patients (stage IIIC or IV)
- 48% received prior systemic therapy
- 30% relapsed at median F/U 32 months
- mRFS 47.1 months, 2 year OS 82%





Gibney GT, et al, Clin Cancer Res, 2014

Potential Synergism of Checkpoint Inhibitors



Adapted from Kluger H, SMR 2014

Phase I Nivolumab plus Ipilimumab

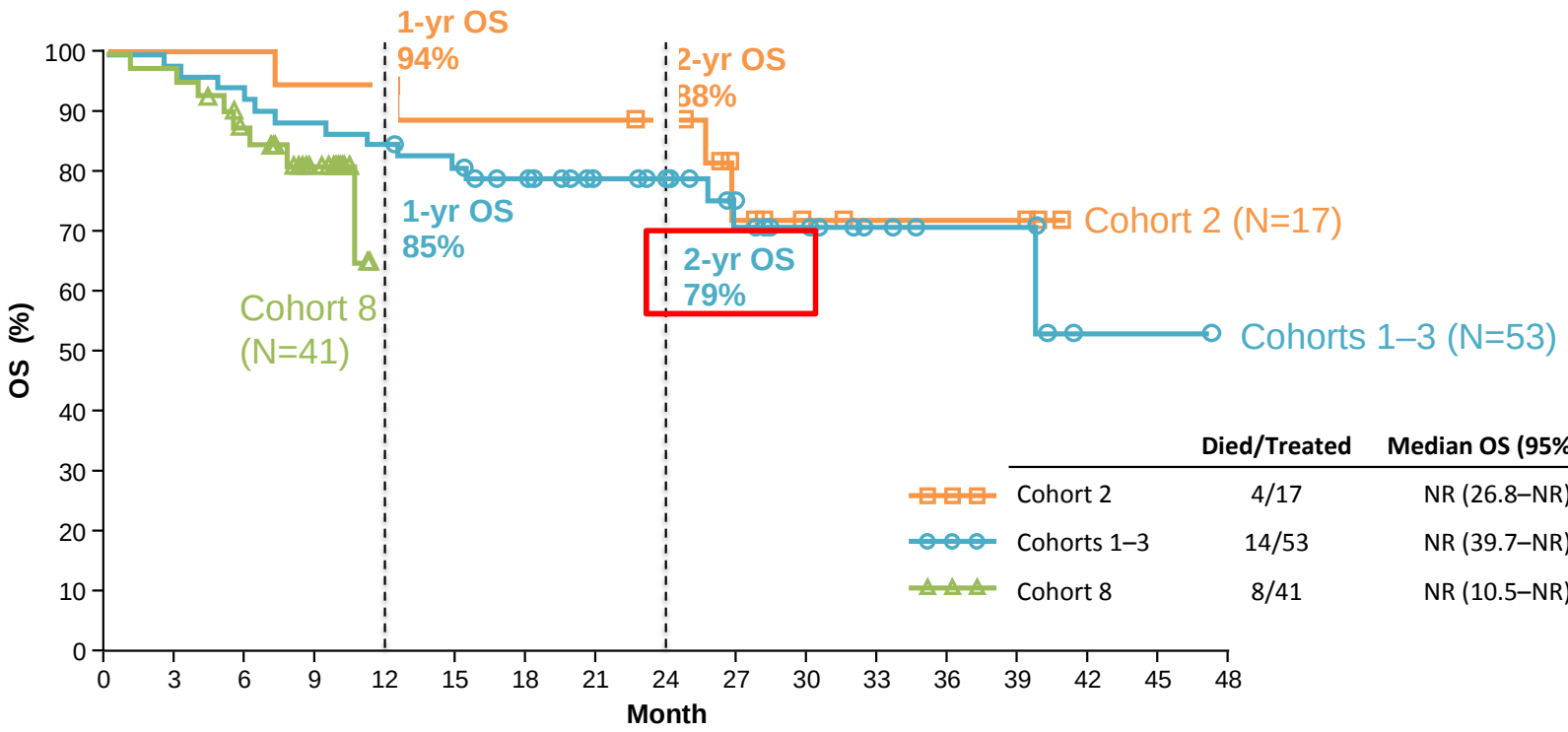
Cohort(s)	Nivo (mg/kg) + Ipi (mg/kg)	N[b]	ORR,[a] %	CR, %	Aggregate Clinical Activity Rate, %	≥80% Tumor Burden Reduction at 36 Weeks,[c] %
1–3		**53**	**42**	**17**	**72**	**42**
1	0.3 + 3	14	21	14	57	36
2	1 + 3	17	47	18	65	53
2a	3 + 1	16	50	25	88	31
3	3 + 3	6	50	0	83	50
8[d]	**1 + 3**	**41**	**44**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

Kluger H, et al, 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

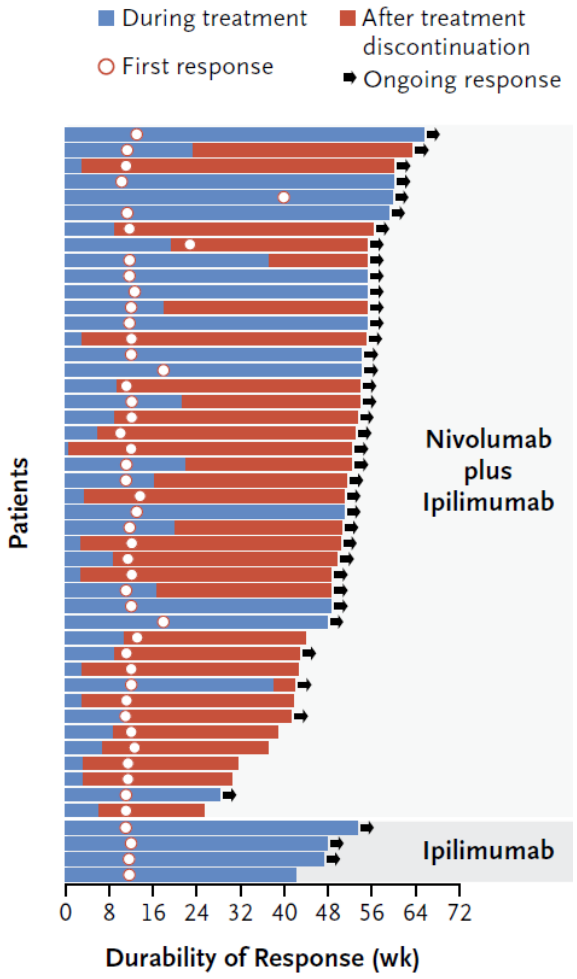
- **Cohort 8 uses the same dosing schedule that is being tested in the phase 3 trial (CA209-067)**

JUNE 2014 data analysis.

Kluger H, et al, SMR, 2014

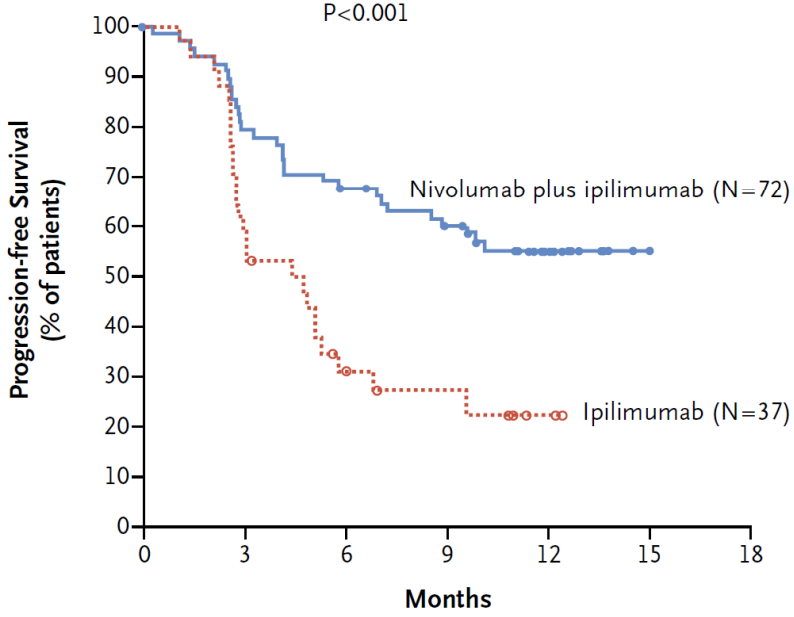
Checkmate-069: Phase II Nivo-Ipi vs Ipi alone

- 142 pts with advanced melanoma blinded treatment randomized 2:1
- Primary endpoint ORR for BRAF WT patients: 61% Nivo-Ipi vs 11% Ipi



	Death or Disease Progression	Median Progression-free Survival
	no. of patients/total no.	*mo (95% CI)*
Nivolumab plus Ipilimumab	30/72	NR
Ipilimumab	25/37	4.4 (2.8–5.7)

Hazard ratio, 0.40 (95% CI, 0.23–0.68)
P<0.001



Postow MA, et al, N Engl J Med, 2015

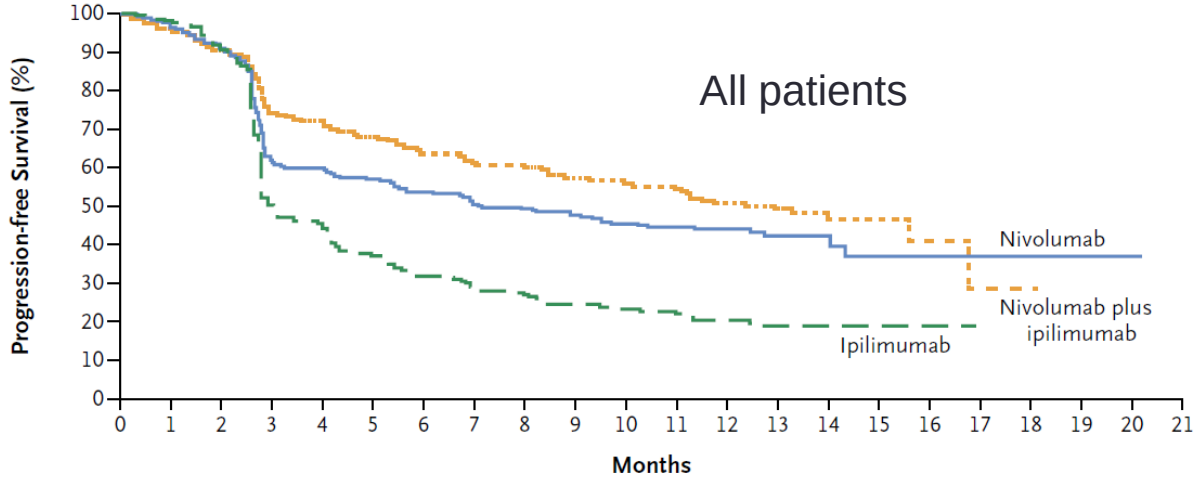
Phase III Nivo-Ipi vs Nivo alone vs Ipi alone (Checkmate-067)

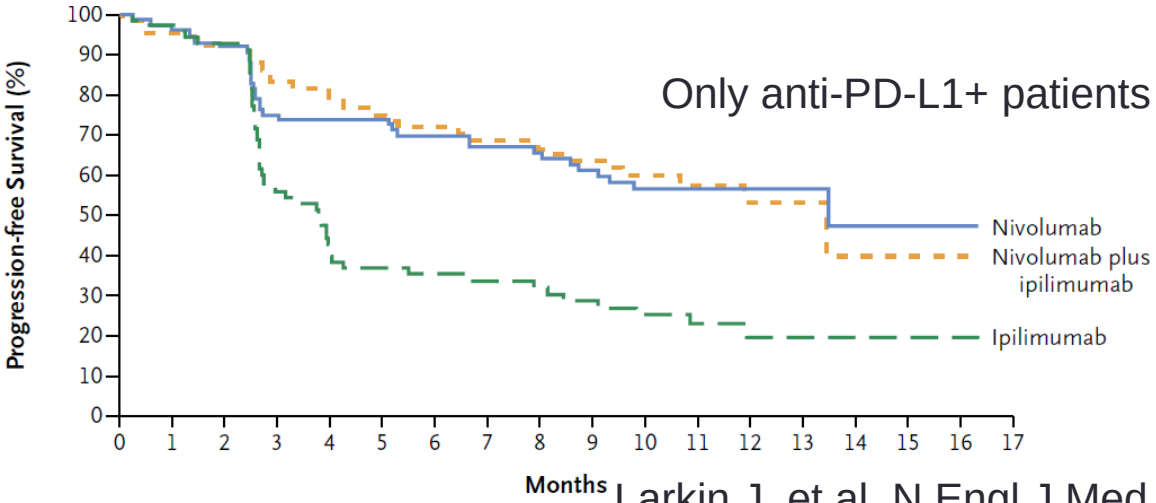
- Randomized 945 previously untreated pts with unresectable stage III/IV melanoma to nivolumab alone, nivolumab plus ipilimumab, or ipilimumab alone.

Overall	ORR	mPFS
Nivo-Ipi	58%	11.5 m
Nivo	44%	6.9 m
Ipi	19%	2.9 m

PD-L1+	ORR	mPFS
Nivo-Ipi	72%	14 m
Nivo	58%	14 m
Ipi	21%	3.9 m

PFS and OS are co-primary endpoints





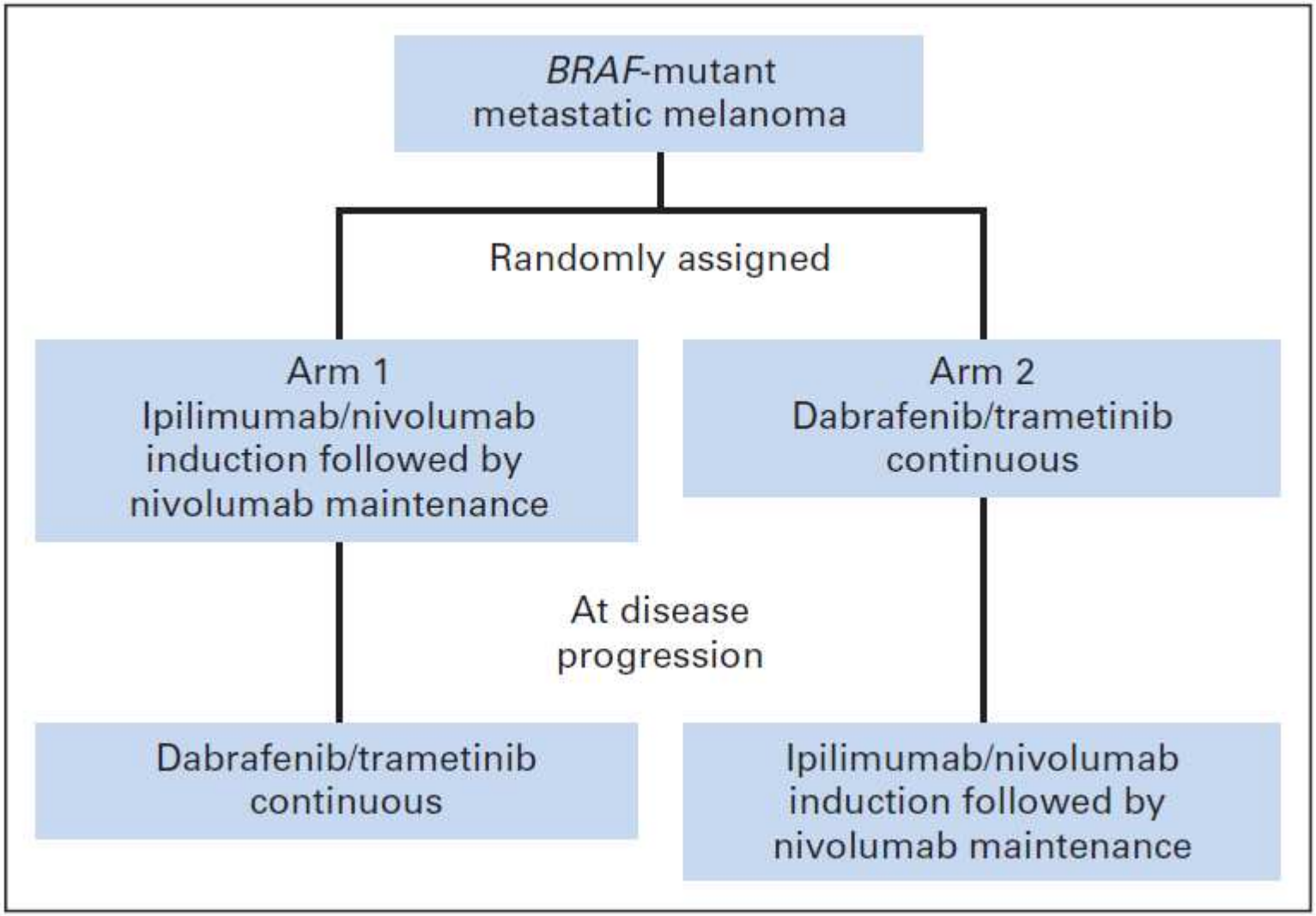
Larkin J, et al, N Engl J Med, 2015

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Larkin J, et al, N Engl J Med, 2015

EA-6134 Protocol



Gibney GT and Atkins MB, J Clin Oncol, 2015

Other promising immunotherapy combinations in melanoma (presented or published)

Ipilimumab plus bevacizumab

Hodi FS, Cancer Immunol Res, 2014

Ipilimumab plus GM-CSF (sargramostim)

Hodi FS, JAMA, 2014

Ipilimumab plus peg-interferon alpha-2b

Kudchadkar R, ASCO Annual Meeting 2014

Ipilimumab plus IDO inhibitor (INCB024360)

Gibney GT, ASCO Annual Meeting 2014

Take home points

- Checkpoint immunotherapies are producing durable clinical responses in a high percentage of patients
- Fewer, but new, toxicities with checkpoint inhibitors compared to IL-2
- Biomarker discovery is evolving and will hopefully allow for better precision medicine.
- Immunotherapy combinations are emerging as the next standard.