Immunotherapy Combinations

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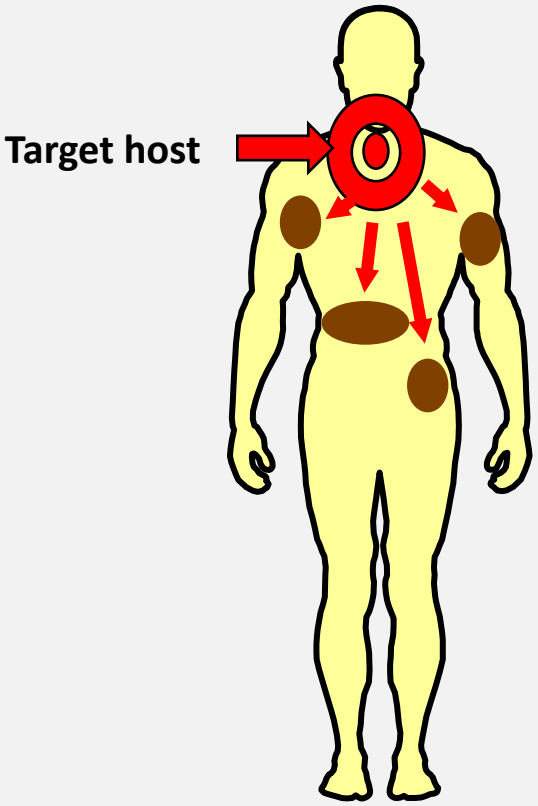
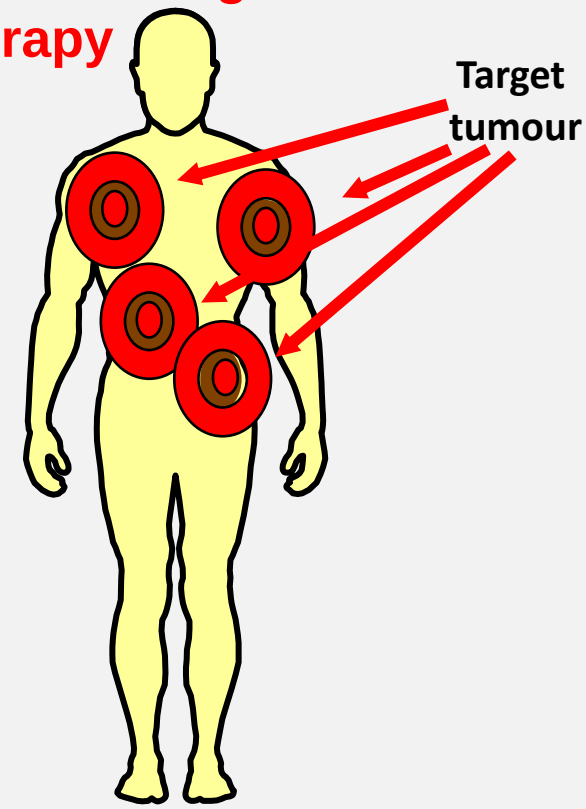
New Treatment Paradigms

Immunotherapy



- Vaccines
- Checkpoint inhibitors
- Cytokines

Conventional Drug Therapy



- Chemotherapy
- ‘inib’

Combination Therapy

- Different mechanisms of action
- Additive or synergistic effects
- Change toxicity profile
- Antigen release to prime the immune system

CTLA-4 Combination Studies

Chemotherapy

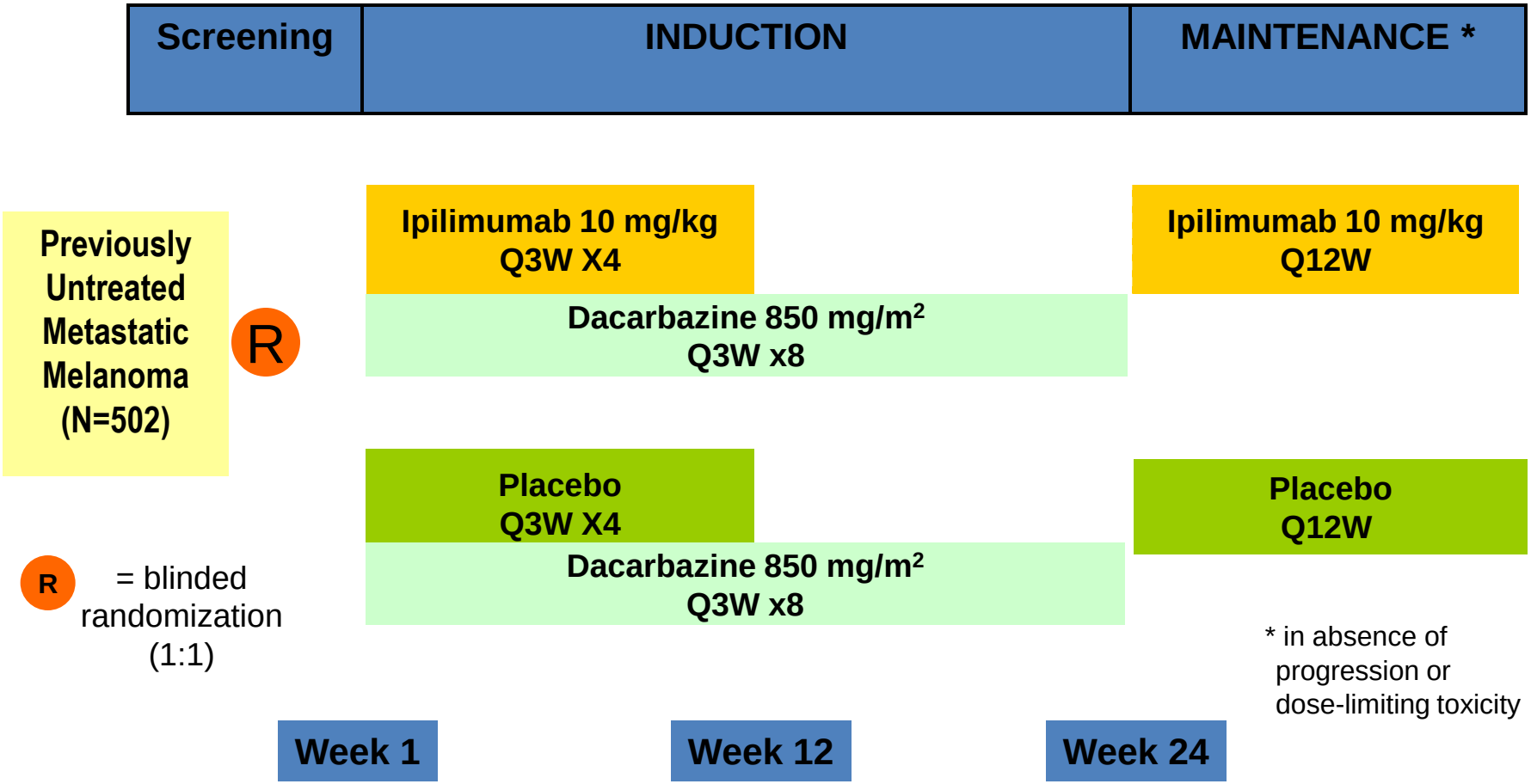
- Ipilimumab + DTIC
- Ipilimumab + fotemustine
- Ipilimumab + temozolomide

Biological agents

- Ipilimumab + bevacizumab
- Tremelimumab + High Dose Interferon
- Ipilimumab + GMCSF

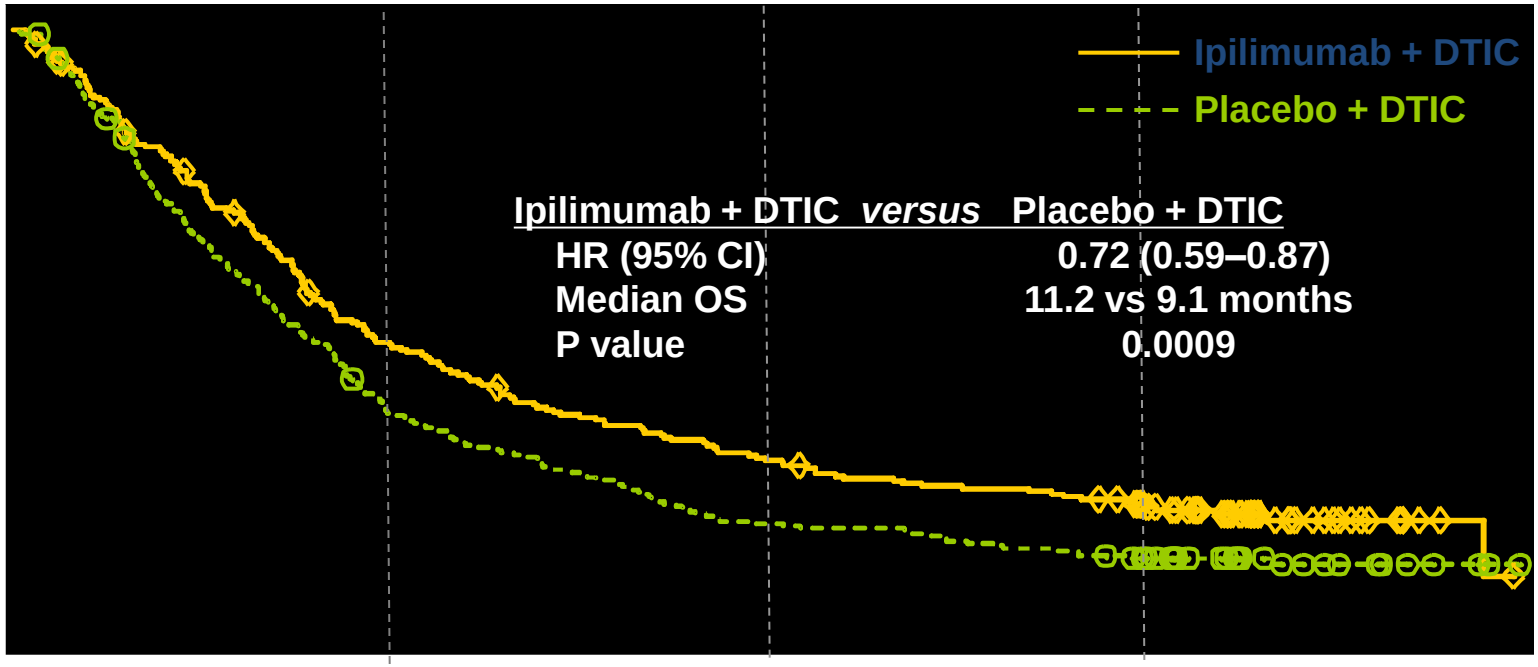
- Radiotherapy

Study 024: Design



Robert NEJM 2011

Study 024: Overall Survival



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

**3-yr survival was a post-hoc analysis*

Robert NEJM 2011

Ipilimumab: selected AEs (%)

		Ipi + DTIC[1] n=247		DTIC + placebo[1]		Ipi + gp100[2] n=380		Ipi + placebo[2] n=131		gp100[2] n=132	
		Any	Grade 3/4	Any	Grade 3/4	Any	Grade 3/4	Any	Grade 3/4	Any	Grade 3/4
Dermatologic:	Pruritus	29.6	2.0	8.8	0	17.6	0.3	24.4	0	10.6	0
	Rash	24.7	1.2	6.8	0	17.6	1.3	19.1	0.8	4.5	0
Gastrointestinal:	Diarrhoea	36.4	4.0	24.7	0	30.3	3.7	27.5	4.6	13.6	0.8
	Colitis	4.5	2.0	0.4	0	5.3	3.2	7.6	5.3	0.8	0
	Perforation	0	0	0	0		0.8%(n=3)		1.5% (n=2)		0
Hepatic	ALT	33.2	21.9	5.6	0.8	0.8	0.5	1.5	0	2.3	0
	AST	29.1	18.2	5.6	1.2	1.1	0.3	0.8	0	0.8	1.5
Endocrine	Hypothyroidism	1.6	0	0.4	0	1.6	0.3	1.5	0	1.5	0
	Hypophysitis	0	0	0	0	0.5	0.5	1.5	1.5	0	0
Death (number and %)			0		0	8* (2.1%)			4 (3%)		2 (1.5%)

Also counted as deaths on treatment

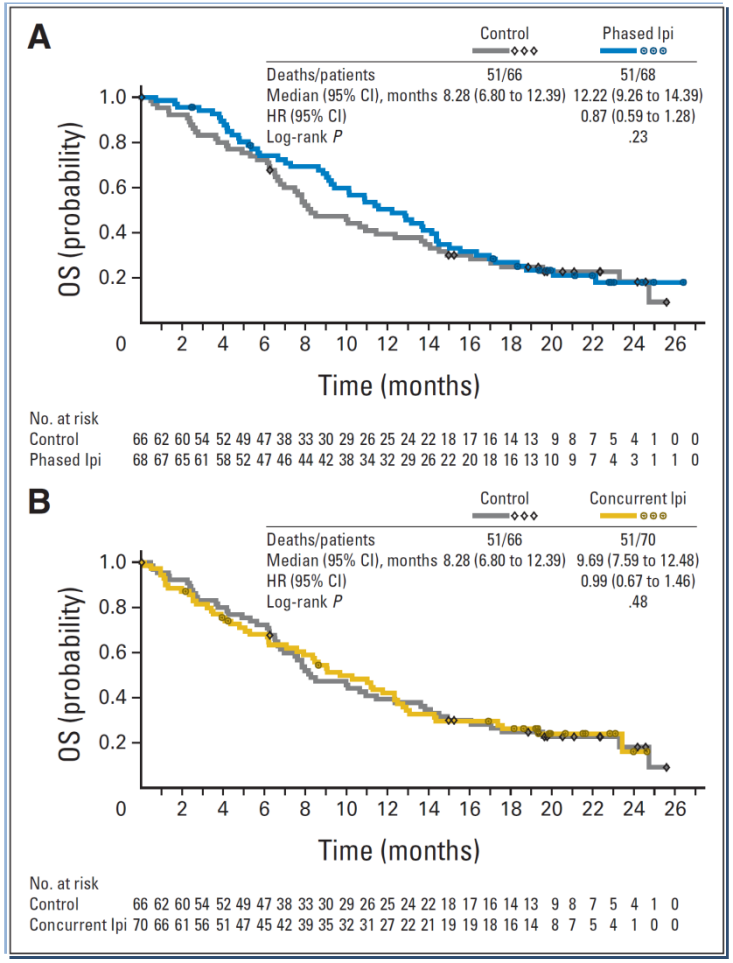
1. Robert C, et al. N Engl J Med. 2011;364:2517–2526
2. Hodi FS, et al. N Engl J Med. 2010;363:711–723

Ipilimumab in NSCLC

n =204

Paclitaxel + carboplatin +/- ipilimumab (concurrent or sequential)

Survival benefit for sequential treatment



Lynch JCO 2012

Ipilimumab + high dose IL-2

Ipi + IL-2 (720,000 IU/kg every 8 hours up to 15 doses).

Ipilimumab

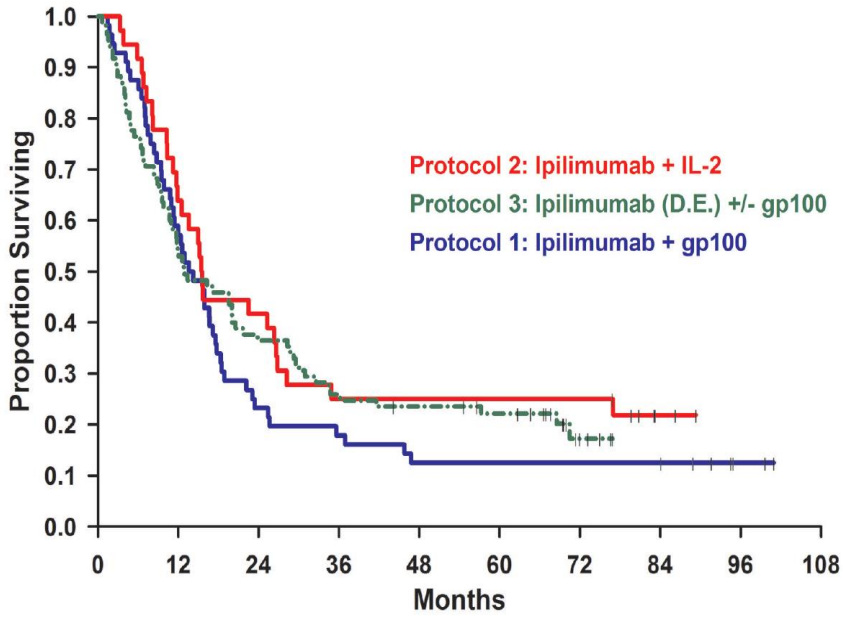
- Ipi cycle 1
- Ipi + IL-2 cycles 2-4
- Ipi dose levels 0.1mg/kg, 0.3 mg/kg, 1 mg/kg, and 2 mg/kg; 24 patients @ 3mg/kg.

n = 36

OR rate 25%, CR 17%

17% grade 3-4 irAEs mostly GI

Median survival 16 months



Prieto CCR 2012

Tremeilimumab and HDI

- Tremelimumab 15mg/kg q 12 wks x 3 cycles
- HDI 20 MU/m^2/day x 5 days then 10MU/m^2 x 3 weekly
- N = 37
- RR = 24%

Table 1. Adverse Events Considered Possibly, Probably, or Definitely Related to the Study Regimen (CTCAE version 3)

Type	All Grades		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Immune mediated						
Diarrhea/colitis	21	57.0	3	8.0	1	2.7
Hyper/pothyroidism	2	5.4	0	0	0	0
Hypogonadism	1	2.7	0	0	0	0
Hepatitis-increased AST/ALT/AP/GGT	8	21.6	3	8.0	1*	2.7
Skin rash	23	62.0	4	11.0	0	0
Constitutional						
Fatigue	37	100	15	40.5	0	0
Gastrointestinal						
Nausea	27	73.0	1	2.7	0	0
Vomiting	17	46.0	1	2.7	0	0
Hematologic						
Neutropenia	19	51.4	5	13.5	1	2.7
Neuropsychiatric						
Depression/anxiety	9	24.3	4	11.0	0	0
Renal						
Increased Cr/dehydration	2	5.4	1	2.7	0	0
Respiratory						
Bronchospasm	1	2.7	1	2.7	0	0
Other						
Cardiac arrhythmia (atrial fibrillation)	1	2.7	1	2.7	0	0
Increased CPK	9	24.3	2	5.4	1	2.7

Abbreviations: AP, alkaline phosphatase; Cr, creatinine; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma-glutamyltransferase.
*GGT.

Tarhini et al JCO 2012

Tremeilimumab and High Dose Interferon

Progression Free Survival

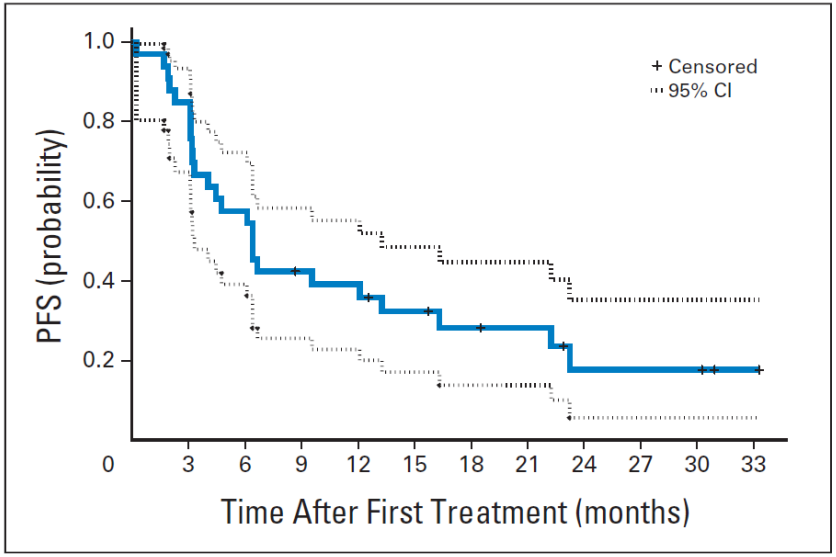


Fig 1. Kaplan-Meier plot of the probability of progression-free survival (PFS; N = 37). The estimated median was 6.4 months (95% CI, 3.3 to 12.1).

Overall Survival

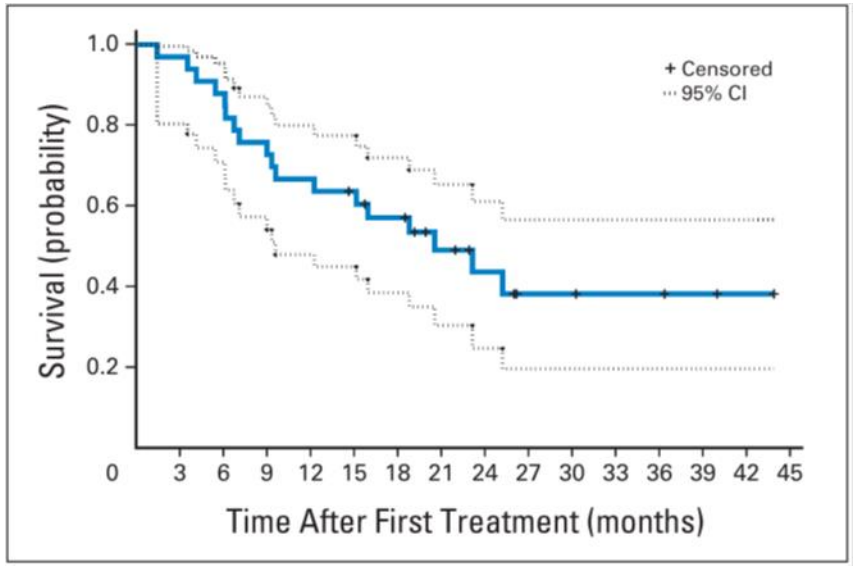


Fig 2. Kaplan-Meier plot of the probability of overall survival (N = 37). The estimated median was 21 months (95% CI, 9.5 months to not reached).

Tarhini et al JCO 2012

Ipilimumab + Bevacizumab

Phase 2

- Ipi 3mg/kg or 10mg/kg
- Bevacizumab 7.5mg/kg or 15mg/kg
- 4 cohorts

n = 46

–8 (17%)PR and 22 (48%) SD

–All responses > 6 months

–Median OS 25 months

<u>Toxicity</u>

28.3% grade 3-4 toxicity

- Temporal arteritis
- Hypophysitis
- Grade 4 hepatitis
- Bilateral uveitis
- Haemorrhagic purpura
- Colitis
- Thyroiditis

Hodi Cancer Immunol Res 2014

GMCSF + Ipilimumab

- Ipilimumab 10mg/kg every 3 weeks x 4 doses, then every 12 weeks maintenance
- Sagramostim 250µg day 1-14 of 3 week cycle
- No limit in number of treatments,
- Treatment allowed through disease progression.
- N = 245

Hodi et al. JAMA 2014

Results

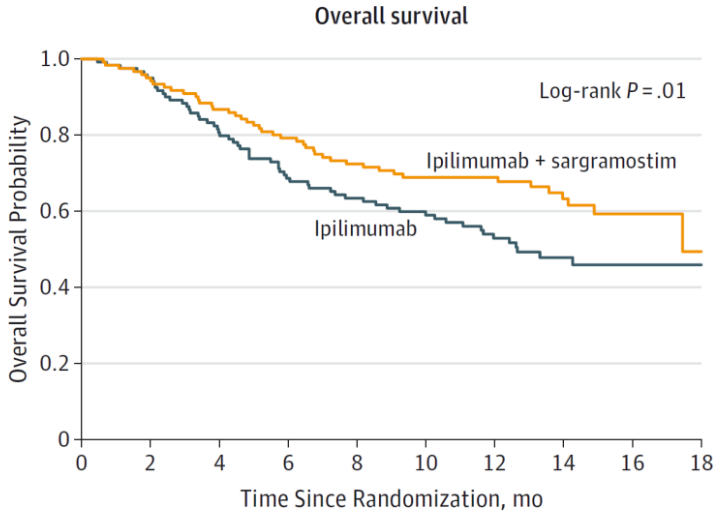
Outcomes	Ipilimumab Plus Sargramostim (n=123)	Ipilimumab Only (n=122)	*P* Value
No. of deaths	44	60	
OS, median (95% CI), mo	17.5 (14.9-Not reached)	12.7 (10.0-Not reached)	.01 (1 Sided)
1-Year survival (95% CI), %	68.9 (60.6-85.5)	52.9 (43.6-62.2)	.01 (1 Sided)
Mortality hazard ratio (95% CI)	0.64 (NA-0.90)	1 [Reference]	
PFS, median (95% CI), mo	3.1 (2.9-4.6)	3.1 (2.9-4.0)	.37 (2 Sided)
Grade 3-5 adverse events (95% CI), %	44.9 (35.8-54.4)	58.3 (49.0-67.2)	.04 (2 Sided)

Toxicity similar except gastrointestinal sig reduced - 16.1% vs 26.7%

Hodi et al. JAMA 2014

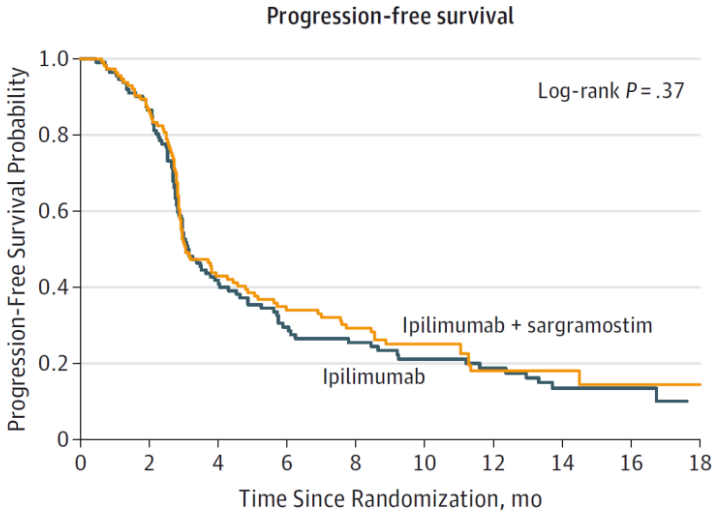
Results

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

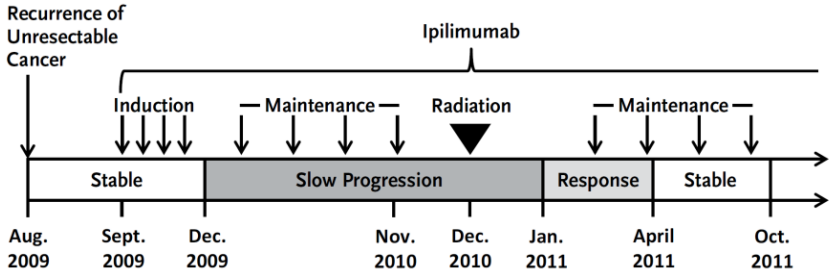
Ipilimumab + sargramostim	123	99	49	36	31	22	10	7	4
Ipilimumab	122	97	46	29	25	19	15	8	5

A, Primary efficacy treatment analysis (stratified hazard ratio [HR] = 0.64; 1-sided 90% repeated CI with an upper bound of 0.90; *P* value was 1-sided and calculated using the stratified log-rank test). B, Intent-to-treat patient population. There was no significant difference in progression-free survival between treatment groups (stratified HR = 0.87 [95% CI, 0.64-1.18]; *P* value was 2-sided and calculated using the stratified log-rank test).

Hodi et al. JAMA 2014

Abscopal Effect

- Radiotherapy
  - Antigen release
  - Triggers immune system
  - Distant impact



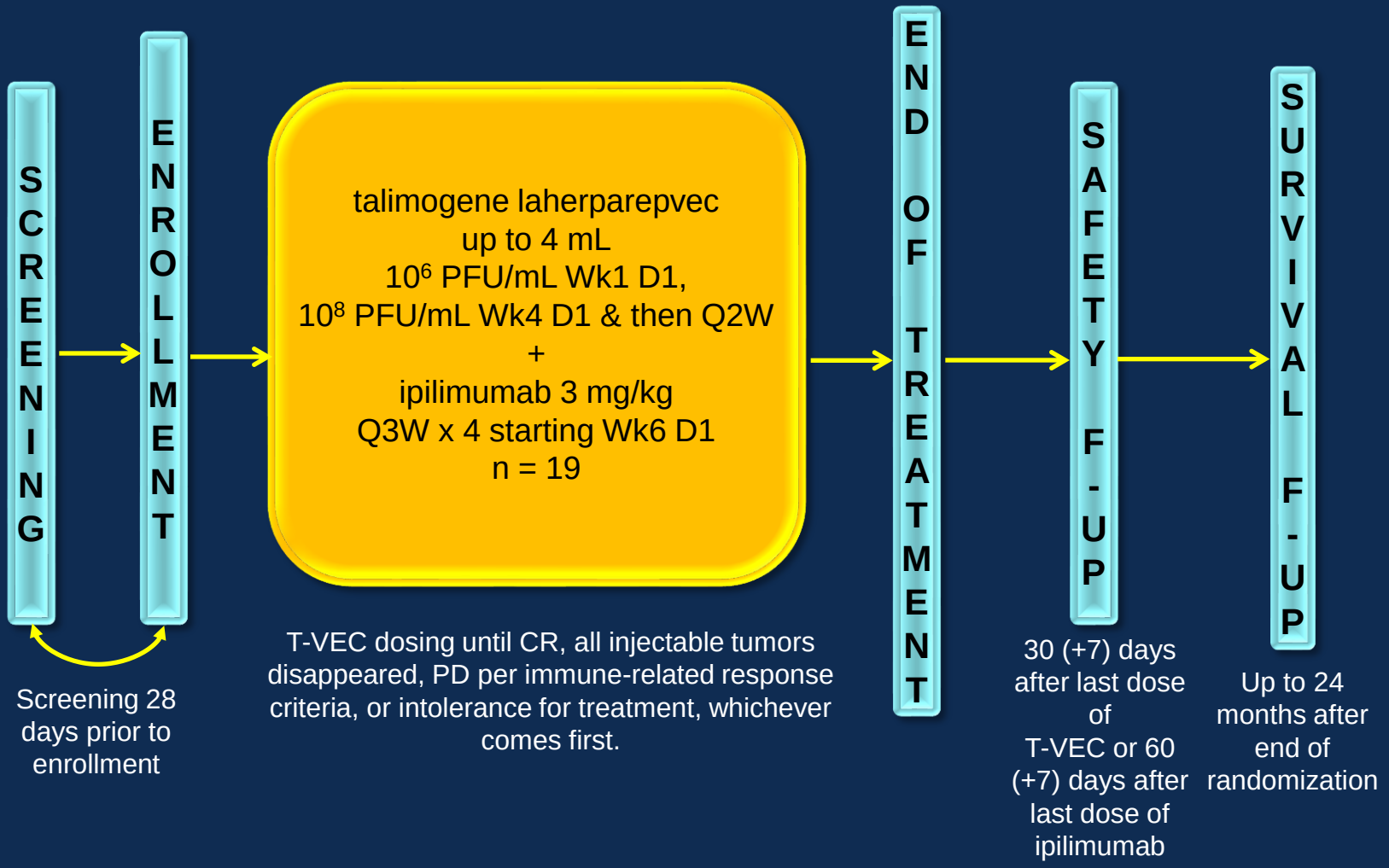
- PERM Study
  - Advanced melanoma
  - Pembrolizumab +/- RT

Postow NEJM 2012

Phase 1b Study of Talimogene Laherparepvec (T-VEC) and Ipilimumab in Previously Untreated IIIB-IV Melanoma

- T-VEC: herpes simplex virus type-1 (HSV-1)–derived oncolytic immunotherapy
- Intra-lesional injection
- Selectively replicates in cancer cells, producing GM-CSF at site of injection
- Lyses cancer cells, releasing tumor-derived antigens
- Creates microenvironment that promotes systemic immune responses against TAA
- Phase 3 OPTiM study of T-VEC in Stage IIIB-IV melanoma met primary endpoint vs GM-CSF of durable response rate (objective responses lasting ≥ 6 months)
- Combining T-VEC (promotes the release of TAA) with an immune checkpoint inhibitor (improves T cell responses)

Study Schema – Phase 1b



- Primary endpoint: Incidence of dose limiting toxicities (DLTs)
- Key secondary endpoints: Overall response rate, safety

PFU: plaque-forming units; Wk: week; D: day; Q2W: every 2 weeks; Q3W: every 3 weeks; CR: complete response; PD: progressive disease; F-Up: follow-up

Treatment-Emergent Adverse Events*

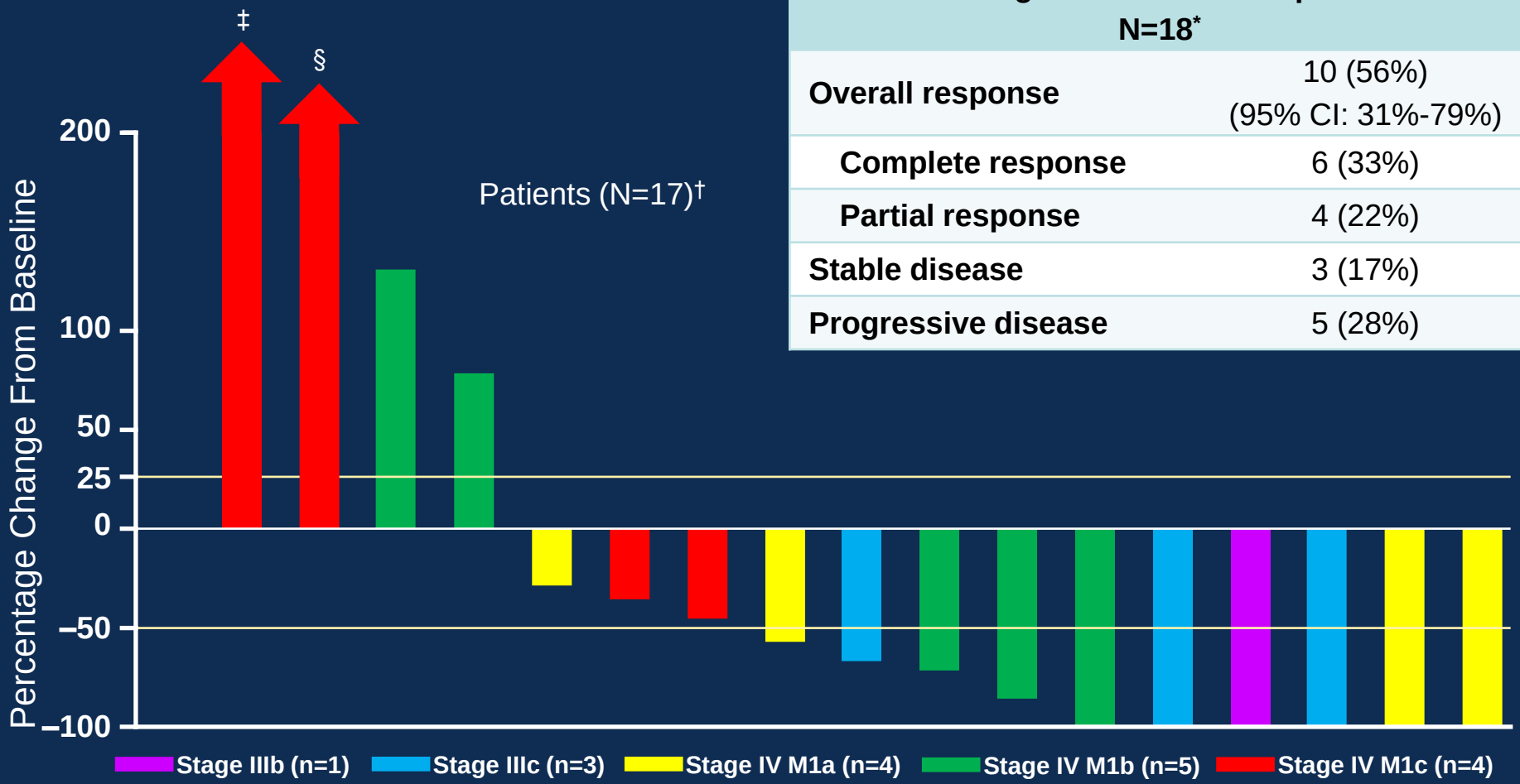
Preferred Term	Total N (%)	Grade 3 N (%)
Any event	19 (100)	5 (26)
Any attributed to T-VEC	17 (90)	3 (16)†
Any attributed to ipilimumab	15 (80)	3 (16)†
Chills	11 (58)	-
Fatigue	11 (58)	1 (5)
Pyrexia	11 (58)	1 (5)
Nausea	9 (47)	2 (11)
Rash	9 (47)	-
Diarrhea	8 (42)	1 (5)
Headache	8 (42)	-
Pruritis	7 (37)	-
Decreased appetite	4 (21)	-
Hyperglycemia	4 (21)	-
Vomiting	4 (21)	1 (5)
ALT increased	3 (16)	-
Back pain	3 (16)	1 (5)
Influenza-like illness	3 (16)	1 (5)
Pain	3 (16)	-
Vision blurred	3 (16)	-

- The only grade 3 event occurring in > 1 patient was nausea
- The only two grade 4 events were in a patient with elevated amylase and lipase (attributed to ipilimumab)
- There was one grade 5 event of metastases to central nervous system (preferred term)

*All events of any grade occurring in > 15% of patients during treatment or up to 30 days after last T-VEC or 60 days after last ipilimumab, whichever is later; †Grade 3 events in these patients: pyrexia attributed to T-VEC; hypophysitis and abdominal distention attributed to ipilimumab; and nausea, diarrhea, fatigue, influenza-like illness, vomiting, adrenal insufficiency, and dehydration attributed to both; ALT: alanine aminotransferase

Maximal Change in Tumor Burden

Investigator-assessed responses N=18*	
Overall response	10 (56%) (95% CI: 31%-79%)
Complete response	6 (33%)
Partial response	4 (22%)
Stable disease	3 (17%)
Progressive disease	5 (28%)



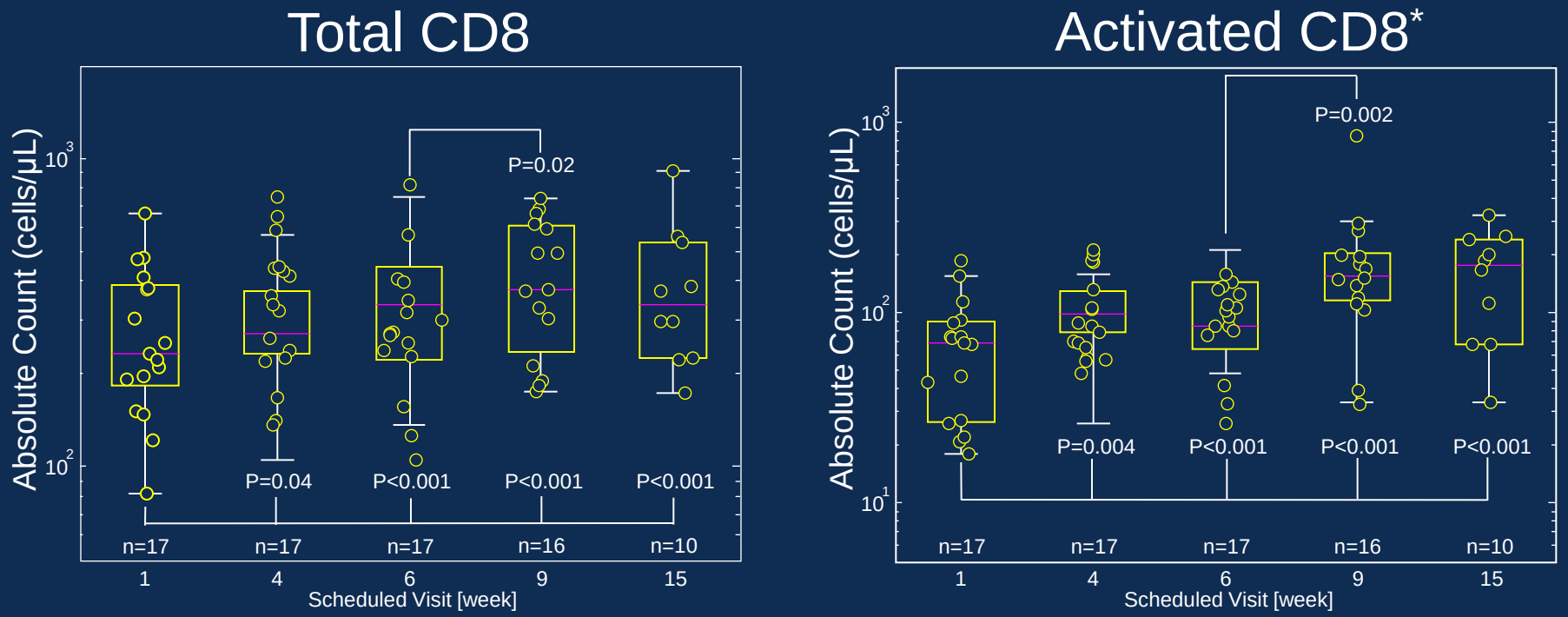
* Efficacy analysis set includes only the patients who received both T-VEC and ipilimumab. Both confirmed and unconfirmed responses and progressions are included

† One patient assessed to have PD by the investigator was not shown in the plot because tumor burden could not be accurately calculated based on missing post-baseline data

‡ Percentage change from baseline for this patient was 538

§ Percentage change from baseline for this patient was 265

Total & Activated CD8* T cells Increase After T-VEC and Combination Treatment

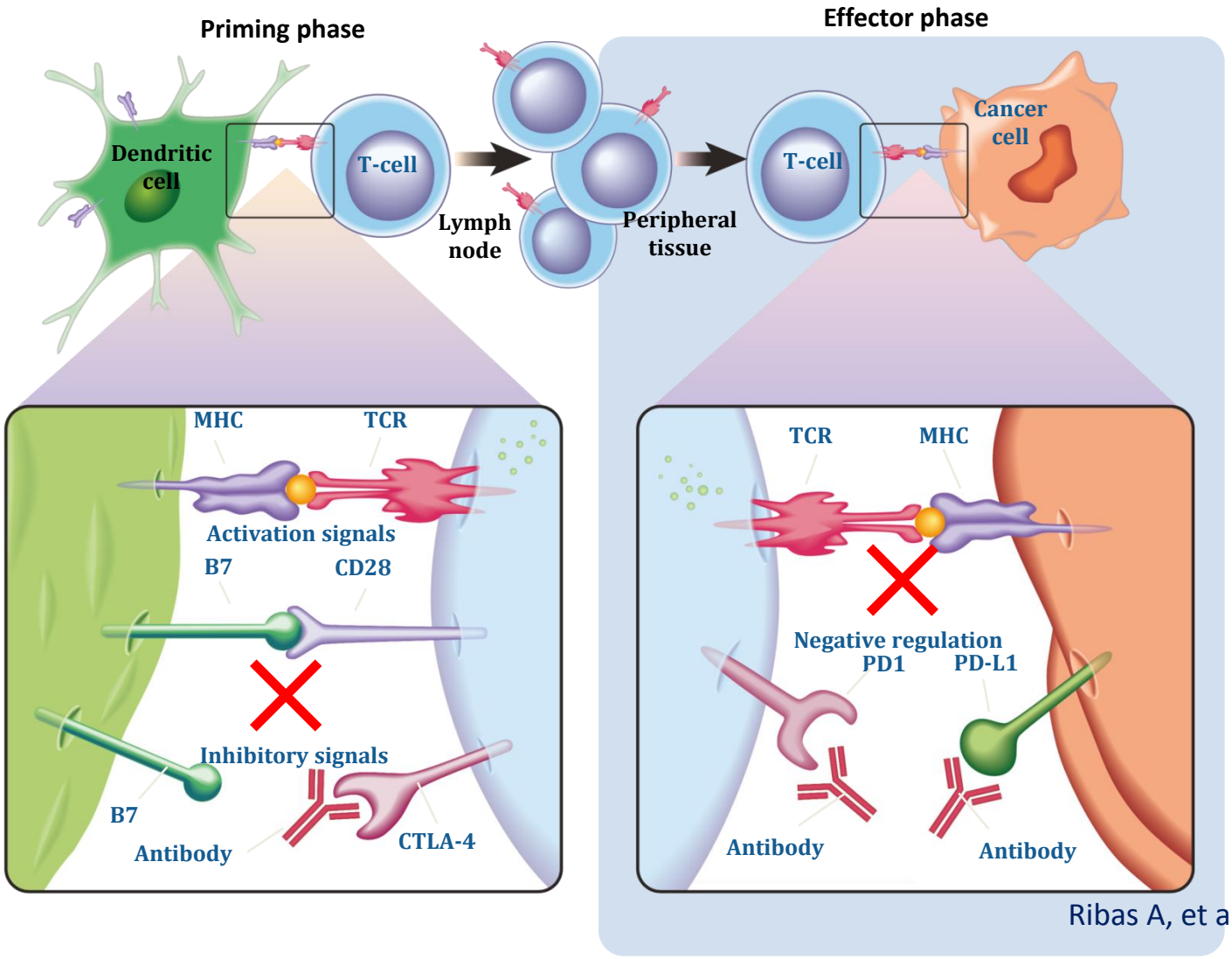


Data points are overlaid on the box plots. Each box plot shows the range between 25th percentile (q1) and 75th percentile (q3) as a yellow box, with a pink line showing the 50th percentile. The whiskers on each box are q3 ± 1.5*(q3 – q1). *P*-values below each post week 1 subset indicate significant changes from baseline level on week 1, and *P*-values above week 9 subset indicate significant changes from week 6 to week 9.

- Total and activated CD8 T cells in the peripheral blood increased from baseline after T-VEC administration at weeks 4 and 6 and further increased at weeks 9 and 15 after ipilimumab
- CD4 T cells expressing ICOS, an activation marker up-regulated by CTLA-4 blockade, significantly increased from baseline at weeks 9 and 15 after ipilimumab, consistent with previous reports,[5] but not during the T-VEC monotherapy period (data not shown)

*Activated CD8 T cells are defined as HLA-DR+CD3+CD4- cells

Targeting The Immune Checkpoints

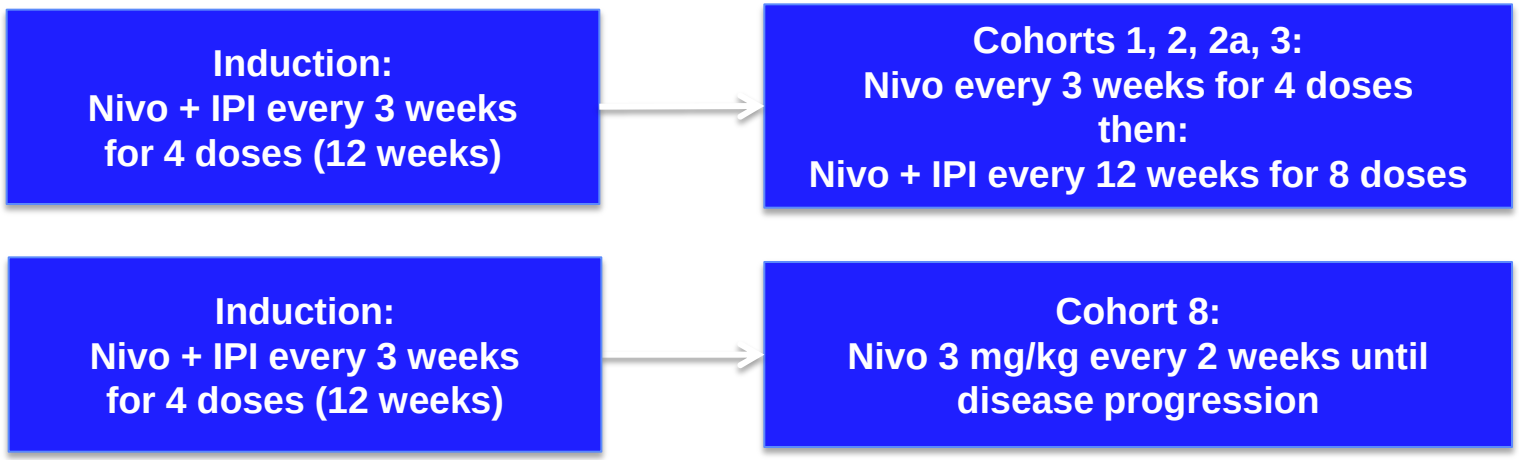


Ribas A, et al. *NEJM* 2012

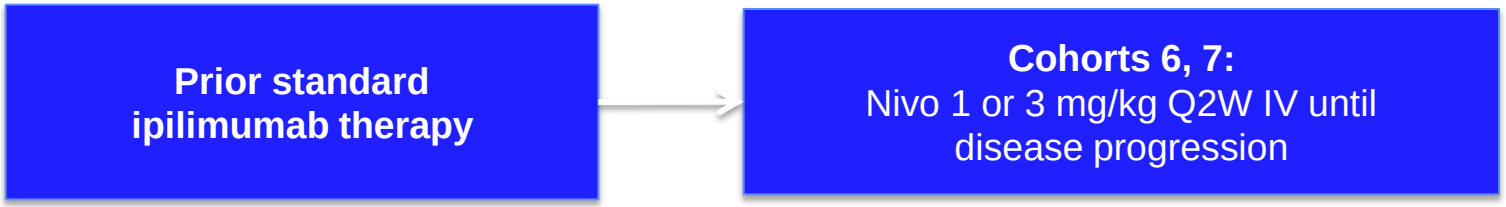
Objectives

- **To report updated safety, survival, and clinical activity of initial concurrent cohorts 1-3 (N=53) with additional follow-up of ~ 1 year**
- **To report responses in a new cohort (cohort 8) of 41 patients using Phase 2/3 dosing regimen (last patient, first treatment Nov. 2013)**

Concurrent Therapy



Sequential Therapy



Sznol ASCO 2014

CA209-004 Phase I Study: Dose Cohorts

		Dose (mg/kg),		Treatment Schedule	
Regimen Cohort No.	N	Nivolumab	Ipilimumab	Induction	Maintenance
Concurrent					
1	14	0.3	3	Nivo Q3W x 8 + IPI Q3W x 4	Nivo + IPI Q12W x 8
2	17	1	3		
2a	16	3	1		
3	6	3	3		
8*	41	1	3	Nivo Q3W x 8 + IPI Q3W x 4	Nivo 3 mg/kg Q2W (Max. 48 doses)
Sequenced					
6	17	1	Prior	Nivo Q2W (Max of 48 doses)	
7	16	3	Prior		

*Insufficient follow-up at this data collection to report survival endpoints

Patient Demographics

Variable	Concurrent Cohorts 1-3 n = 53	Cohort 8 n = 41	All Concurrent n=94	Sequenced regimen n = 33
Median age, years (range)	58 (22–79)	56 (22–80)	58 (22–80)	64 (23–89)
Male, n (%)	32 (60)	18 (44)	50 (53)	18 (55)
ECOG performance status, n (%)				
0	44 (83)	25 (61)	15 (88)	22 (67)
1	8 (15)	11 (27)	1 (6)	11 (33)
Unknown	1 (2)	5 (12)	1 (6)	0
M-stage at study entry, n (%)				
M1c	29 (55)	21 (51)	50 (53)	17 (52)
Lactate dehydrogenase level, n (%)				
≤Upper limit of the normal range	33 (62)	25 (61)	58 (62)	21 (64)
>Upper limit of the normal range	20 (38)	16 (39)	36 (38)	12 (36)
Systemic cancer therapy, n (%)	21 (40)	21 (51)	42 (45)	33 (100)
Immunotherapy	10 (19)	12 (29)	22 (23)	33 (100)
Prior ipilimumab therapy	0	0	0	33 (100)
B-RAF inhibitor	2 (4)	3 (7)	5 (5)	6 (18)
Number of prior systemic cancer therapies, n (%)				
0	32 (60)	20 (49)	52 (55)	0
1	15 (28)	11 (27)	26 (28)	17 (52)
≥2	6 (11)	10 (24)	16 (17)	16 (48)

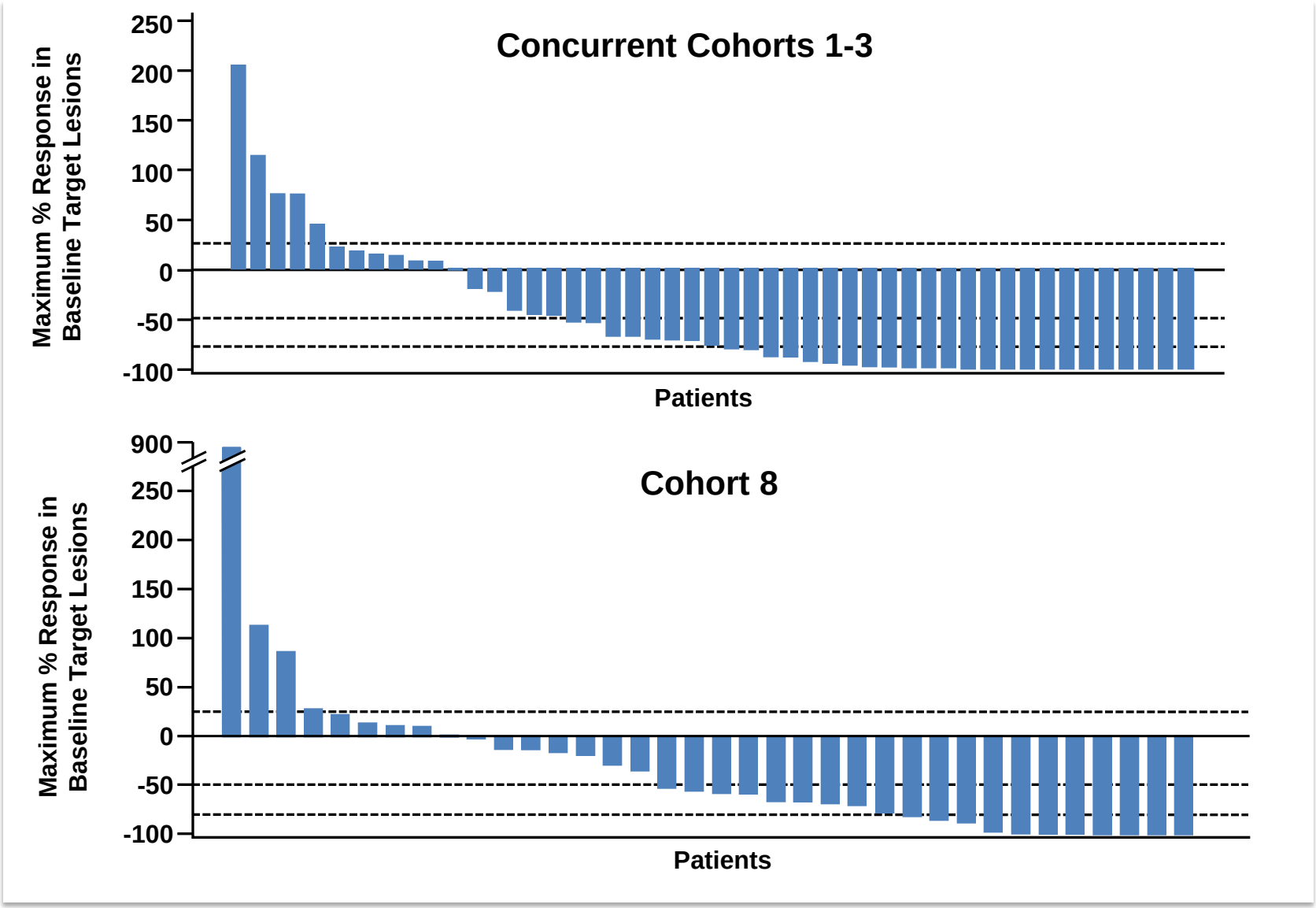
Activity Summary: Concurrent and Sequenced Cohorts from 004

Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR[a], %	CR, %	Aggregate Clinical Activity Rate	≥80% tumor burden reduction at 36 wks[b], %
Concurrent Cohorts 1-3	53	42	17	70	42
0.3 + 3	14	21	14	57	36
1 + 3	17	53	18	65	53
3 + 1	16	44	25	81	31
3 + 3	6	50	0	83	50
1 + 3 [Cohort 8][c]	40	43	10[d]	53	28
Sequenced	33	31	3	44	31

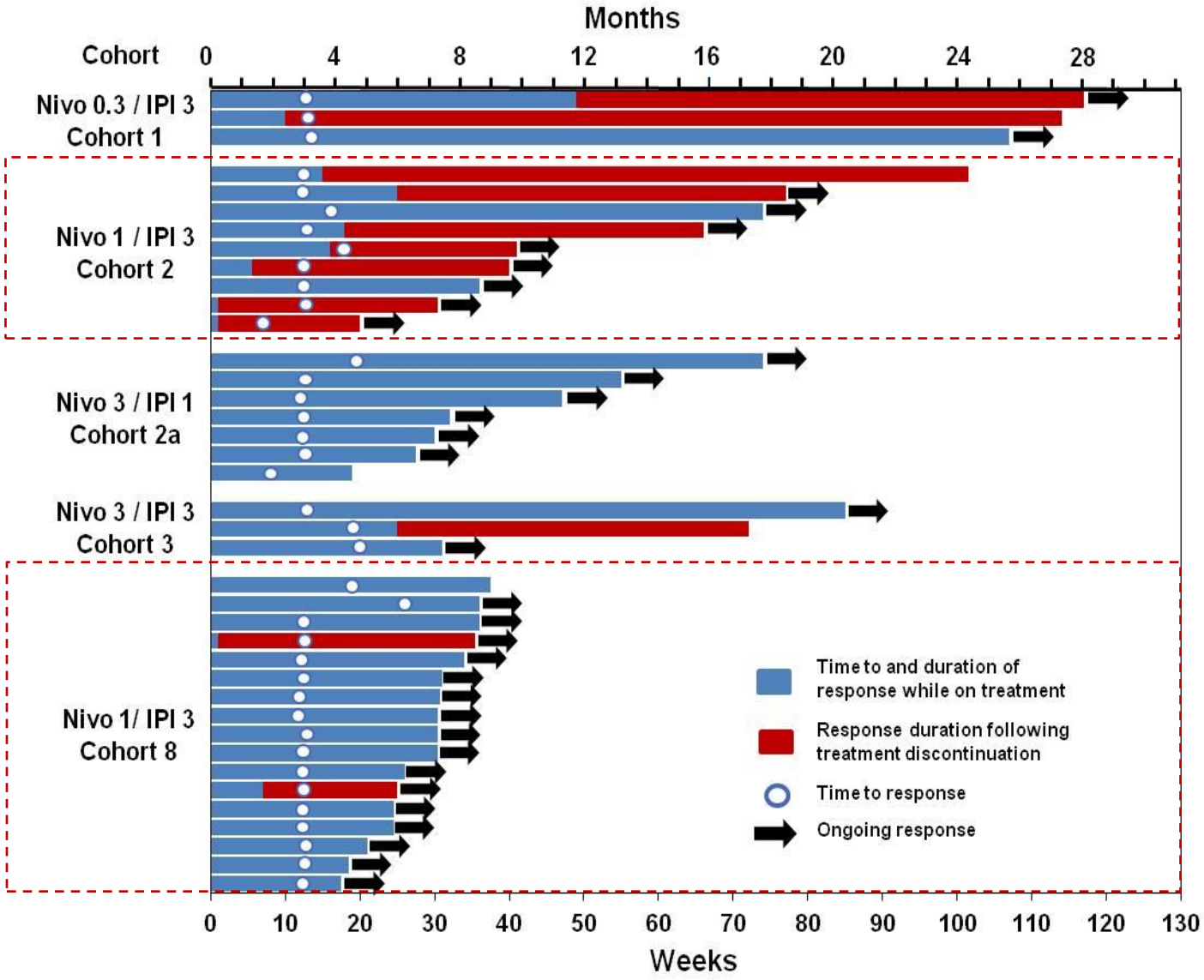
[a]per RECIST, [CR+PR]/N x 100; [b] Best overall response; [c]Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. [d]2 confirmed and 2 unconfirmed responses

n: no. response-evaluable pts.

Response in Target Lesions



Characteristics of Response



Median duration of response in Cohorts 1-3 and cohort 8 not reached

18/22 responses ongoing

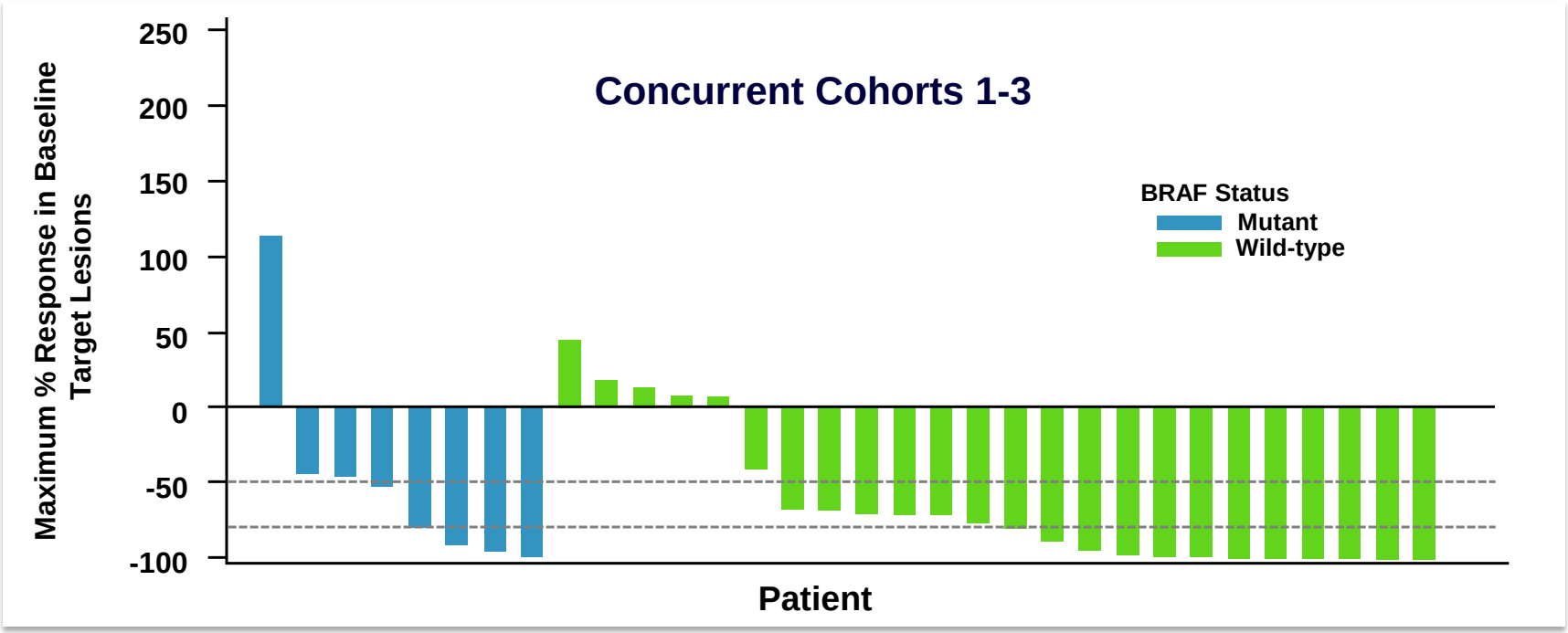
Safety Overview

AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	**96**	**62**	**95**	**61**	**96**	**62**
Select AEs						
Gastrointestinal	**43**	**9**	**34**	**20**	**39**	**14**
Hepatic	**30**	15	**12**	**12**	**22**	**14**
Skin	**79**	**4**	**73**	**15**	**77**	**9**
Endocrine	**17**	**4**	**22**	**2**	**19**	**3**
Renal	**6**	**6**	**0**	**0**	**3**	**3**
Other						
Uveitis	**6**	**4**	**2**	**2**	**4**	**3**
Pneumonitis	**6**	**2**	**2**	**2**	**4**	**2**
Lipase increased	**26**	**19**	**15**	**10**	**21**	**15**
Amylase increased	**21**	**6**	**12**	**7**	**17**	**6**

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

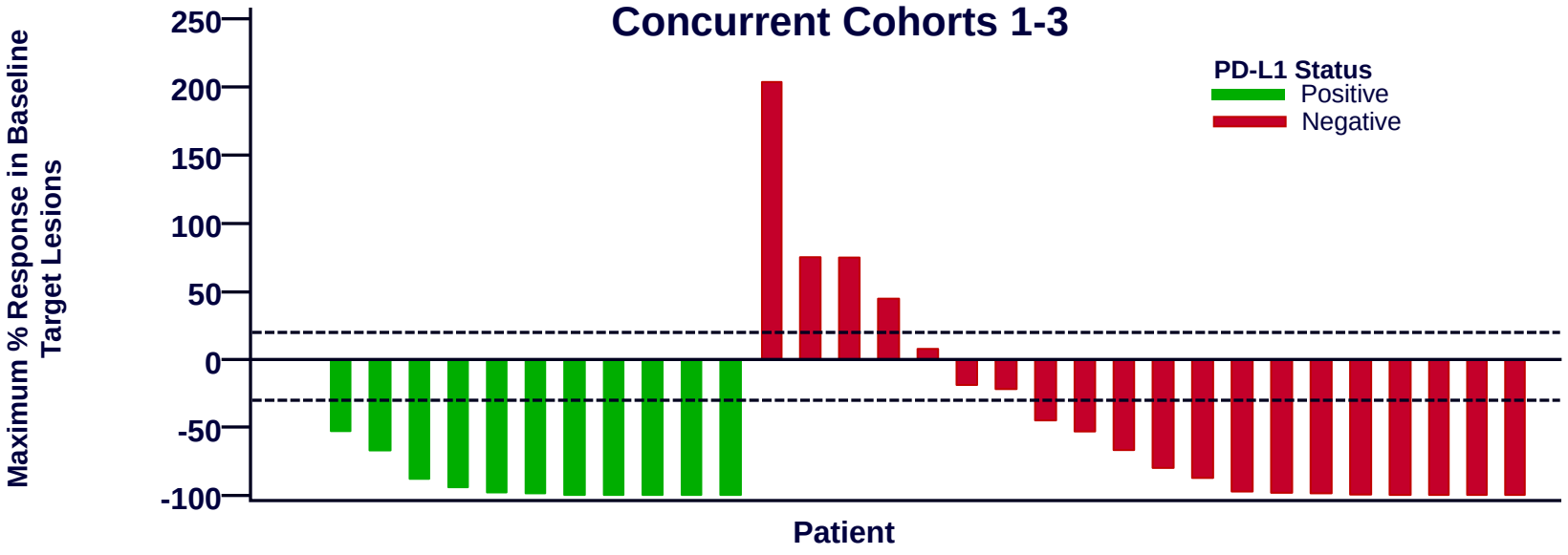
ORR by BRAF Status for Concurrent Cohorts

Nivolumab (mg/kg) + IPI (mg/kg) [n]	Evaluable Samples	ORR, n (%)	
BRAF Status		WT	MT
Concurrent Cohorts 1-3 [53]	36	13/26 (50)	2/10 (20)
Cohort 8 [41; Nivo 1 + IPI3]	38	9/26 (35)	6/12 (50)
Sequenced [33]	24	5/15 (33)	3/9 (33)

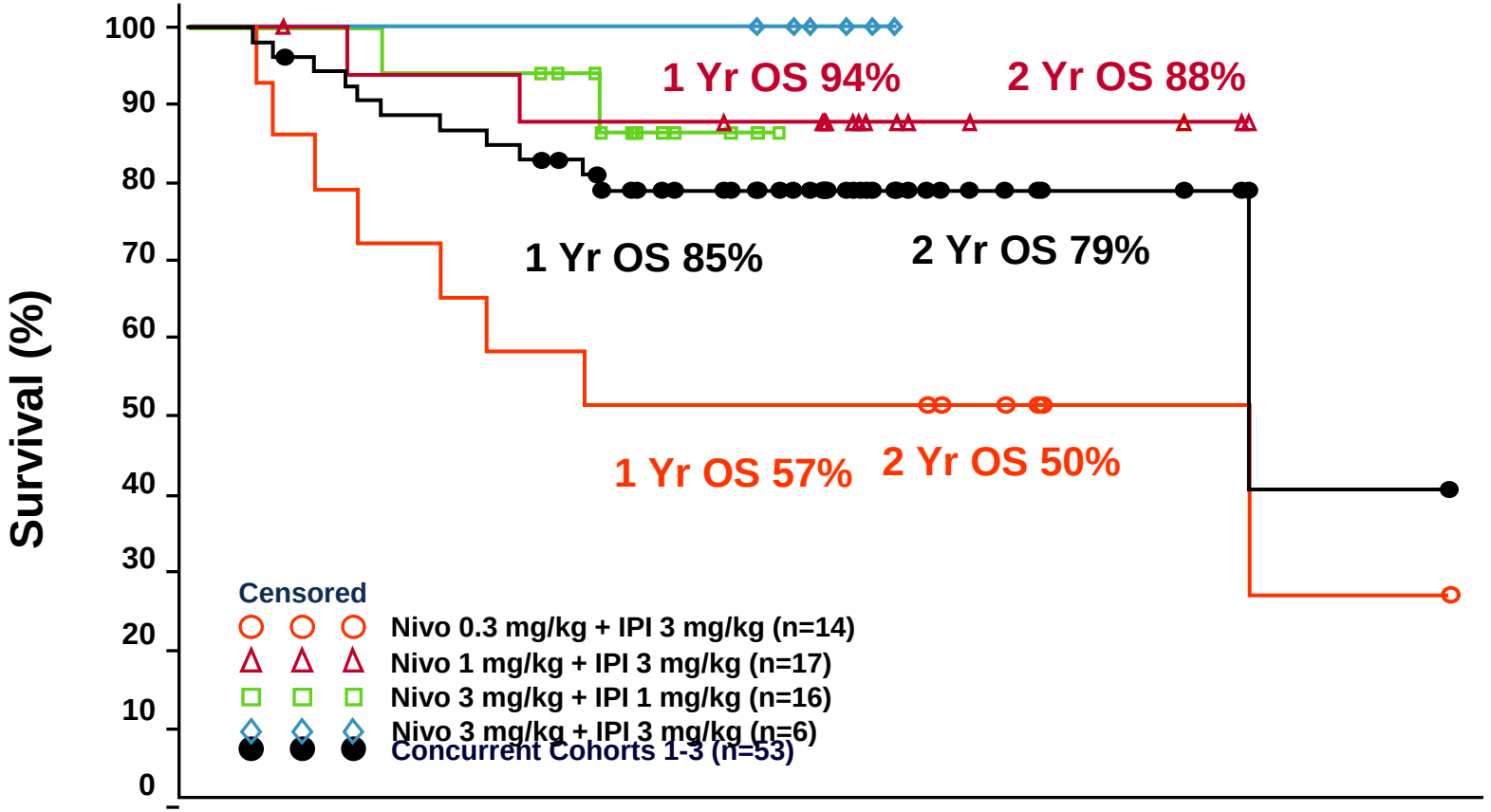


ORR by PD-L1 Status (5% cutoff)

Cohort [n] PD-L1 Status	Evaluable Samples	ORR, n (%) PD-L1+	 PD-L1-
Concurrent Cohorts 1-3 [53]	36	8/14 (57)	9/22 (35)
Cohort 8 [41; Nivo1 + IPI3]	20	0/0	8/20 (40)
Sequenced [33]	23	5/8 (63)	3/15 (20)



Overall Survival for Concurrent Therapy by Dose Cohort



Pts at Risk																	
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

Ipilimumab and Targeted therapy

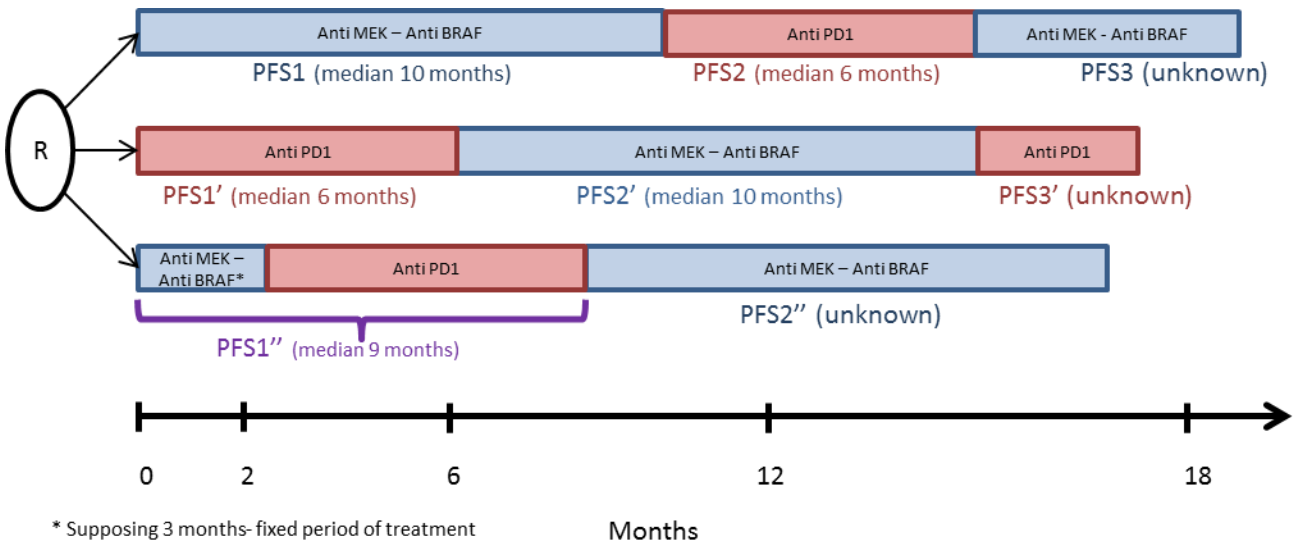
Ipilimumab and vemurafenib – liver toxicity

Dabrafenib + ipilimumab – deliverable

Dabrafenib + trametinib + ipilimumab – significant toxicity

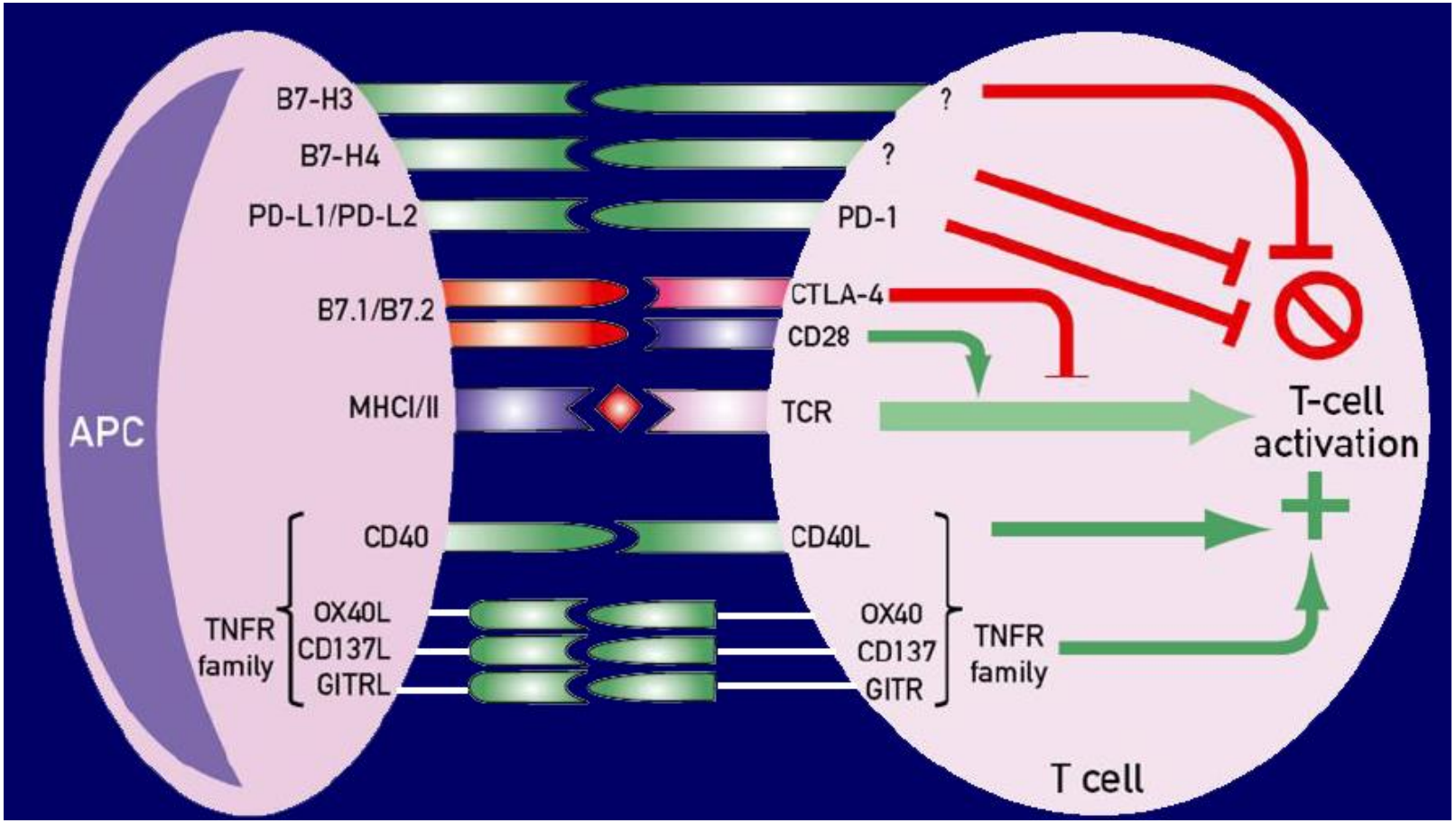
Ribas NEJM 2013
Puzanov ASCO 2014

Sequencing Study



* Supposing 3 months- fixed period of treatment

T cell: APC interface



Peggs KS, et al. Clin Exp Immunol 2009;157:9–19

Conclusions

- Promising combinations identified, will the results hold up in randomised studies?
- Trial design
- How to test all the possible combinations
  - Surrogate endpoints
  - Biomarkers to enrich population
- Implications for adjuvant therapy
- Implications for other cancers

THANK YOU

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