GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Immunotherapy of cancer: Immune checkpoints in melanoma

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Science Breakthrough of Year 2013

PD-1 & CTLA-4 BLOCADES
CELL-BASED THERAPIES

ESMO Preceptorship Program

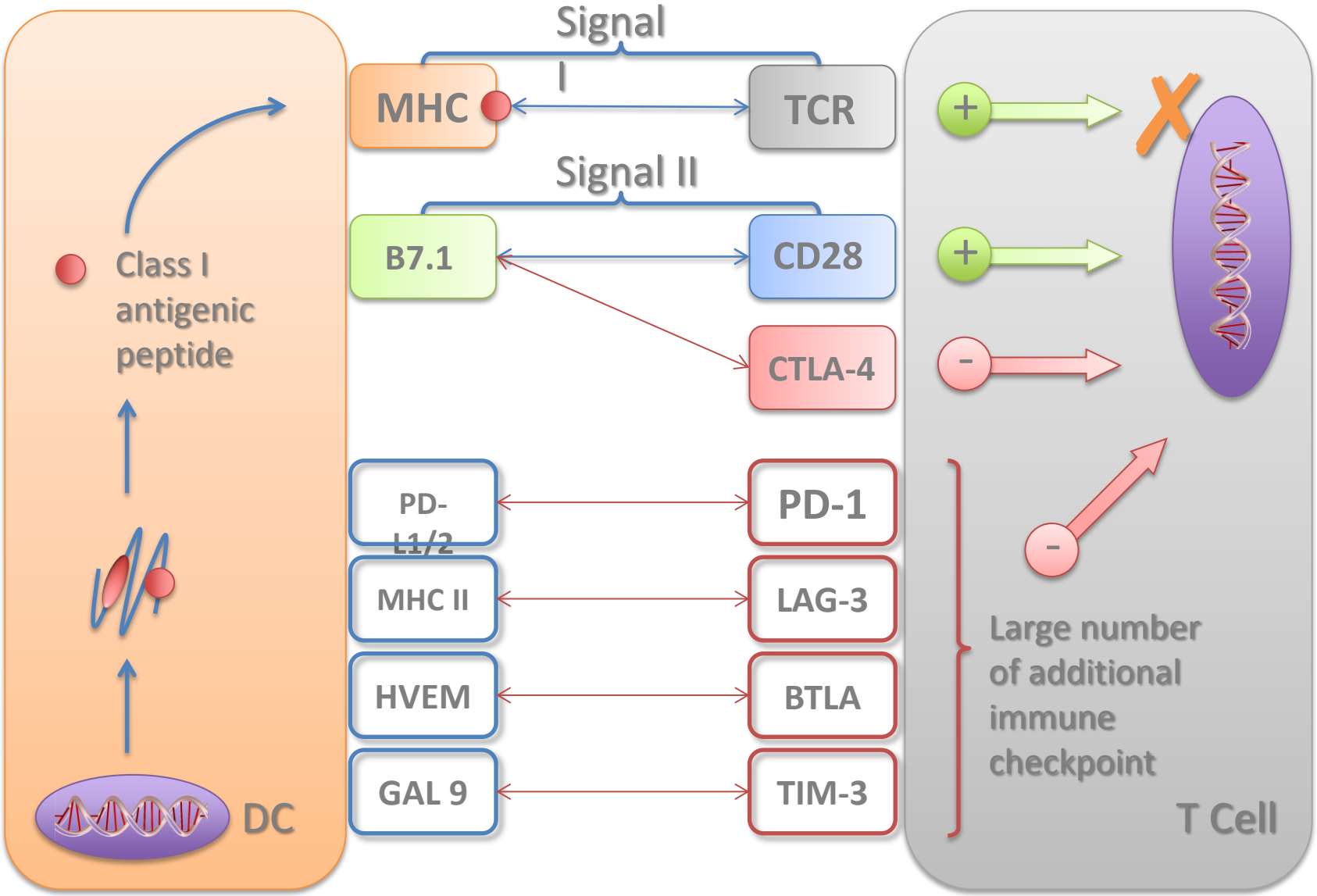
19-20 November 2014, Lausanne, Switzerland

Summary of overall survival data (not randomized)

Treatment Option	Response rate	1 year OS rate	2 year OS rate
Historical control: M1c (Balch, *JCO* 2009)	NR	33%	19%
High dose IL-2 (Schwartzentruber, *NEJM* 2011)	6%	48%	27%
BRAF inhibition (McArthur, *Lancet Oncol* 2014)	57%	56%	NA
MEK inhibition (Kim, *JCO* 2013)	22%	59%	NA
BRAFi + MEKi (Flaherty, ASCO 2014)	75%	80%	51%
CTLA-4 blockade (Hodi, *NEJM* 2010; Wolchok, *Ann Oncol* 2013)	11%	46%	24%
PD-1 blockade (pembrolizumab) (Ribas, ASCO 2014 & Kefford, ASCO 2014)	34%	69%	(60%)
PD-1 blockade (nivolumab) (Topalian, *JCO* 2014)	31%	62%	43%
CTLA-4 + PD-1 blockade (Kluger, ESMO 2014)	**41%**	**85%**	**79%**

NA: Not Available, NR: Not Relevant

T cell activation and immune checkpoints



Overview of checkpoint blockade

Combinations

Single agent

Ipi + bevacizumab[7]:
- Ph1: Ipi + bev
- RR 17%, DCR 67%
- HR OS/PFS: NR/NR

Checkmate 067[8]:
- Ph3: Ipi/nivo/combo
- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

BMS-024[2]: Phase 3
- DTIC vs DTIC + ipi, 1st
- RR 34%, mPFS 2.6
- HR OS: 0.72, mOS 11

BMS-020[1]: Phase 3
- Ipi/gp100/combo 2nd
- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

Adjuvant

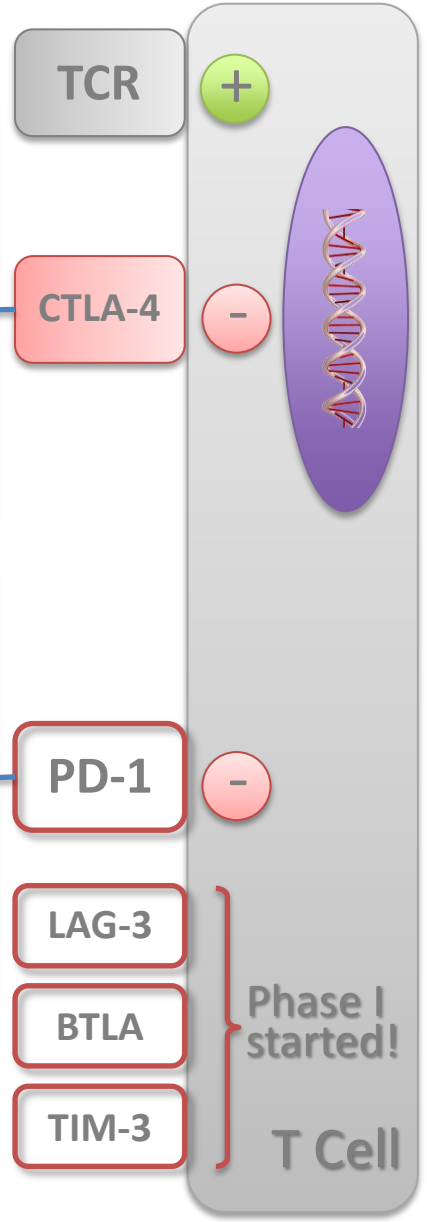
EORTC-18071[3]: Phase 3
- Ipi (10mg) vs placebo
- mRFS: 26 vs 17
- HR RFS/OS: 0.75/NA

CA-209-003[5]: Phase 1
- Nivolumab, 2nd +
- RR 31%, mOS: 17
- HR OS/PFS: NR/NR

Keynote-001[4]: Phase 1
- Keytruda, Ipi-N or T
- RR 34%, mOS 26
- HR OS/PFS: NR/NR

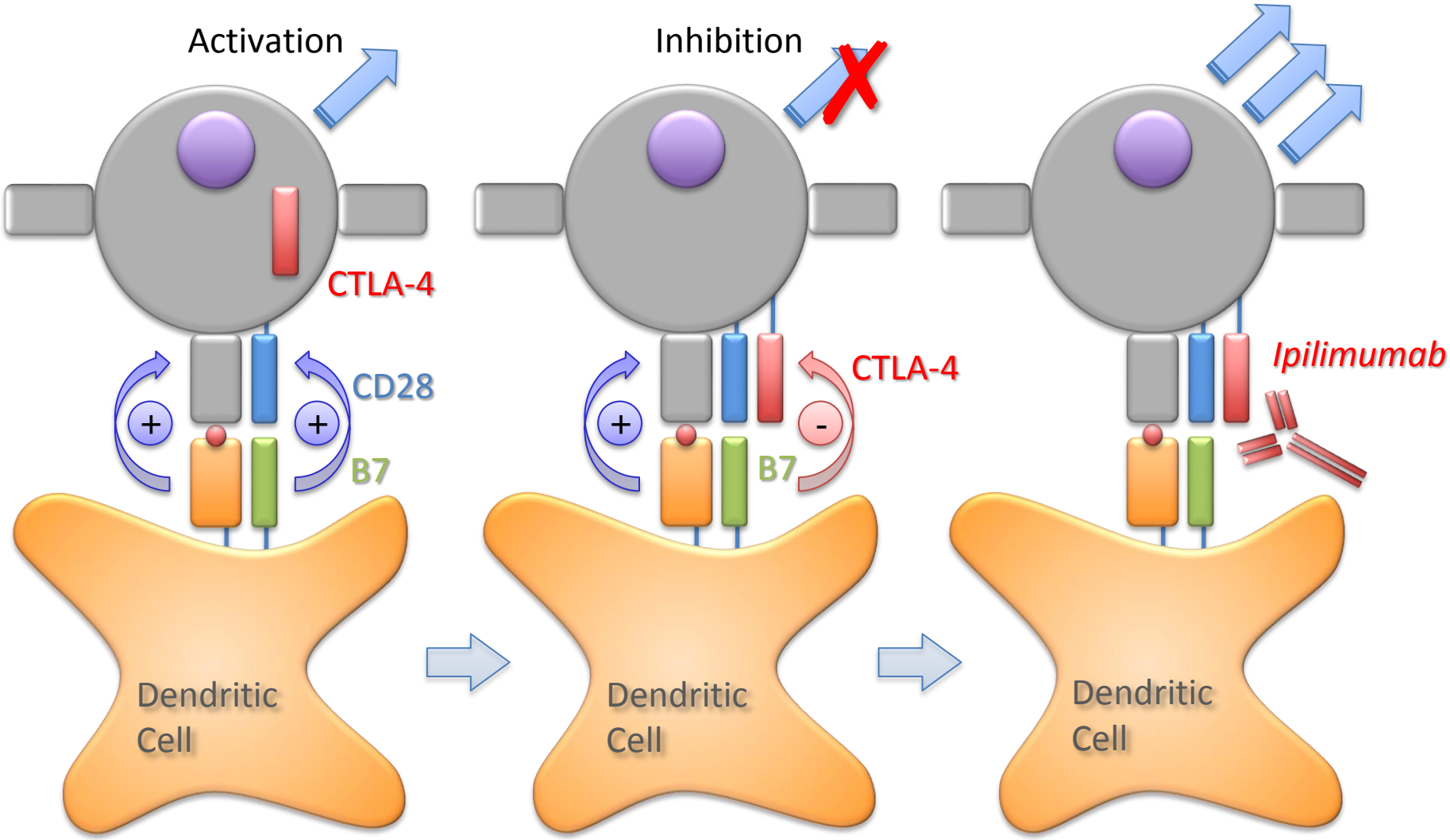
CA-209-037[8]: Phase 3
- Nivo vs ICC, 2nd
- RR 32%,
- HR OS/PFS: NA/NA

CA-209-066[6]: Phase 3
- Nivo vs DTIC, 1st
- RR 40%,
- HR OS/PFS: 0.42/0.43



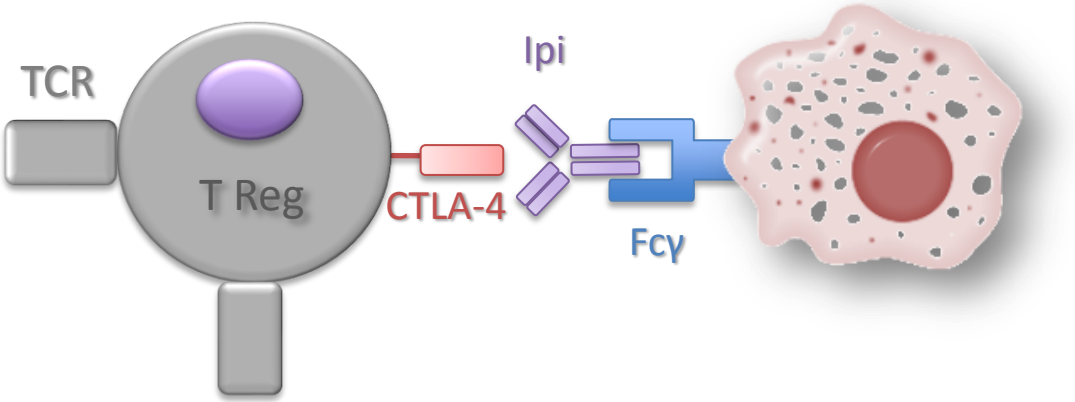
1 Hodi, *NEJM* 2010; 2 Robert, *NEJM* 2011; 3 Eggermont, ASCO 2014;
4 Robert, *Lancet Oncol* 2014; 5 Topalian, *JCO* 2014; 6 Robert, *NEJM* 2014;
7 Hodi *Cancer Immunol Res* 2014; 8 ASCO/ESMO/SMR 2014
(Time units in months unless specified, NA: Not Available, NR: Not Relevant)

CTLA-4 blockade, traditional mechanism of action

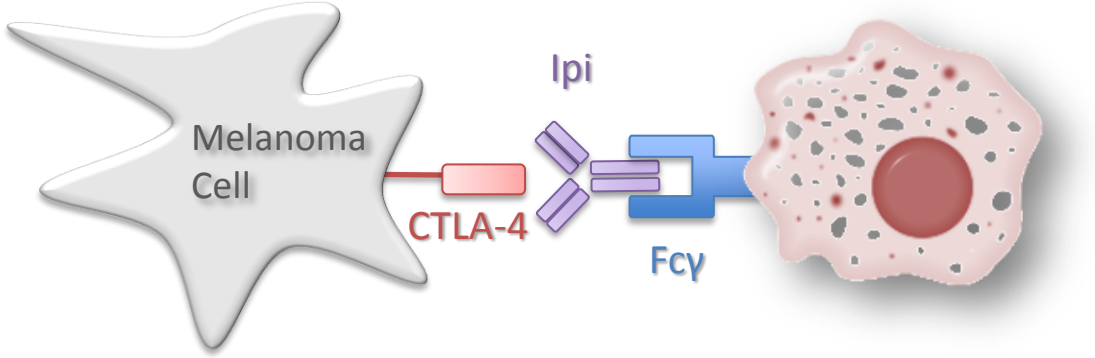


Other biological mechanisms of action

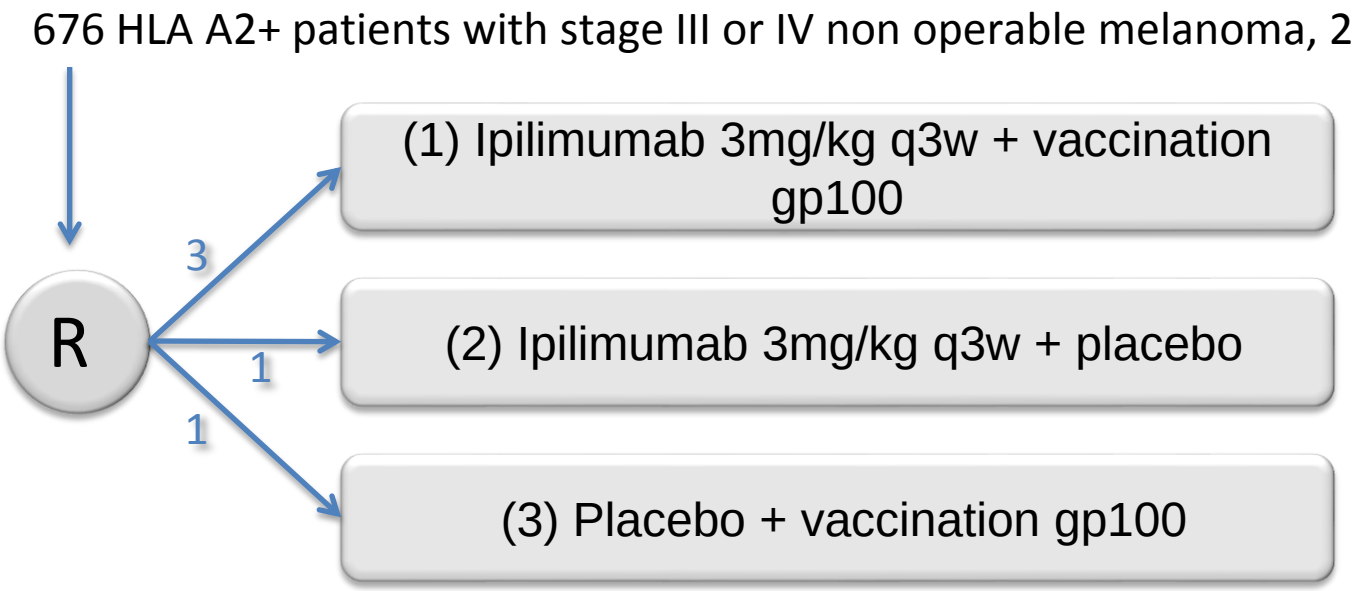
- Fc-γ dependent T-Reg depletion by ADCC that increase the Teff / Treg ratio as shown in mice:
  - Simpson & al. *J. Exp. Med.* 2013
  - Buillard & al. *J. Exp. Med.* 2013



- Reports of CTLA-4 expression at the surface of melanoma cells and ipilimumab mediated ADCC
  - Laurent & al. *J. Transl. Med.* 2013



Design of BMS 020 Phase III study:



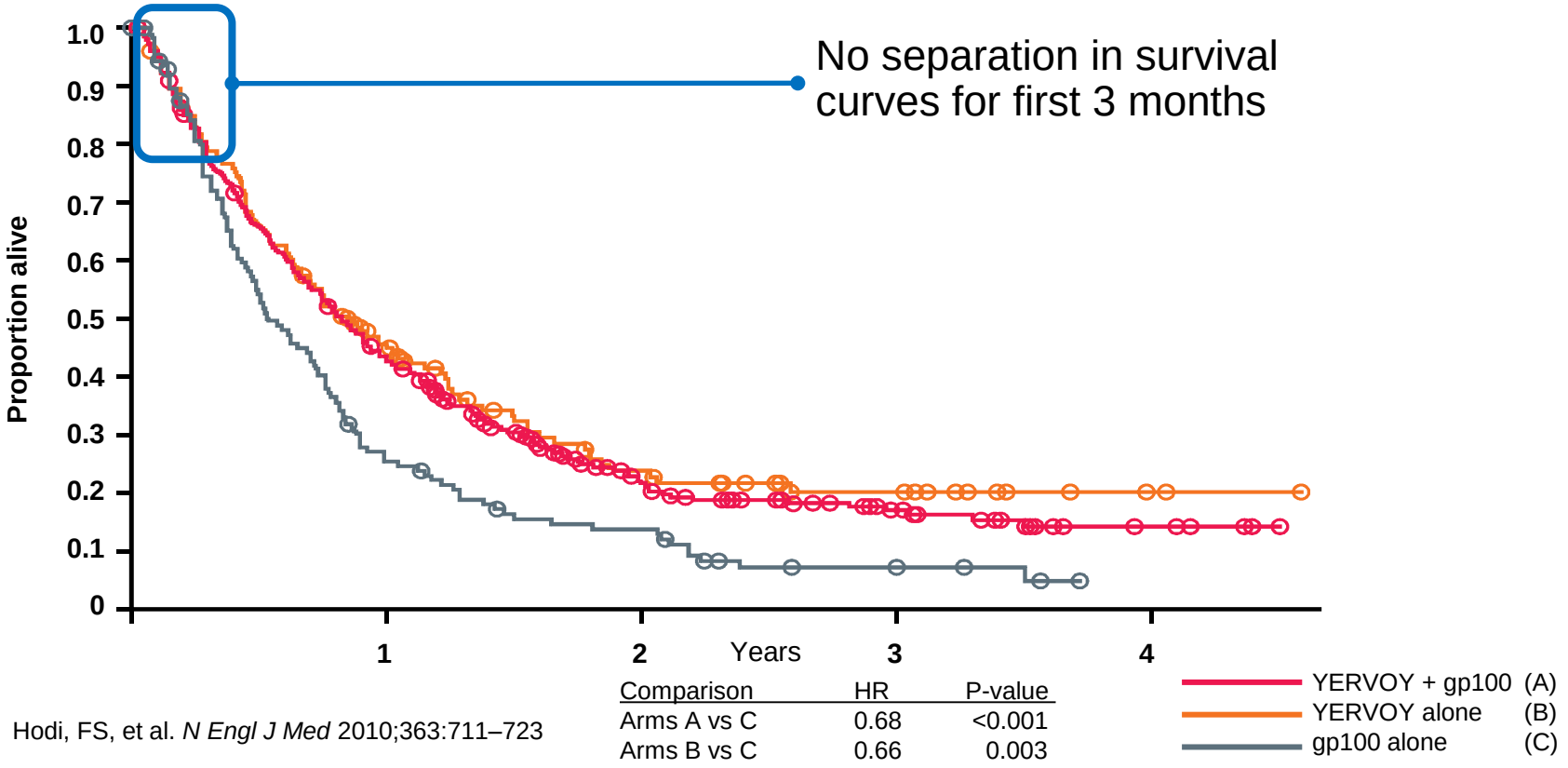
Methodology:

Primary endpoint: Overall survival (OS)

Secondary endpoint: PFS, response rate

Hodi & al, NEJM, 2010

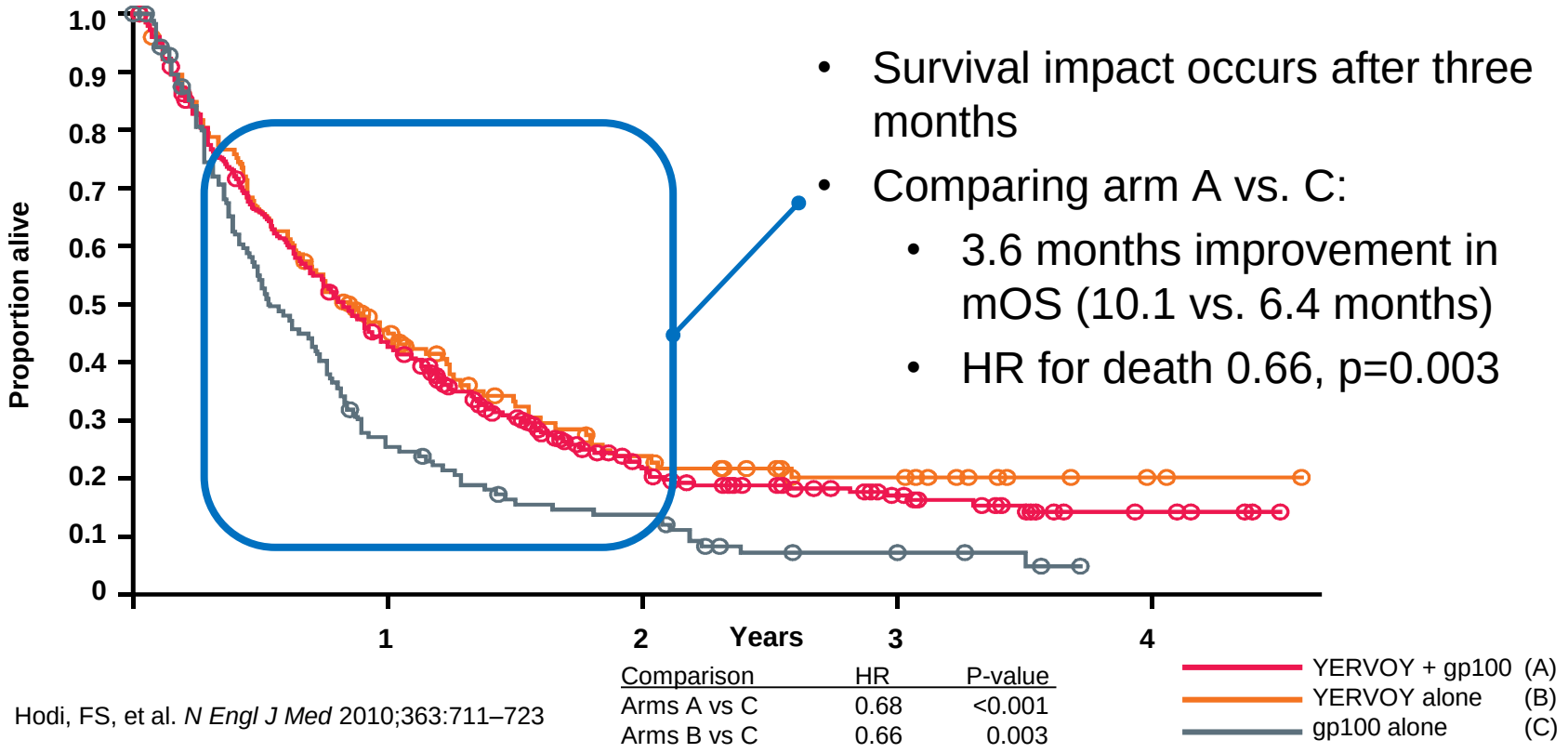
Improved Survival with Ipilimumab (> 4.5 Years of Follow-Up)



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

Improved Survival with Ipilimumab (> 4.5 Years of Follow-Up)

Survival Rate*	YERVOY + gp100 N=403 (95% CI)	YERVOY + placebo N=137 (95% CI)	gp100 + placebo N=136 (95% CI)
1 year	44% (0.39,0.49)	46% (0.37,0.54)	25% (0.18,0.33)
2 year	22% (0.17,0.26)	24% (0.16,0.32)	14% (0.08,0.2)



- Survival impact occurs after three months
- Comparing arm A vs. C:
  - 3.6 months improvement in mOS (10.1 vs. 6.4 months)
  - HR for death 0.66, p=0.003

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

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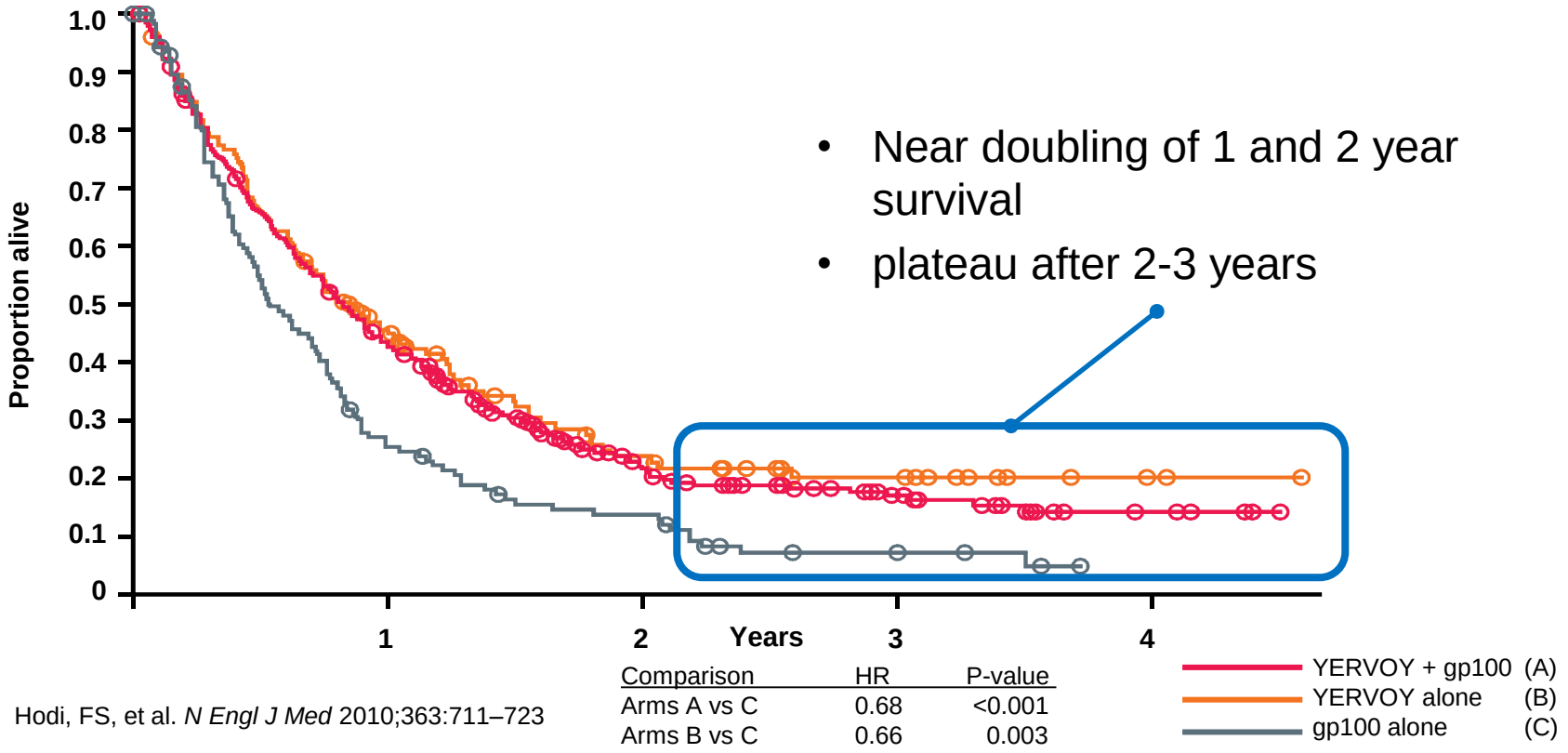
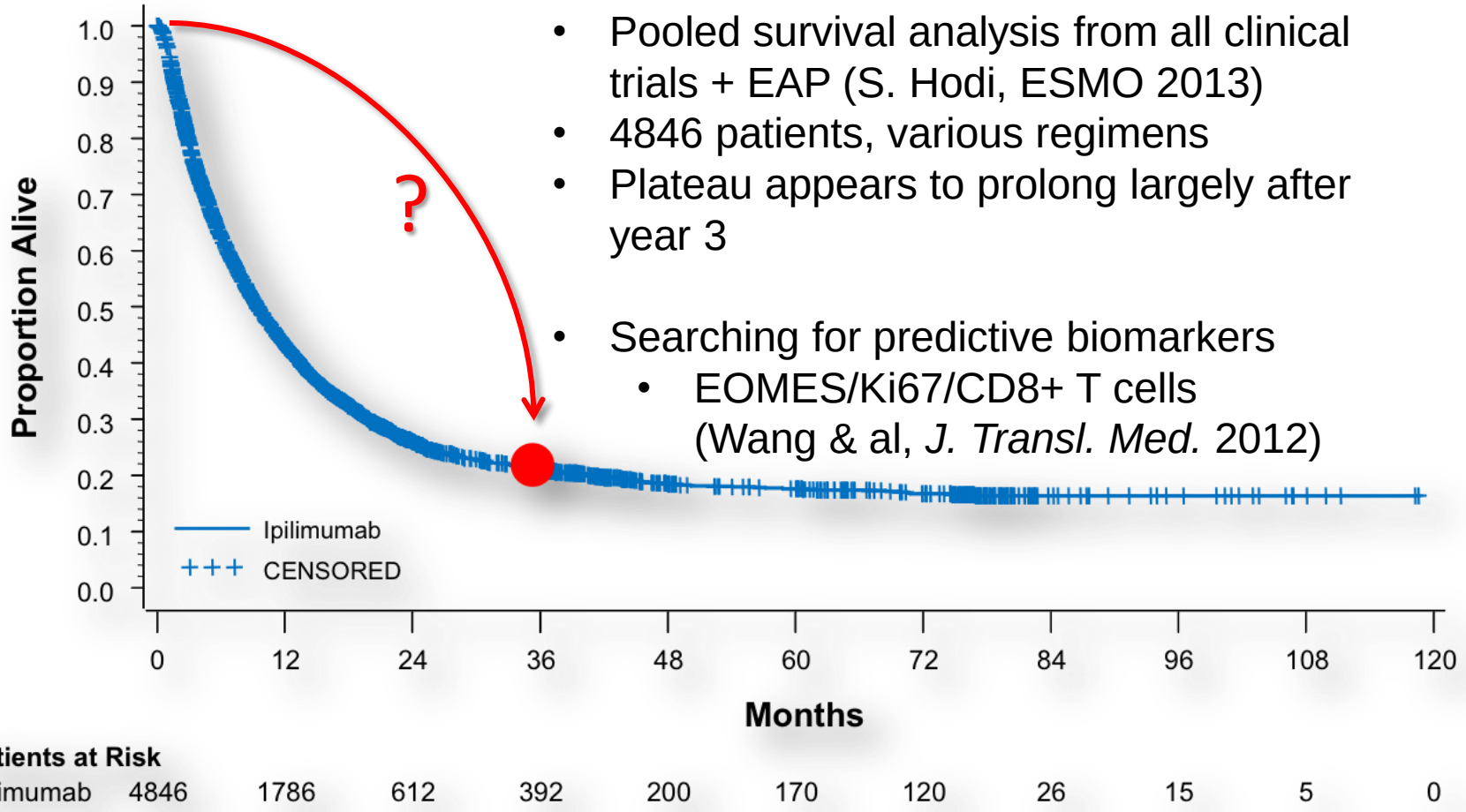


- Near doubling of 1 and 2 year survival
- plateau after 2-3 years

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

Pooled survival analysis from all phase I-III, including BMS EAP:

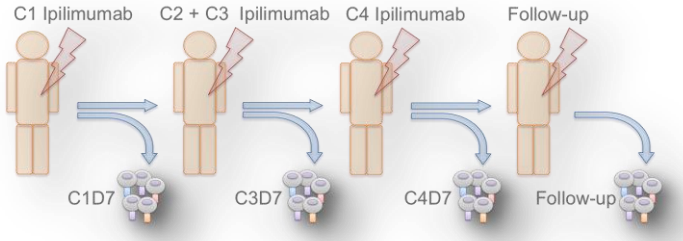


- Pooled survival analysis from all clinical trials + EAP (S. Hodi, ESMO 2013)
- 4846 patients, various regimens
- Plateau appears to prolong largely after year 3

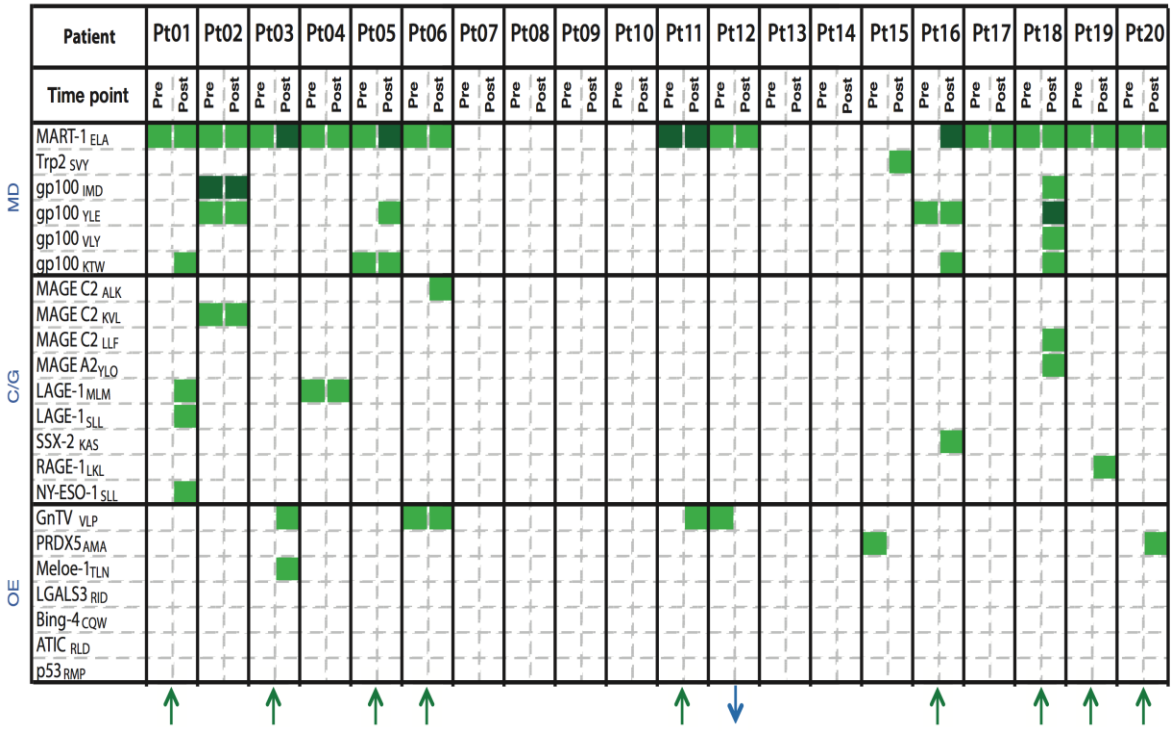
- Searching for predictive biomarkers
  - EOMES/Ki67/CD8+ T cells (Wang & al, *J. Transl. Med.* 2012)

Hodi & al, NEJM, 2010

Impact of ipi on existing / new antigenic specificities



- Systematic blood collections of patients treated by ipilimumab in our institution and at NKI (Amsterdam), pre- , during and post-treatment
- Large scale analysis of antigenic specificities (Ton Schumacher)
  - UV–induced peptide exchange and (pMHC) combinatorial coding
  - Screening of 145 melanoma epitopes



Conclusions:

- Pre-existing response remained unaltered
- Appearance of new antigenic specificities
- Confirms the clinical role in T cell priming

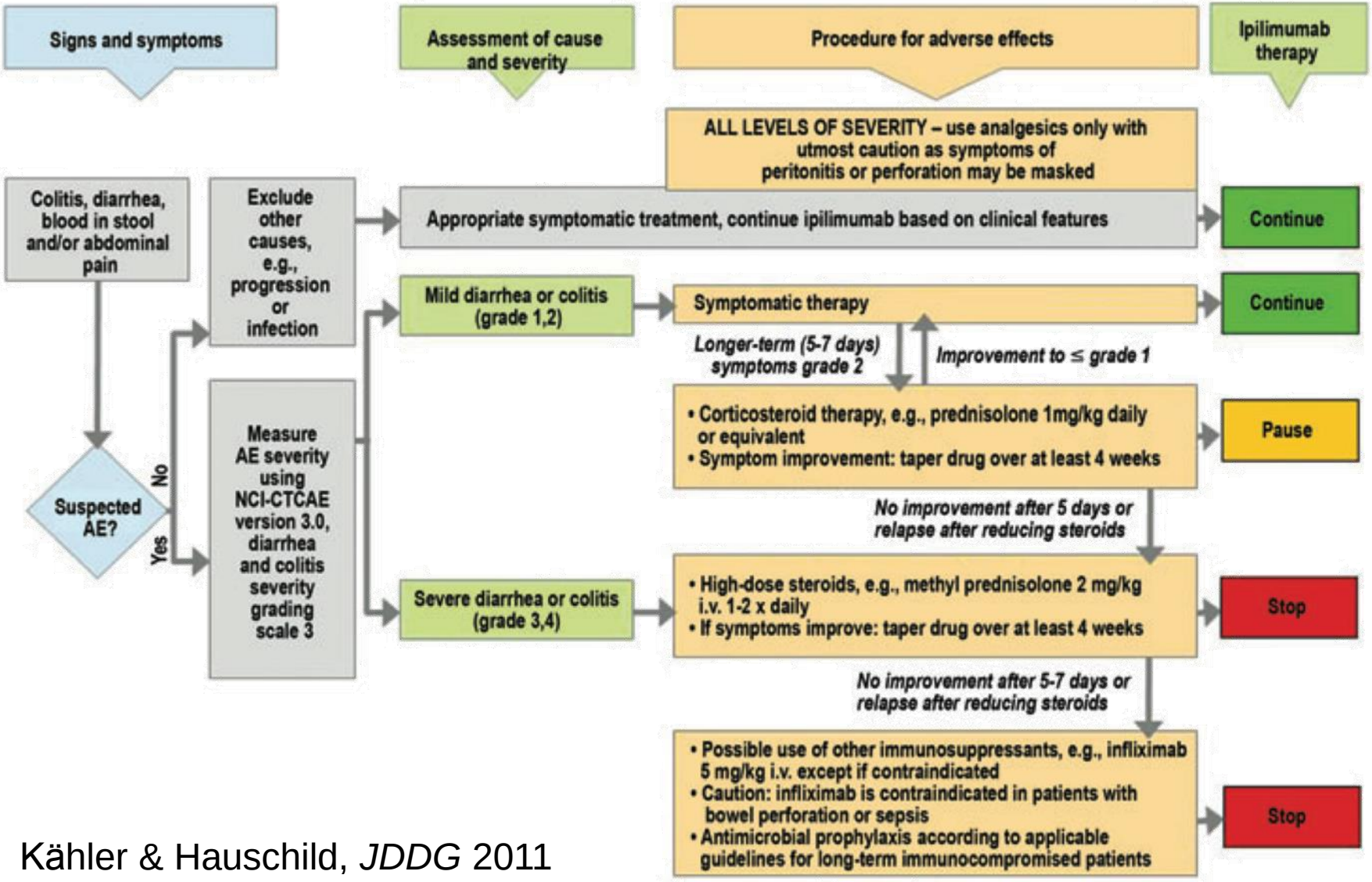
Kvisborg, *Science Transl. Med.* 2014

irAE associated with ipilimumab (Hodi & al. *NEJM*, 2010)

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)			gp100 Alone (N=132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)								
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)	128 (97.0)	54 (40.9)	8 (6.1)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)	104 (78.8)	15 (11.4)	0
Gastrointestinal disorders									
Diarrhea	146 (38.4)	16 (4.2)	1 (0.3)	43 (32.8)	7 (5.3)	0	26 (19.7)	1 (0.8)	0
Nausea	129 (33.9)	5 (1.3)	1 (0.3)	46 (35.1)	3 (2.3)	0	52 (39.4)	3 (2.3)	0
Constipation	81 (21.3)	3 (0.8)	0	27 (20.6)	3 (2.3)	0	34 (25.8)	1 (0.8)	0
Vomiting	75 (19.7)	6 (1.6)	1 (0.3)	31 (23.7)	3 (2.3)	0	29 (22.0)	3 (2.3)	0
Abdominal pain	67 (17.6)	6 (1.6)	0	20 (15.3)	2 (1.5)	0	22 (16.7)	6 (4.5)	1 (0.8)
Other									
Fatigue	137 (36.1)	19 (5.0)	0	55 (42.0)	9 (6.9)	0	41 (31.1)	4 (3.0)	0
Decreased appetite	88 (23.2)	5 (1.3)	1 (0.3)	35 (26.7)	2 (1.5)	0	29 (22.0)	3 (2.3)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	0	16 (12.2)	0	0	23 (17.4)	2 (1.5)	0
Headache	65 (17.1)	4 (1.1)	0	19 (14.5)	3 (2.3)	0	19 (14.4)	3 (2.3)	0
Cough	55 (14.5)	1 (0.3)	0	21 (16.0)	0	0	18 (13.6)	0	0
Dyspnea	46 (12.1)	12 (3.2)	2 (0.5)	19 (14.5)	4 (3.1)	1 (0.8)	25 (18.9)	6 (4.5)	0
Anemia	41 (10.8)	11 (2.9)	0	15 (11.5)	4 (3.1)	0	23 (17.4)	11 (8.3)	0
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0	22 (16.7)	0	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0	14 (10.6)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0	6 (4.5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0	1 (0.8)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0	18 (13.6)	1 (0.8)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)	2 (1.5)	0	0
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)	0	0	0
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0	0	0	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	0	0	0

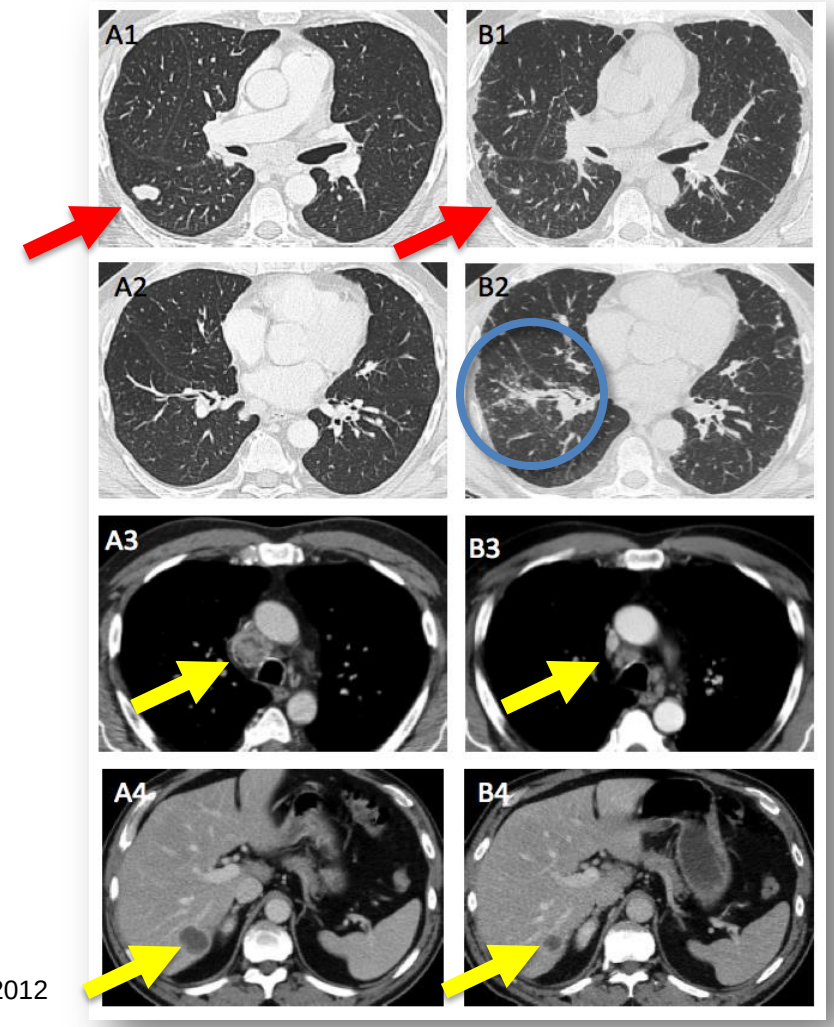
Example: guidelines for managing GI irAE



Kähler & Hauschild, *JDDG* 2011

Illustration: Lung toxicity.
Baseline and Week 12 Tumour Assessment

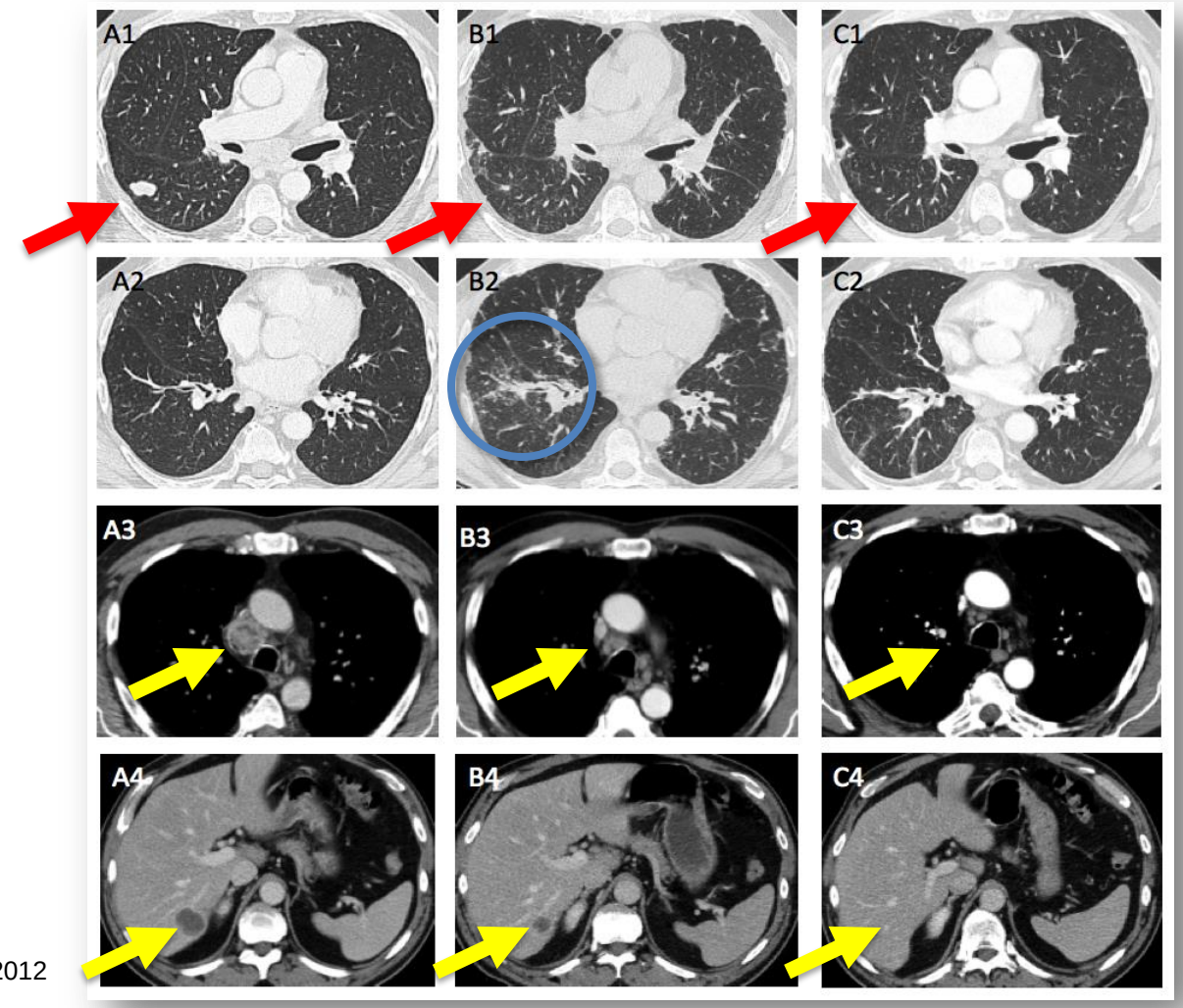
Time points: Baseline Week 12



Berthod G. & al. *JCO* 2012

One Month Steroids: Toxicity Management and Further Tumour Regression

Time points: Baseline Week 12 Week 16



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Overview of checkpoint blockade

Combinations

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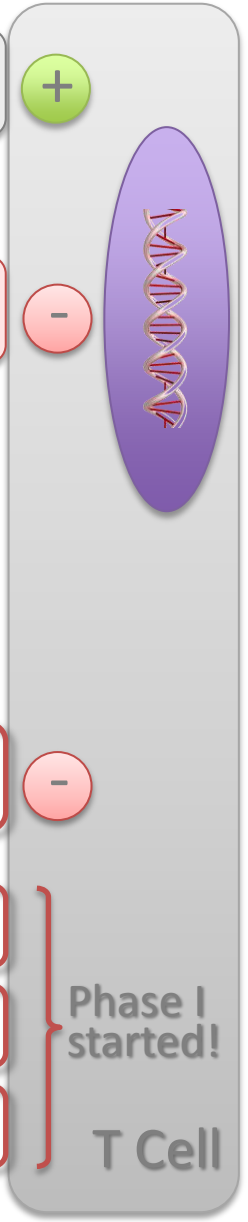

1 Hodi, *NEJM* 2010; 2 Robert, *NEJM* 2011; 3 Eggermont, ASCO 2014;
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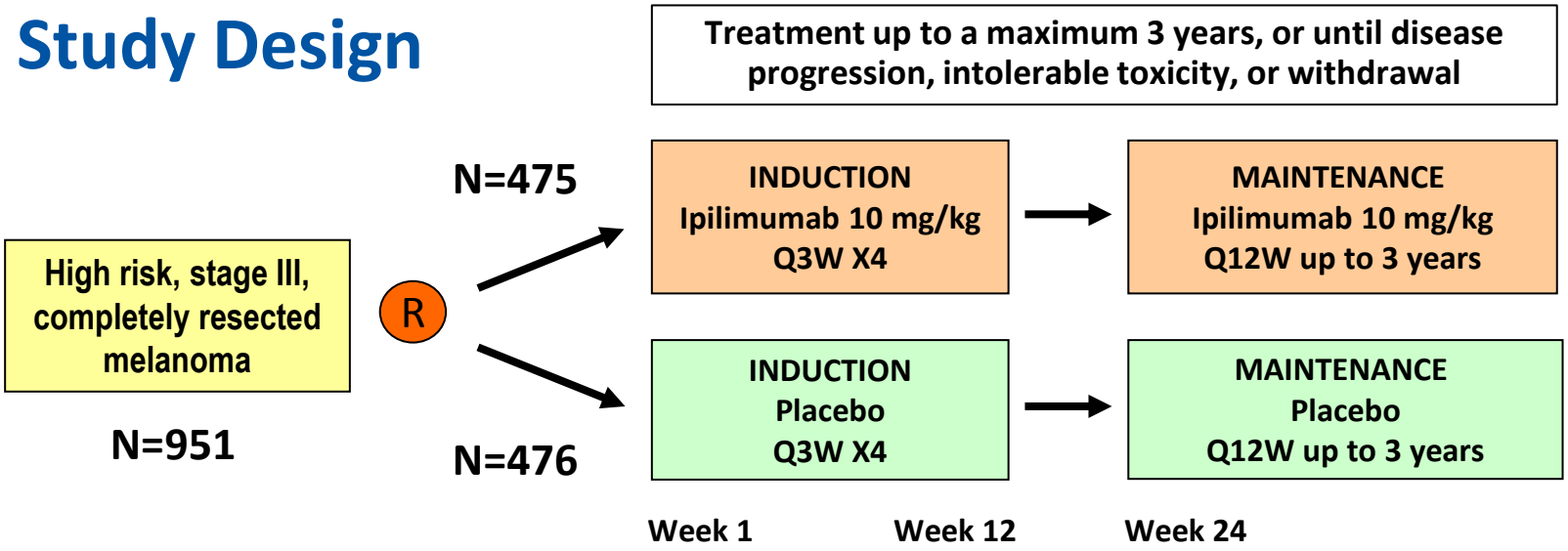
(Time units in months unless specified, NA: Not Available, NR: Not Relevant)

EORTC 18071: Study Design



Primary endpoint:

- RFS by independent review committee: time to local, regional, distant metastasis or death

Secondary endpoints:

- OS, distant metastasis-free survival, AE profile, health related QoL

Stratification factors:

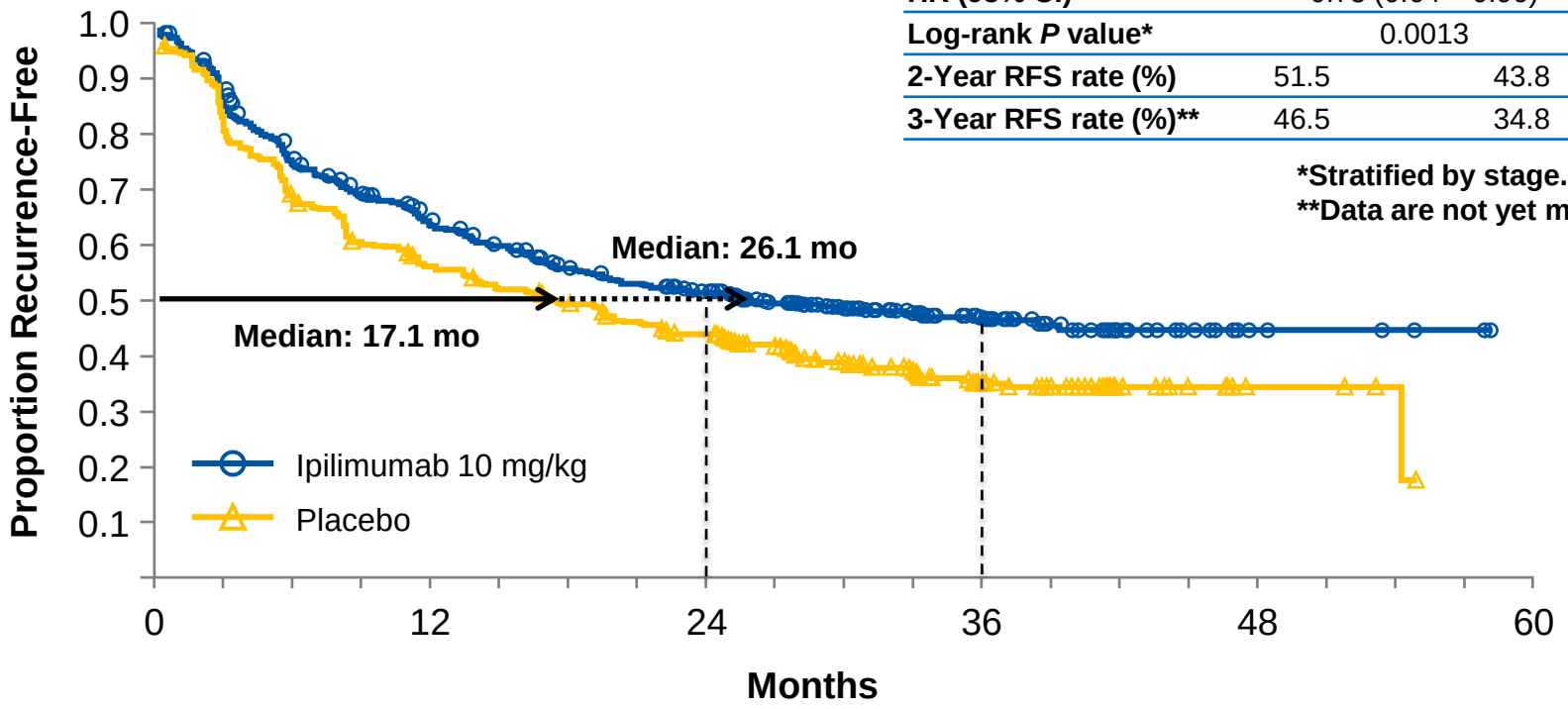
- Stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIc ≥4 nodes)
- Regions (North America, European countries and Australia)

Primary Endpoint: Recurrence-free Survival

(2.7 years /56% of overall patients reached an RFS event)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
Median RFS, mo	26.1	17.1
HR (95% CI)	0.75 (0.64 – 0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

***Stratified by stage.**
****Data are not yet mature.**



Patients at Risk

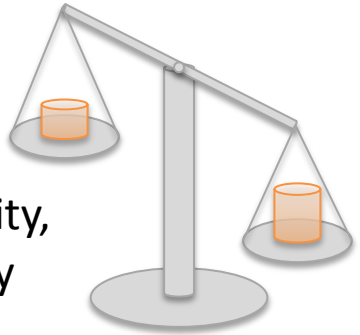
Ipilimumab	475	276	205	67	5	0
Placebo	476	260	193	62	4	0

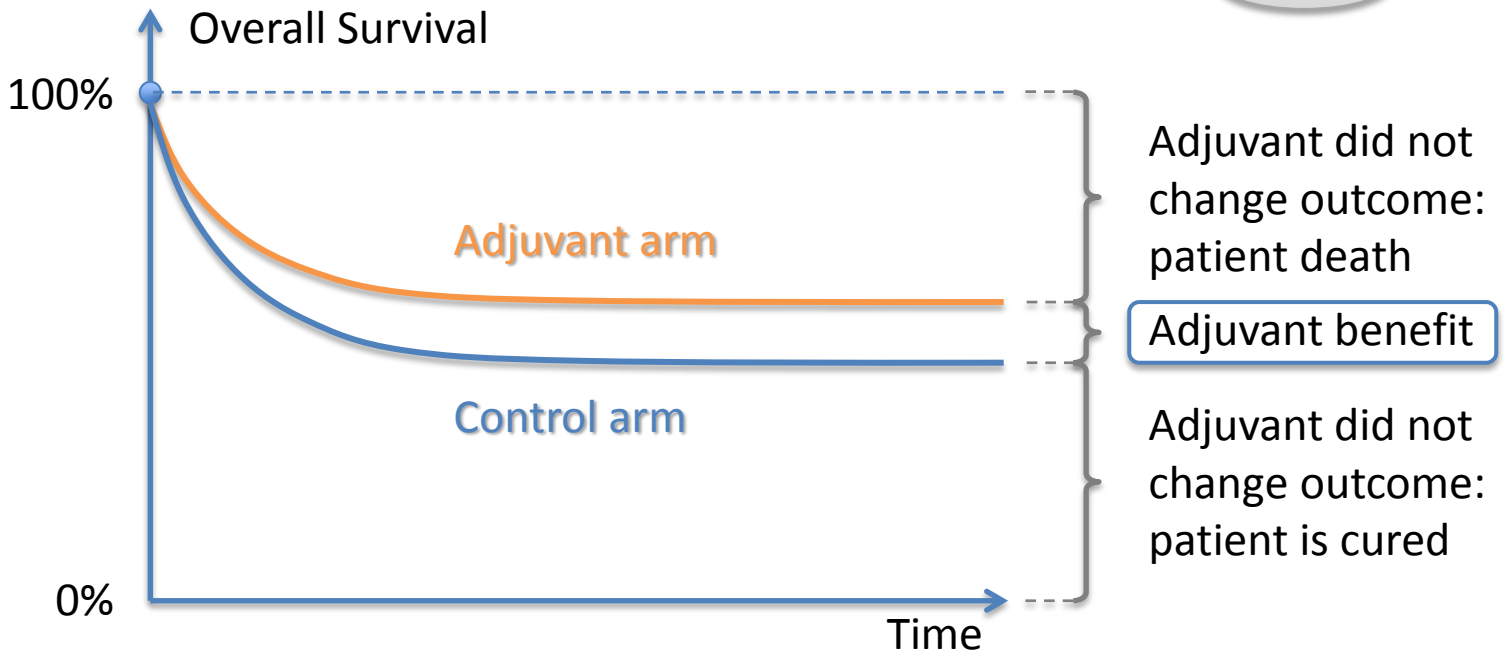
Safety: Immune-related Adverse Events

	% Patients			
	Ipilimumab (n = 471)		Placebo (n =474)	
	All grades	Grade 3-4	All grades	Grade 3-4
Any IrAE	90.4	42.0	38.6	2.5
Dermatologic	63.3	4.5	20.9	0
Rash	34.4	1.3	11.0	0
Gastrointestinal	46.3	15.9	17.7	0.8
Diarrhea	41.4	9.6	16.7	0.4
Colitis*	15.9	7.6	1.3	0.2
Endocrine	37.6	8.5	6.5	0
Hypophysitis	18.3	5.1	0.4	0
Hypothyroidism	8.9	0.2	0.8	0
Hepatic	25.1	10.6	4.4	0.2
LFT increase	19.7	5.3	4.0	0
Neurologic	4.5	1.9	1.9	0
Other	23.6	7.9	4.4	1.7

*GI perforations: ipilimumab, 6 related (1.3%); placebo, 3 unrelated (0.6%).

Cost/benefit in adjuvant therapy

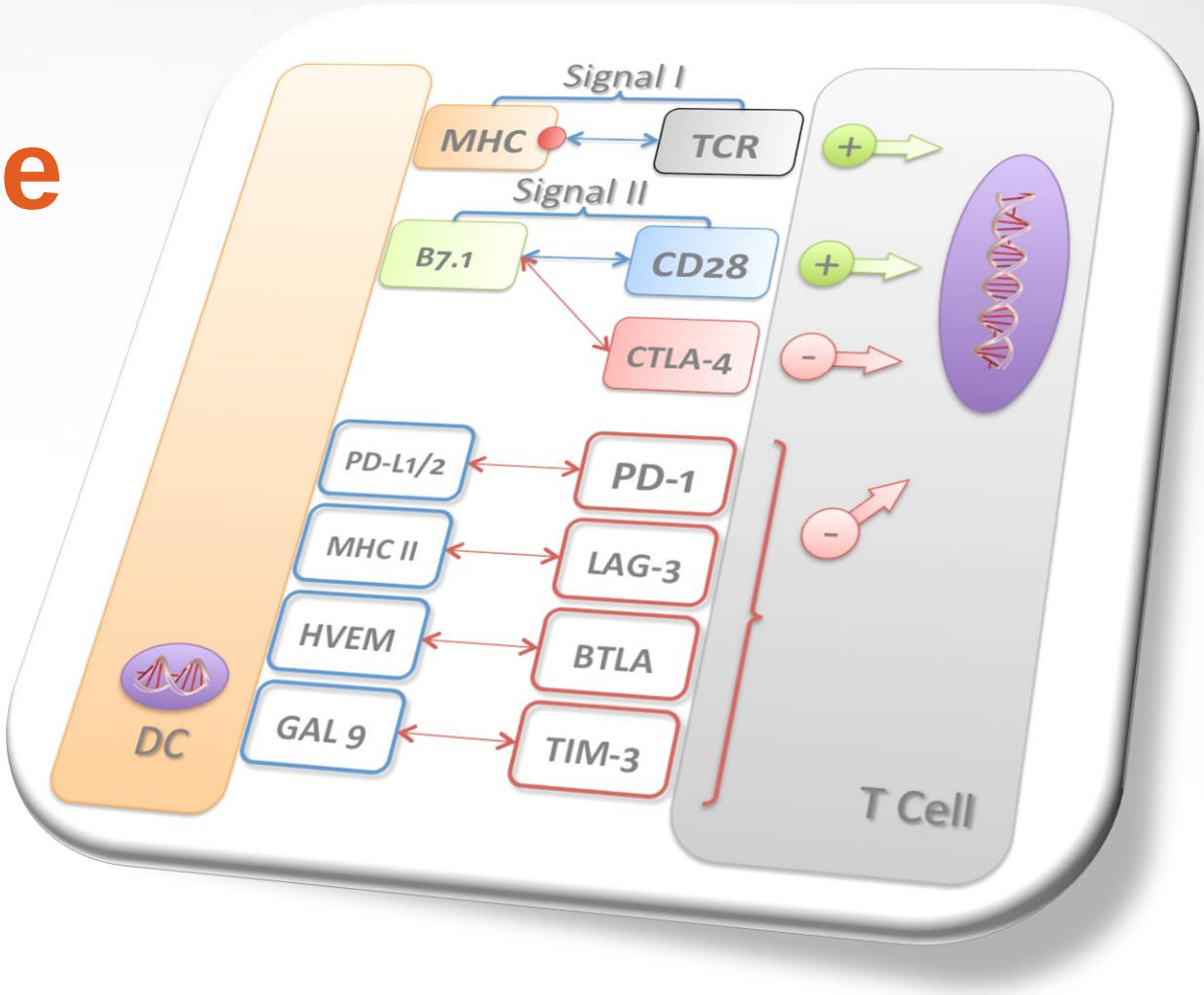




In typical adjuvant trials, this results in a large number of **patients needed to treat**:

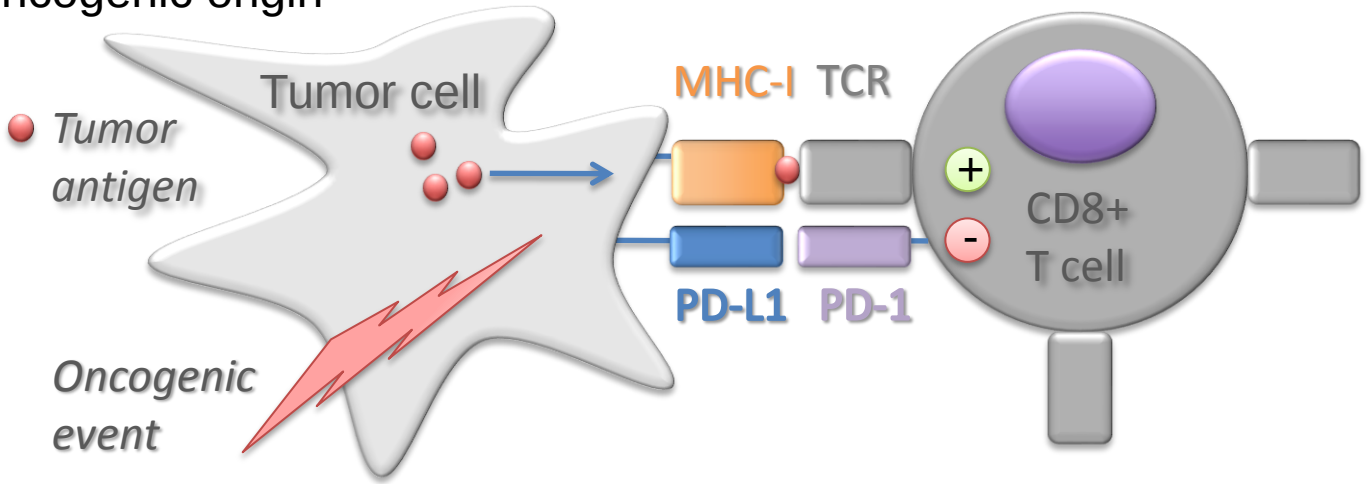
- Adjuvant Interferon - Cochrane Review (Mocellin 2013):
  - 35 participants in order to prevent 1 death
  - 97% of patients exposed for no benefit

PD-1 Blockade

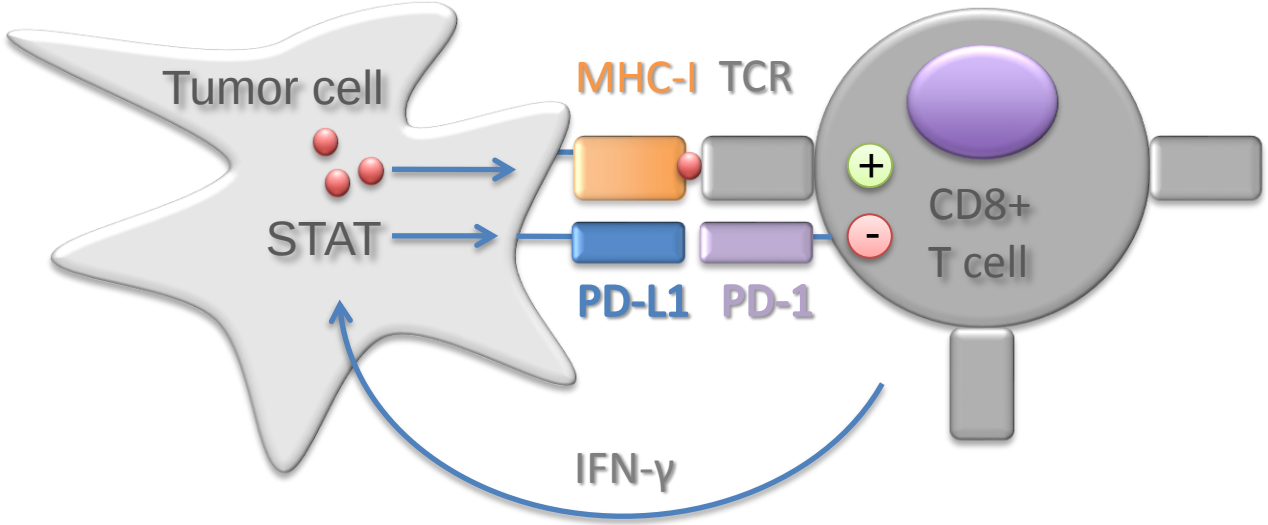


Biology of PD-L1 expression

1 Oncogenic origin



2 Induced by chronic inflammation



Clinical development status of PD-1/PD-L1 mAB

Target	Agent	Molecule	Company	Development
PD-1	**Nivolumab**-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II, III multiple tumors
	Pembrolizumab MK-3475	Humanized IgG4 mAb	MSD	Phase II, III
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	STOP
	MedI-4736	Engineered human IgG1 mAb	MedImmune	Phase I
	MPDL-3280A	Engineered human IgG1 mAb	Genentech	Phase I-II

Pembrolizumab & nivolumab monotherapies

Efficacy data phase 1

Note: data not randomized head to head and should not be compared

	PD-1 monotherapy (Merck) **Pembrolizumab** (Keytruda)	PD-1 monotherapy (BMS) **Nivolumab**
Study design	Phase 1 Keynote 001 (n=411)	Phase 1 CA209-003 (n=107)
Patient inclusion	Ipi-N, Ipi-T, Ipi-R (Previous BRAFi only for Ipi-R)	2nd line or more
Primary endpoints	Safety, ORR	Safety, tolerability
2nd endpoints	OS, PFS, DoR, PK, biomarkers	Efficacy, dose response
mOS	**25.9 months**	**20.3 months**
Landmark OS	**1-yr OS: 69% (Ipi-N 74%)** **18-mo OS: 62%**	**1-yr OS 63%** **2-yr OS 48%** **3-yr OS 41%**
mPFS	**5.4 months (5.5 Ipi-N)**	**9.7 months**
ORR	**Overall 34%** **(39% for Ipi-N)**	**32% (41% for 3mg/kg)**
DoR	**NR**	**22.9 months** **(18.2 for 3mg/kg)**

Data from presentations from ASCO 2014 & ESMO 2014 & SMR 2014

Overview of checkpoint blockade

Combinations

Single agent

Ipi + bevacizumab[6]:
- Ph1: Ipi + bev
- RR 17%, DCR 67%
- HR OS/PFS: NR/NR

Checkmate 067[8]:
- Ph3: Ipi/nivo/combo
- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

BMS-024[2]: Phase 3
- DTIC vs DTIC + ipi, 1st
- RR 34%, mPFS 2.6
- HR OS: 0.72, mOS 11

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Adjuvant

EORTC-18071[3]: Phase 3
- Ipi (10mg) vs placebo
- mRFS: 26 vs 17
- HR RFS/OS: 0.75/NA

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- Nivolumab, 2nd +
- RR 31%, mOS: 17
- HR OS/PFS: NR/NR

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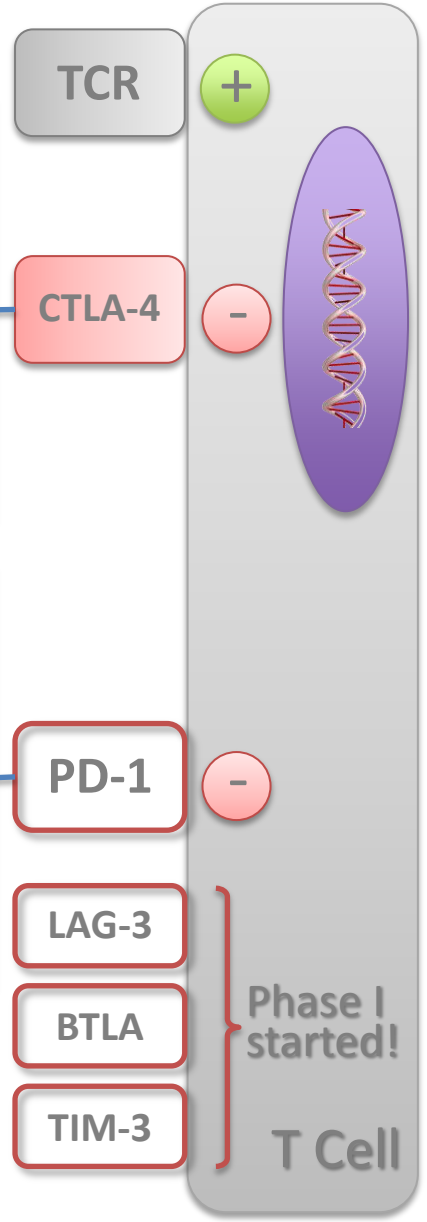
- Keytruda, Ipi-N or T
- RR 34%, mOS 26
- HR OS/PFS: NR/NR

CA-209-037[8]: Phase 3
- Nivo vs ICC, 2nd
- RR 32%,
- HR OS/PFS: NA/NA

CA-209-066[6]: Phase 3
- Nivo vs DTIC, 1st
- RR 40%,
- HR OS/PFS: 0.42/0.43



1 Hodi, *NEJM* 2010; 2 Robert, *NEJM* 2011; 3 Eggermont, ASCO 2014;
4 Robert, *Lancet Oncol* 2014; 5 Topalian, *JCO* 2014; 6 Robert, *NEJM* 2014;
7 Hodi *Cancer Immunol Res* 2014; 8 ASCO/ESMO/SMR 2014

(Time units in months unless specified, NA: Not Available, NR: Not Relevant)

MK-3475: ORR by Dosing Regimen and Prior Ipilimumab

Lambrolizumab Dose	Prior IPI Treatment	RECIST 1.1, Independent Central Review			irRC, Investigator Assessment	
		N	ORR, % (95% CI)	Response Duration Range, mo	N	ORR, % (95% CI)
Total		117	38 (25–44)*	1.9+ – 10.8+	135	37 (29–45)
10 mg/kg Q2W	Naive	39	49 (32–65)	1.9+ – 10.8+	41	56 (40–72)
	Treated	13	62 (32–86)	2.8+ – 8.3+	16	56 (30–80)
	Total	52	52 (38–66)	1.9+ – 10.8+	57	56 (42–69)
10 mg/kg Q3W	Naive	19	26 (9–51)	2.6 – 5.6+	24	33 (16–55)
	Treated	26	27 (12–48)	2.8+ – 8.3+	32	22 (9–40)
	Total	45	27 (15–42)	2.6 – 8.3+	56	27 (16–40)
2 mg/kg Q3W	Naive	20	25 (9–49)	2.1+ – 5.5+	22	14 (3–35)

***Including unconfirmed responses, ORR was 44% across all doses and 56% for 10 mg/kg Q2W, 36% for 10 mg/kg Q3W, and 35% for 2 mg/kg Q3W.**
"+" indicates censored observation.

Ribas, ASCO 2013
Hamid & al. *NEJM* 2013

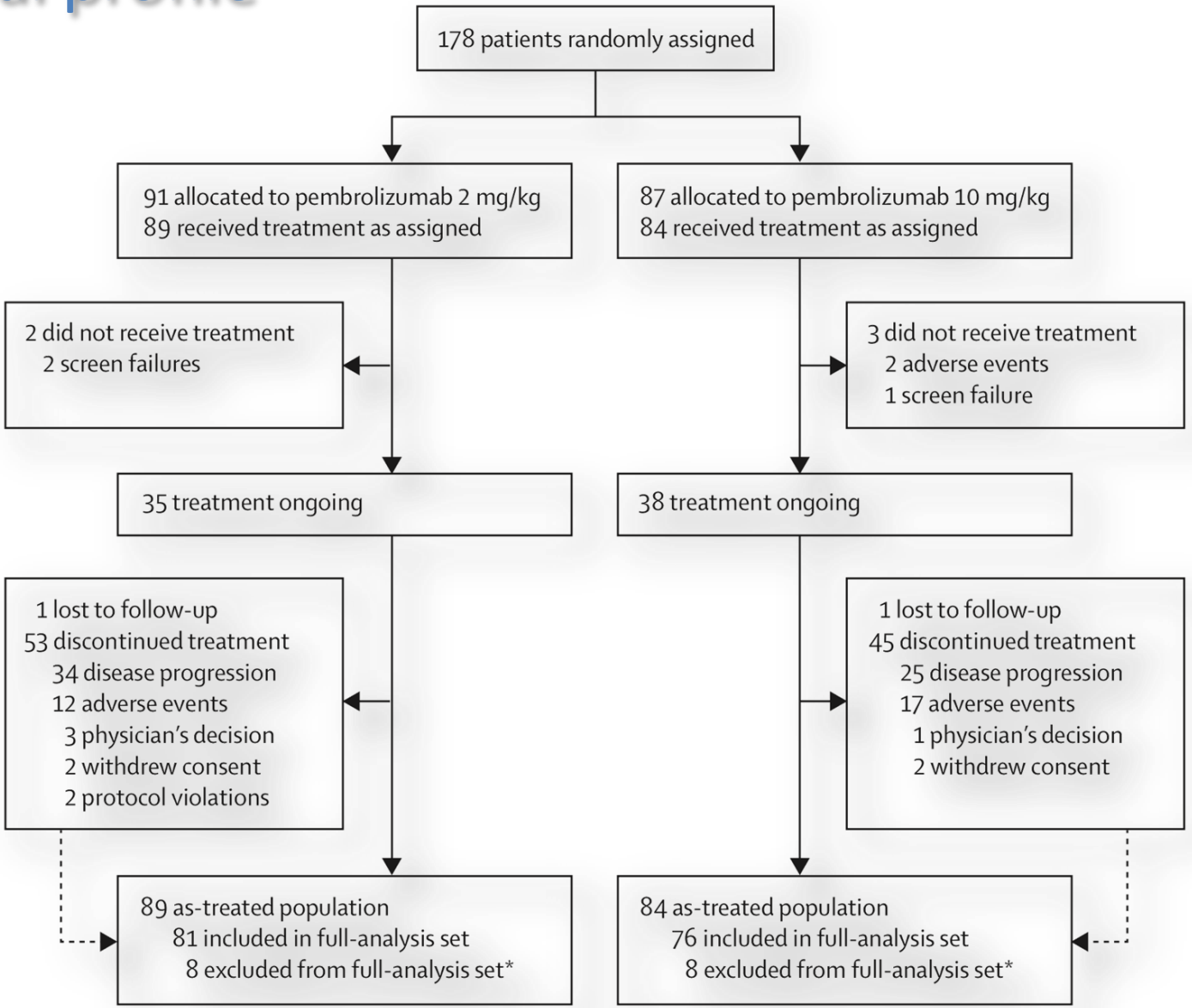
Keynote-001 Update: SMR 2014

ORR (RECIST v1.1), Central Review	Total N=360	IPI Naïve n=165	IPI Treated n=195
CR, % (95% CI)	8 (5-11)	10 (6-15)	6 (3-10)
ORR, % (95% CI)	34 (29-39)	39 (32-47)	29 (23-36)
DCR, % (95% CI)	54 (49-59)	55 (47-62)	54 (47-61)

Compared with previous data analysis (cutoff, Octoer 13th, 2013), CR rate increased From 5% to 8%

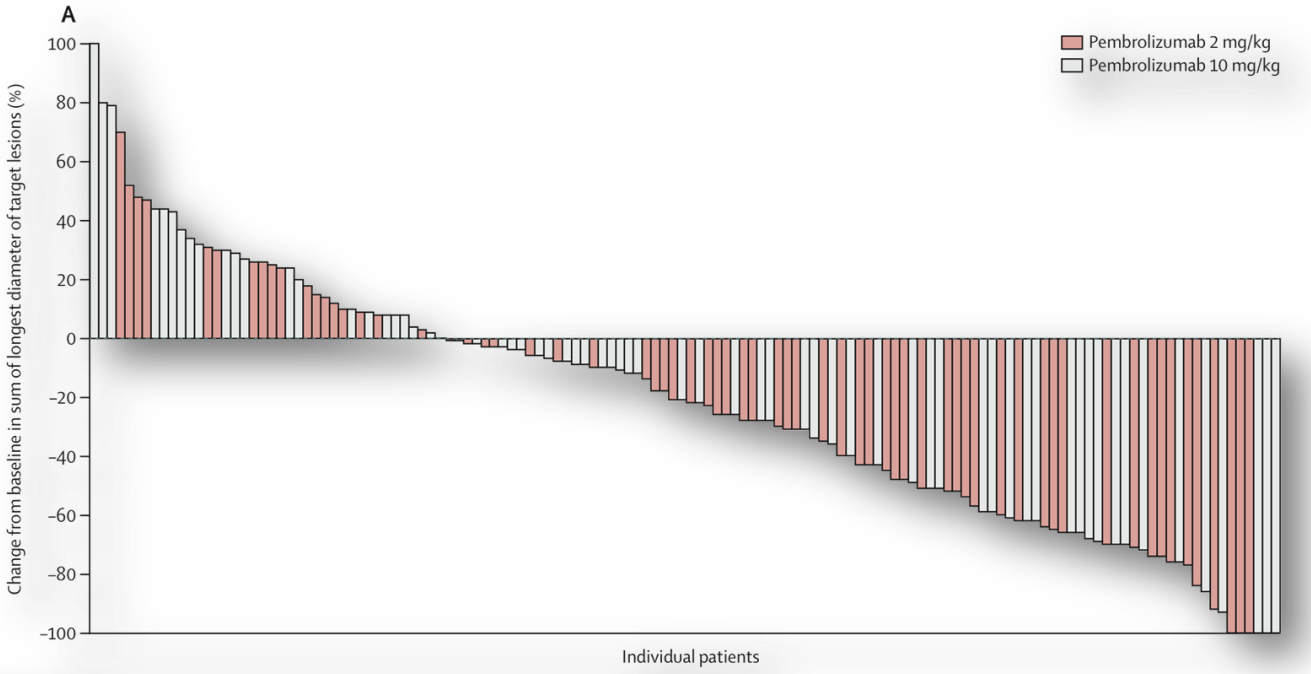
Society for Melanoma Research (SMR) 2014

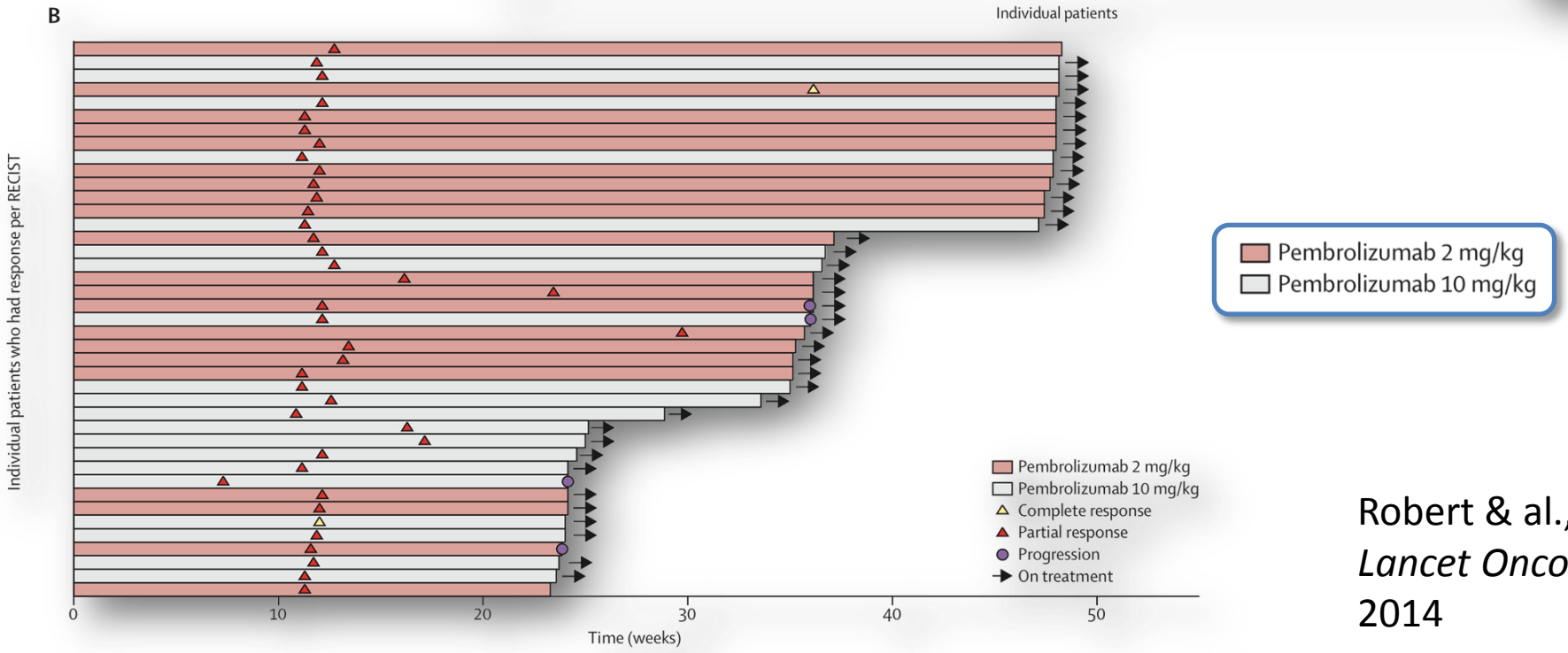
Keynote-001 (international expansion cohort): trial profile



Robert & al., *Lancet Oncol* 2014

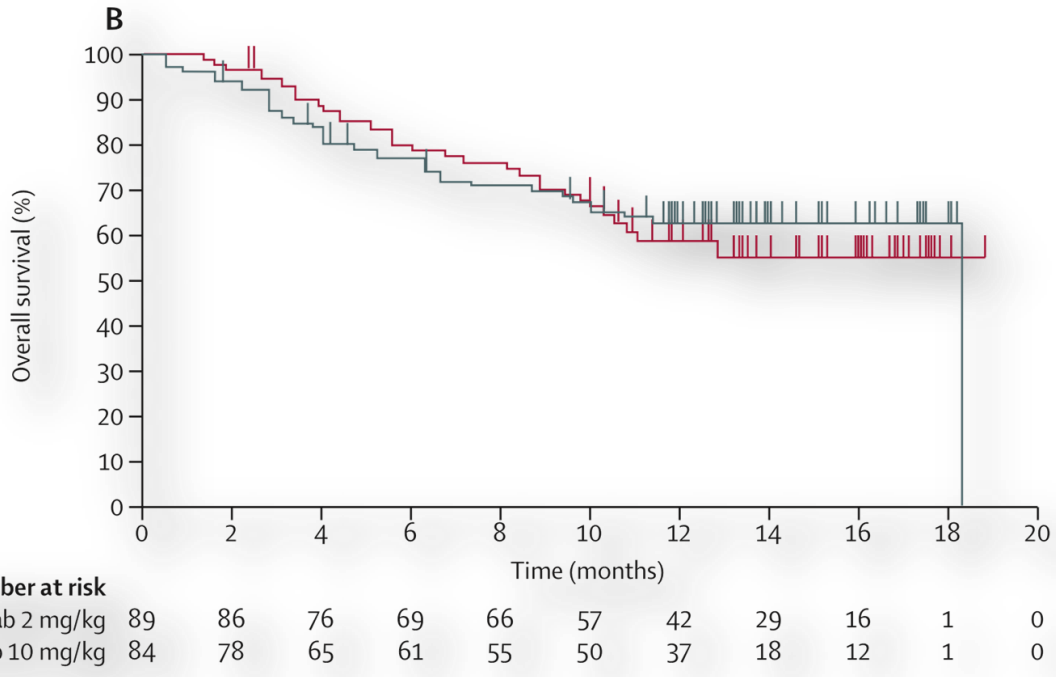
Keynote-001 (expansion): response pattern

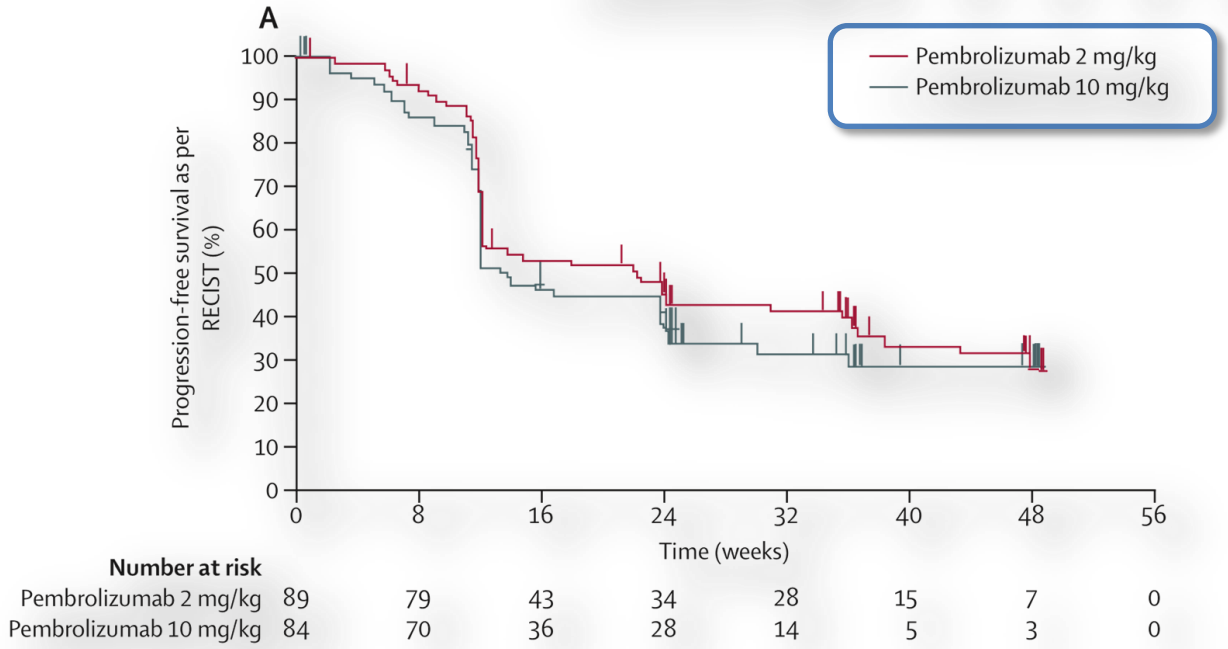




Robert & al., *Lancet Oncol* 2014

Keynote-001 (expansion): OS and PFS





Robert & al., *Lancet Oncol* 2014

Safety and tolerability of checkpoint inhibitors

- *Pembrolizumab ph1 Keynote-001*

Adverse event, %	Total (n=411)	
	All grades	*Grade 3/4*
Fatigue	36	2
Pruritus	24	<1
Rash	20	<1
Diarrhoea	16	<1
Arthralgia	16	0
Nausea	12	<1
Vitiligo	11	0
Asthenia	9	0
Cough	9	0
Myalgia	9	0
Headache	8	<1
Hypothyroidism	8	<1
Decreased appetite	7	<1
Dyspnea	7	<1
Chills	6	0
Pyrexia	6	0
ALT increased	5	<1

- *Nivolumab ph1 CA209-003 selected AEs*

Adverse event, n (%)	*All grades*	*Grade 3/4*
Any select AE	54 (58)	5 (5)
Skin	36 (38)	0
Gastrointestinal	18 (19)	2 (2)
Endocrinopathies	13 (14)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion reaction	6 (6)	0
Pulmonary	4 (4)	0
Renal	2 (2)	1 (1)

Data from ASCO 2014 & ESMO & SMR 2014 presentations

Note: data not randomized head to head and should not be compared directly

AE: PD-1 compared to CTLA-4 blockade

Drug-Related Event	All Grades (N=135)	Grade 3 or 4 (N=135)
	number (percent)	
Any	107 (79)	17 (13)
Hypothyroidism	11 (8)	1 (1)
Gastrointestinal disorder		
Diarrhea	27 (20)	1 (1)
Nausea	13 (10)	0
Abdominal pain	7 (5)	1 (1)
Generalized symptom		
Fatigue	41 (30)	2 (1)
Myalgia	16 (12)	0
Headache	14 (10)	0
Asthenia	13 (10)	0
Pyrexia	10 (7)	0
Chills	9 (7)	0
Decreased appetite	6 (4)	1 (1)
Increase in aminotransferase level		
AST	13 (10)	2 (1)
ALT	11 (8)	0
Renal failure	3 (2)	2 (1)
Respiratory disorder		
Cough	11 (8)	0
Dyspnea	6 (4)	0
Pneumonitis	6 (4)	0
Skin disorder		
Rash	28 (21)	3 (2)
Pruritus	28 (21)	1 (1)
Vitiligo	12 (9)	0

αPD-1 MAB

Hamid & al. *NEJM* 2013

Adverse Event	Ipilimumab Alone (N=131)		
	Total	Grade 3	Grade 4
	number of patients (percent)		
Any immune-related event	80 (61.1)	16 (12.2)	3 (2.3)
Dermatologic	57 (43.5)	2 (1.5)	0
Pruritus	32 (24.4)	0	0
Rash	25 (19.1)	1 (0.8)	0
Vitiligo	3 (2.3)	0	0
Gastrointestinal	38 (29.0)	10 (7.6)	0
Diarrhea	36 (27.5)	6 (4.6)	0
Colitis	10 (7.6)	7 (5.3)	0
Endocrine	10 (7.6)	3 (2.3)	2 (1.5)
Hypothyroidism	2 (1.5)	0	0
Hypopituitarism	3 (2.3)	1 (0.8)	1 (0.8)
Hypophysitis	2 (1.5)	2 (1.5)	0
Adrenal insufficiency	2 (1.5)	0	0
Increase in serum thyrotropin level	1 (0.8)	0	0
Decrease in serum corticotropin level	2 (1.5)	0	1 (0.8)
Hepatic	5 (3.8)	0	0
Increase in alanine aminotransferase	2 (1.5)	0	0
Increase in aspartate aminotransferase	1 (0.8)	0	0
Hepatitis	1 (0.8)	0	0
Other	6 (4.6)	2 (1.5)	1 (0.8)

αCTLA-4 MAB

Hodi & al, *NEJM* 2010

Overview of checkpoint blockade

Combinations

Single agent

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- Ph1: Ipi + bev
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- HR OS/PFS: NR/NR

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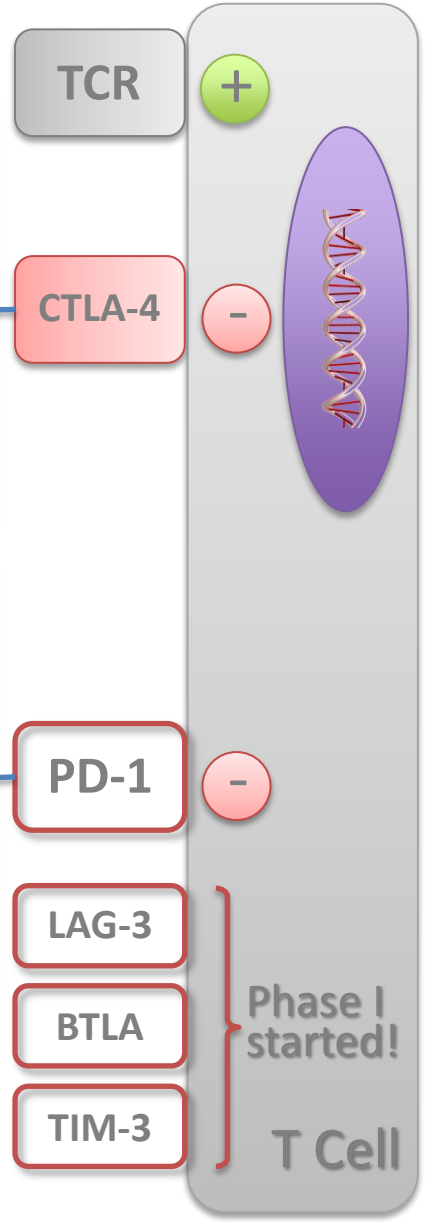

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(Time units in months unless specified, NA: Not Available, NR: Not Relevant)

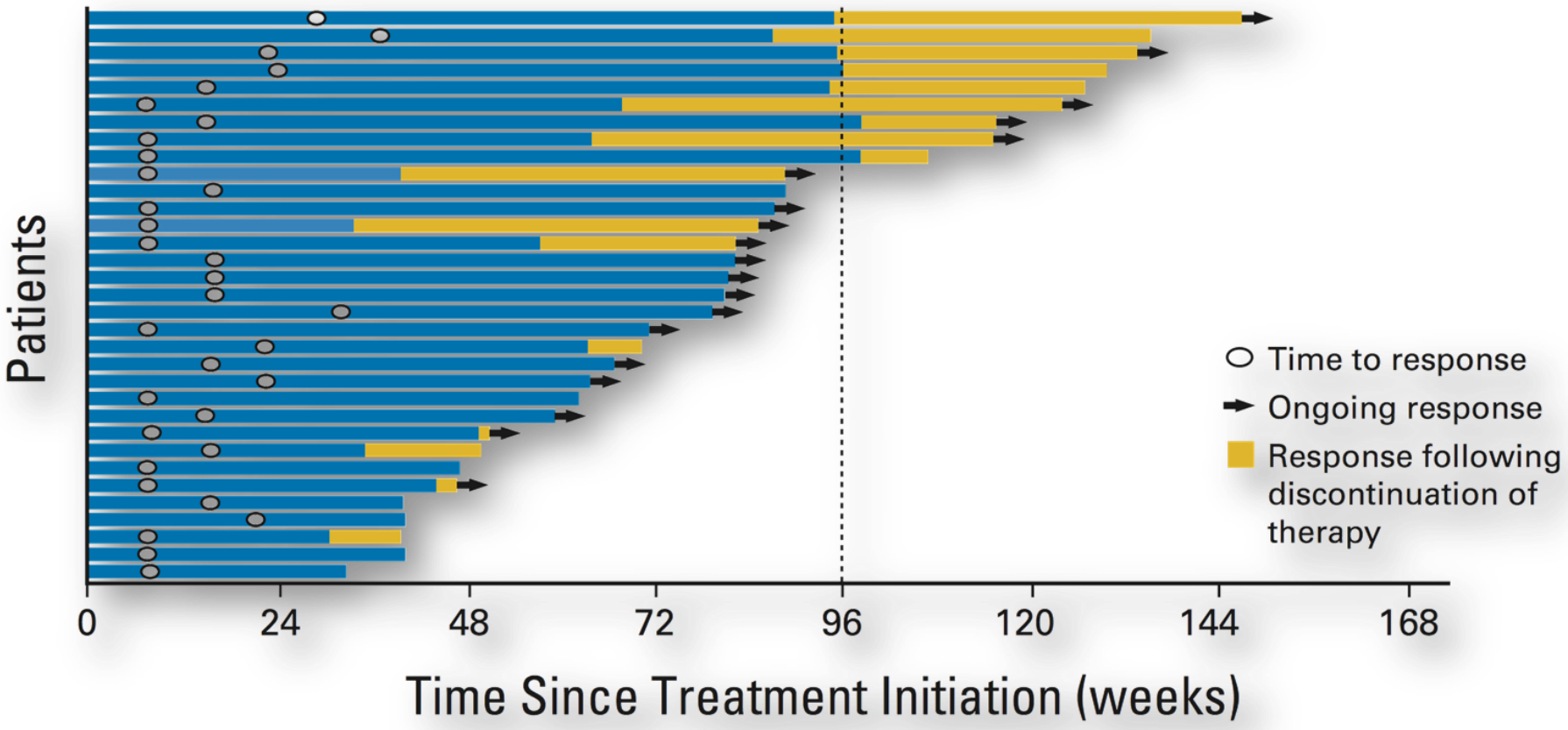
Nivolumab Phase 1: CA209-003 Response rates

Dose, mg/kg	ORR %, (n/N)	Median Duration of Response, Weeks (range)
All doses	32 (34/107)	99.4 (17.0+ to 117.0+)
0.1	35 (6/17)	NR (24.1 to 80.1+)
0.3	28 (5/18)	NR (18.4 to 93.3+)
1	34 (12/35)	104 (17.0+, 108.1+)
3*	**41 (7/17)**	**75 (40.1+ to 115.4+)**
10	20 (4/20)	112 (73.9 to 117.0+)

* 3mg/kg is the dose selected for phase III studies

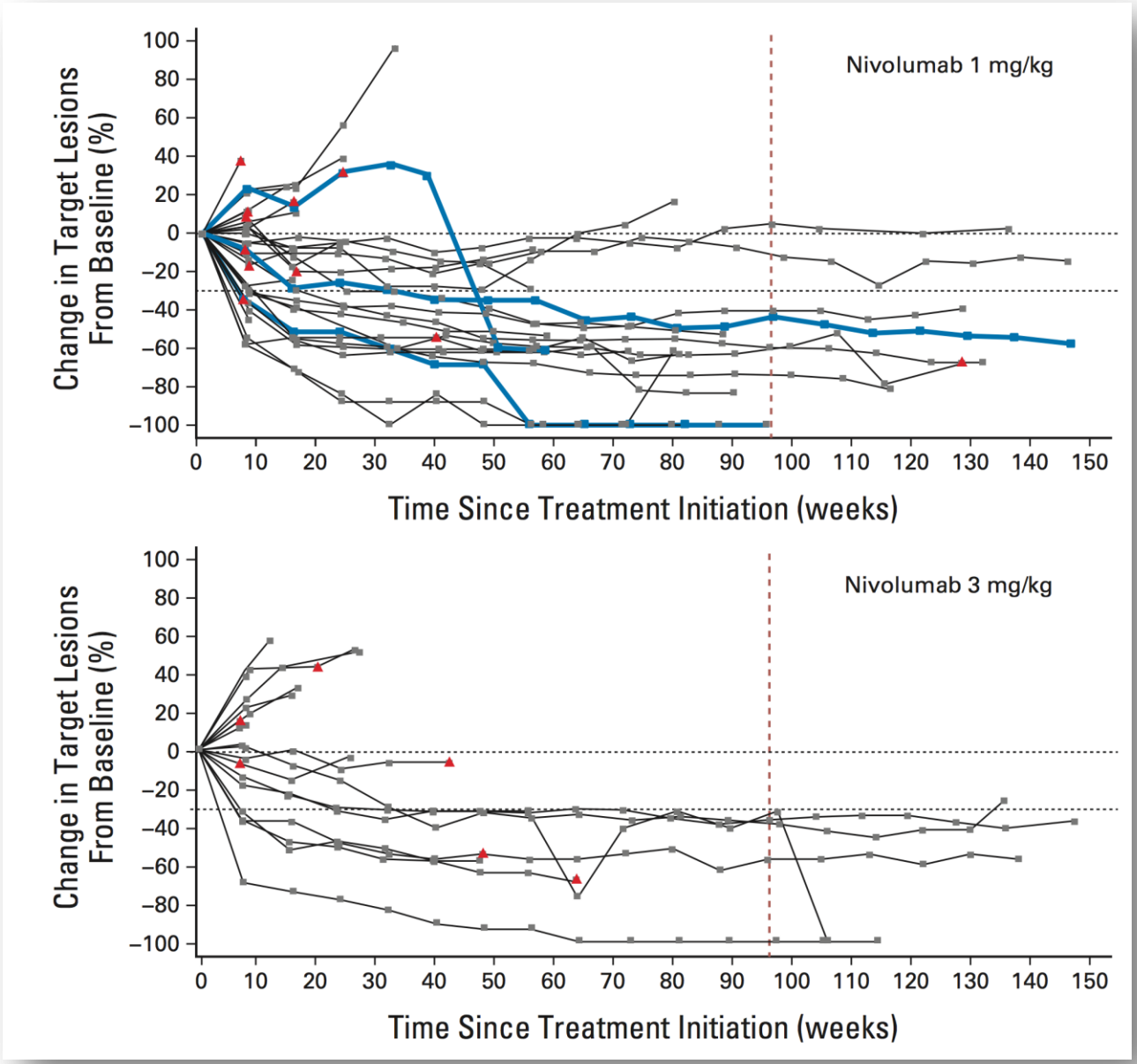
S. Hodi, ASCO 2014, CA209-003

Updated nivolumab single agent data



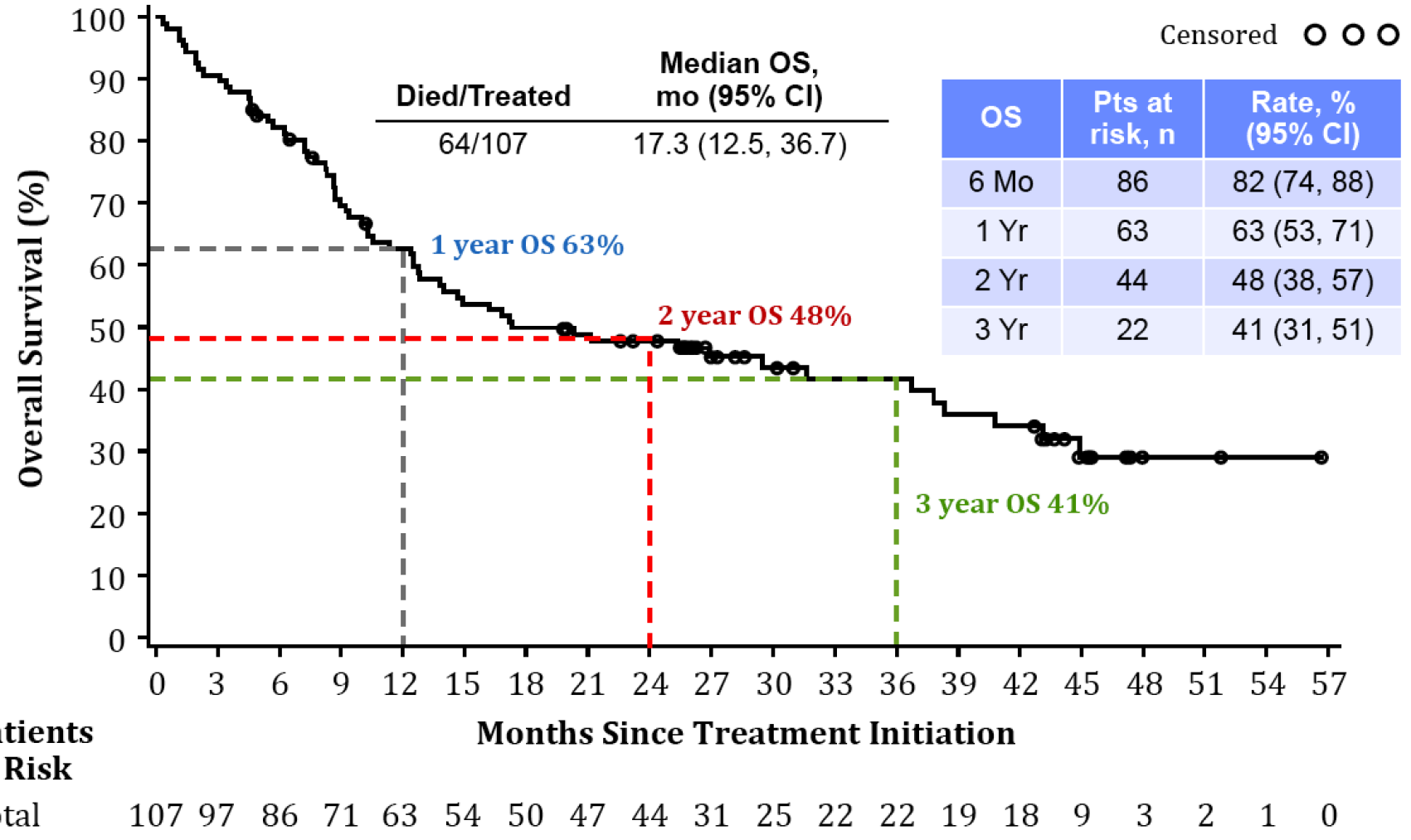
Topalian & al., *JCO* 2014

Spider plots of nivolumab single agent



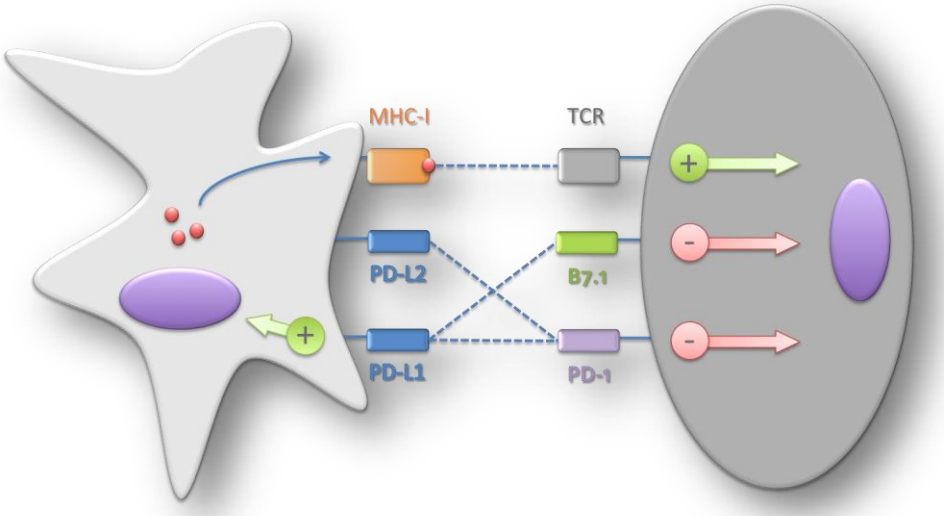
Topalian & al.
JCO 2014

CA209-003: overall survival is 48% at 2 years and 41% at 3 years

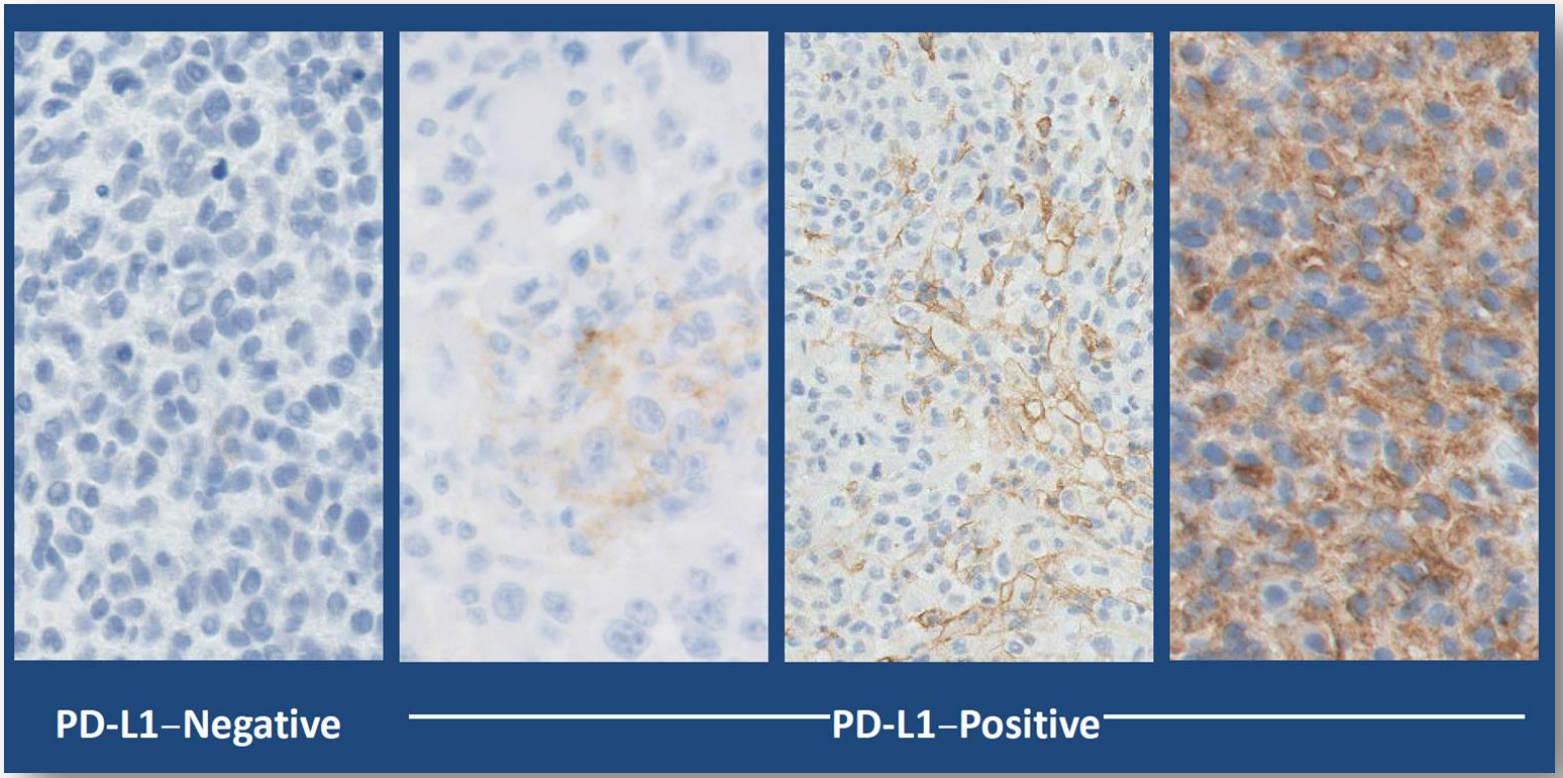


S. Hodi, ASCO 2014, CA209-003

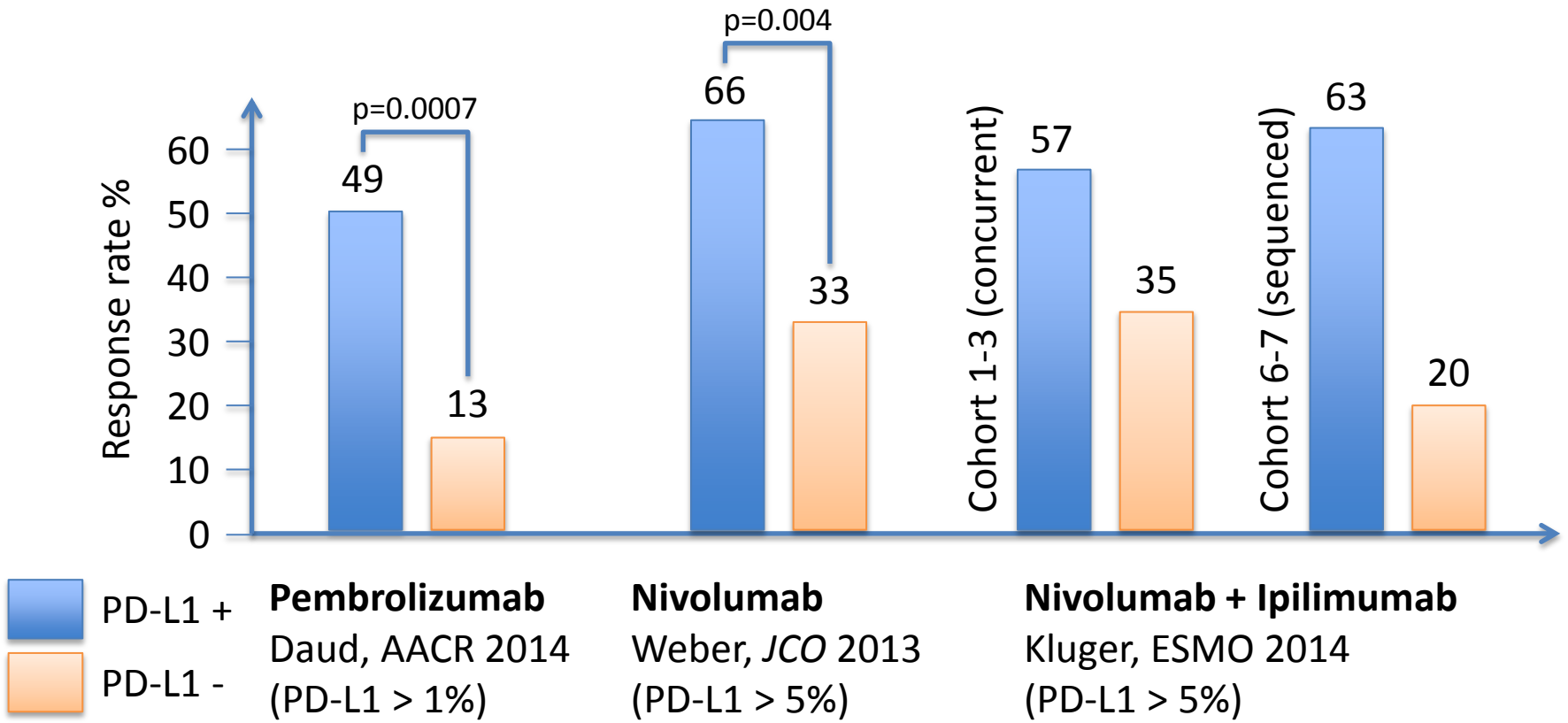
PD-L1 as a predictive biomarker?



Daud & al., AACR 2014



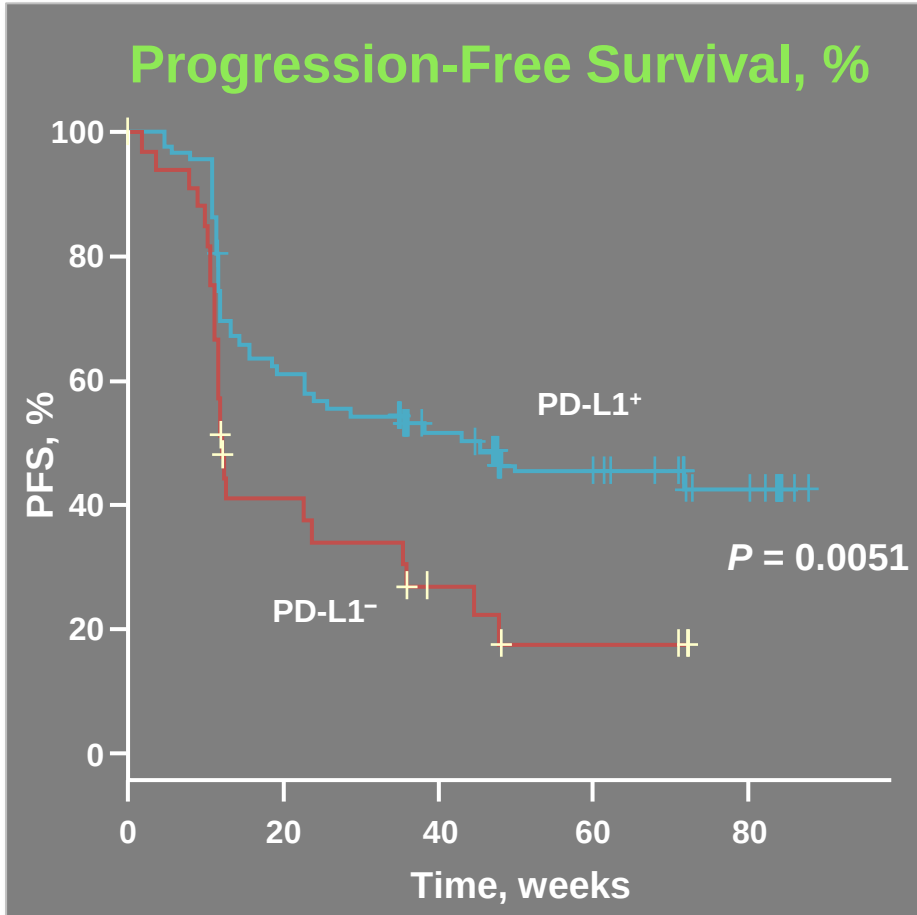
PD-L1 as a predictive biomarker for CTLA-4 + PD-1 double blockade

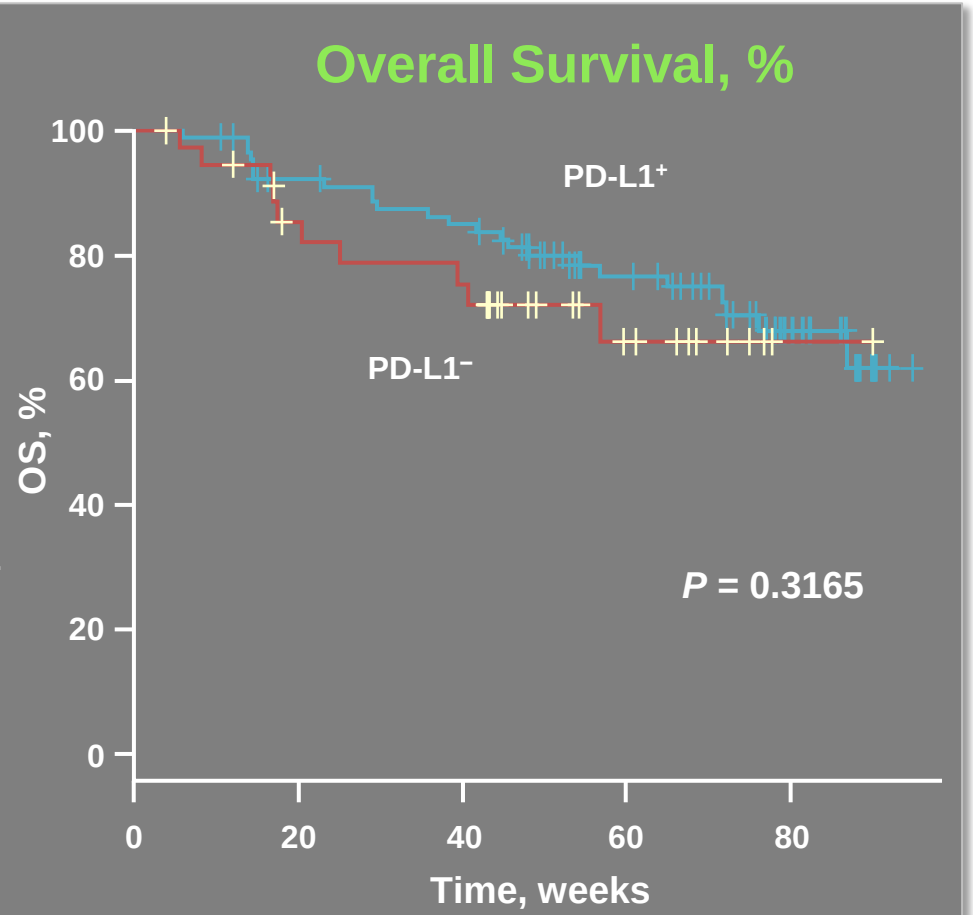


Caveats:

- Sensitivity of results with respect to PD-L1 positivity cutoff (%), type of cells (tumor / µ-environment), antibody used, number of samplings, time of sampling, … and impact on other endpoints…

Impact on survival: PFS and OS based on tumor PD-L1 expression (Central Review, RECIST v1.1)





Kefford, ASCO 2014

Nivolumab Monotherapy
Efficacy data phase 3

Note: data not randomized head to head and should not be compared

	PD-1 monotherapy (BMS) **Nivolumab**	
Study design	**Phase 3 (Checkmate 037)** Nivolumab vs ICC	**Phase 3 (CA209-066)** Nivolumab vs DTIC
Patient inclusion	After Ipi / BRAFi if BRAFmut	1st line (BRAFwt)
Primary endpoints	ORR & OS	OS
2nd endpoints	PFS, PD-L1 expression	PFS, ORR, PD-L1 expression
mOS	NR	**HR =0.42 p<0.0001 1 yr-OS 73%**
Landmark OS	NR	NR
mPFS	NR (95% ongoing)	**mPFS = 5.1 HR =0.43 p<0.0001**
ORR	**32% (3% CR)**	**40% (8% CR)**
DoR		**NR**

Data from presentation from Checkmate 037 ESMO 2014 & CA209-066 SMR 2014

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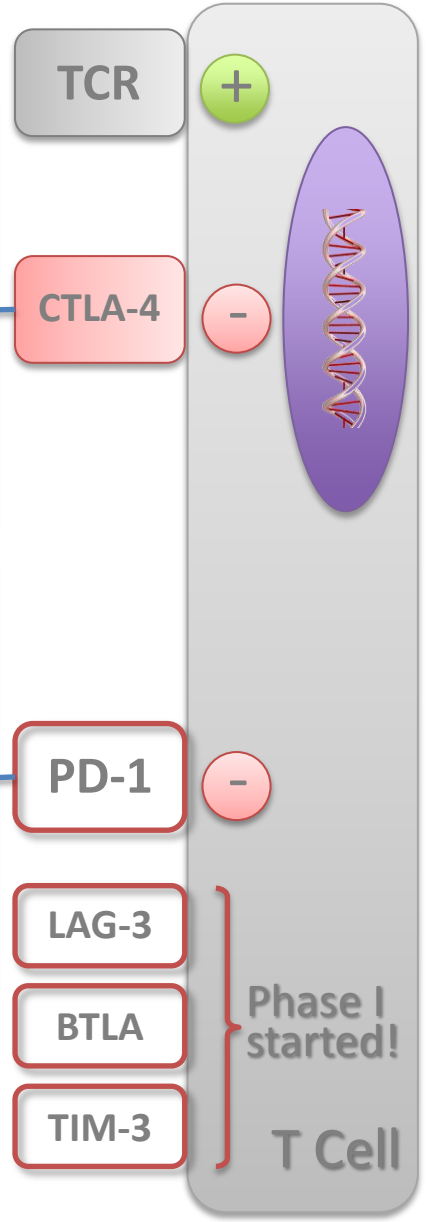

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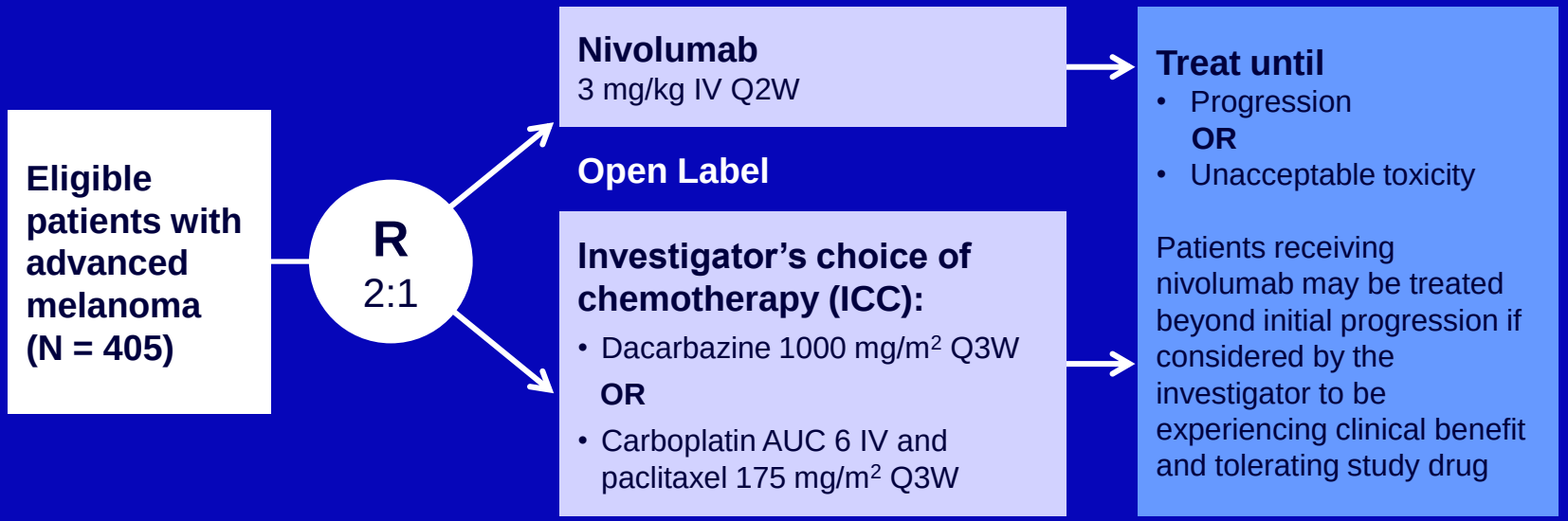
Phase 3 CA209-037: Study Design



Stratified by:

- **PD-L1 expression:** PD-L1 positive vs PD-L1 negative/indeterminate (positive: ≥5% tumor cell surface staining cut-off by immunohistochemistry)
- **BRAF status:** BRAF wild-type vs BRAF V600 mutant
- **Best overall response (BOR) to prior ipilimumab:** Clinical benefit (BOR=CR/PR/SD) vs no clinical benefit (BOR=PD)

AUC = area under the curve; CR = complete response; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-L1 = programmed death ligand 1; PR = partial response; Q2W = every 2 weeks; SD = stable disease.

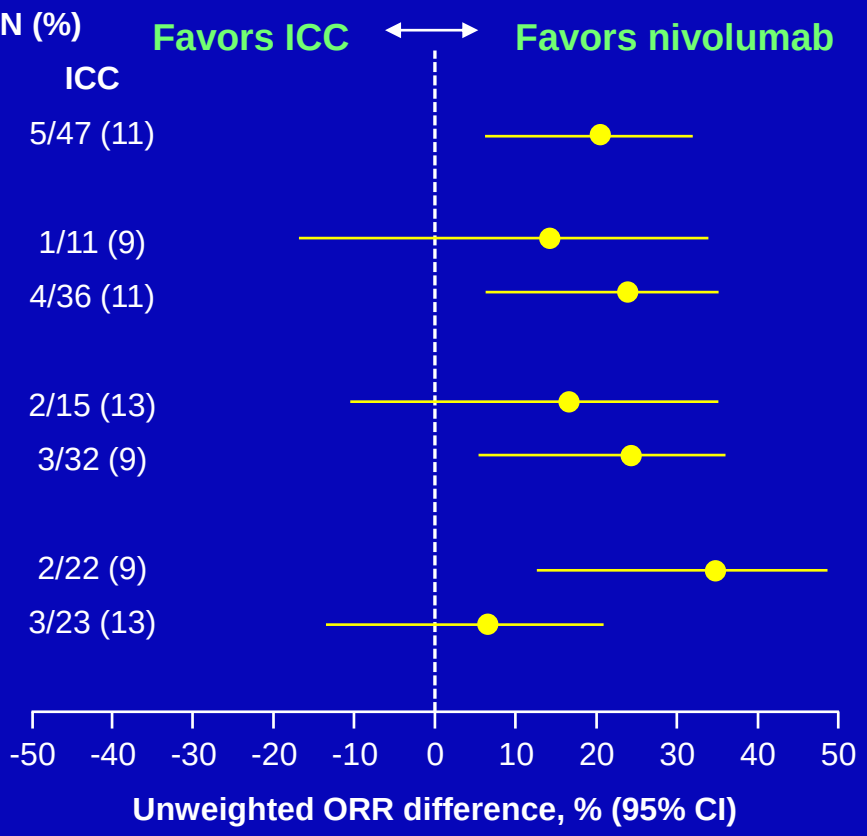
Co-Primary Endpoint: ORR

Treatment	N	CR+PR, n	ORR[a], % (95% CI)	Best Overall Response[a], %				
				CR	PR	SD	PD	UNK
Central review[b]								
Nivolumab	120	38	32 (24–41)	3	28	23	35	10
ICC	47	5	11 (4–23)	0	11	34	32	23
Investigator assessed								
Nivolumab	120	31	26 (18–35)	2	24	27	46	2
ICC	47	5	11 (4–23)	0	11	23	62	4

[a]Confirmed response.
[b]Independent radiology review committee based on RECIST 1.1.

Comparison of ORR in Patient Subgroups By Central Review per RECIST 1.1

	N	ORR, n/N (%)	
		Nivolumab	ICC
OVERALL	167	38/120 (32)	5/47 (11)
BRAF Status			
Mutant	37	6/26 (23)	1/11 (9)
Wild-type	130	32/94 (34)	4/36 (11)
Prior ipilimumab benefit			
Yes	55	12/40 (30)	2/15 (13)
No	112	26/80 (33)	3/32 (9)
PD-L1 status			
Positive[a]	77	24/55 (44)	2/22 (9)
Negative	87	13/64 (20)	3/23 (13)



- Consistently higher clinical activity was observed for nivolumab versus ICC regardless of pre-treatment PD-L1 expression status, BRAF mutation status and prior ipilimumab benefit

[a]PD-L1 positivity was defined as a tumor specimen with ≥5% tumor cell membrane staining measured by BMS/Dako immunohistochemistry assay. Three patients had indeterminate PD-L1 status by immunohistochemical staining.

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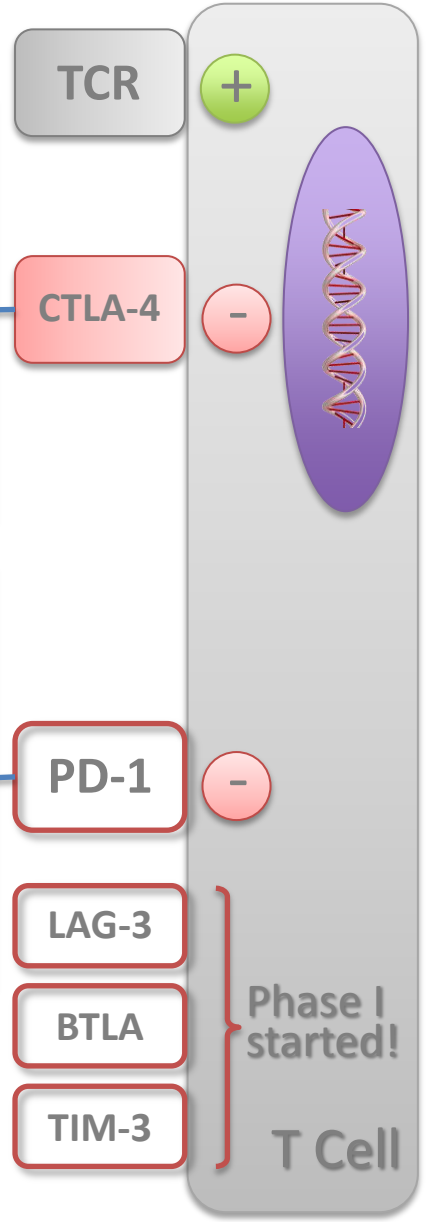
- RR 40%,
- HR OS/PFS: 0.42/0.43



1 Hodi, *NEJM* 2010; 2 Robert, *NEJM* 2011; 3 Eggermont, ASCO 2014;
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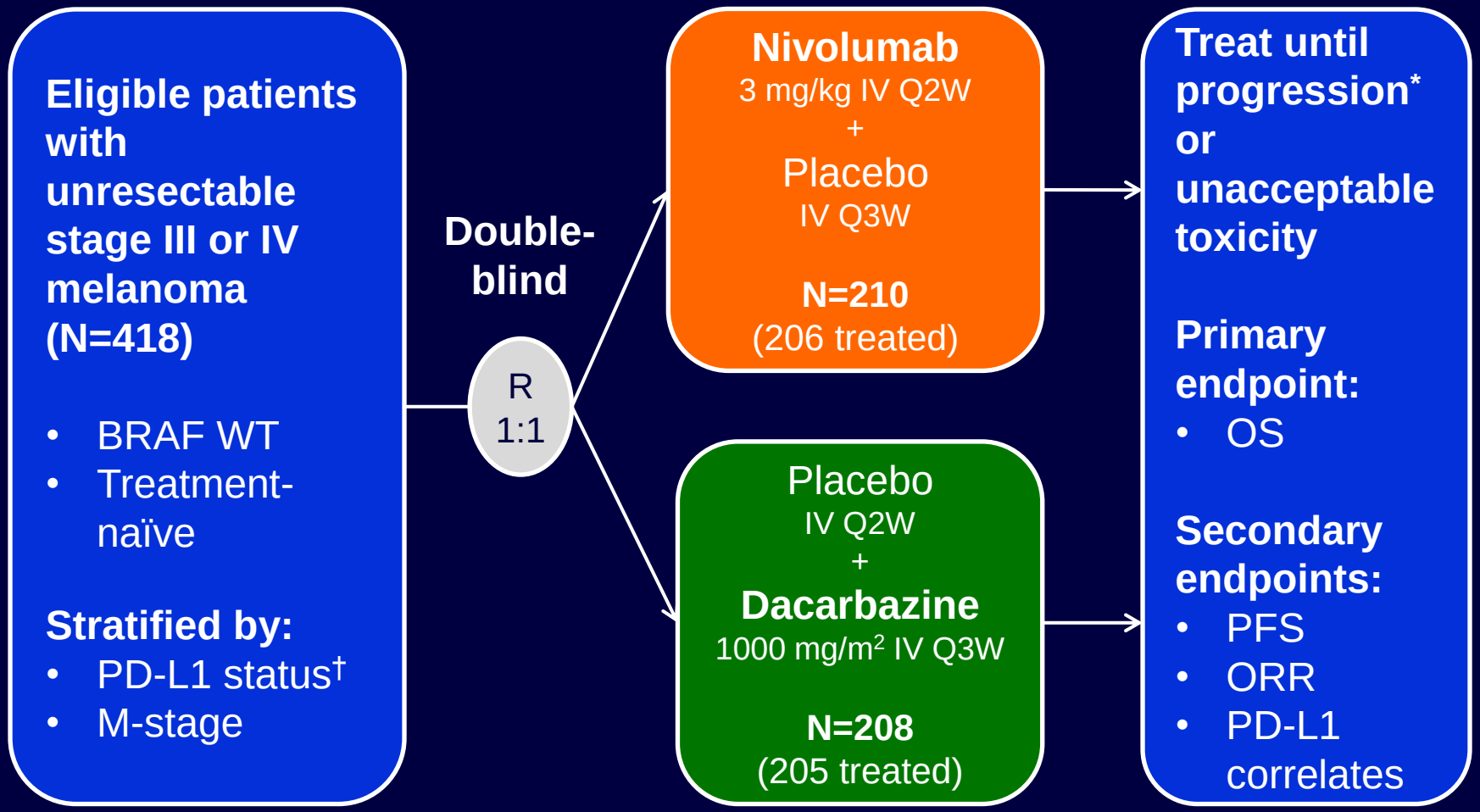
Phase 3 CA209-066: Study Design

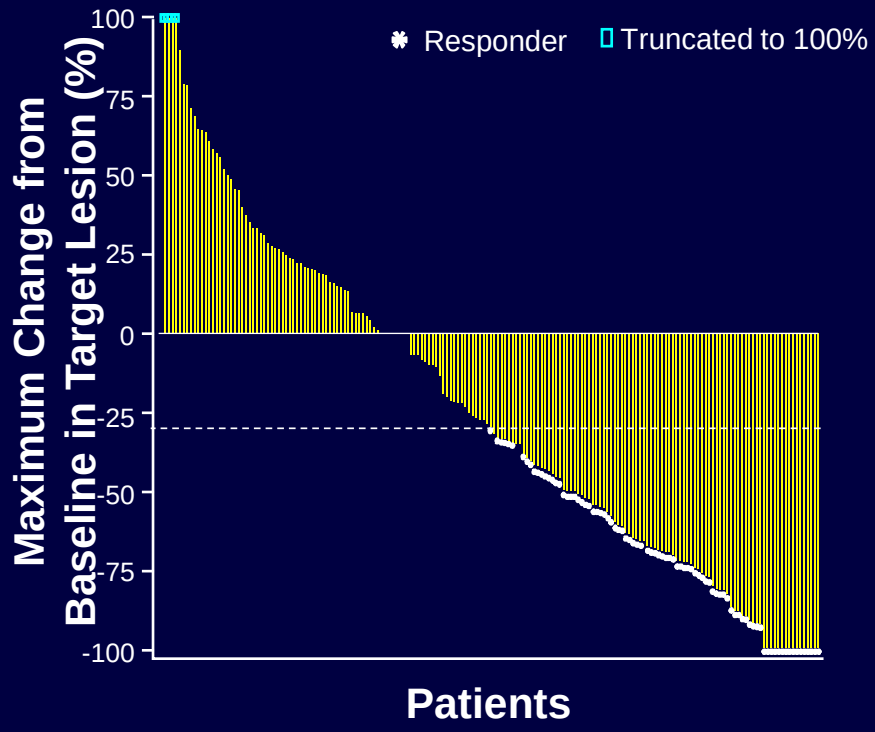


†PD-L1 positive: ≥ 5% tumor cell surface staining.

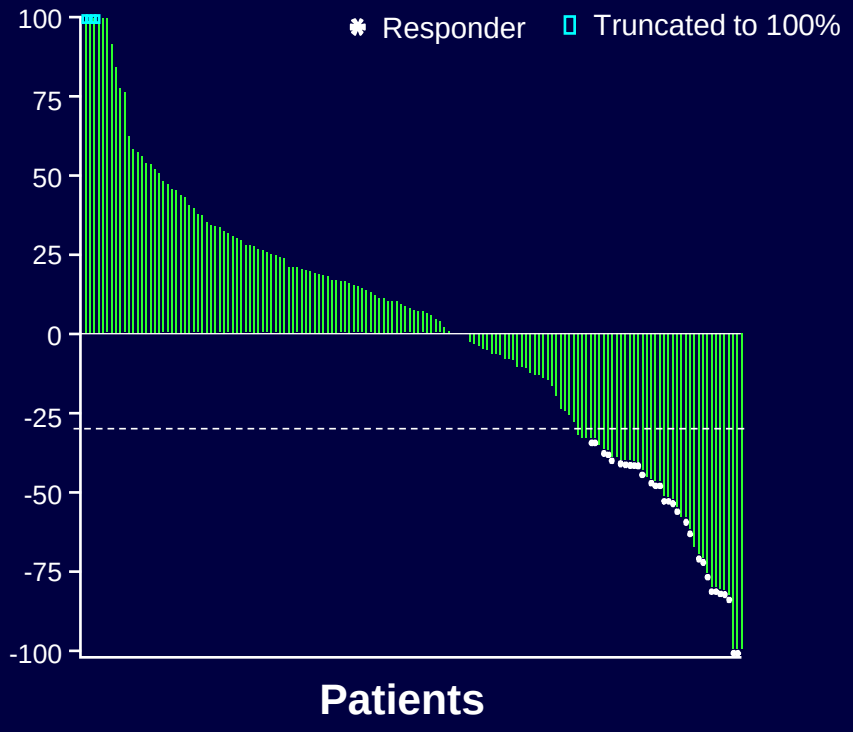
*Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Objective Response by RECIST v1.1

Nivolumab
ORR 40% (95% CI, 33–47%)



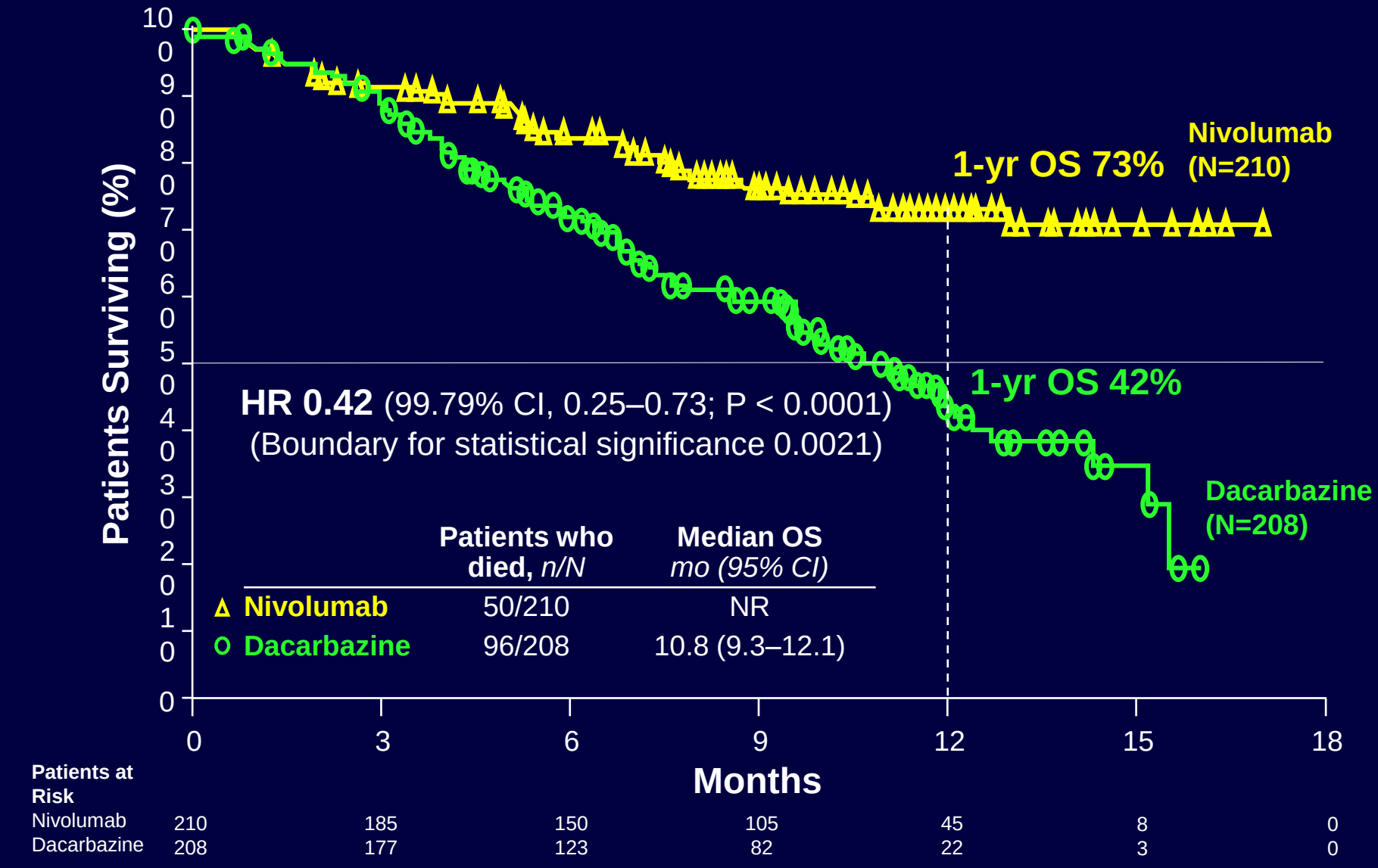
Dacarbazine
ORR 14% (95% CI, 10–19%)



Odds ratio for response 4.06 (95% CI, 2.52–6.54; P < 0.0001)

Showing only patients with both baseline and at least one post-baseline measurement of target lesion

Primary Endpoint: Overall Survival



NR=not reached. Based on 5 August 2014 database lock

Follow-up since randomization: 5.2–16.7 m

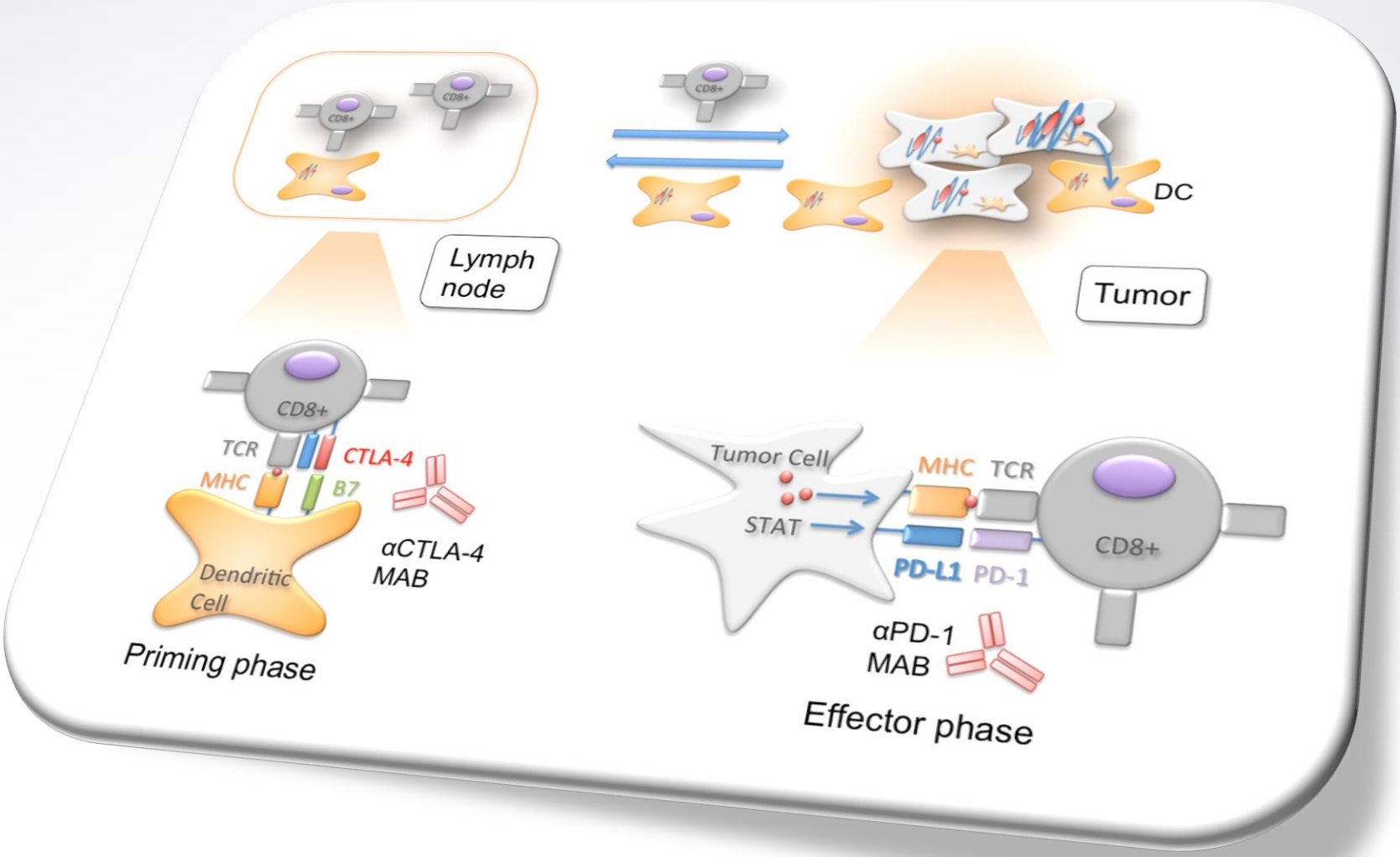
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.

Ipilimumab and nivolumab combo



Overview of checkpoint blockade

Combinations

Single agent

Ipi + bevacizumab[6]:
- Ph1: Ipi + bev
- RR 17%, DCR 67%
- HR OS/PFS: NR/NR

Checkmate 067[8]:
- Ph3: Ipi/nivo/combo
- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

BMS-024[2]: Phase 3
- DTIC vs DTIC + ipi, 1st
- RR 34%, mPFS 2.6
- HR OS: 0.72, mOS 11

BMS-020[1]: Phase 3
- Ipi/gp100/combo 2nd
- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

Adjuvant

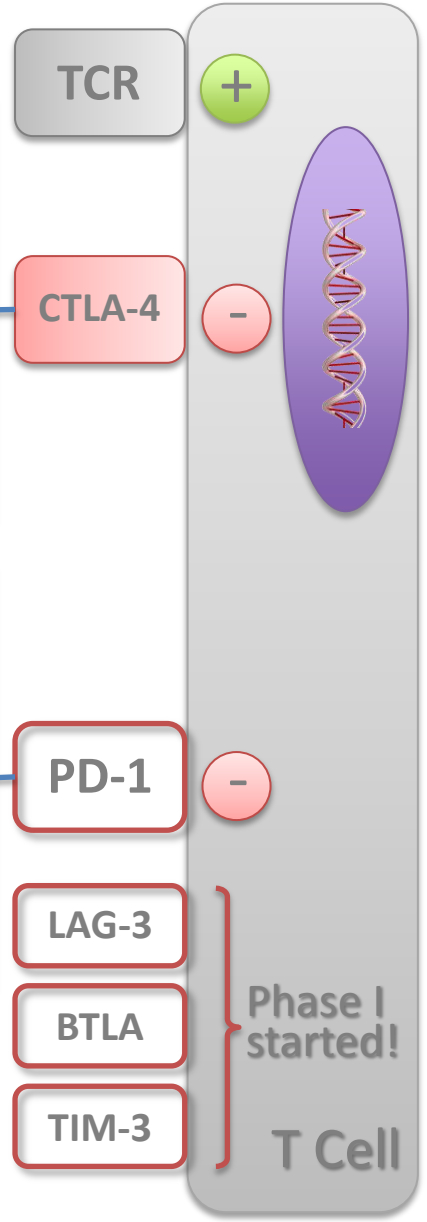
EORTC-18071[3]: Phase 3
- Ipi (10mg) vs placebo
- mRFS: 26 vs 17
- HR RFS/OS: 0.75/NA

CA-209-003[5]: Phase 1
- Nivolumab, 2nd +
- RR 31%, mOS: 17
- HR OS/PFS: NR/NR

Keynote-001[4]: Phase 1
- Keytruda, Ipi-N or T
- RR 34%, mOS 26
- HR OS/PFS: NR/NR

CA-209-037[8]: Phase 3
- Nivo vs ICC, 2nd
- RR 32%,
- HR OS/PFS: NA/NA

CA-209-066[6]: Phase 3
- Nivo vs DTIC, 1st
- RR 40%,
- HR OS/PFS: 0.42/0.43



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(Time units in months unless specified, NA: Not Available, NR: Not Relevant)

Nivolumab and ipilimumab combination

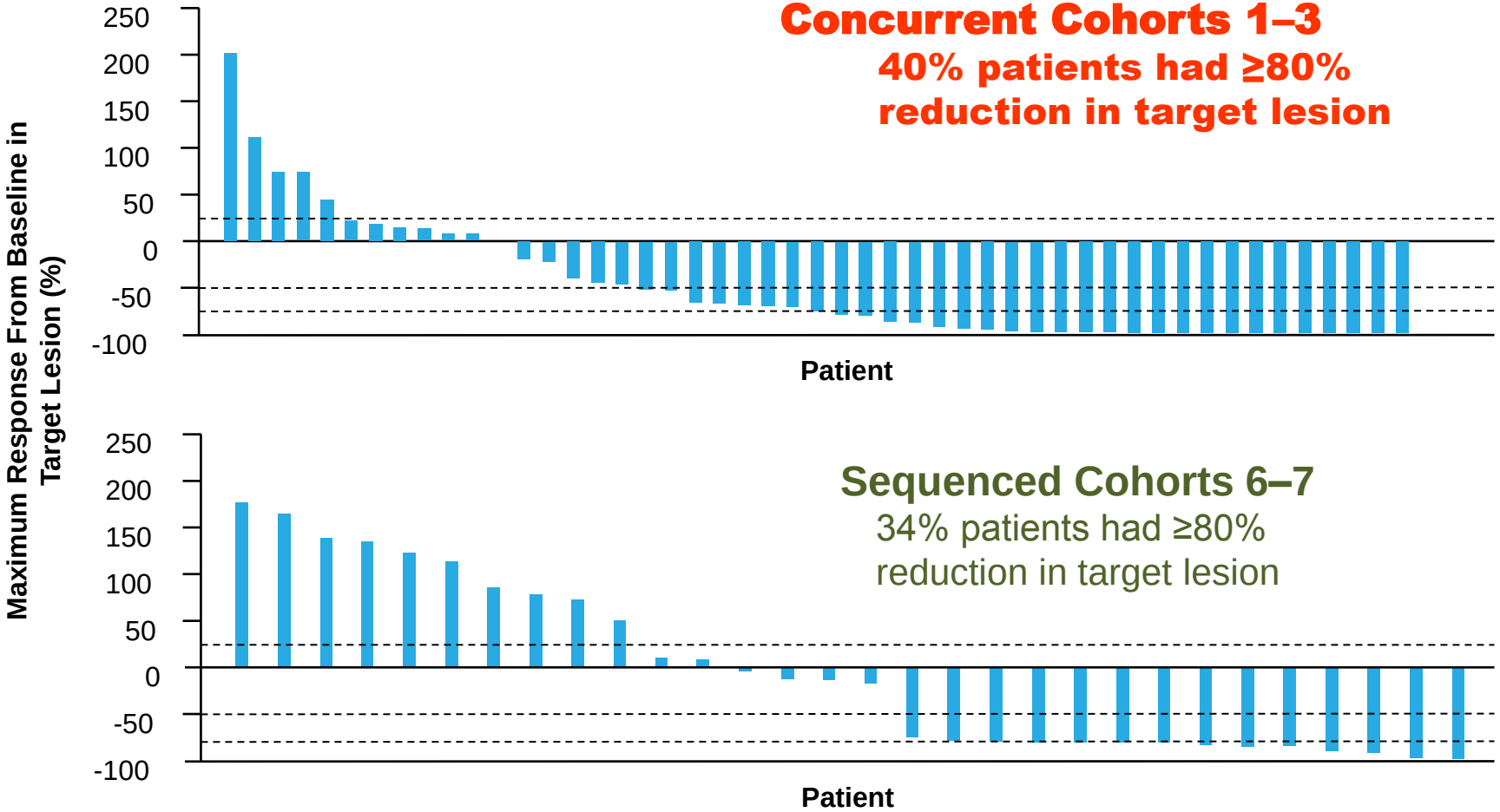
Phase I data

Note: data not randomized head to head and should not be compared

	PD-1 / CTLA-4 dual therapy (BMS) **Nivolumab / Ipilimumab**
Study design	Phase 1, CA209-004
Patient inclusion	Up to 3 systemic lines of treatment ECOG PS 0/1
Primary endpoints	Safety, tumor response
2nd endpoints	pharmacokinetics
mOS	NR
Landmark OS	**1-yr OS: 85%, 2-yr OS 79% (cohort 1-3)** **(Nivo 1mg/Ipi 3mg: 1yr OS 94%,2yr OS 88%)**
mPFS	**6.2 months (9 mo for ph2/3 dose)**
ORR	**40% (43% for ph2/3 dose)**

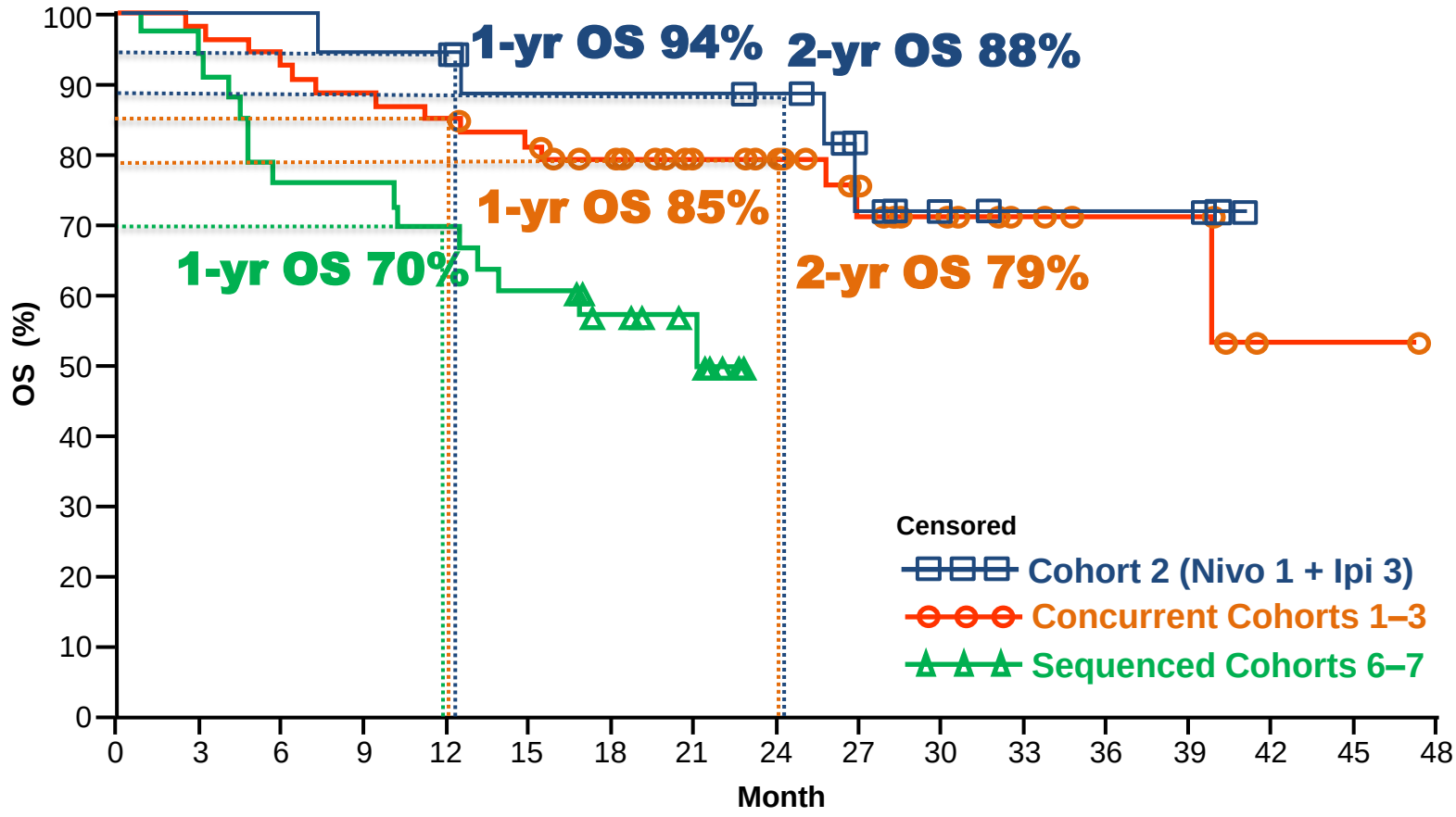
Data from ASCO, ESMO & SMR 2014

Maximum Response in Target Lesion



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
Concurrent Cohorts 1–3	53	52	49	47	45	42	37	30	25	16	11	7	5	5	1	1	0
Sequenced Cohorts 6–7	33	31	25	25	23	20	12	8	0	0	0	0	0	0	0	0	0

Cohort 2 dose is similar to the dose/schedule used in phase 3 clinical studies

June 2014 data analysis.

Treatment-Related AEs Reported in ≥15% of Patients

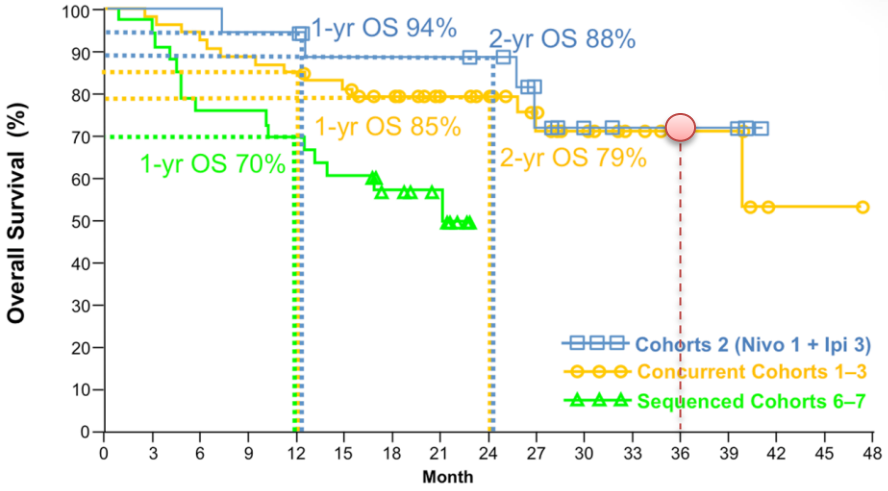
Patients with an event, %	All Concurrent Cohorts (N = 94)		All Sequenced Cohorts (N = 33)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
All drug-related AEs	**97**	**64**	**85**	**24**
Rash	64	6	24	0
Pruritus	52	0	21	0
Fatigue	45	1	21	0
Diarrhea	38	7	12	0
Nausea	23	2	9	0
Lipase increased	22	15	18	12
Pyrexia	22	0	3	0
AST increased	19	11	0	0
ALT increased	18	12	3	0
Amylase increased	17	6	9	2

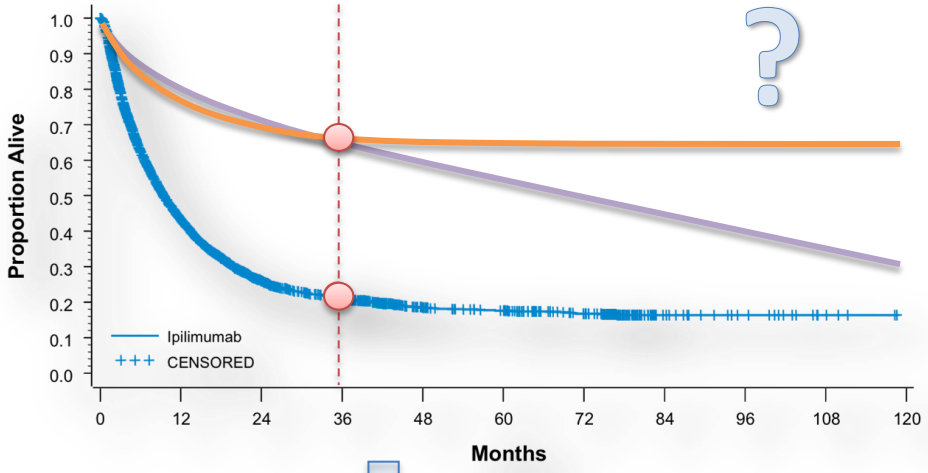
Sorted from high to low by total AEs of any grade reported in all concurrent cohorts (1–3 and 8; N = 94).
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Overall survival data: long term benefits?

- Pooled survival analysis of all ipilimumab trials show a prolonged plateau after year 2-3 (Hodi, ESMO 2013, Abstract 24LBA)
- This behavior is induced by ipilimumab single agent with a 2 year survival of 24% and a 3 year survival of 21%

In the ipi / nivo concurrent cohorts, 2 year survival reaches 80-90% and 3 year survival around 70%...

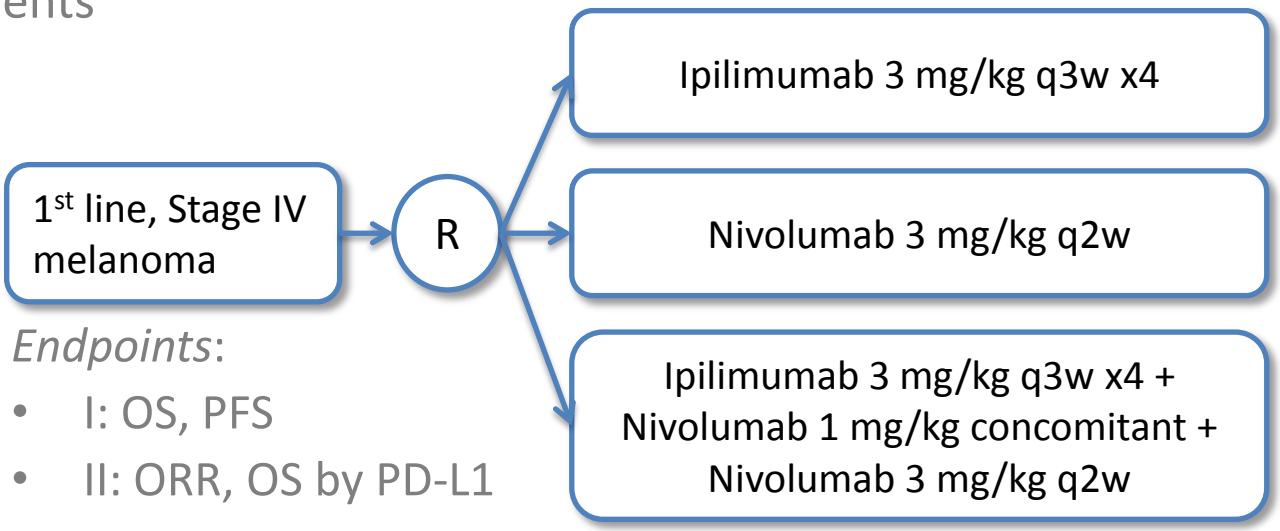




CheckMate 067 phase III trial

Overall survival vs. toxicity data

- Unprecedented 1 year and 2 year survival rates for Ipi/PD-1 combo
- Limitations:
  - Patient number is low and follow-up is still short
  - Not randomized head to head
- Higher toxicity of Ipi/PD-1 combo (not randomized), but manageable
- Randomized phase III, **CheckMate 067**, has just finished recruiting 915 patients



Endpoints:

- I: OS, PFS
- II: ORR, OS by PD-L1

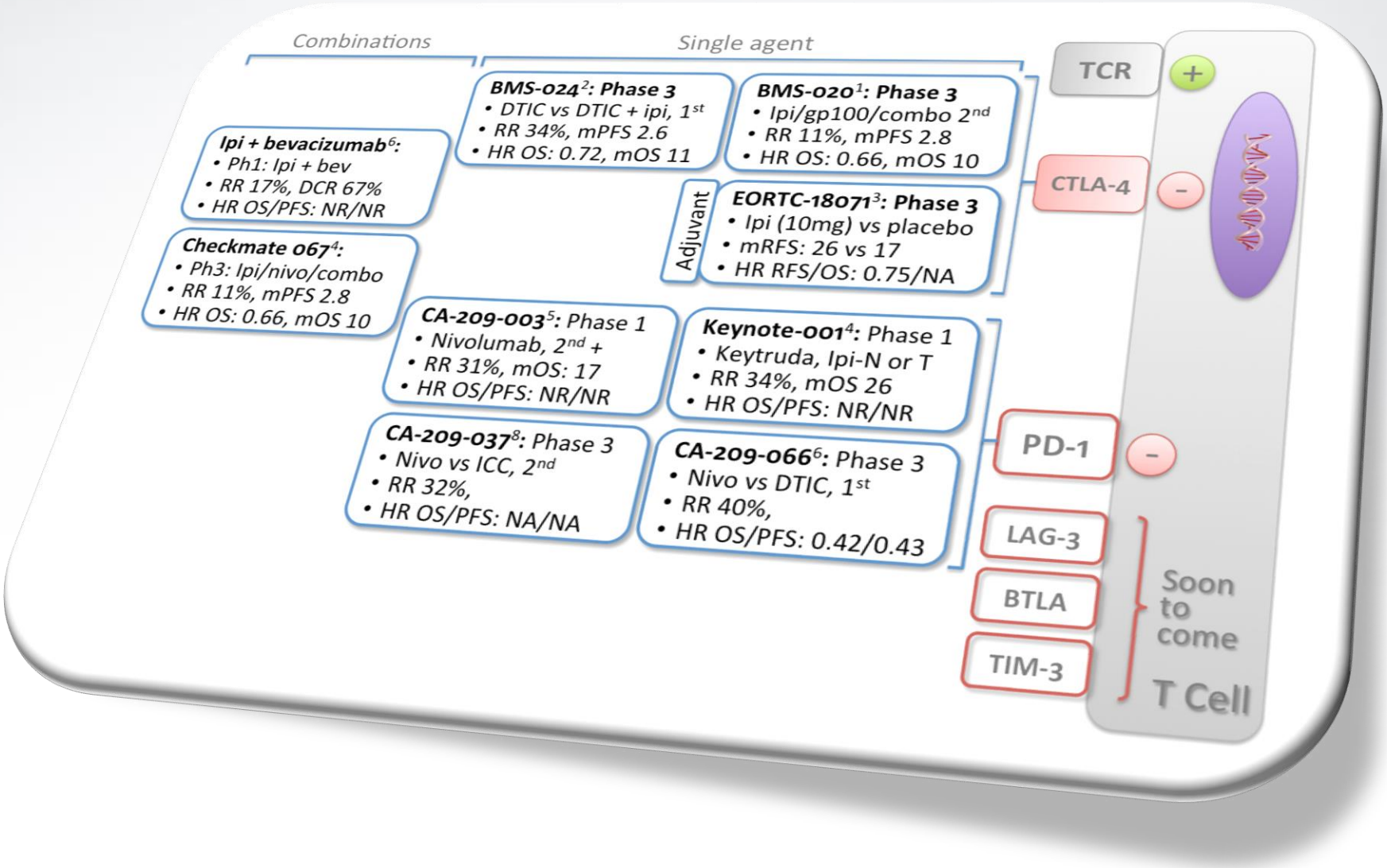
- This study aims at providing a definitive answer on the OS benefit vs. toxicity of the combination therapy. Results expected by October 2016.

Summary of overall survival data (not randomized)

Treatment Option	Response rate	1 year OS rate	2 year OS rate
Historical control: M1c (Balch, *JCO* 2009)	NR	33%	19%
High dose IL-2 (Schwartzentruber, *NEJM* 2011)	6%	48%	27%
BRAF inhibition (McArthur, *Lancet Oncol* 2014)	57%	56%	NA
MEK inhibition (Kim, *JCO* 2013)	22%	59%	NA
BRAFi + MEKi (Flaherty, ASCO 2014)	75%	80%	51%
CTLA-4 blockade (Hodi, *NEJM* 2010; Wolchok, *Ann Oncol* 2013)	11%	46%	24%
PD-1 blockade (pembrolizumab) (Ribas, ASCO 2014 & Kefford, ASCO 2014)	34%	69%	(60%)
PD-1 blockade (nivolumab) (Topalian, *JCO* 2014)	31%	62%	43%
CTLA-4 + PD-1 blockade (Kluger, ESMO 2014)	**41%**	**85%**	**79%**

NA: Not Available, NR: Not Relevant

Thank you!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TCR
+
CTLA-4
-
PD-1
-
LAG-3
BTLA
TIM-3
Soon to come
T Cell