GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Immuno-oncology clinical studies across tumour types: Melanoma

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Disclosure Slide

- OM is an occasional consultant for BMS, Roche and GSK
- OM has received honoraria from BMS, Roche and GSK to participate in advisory boards and to speak at sponsored meetings
- OM declares no conflicts of interest

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

Overview of checkpoint blockade

Combinations

Ipi + bevacizumab[8]:
- Ph1: Ipi + bev
- RR 17%, DCR 67%

Ipi + T-vec[9]:
- Ph1, IT injection
- RR 41%, CR 24%

Ipi + GM-CSF[10]: low tox
- Ph2: Ipi/ipi + GM-CSF
- mOS 17.5 vs 12.7

Checkmate 067[11]:
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- RR 11%, mPFS 2.8
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- RR 31%, mOS: 17
- HR OS/PFS: NR/NR

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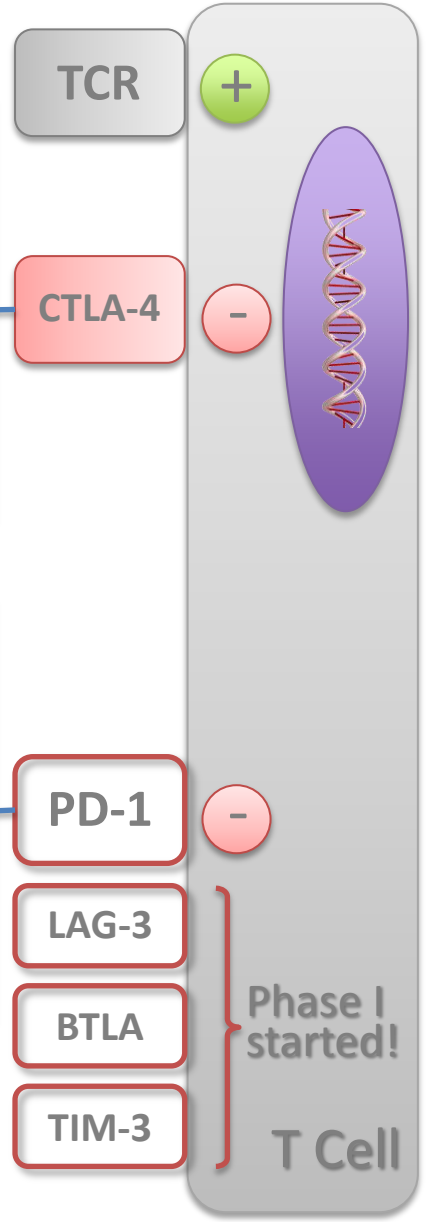
- Keytruda, Ipi-N or T
- RR 34%, mOS 26
- HR OS/PFS: NR/NR

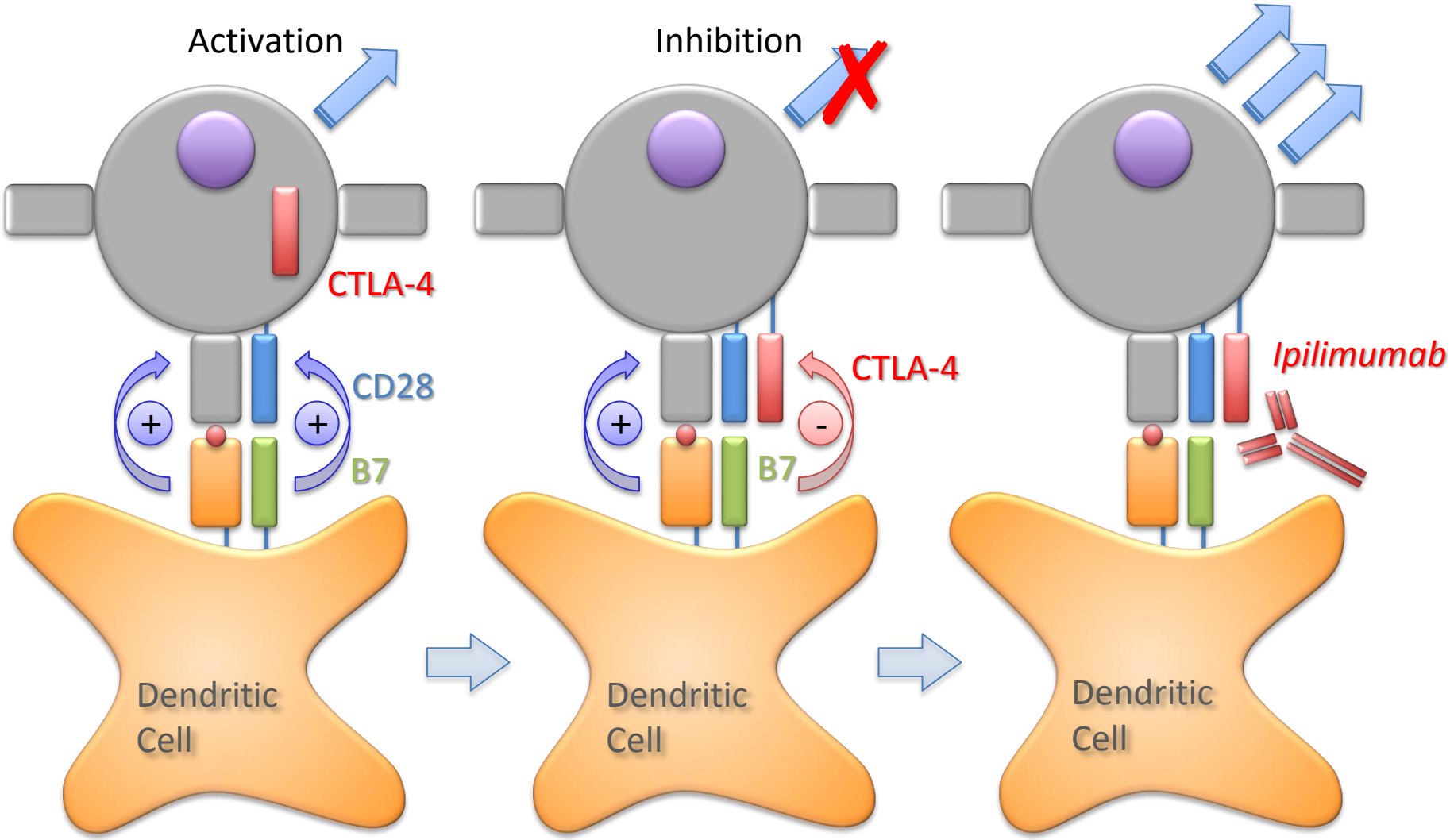
CA-209-037[11]: Phase 3
- Nivo / ICC, 2nd line
- RR 32%,
- HR OS/PFS: NA/NA

CA-209-066[6]: Phase 3
- Nivo / DTIC, 1st line
- RR 40%,
- HR OS/PFS: 0.42/.43



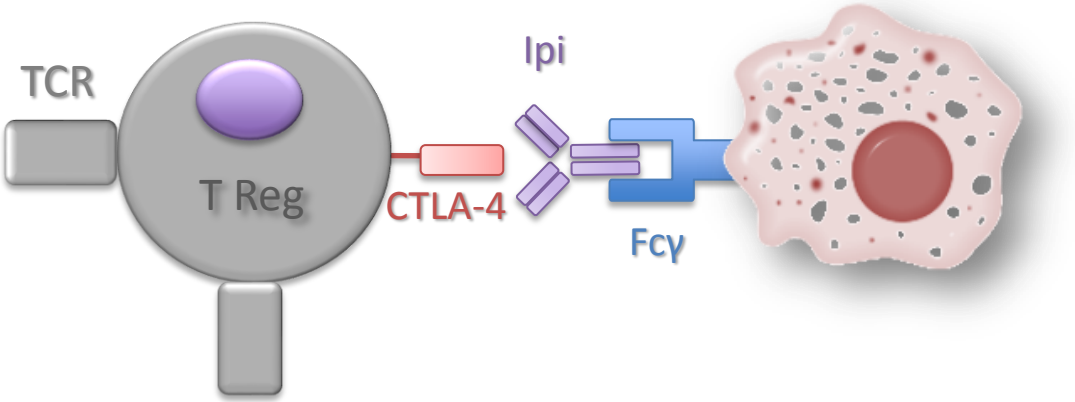
1 Hodi, *NEJM* 2010; 2 Robert, *NEJM* 2011; 3 Eggermont, ASCO 2014;
4 Robert, *Lancet Oncol* 2014; 5 Topalian, *JCO* 2014; 6 Robert, *NEJM* 2014;
8 Hodi *Cancer Immunol Res* 2014; 9 Puzanov, ASCO 2014; 10 Hodi, *JAMA* 2014
11 ASCO/ESMO/SMR 2014 (Time units in months unless specified, NA: Not Available, NR: Not Relevant)

CTLA-4 blockade, traditional mechanism of action

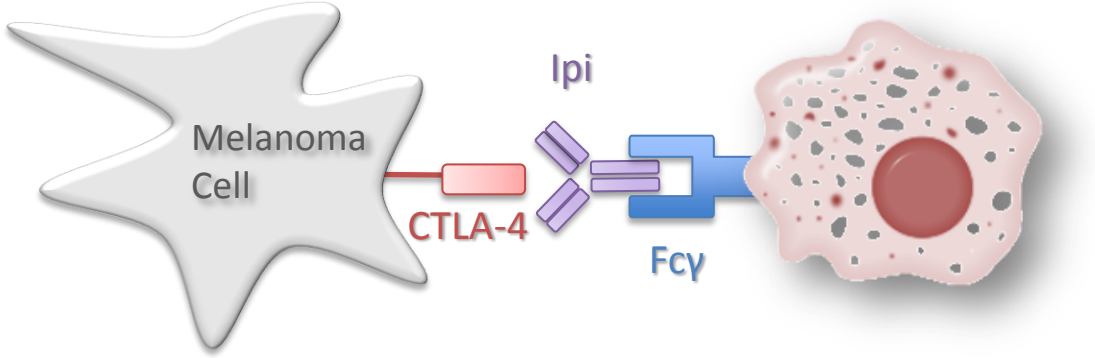


Other biological mechanisms of action

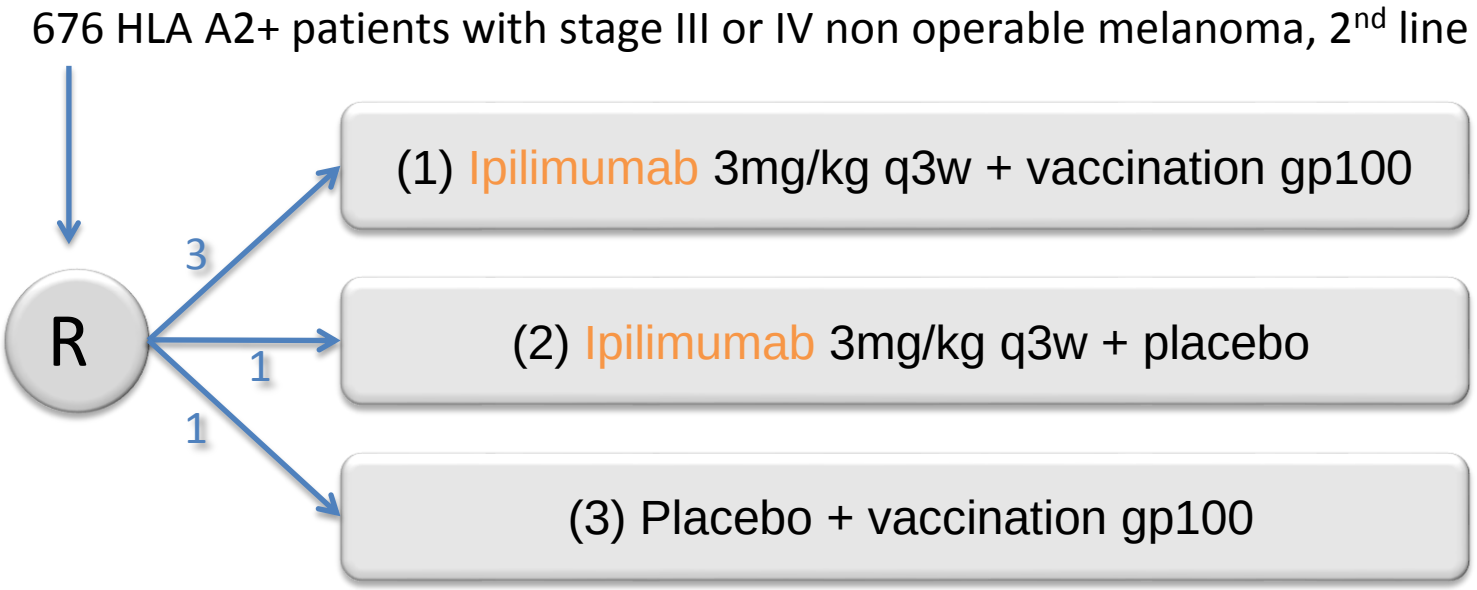
- Fc-γ dependent T-Reg depletion by ADCC that increase the Teff / Treg ratio as shown in mice:
  - Simpson & al. *J. Exp. Med.* 2013
  - Buillard & al. *J. Exp. Med.* 2013



- 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:

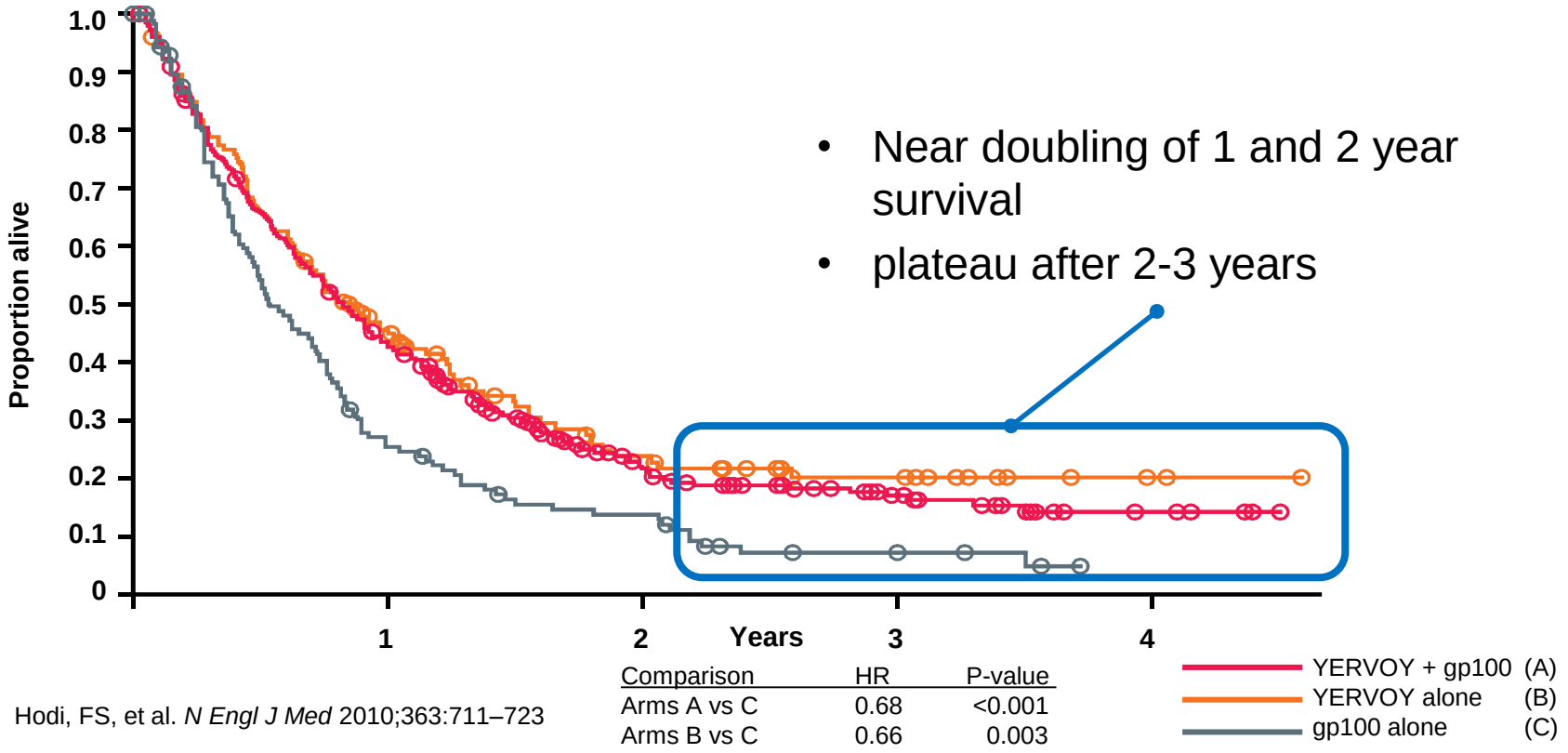
Primary endpoint: Overall survival (OS)

Secondary endpoint: PFS, response rate

Hodi & al, NEJM, 2010

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

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)



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

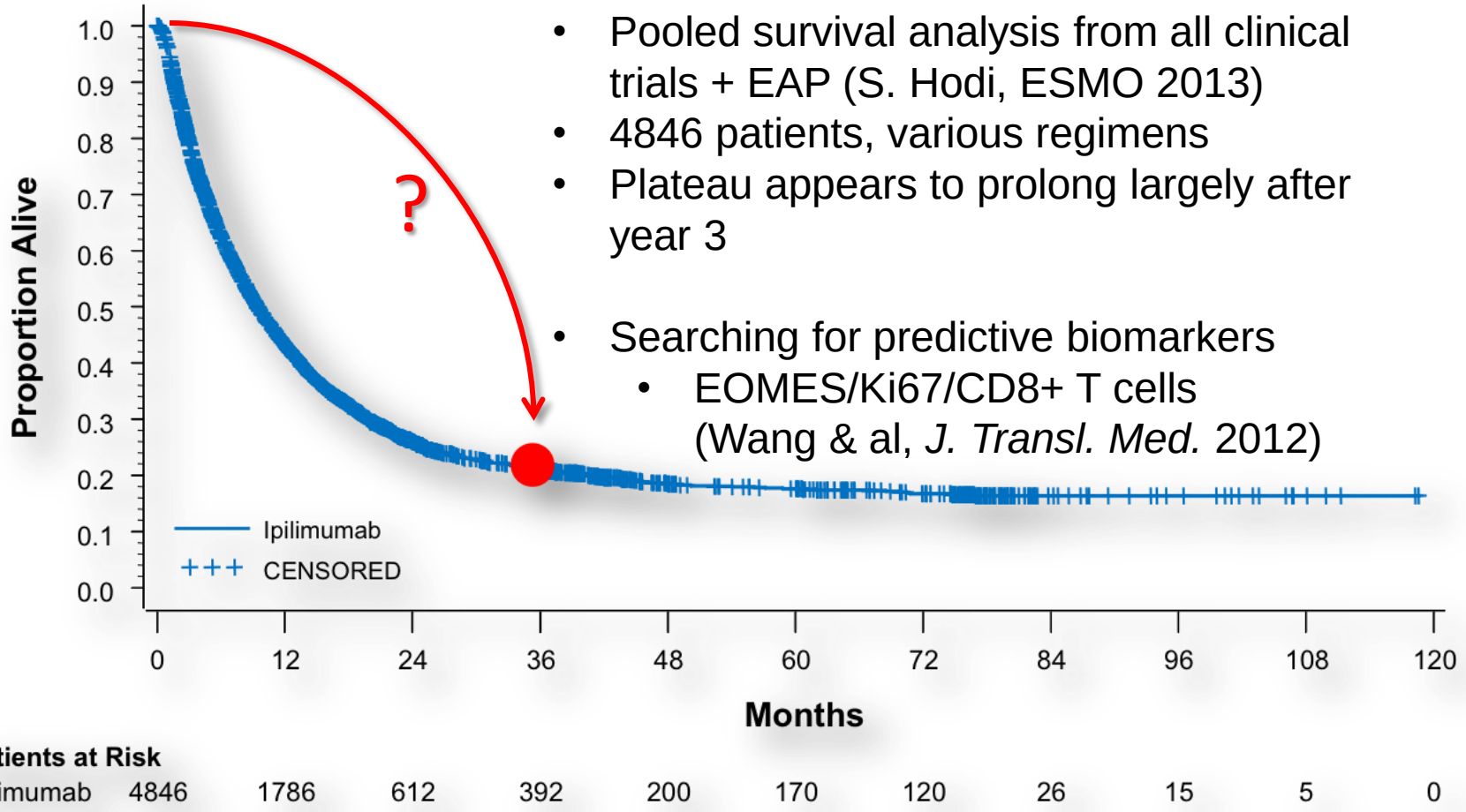
Hodi, FS, et al. *N Engl J Med* 2010;363:711–723

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

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

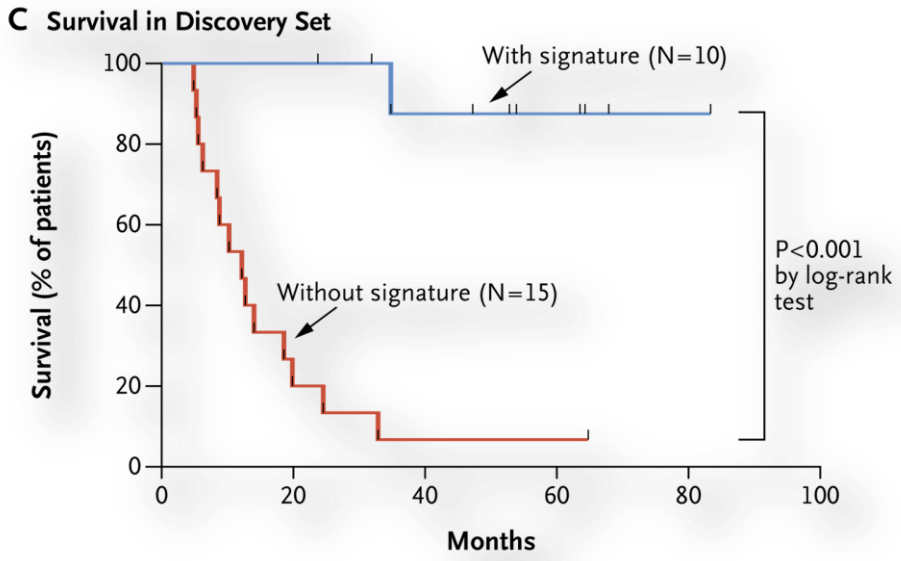


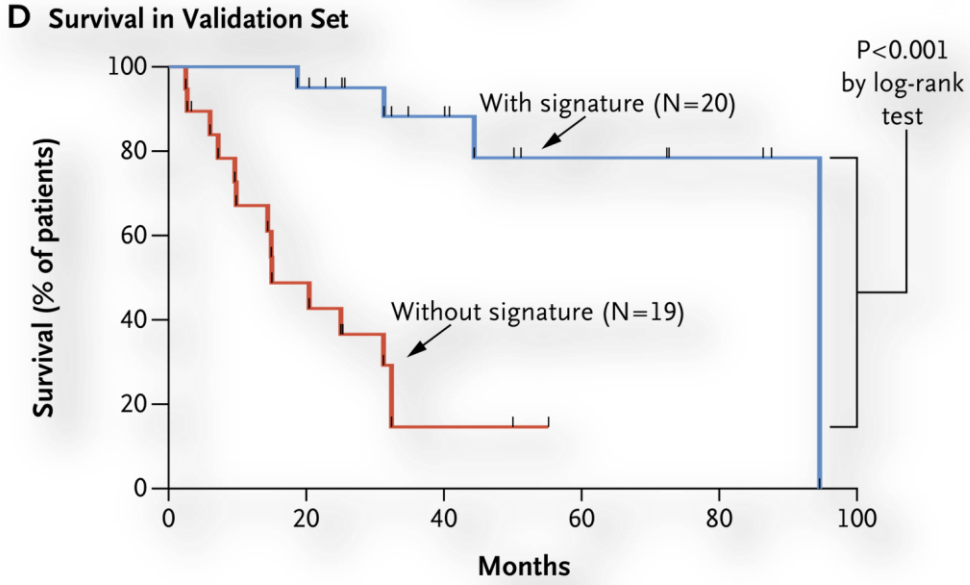
- Pooled survival analysis from all clinical trials + EAP (S. Hodi, ESMO 2013)
- 4846 patients, various regimens
- Plateau appears to prolong largely after year 3

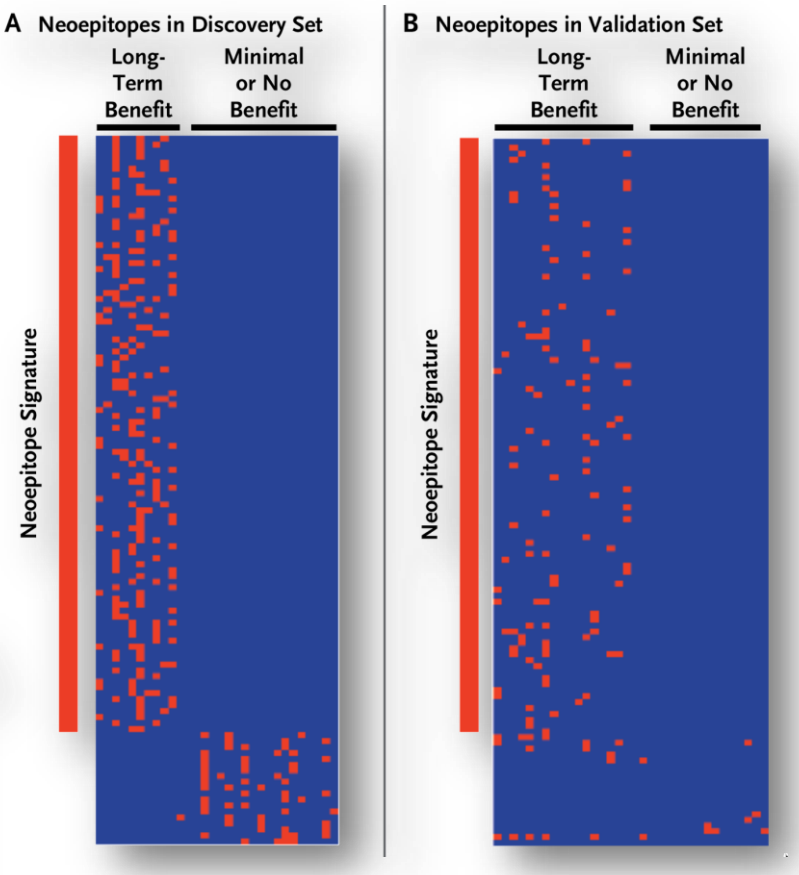
- Searching for predictive biomarkers
  - EOMES/Ki67/CD8+ T cells (Wang & al, *J. Transl. Med.* 2012)

Hodi & al, NEJM, 2010

Neoantigens as a predictive biomarker for ipi?



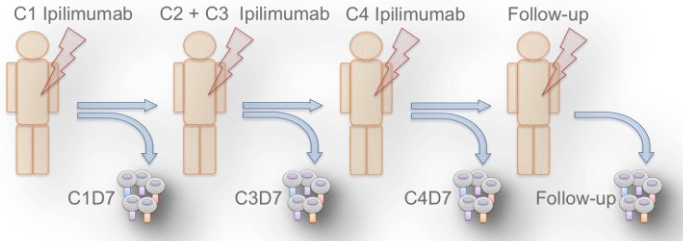




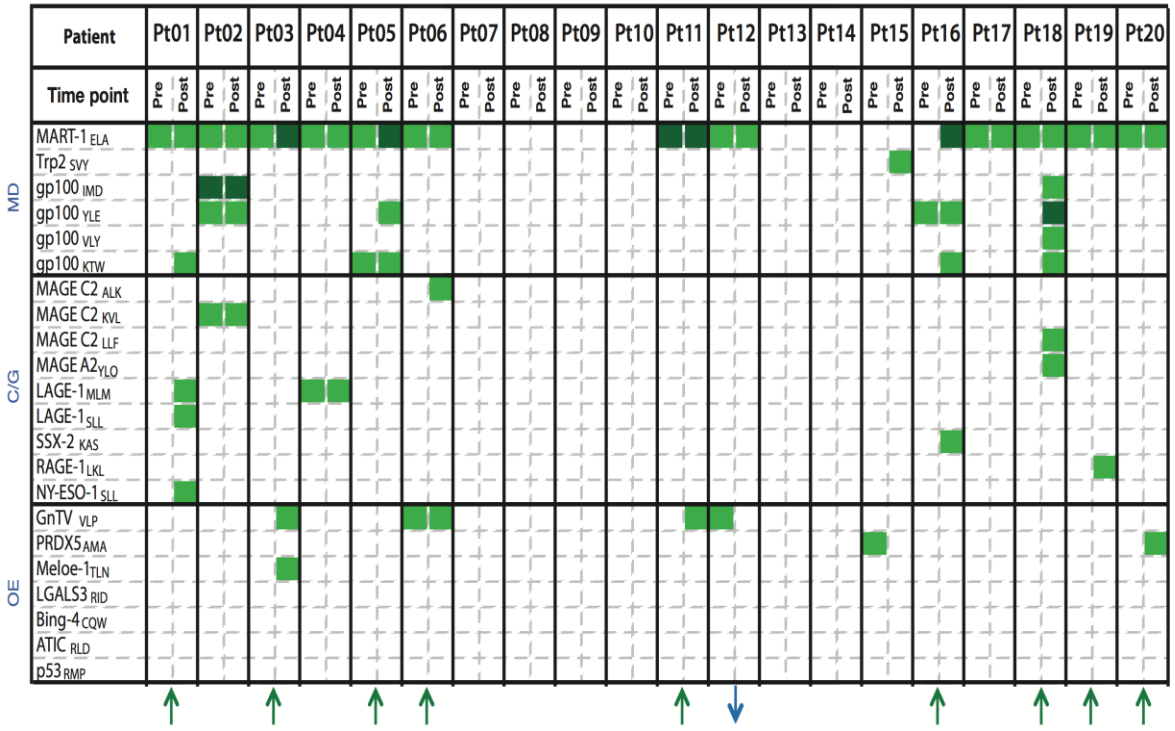
- Neoantigen signature associated with response to ipi[1]

1 Snyder & al. *NEJM* 2014

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

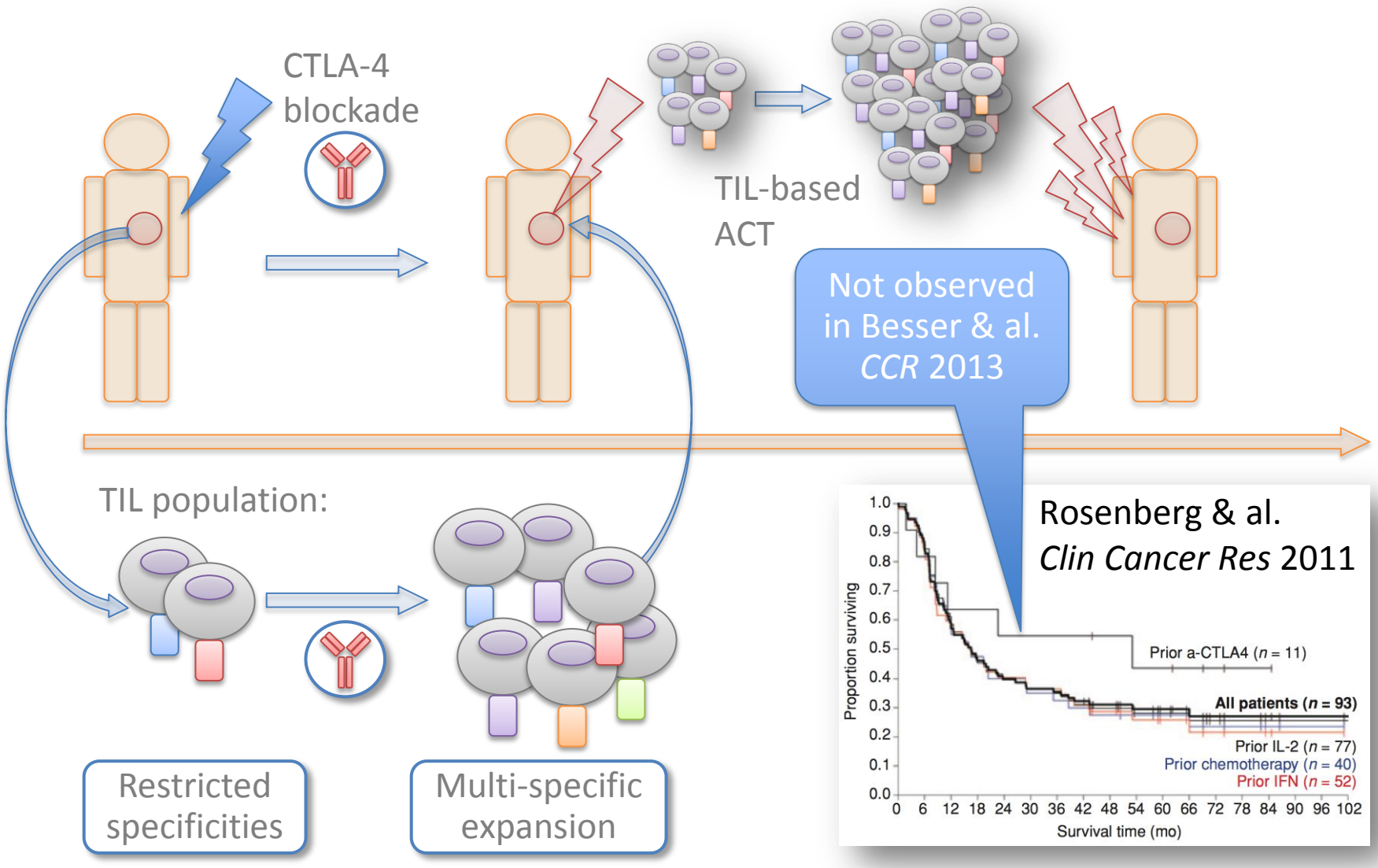


Conclusions:

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

Kvisborg, *Science Transl. Med.* 2014

Could the broadening of T cell specificities synergize with TIL-based ACT approaches?



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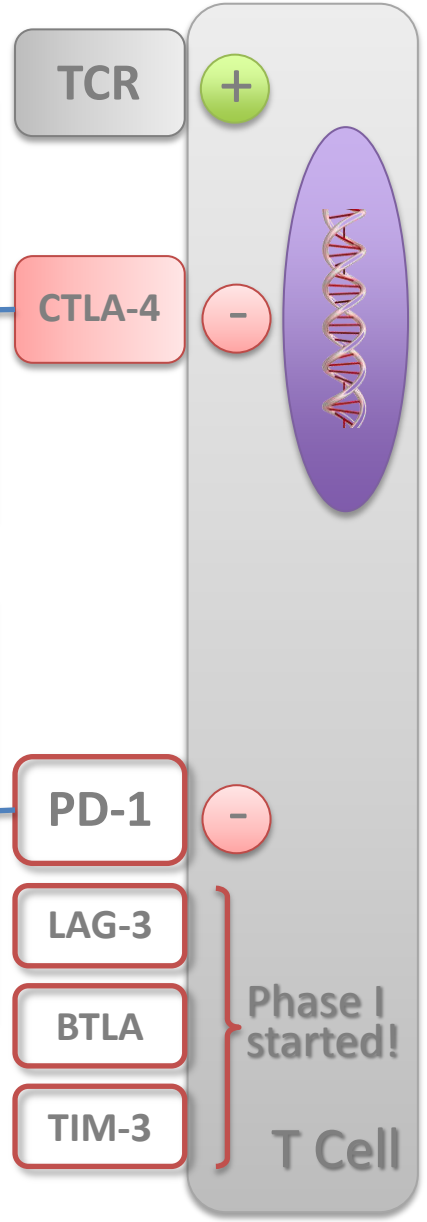

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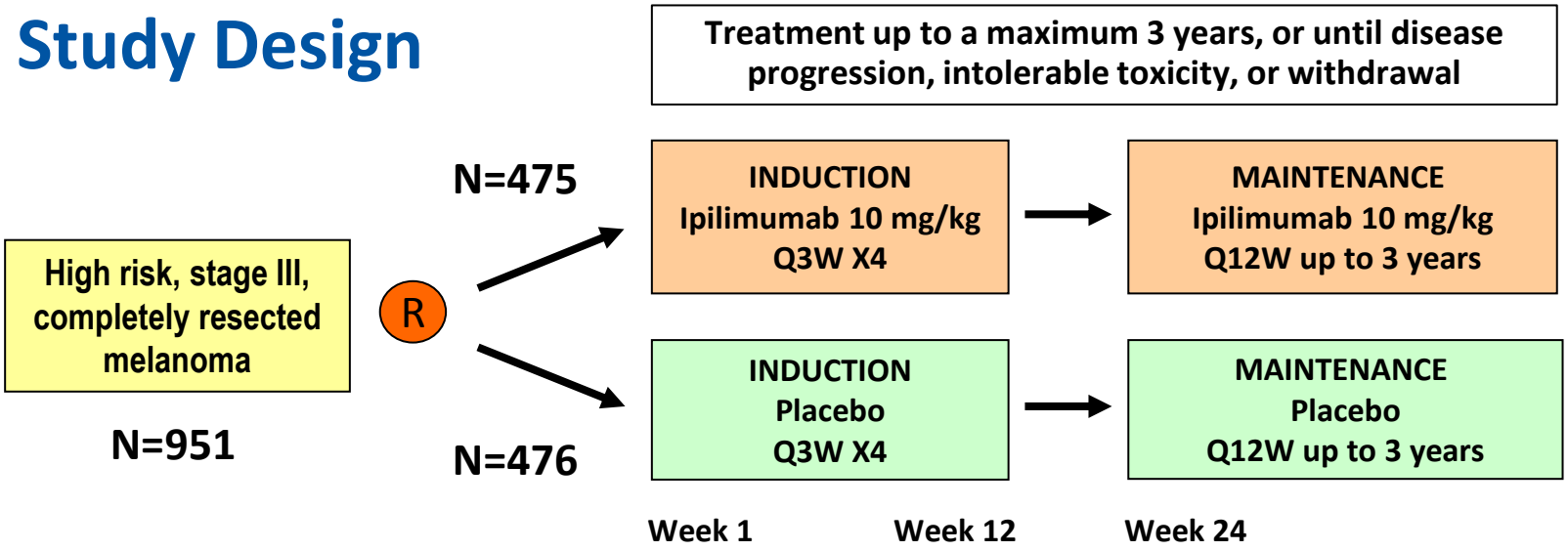
EORTC 18071: Study Design



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:

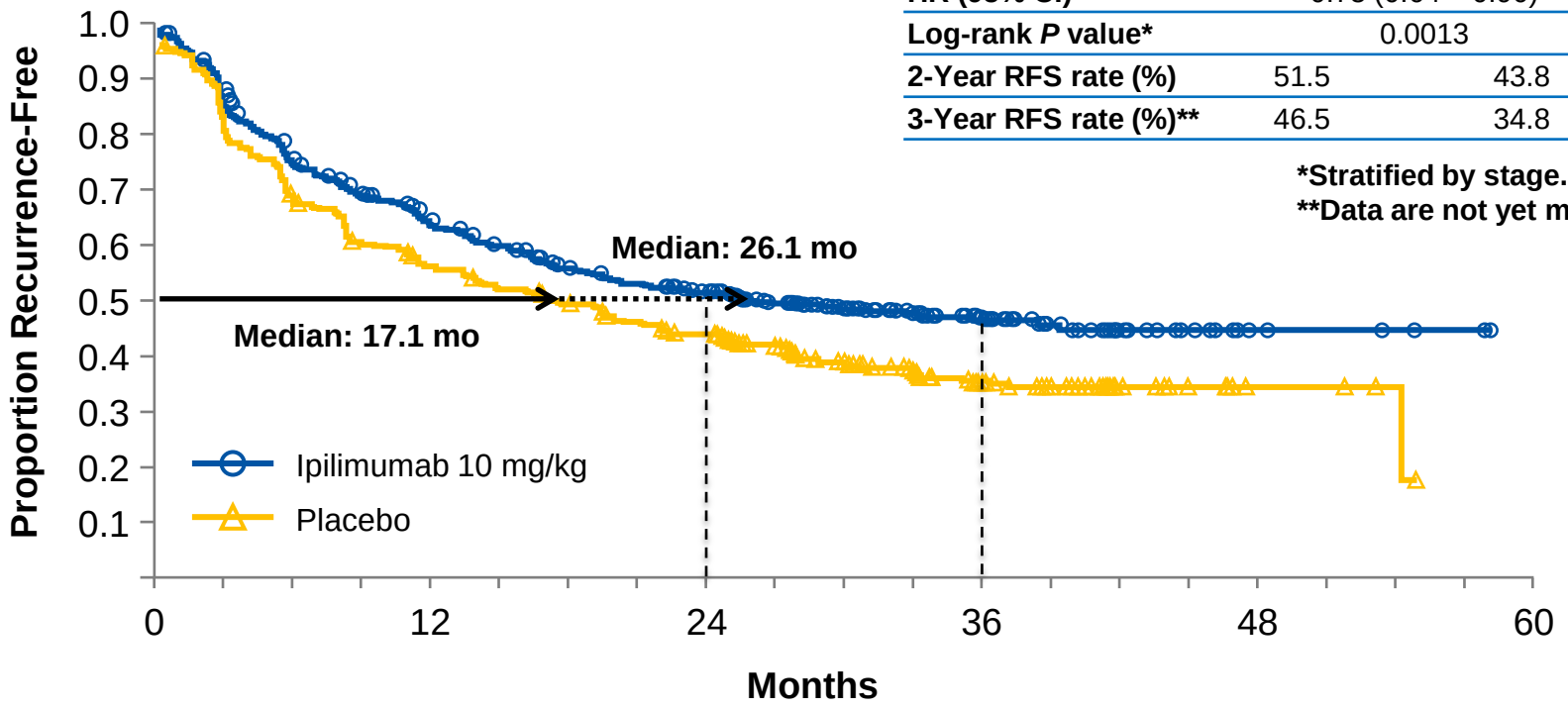
- Stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIc ≥4 nodes)
- Regions (North America, European countries and Australia)

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

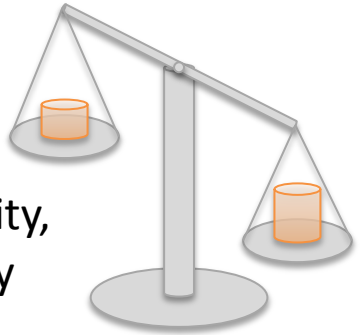
Ipilimumab	475	276	205	67	5	0
Placebo	476	260	193	62	4	0

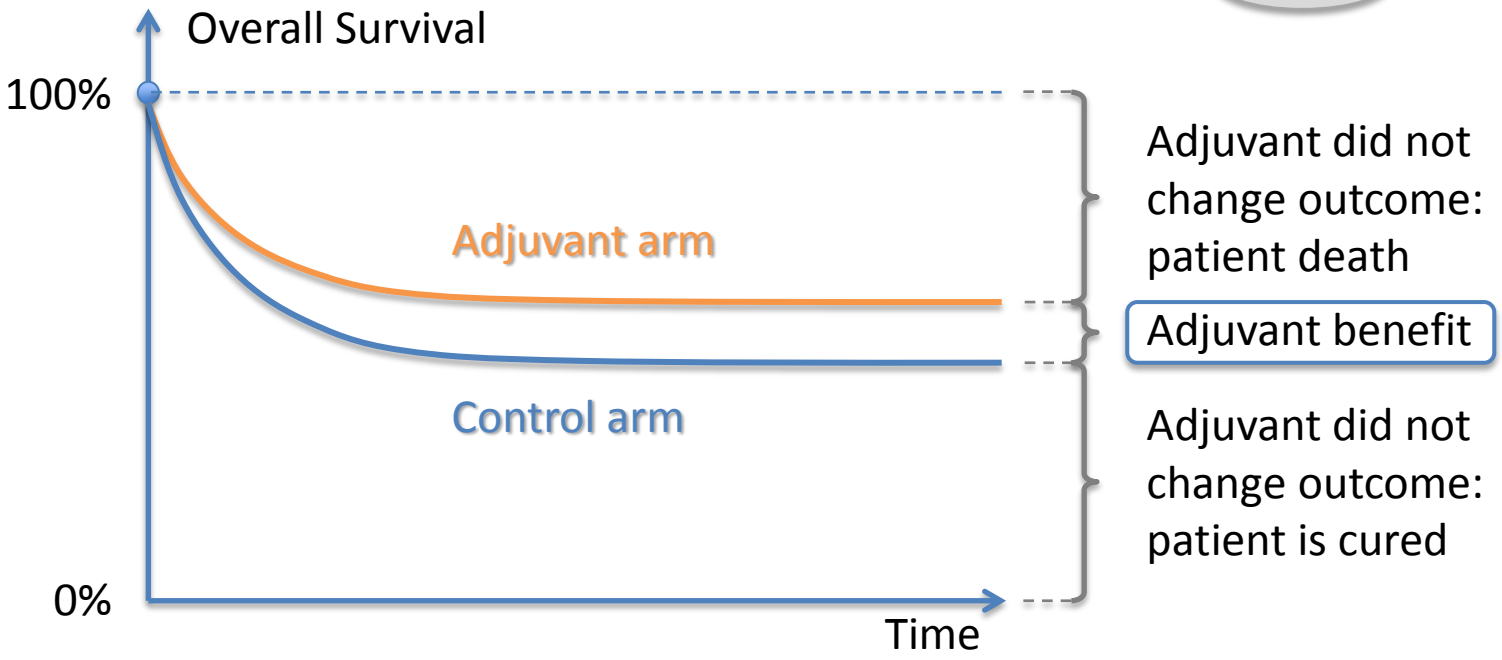
Safety: Immune-related Adverse Events

	% 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 the adjuvant setting

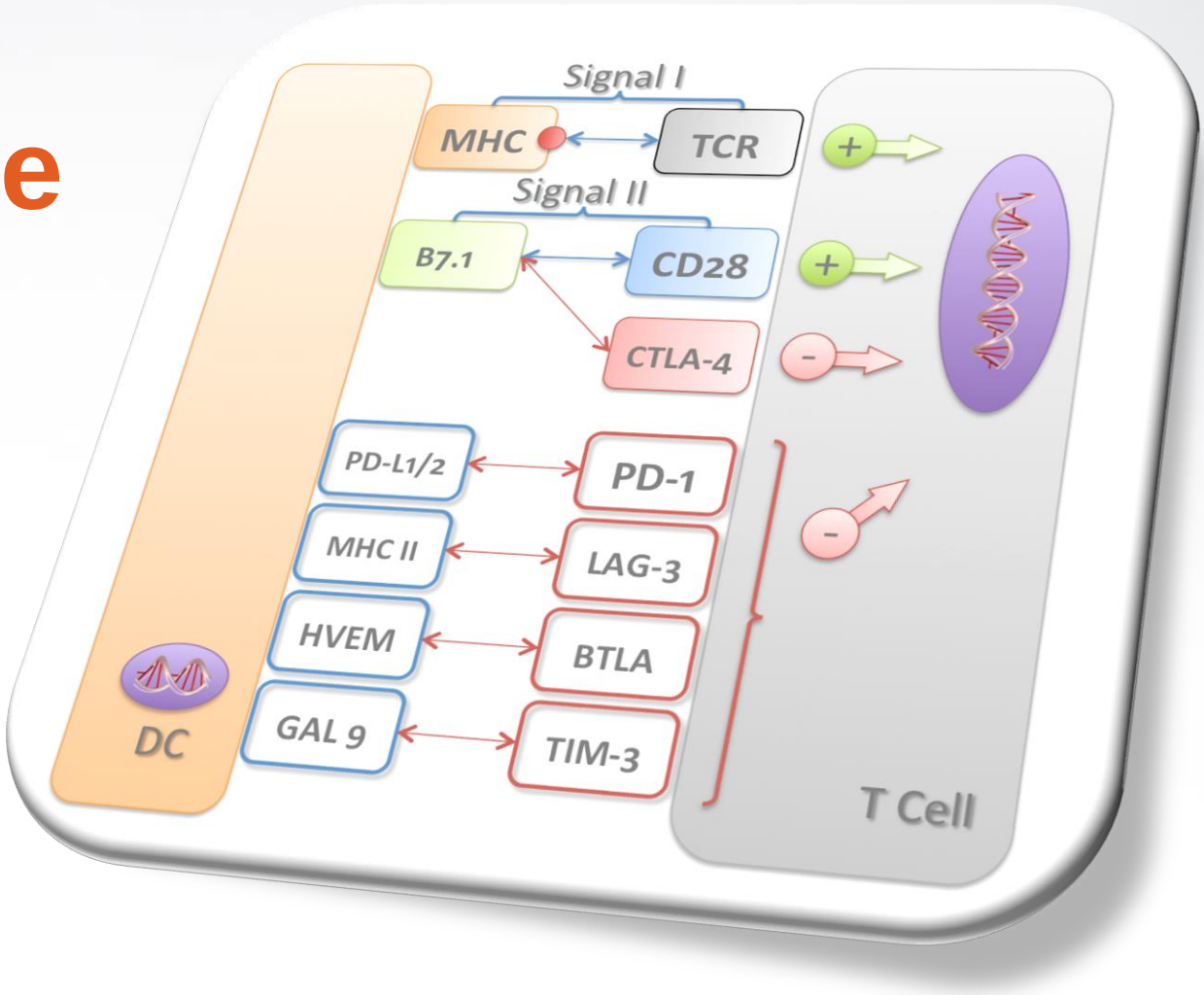




In typical adjuvant trials, this results in a large number of **patients needed to treat**:

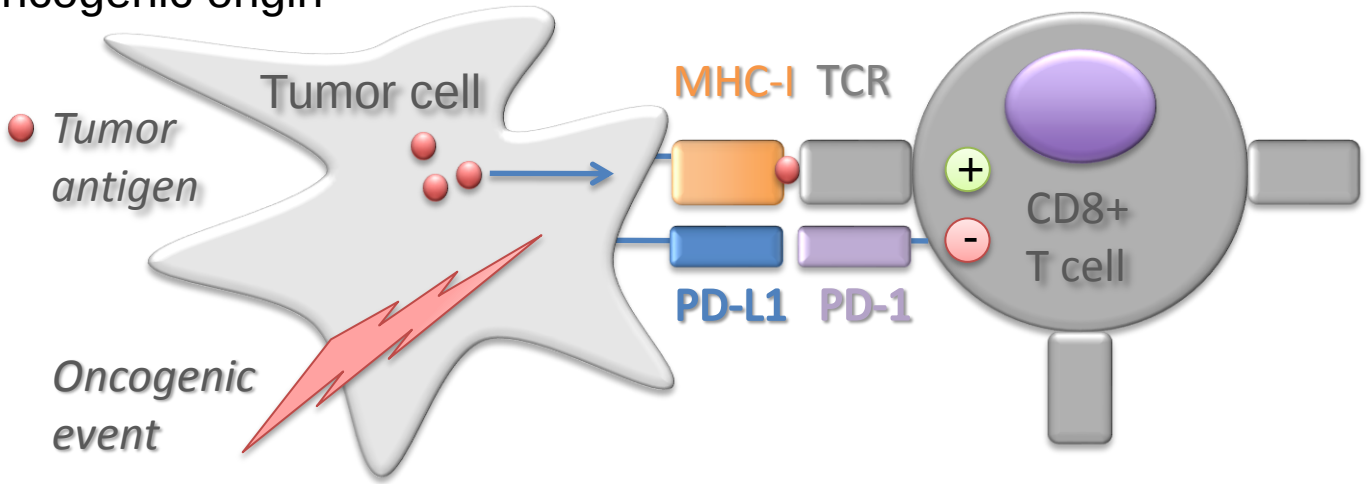
- Adjuvant Interferon - Cochrane Review (Mocellin 2013):
  - 35 participants in order to prevent 1 death
  - 97% of patients exposed for no benefit

PD-1 Blockade

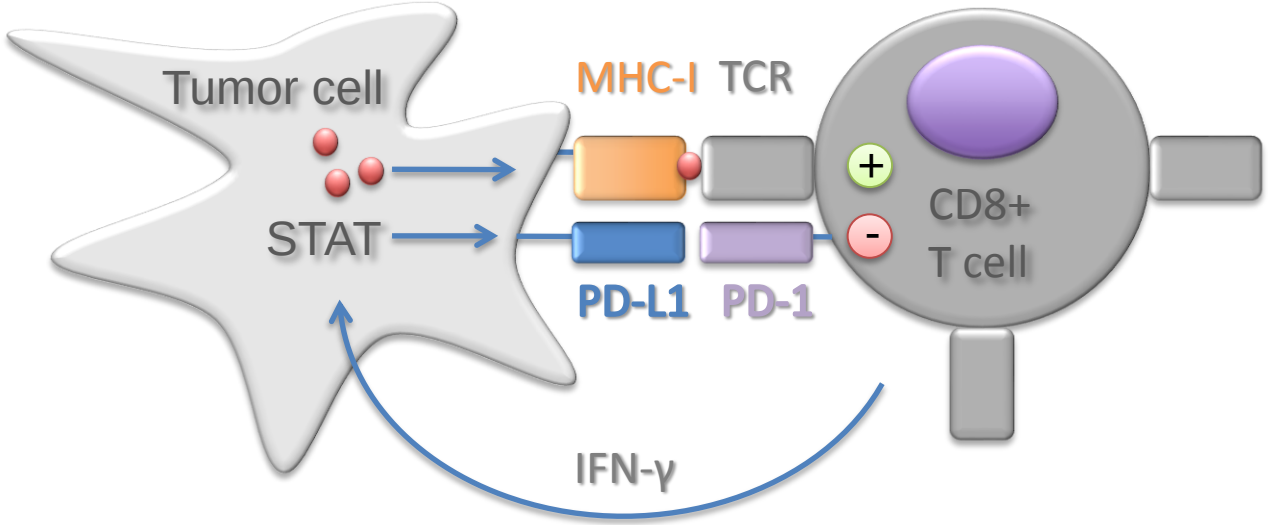


Biology of PD-L1 expression

1 Oncogenic origin



2 Induced by chronic inflammation



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

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Keynote-001[4]: Phase 1
- Keytruda, Ipi-N or T
- RR 34%, mOS 26
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- RR 32%,
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- Nivo / DTIC, 1st line
- RR 40%,
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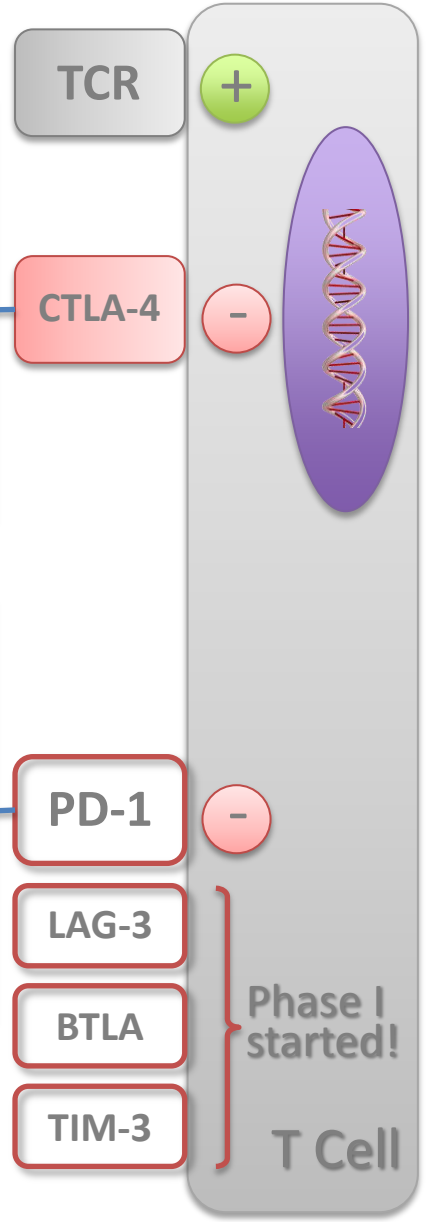

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11 ASCO/ESMO/SMR 2014 (Time units in months unless specified, NA: Not Available, NR: Not Relevant)

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

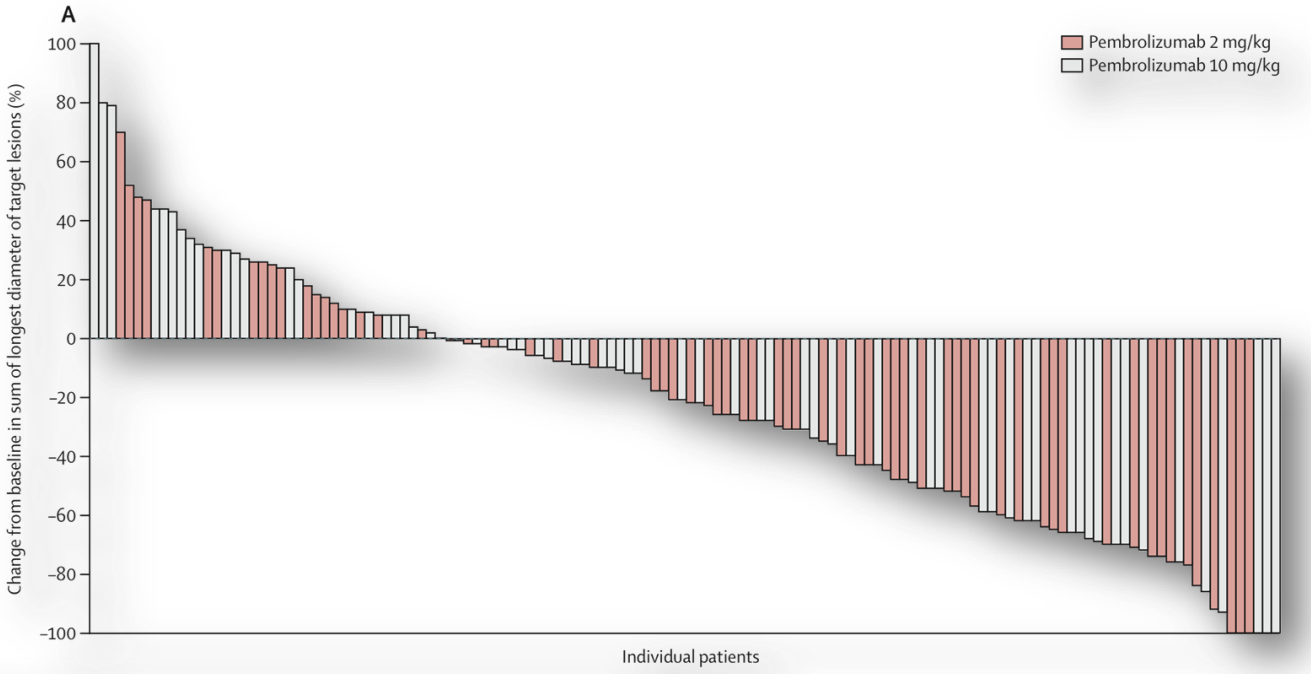
Keynote-001 Update: SMR 2014

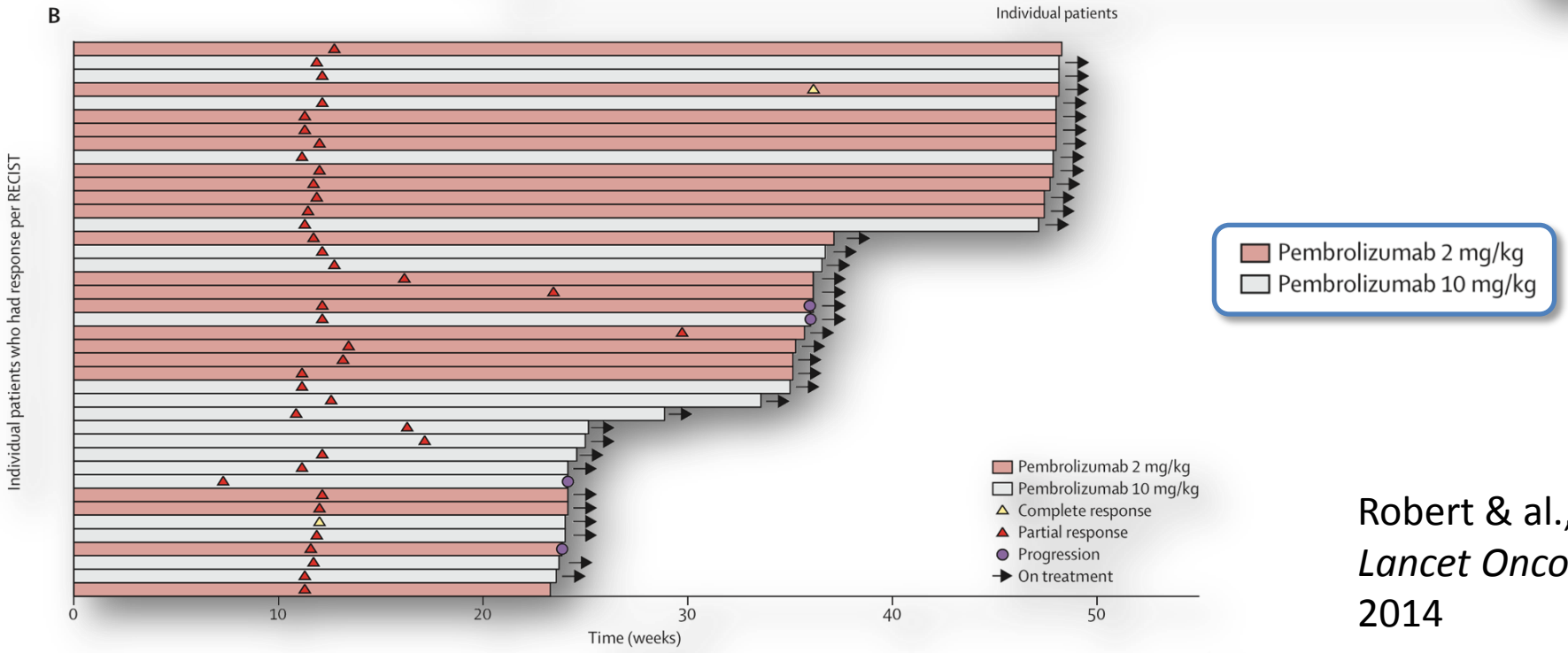
ORR (RECIST v1.1), Central Review	Total N=360	IPI Naïve n=165	IPI Treated n=195
CR, % (95% CI)	8 (5-11)	10 (6-15)	6 (3-10)
ORR, % (95% CI)	34 (29-39)	39 (32-47)	29 (23-36)
DCR, % (95% CI)	54 (49-59)	55 (47-62)	54 (47-61)

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

Society for Melanoma Research (SMR) 2014

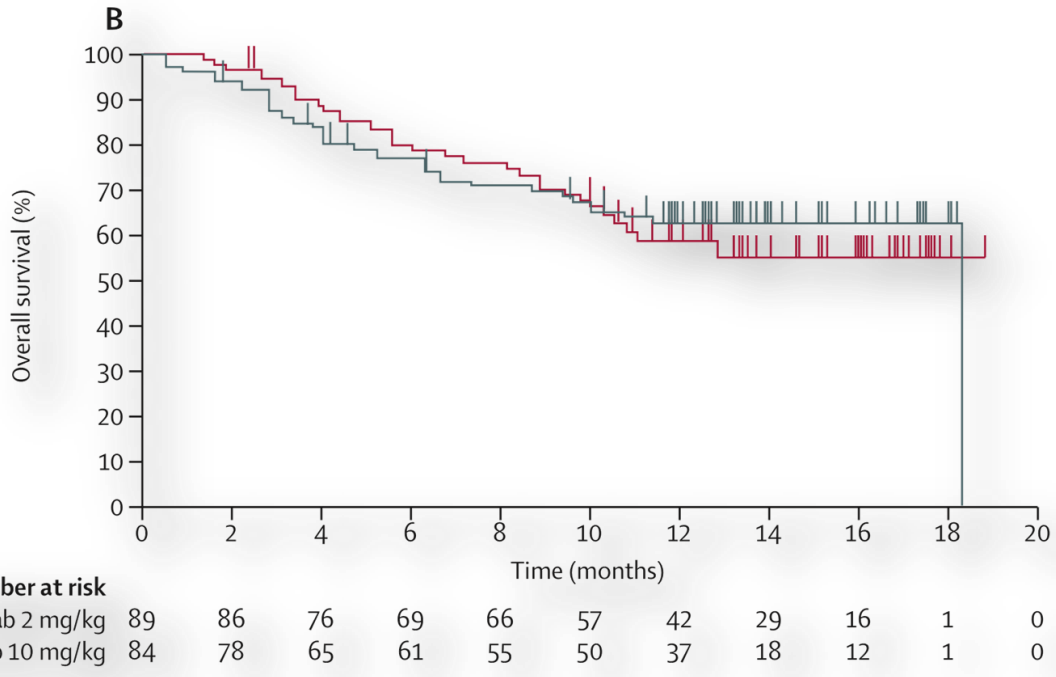
Keynote-001 (expansion): response pattern

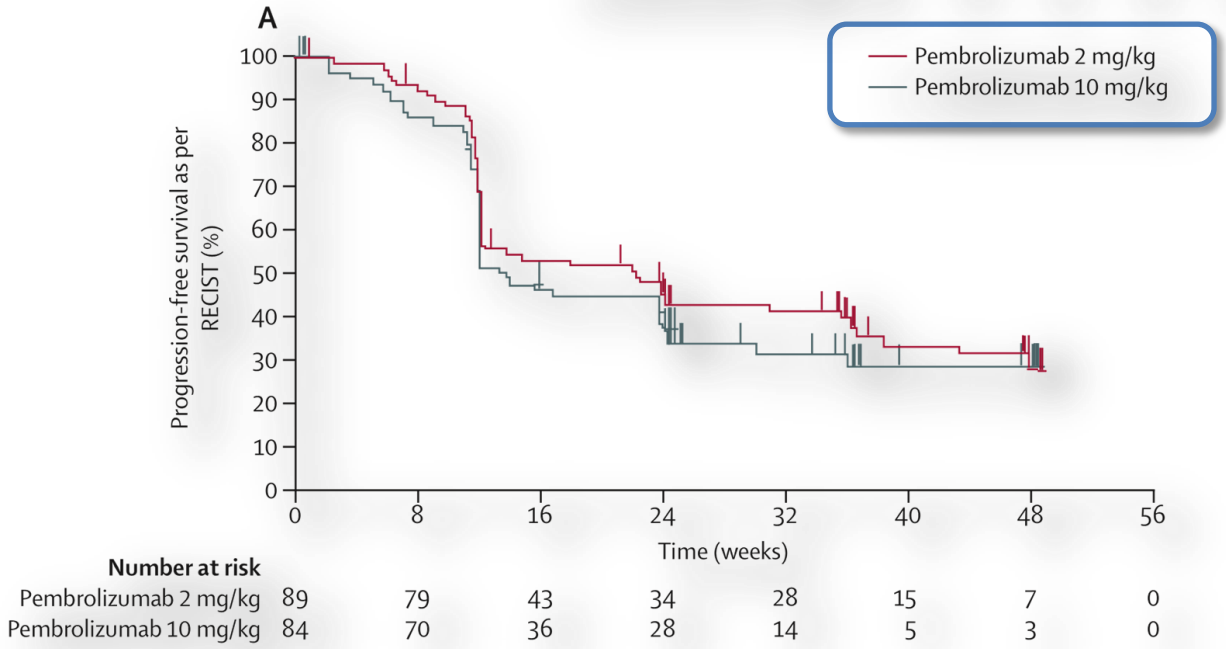




Robert & al., *Lancet Oncol* 2014

Keynote-001 (expansion): OS and PFS





1 year OS:

- 58% (95% CI 47–68) in the 2 mg/kg group
- 63% (51–72) in the 10 mg/kg group

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

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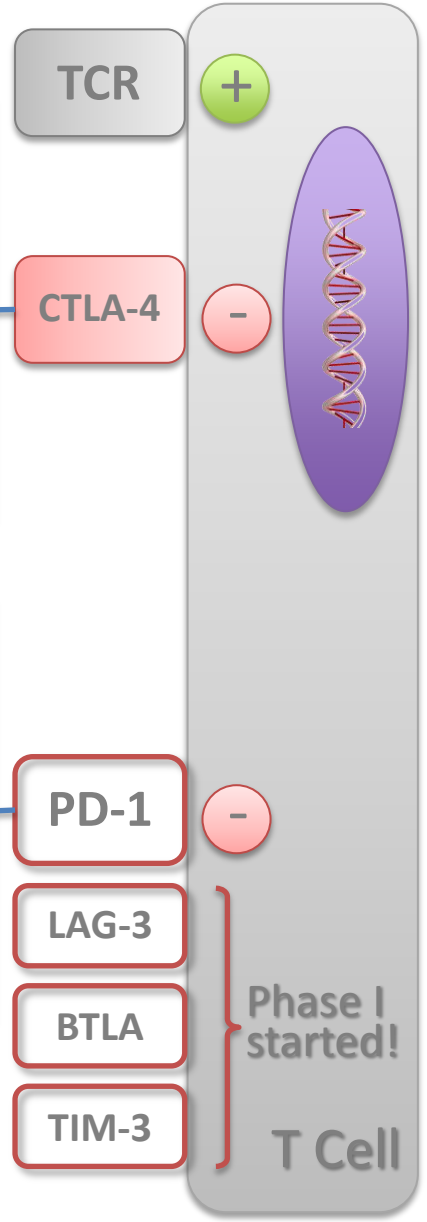

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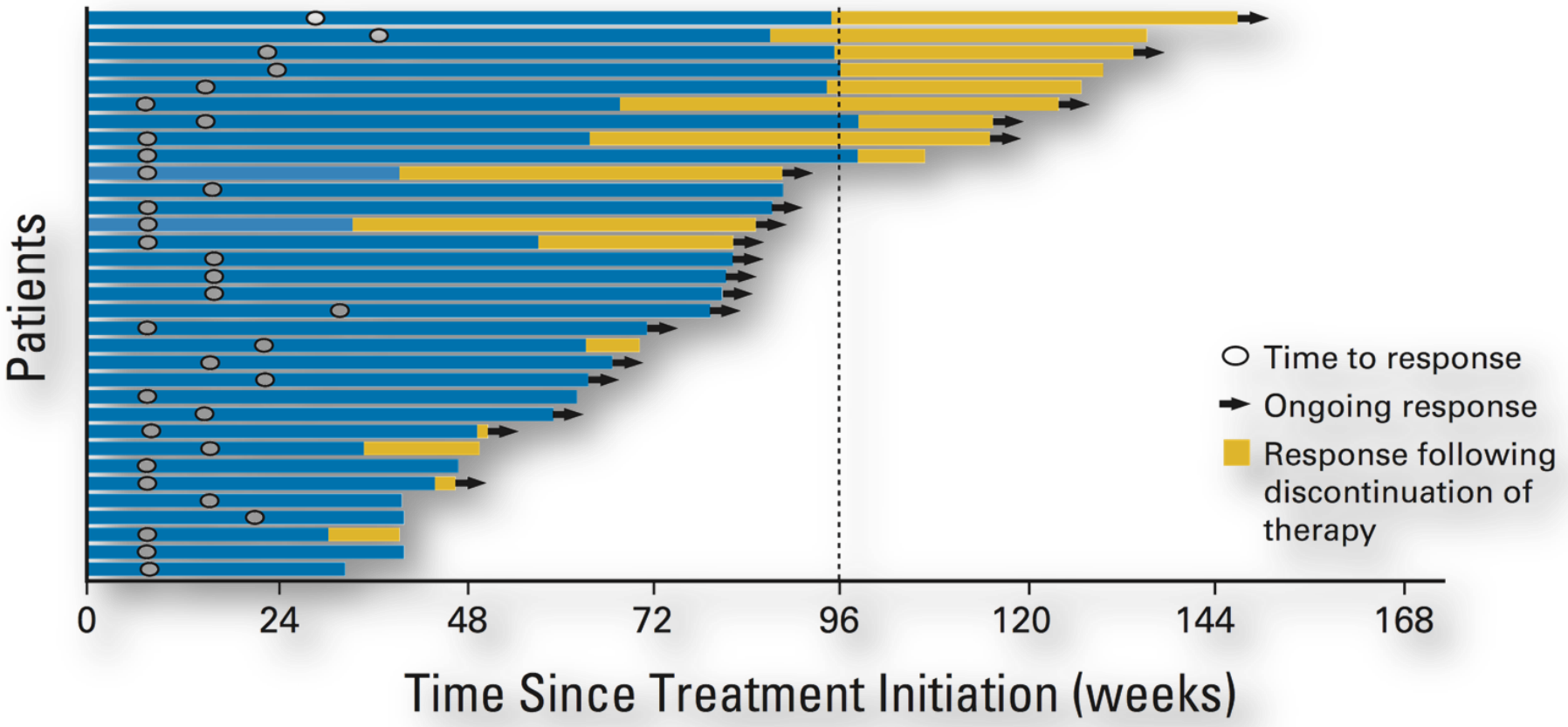
Nivolumab Phase 1: CA209-003, response rates, ASCO 2014 update

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

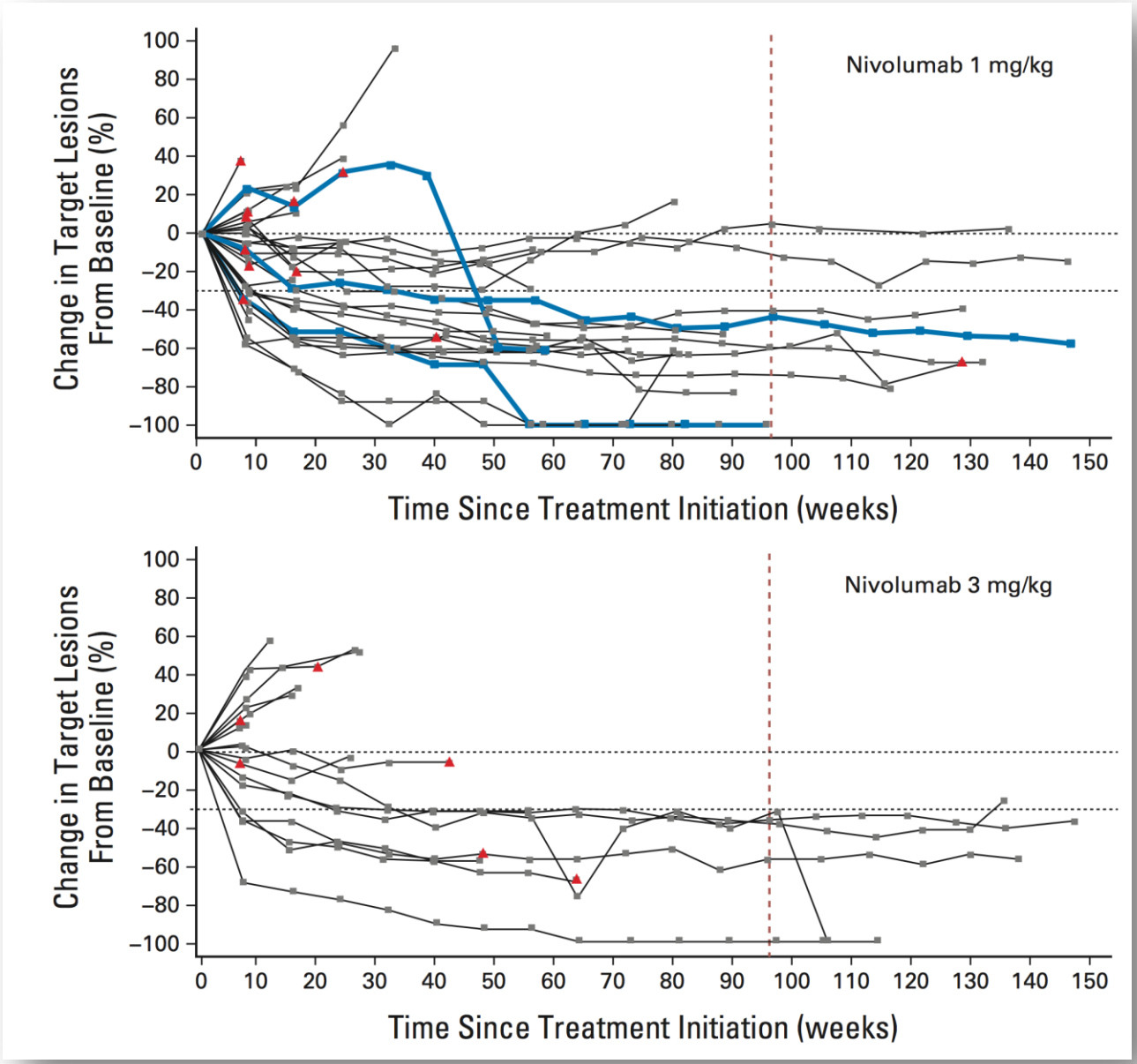
Adapted from S. Hodi, ASCO 2014, CA209-003

Updated nivolumab single agent data



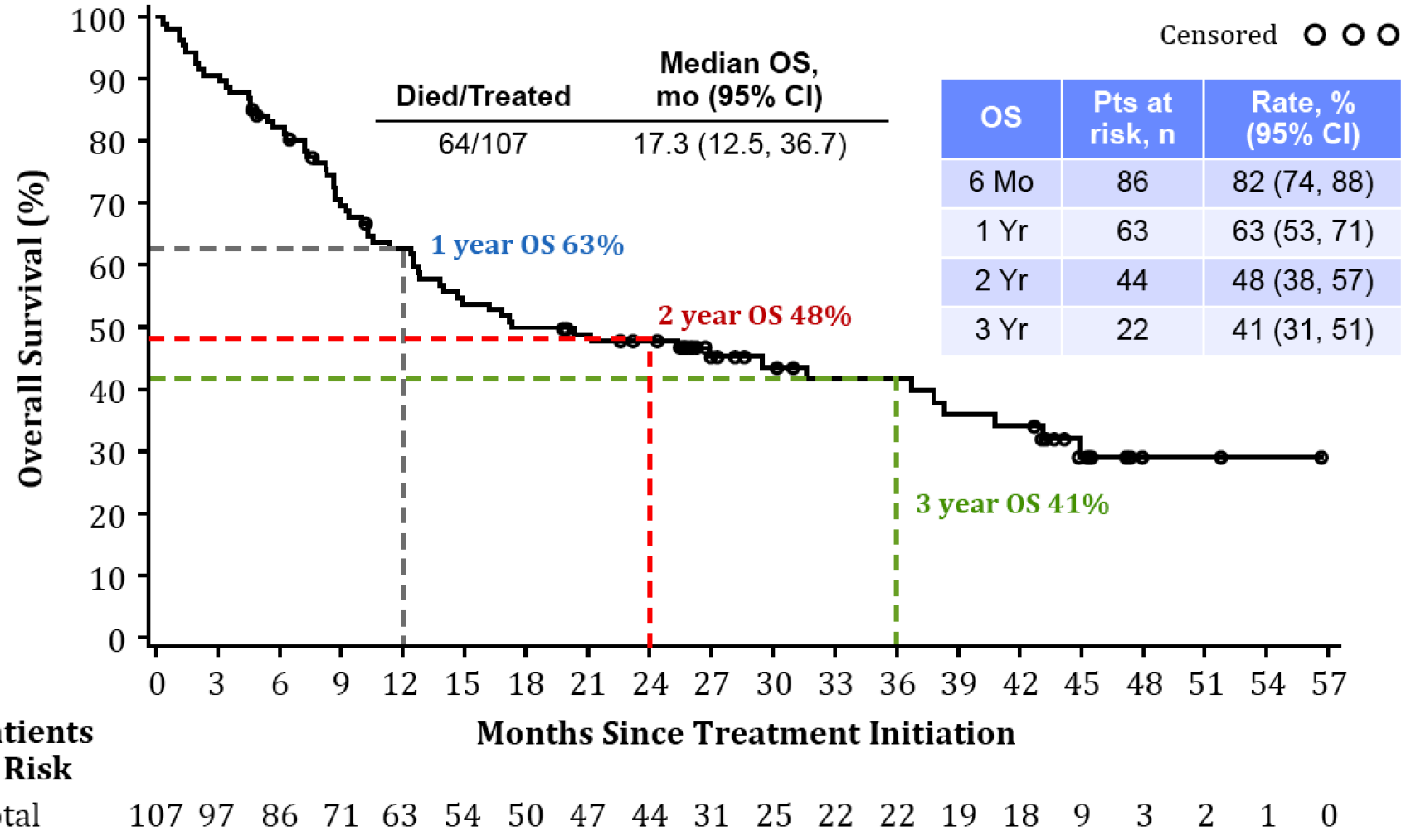
Topalian & al., *JCO* 2014

Spider plots of nivolumab single agent



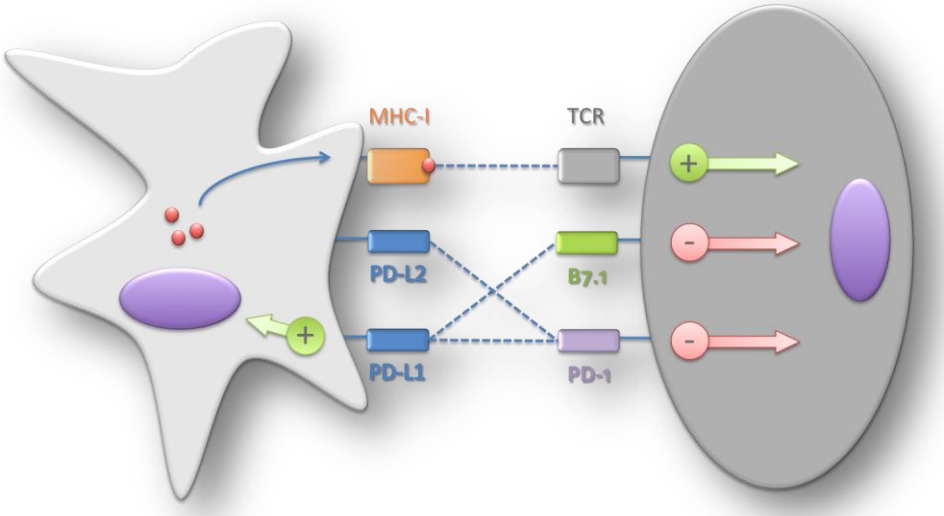
Topalian & al.
JCO 2014

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

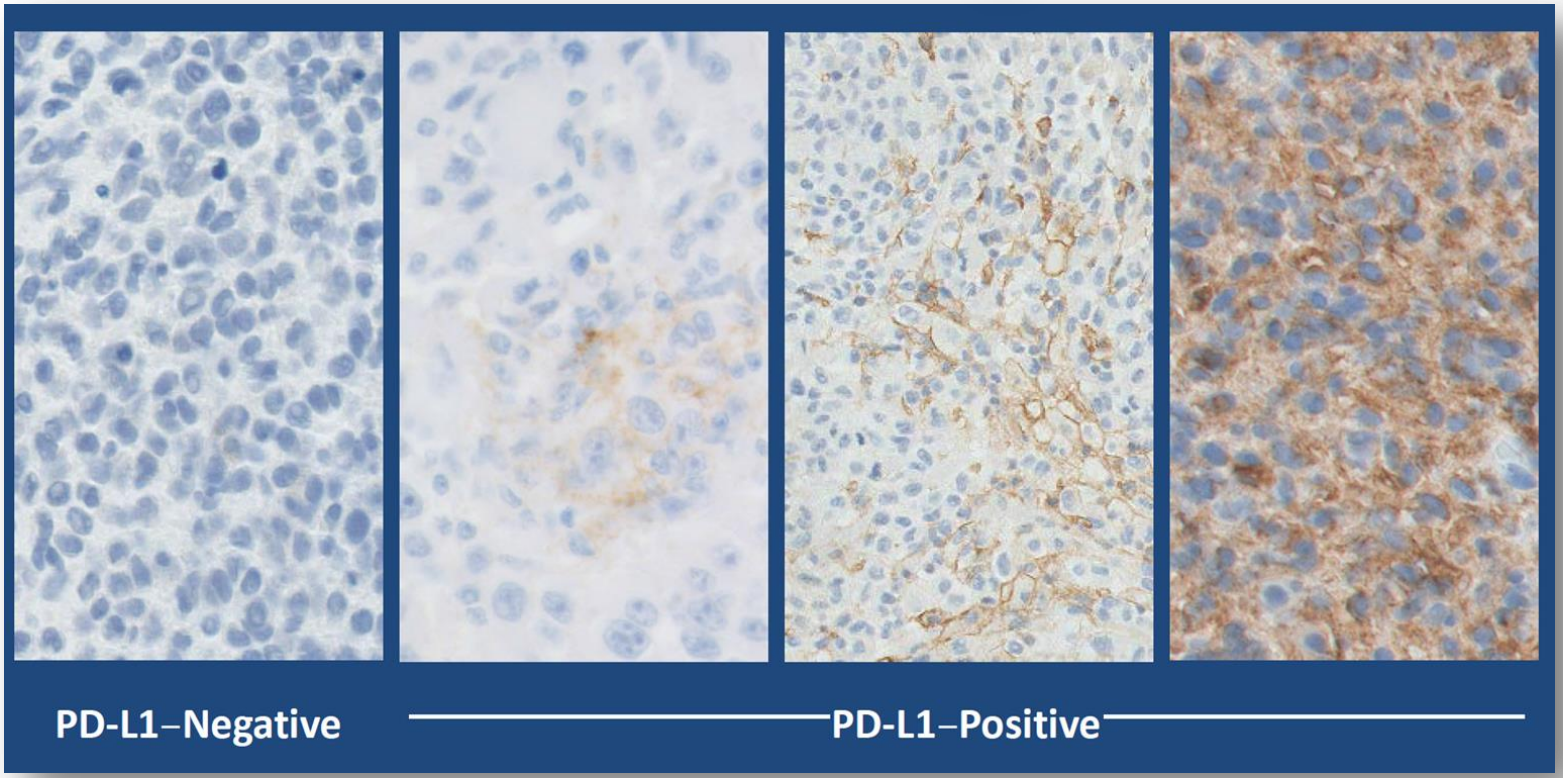


S. Hodi, ASCO 2014, CA209-003

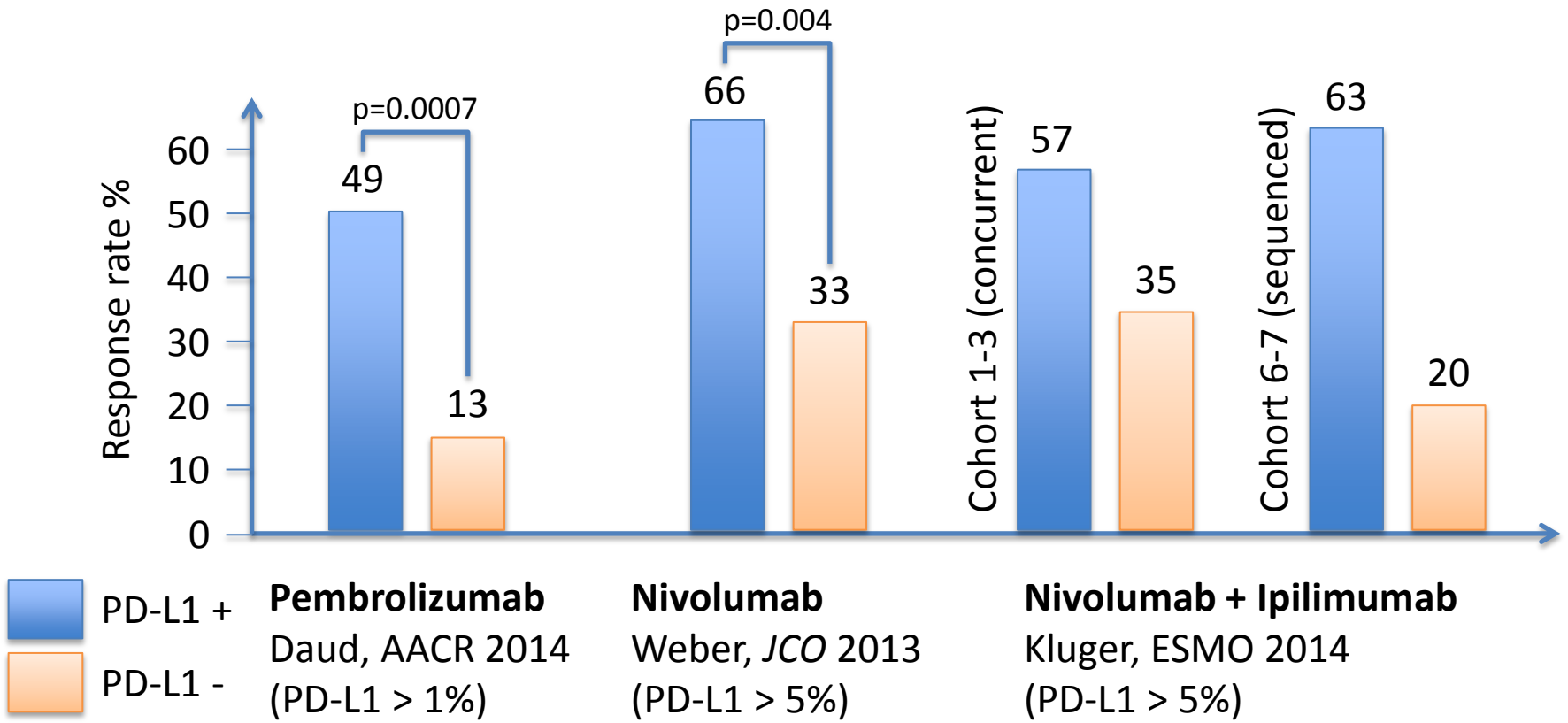
PD-L1 as a predictive biomarker?



Daud & al., AACR 2014



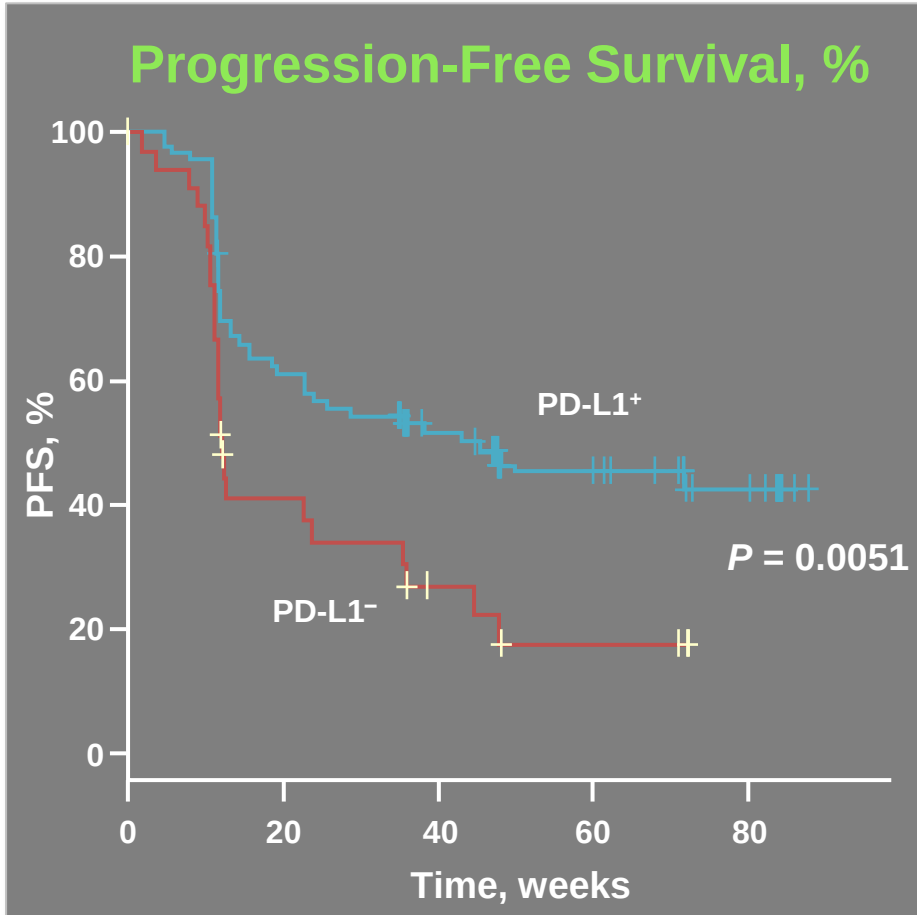
PD-L1 as a predictive biomarker for CTLA-4 + PD-1 double blockade

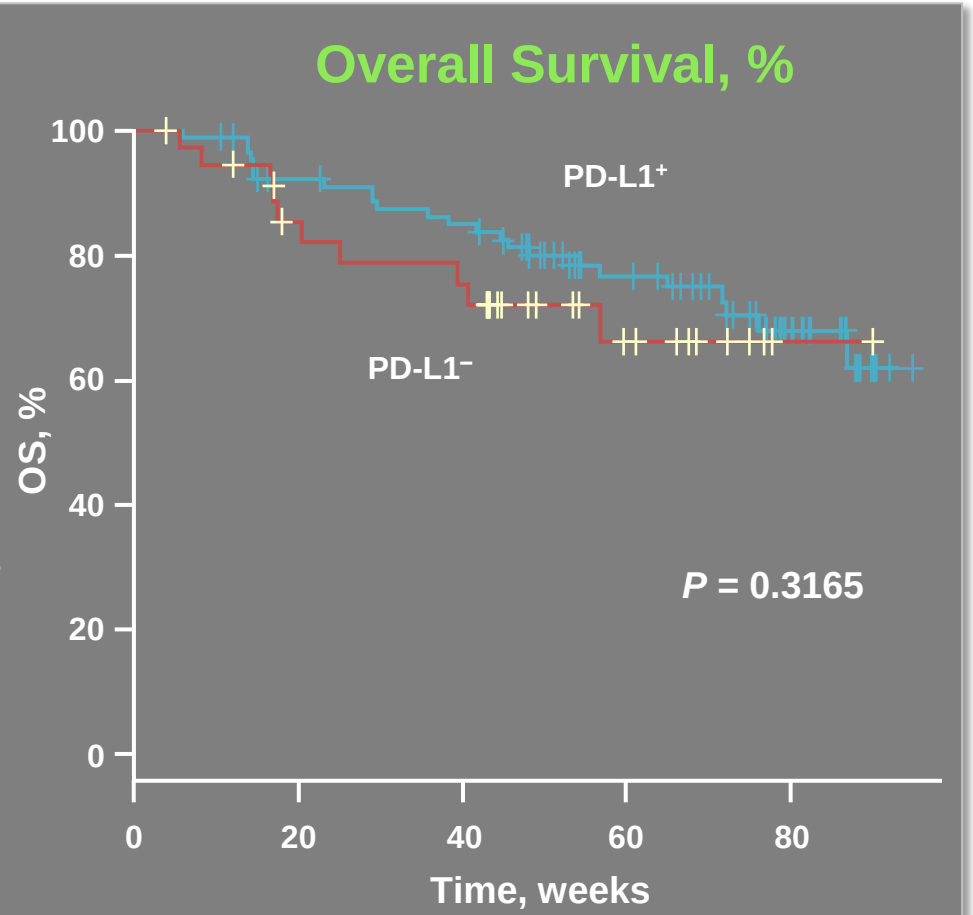


Caveats:

- 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 (CA209-037)** Nivolumab vs ICC	**Phase 3 (CA209-066)** Nivolumab vs DTIC
Patient inclusion	Prior 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

Overview of checkpoint blockade

Combinations

Single agent

Ipi + bevacizumab[8]:
- Ph1: Ipi + bev
- RR 17%, DCR 67%

Ipi + T-vec[9]:
- Ph1, IT injection
- RR 41%, CR 24%

Ipi + GM-CSF[10]: low tox
- Ph2: Ipi/ipi + GM-CSF
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Checkmate 067[11]:
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- RR 11%, mPFS 2.8
- HR OS: 0.66, mOS 10

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- HR OS: 0.72, mOS 11

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Adjuvant

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- mRFS: 26 vs 17
- HR RFS/OS: 0.75/NA

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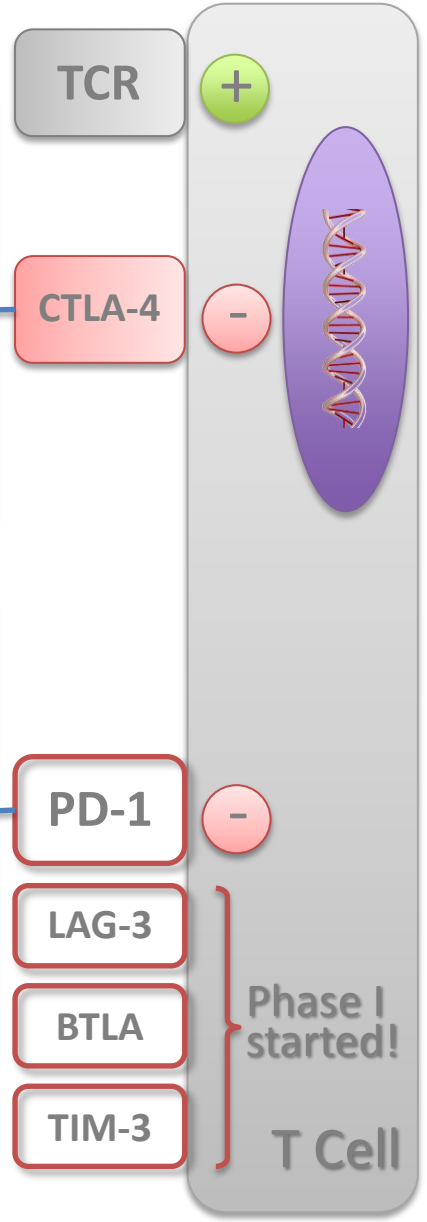

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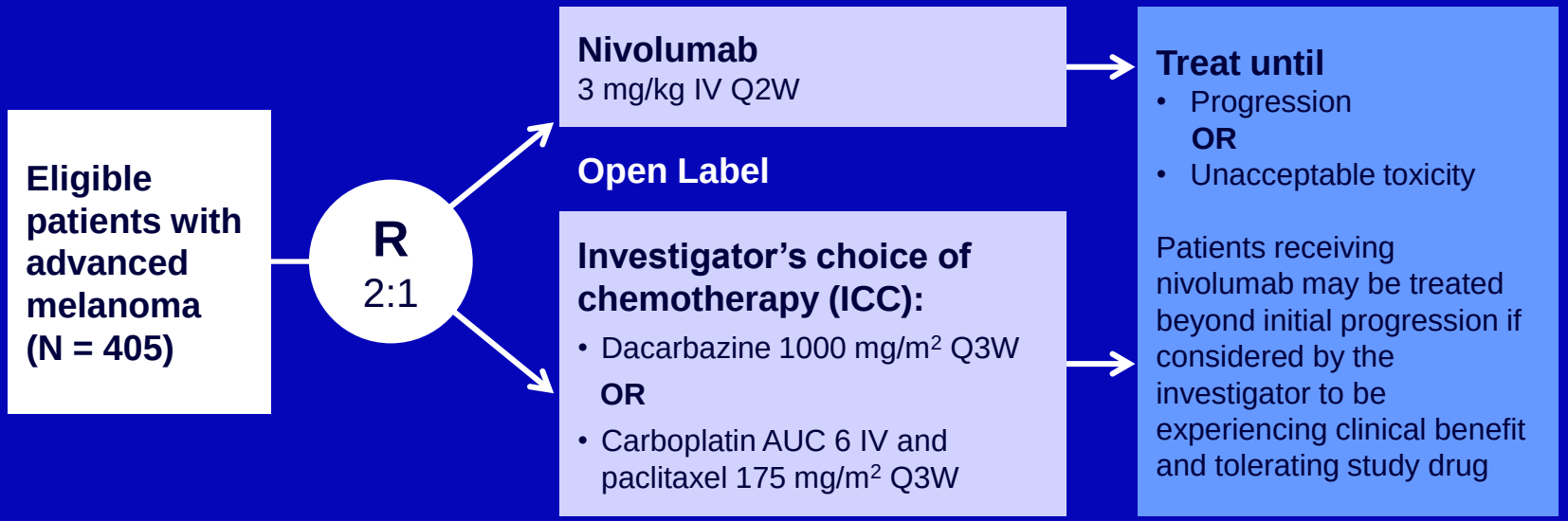
Phase 3 CA209-037: Study Design



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.

Presented at SMR 2014 by Sandra P D'Angelo.

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.

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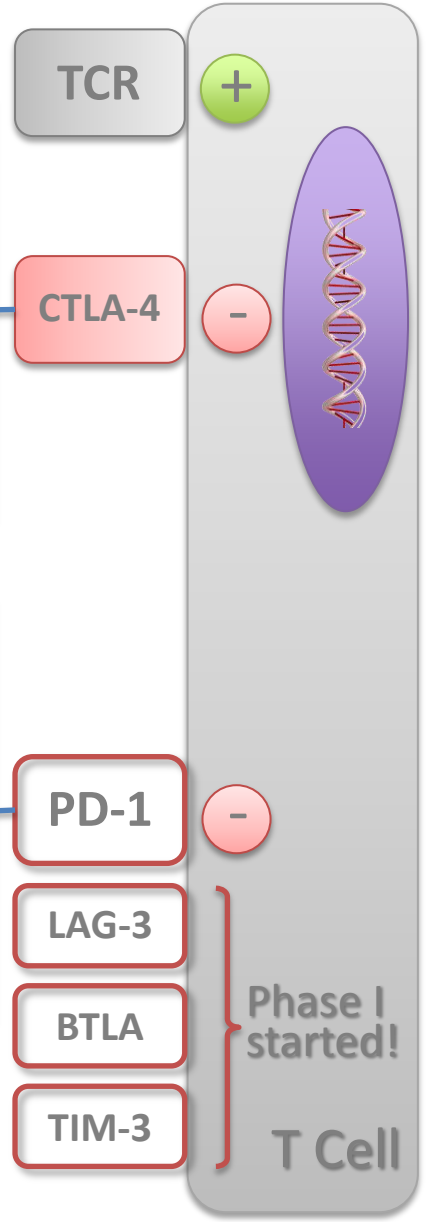

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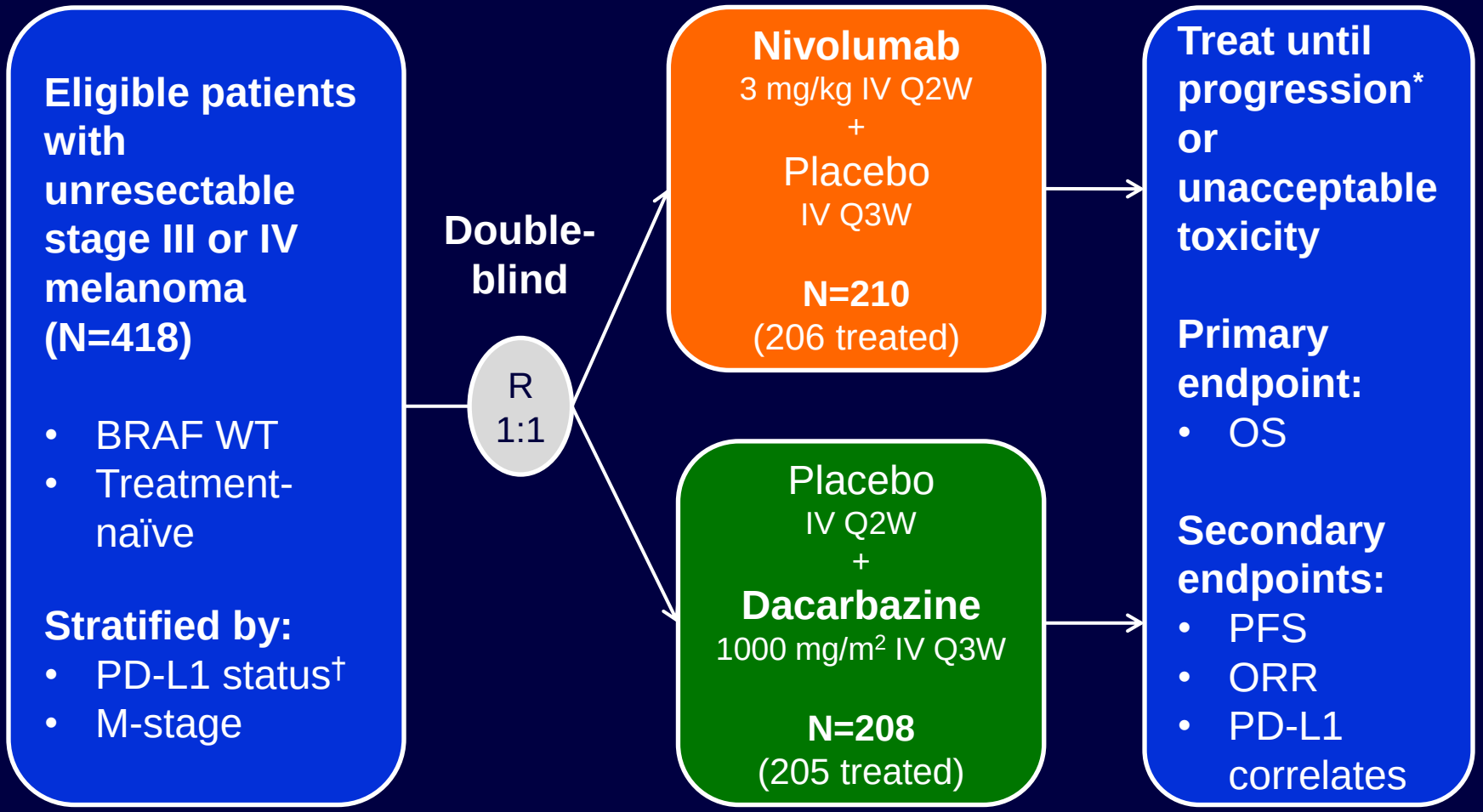
Phase 3 CA209-066: Study Design

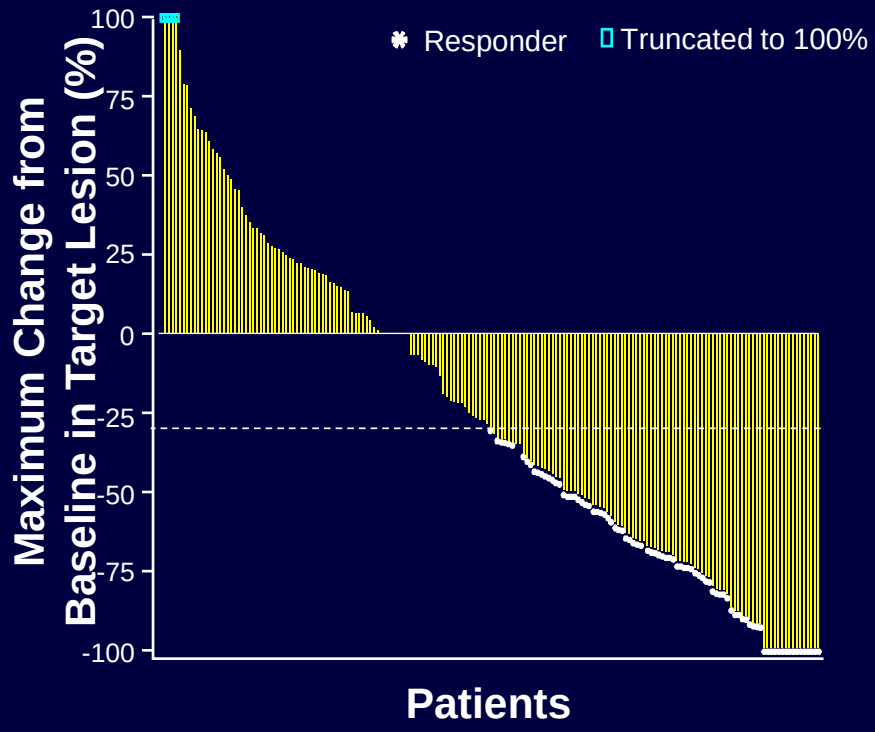


†PD-L1 positive: ≥ 5% tumor cell surface staining.

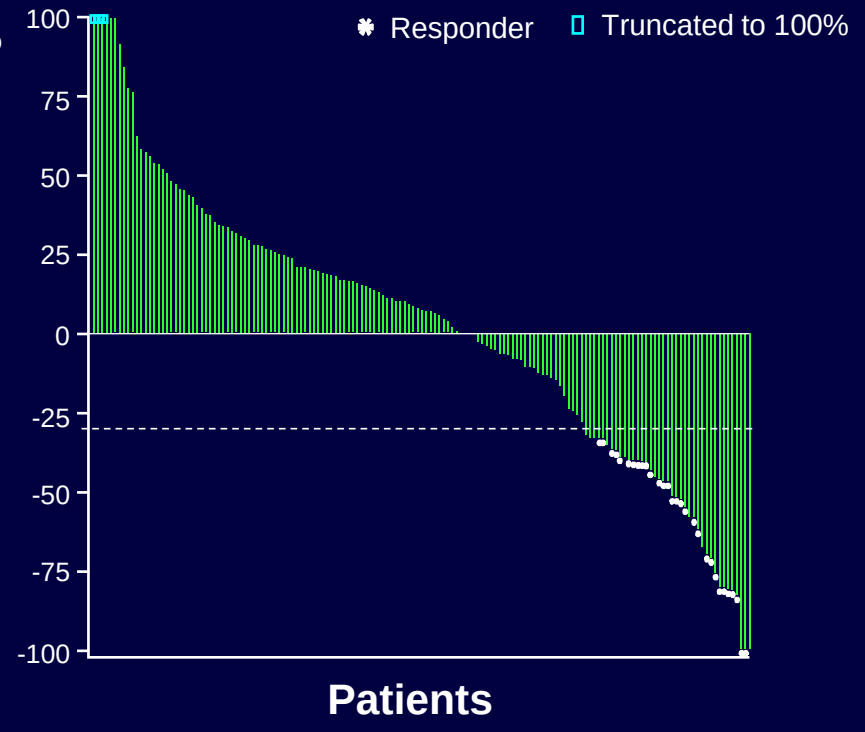
*Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Objective Response by RECIST v1.1

Nivolumab
ORR 40% (95% CI, 33–47%)



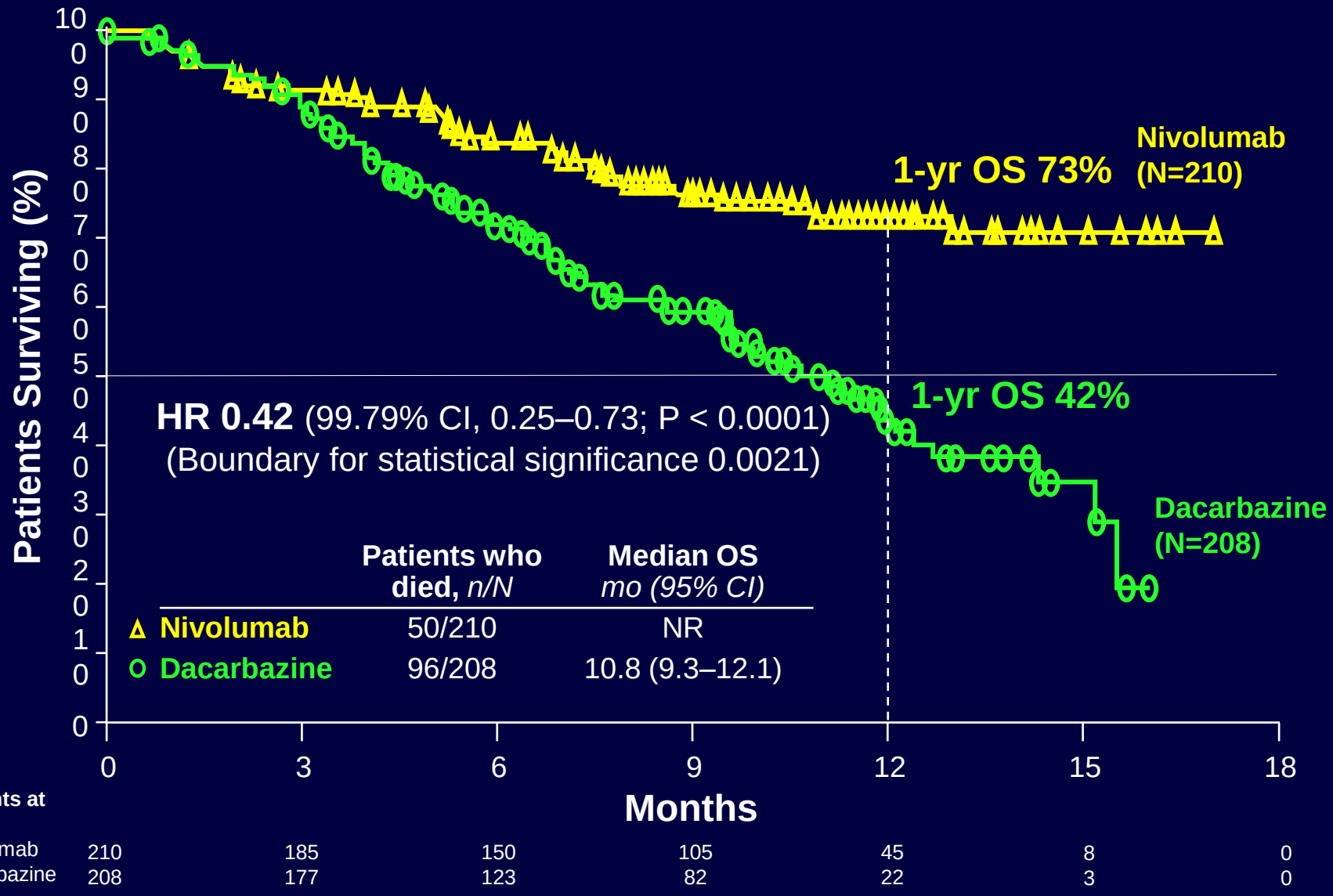
Dacarbazine
ORR 14% (95% CI, 10–19%)



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

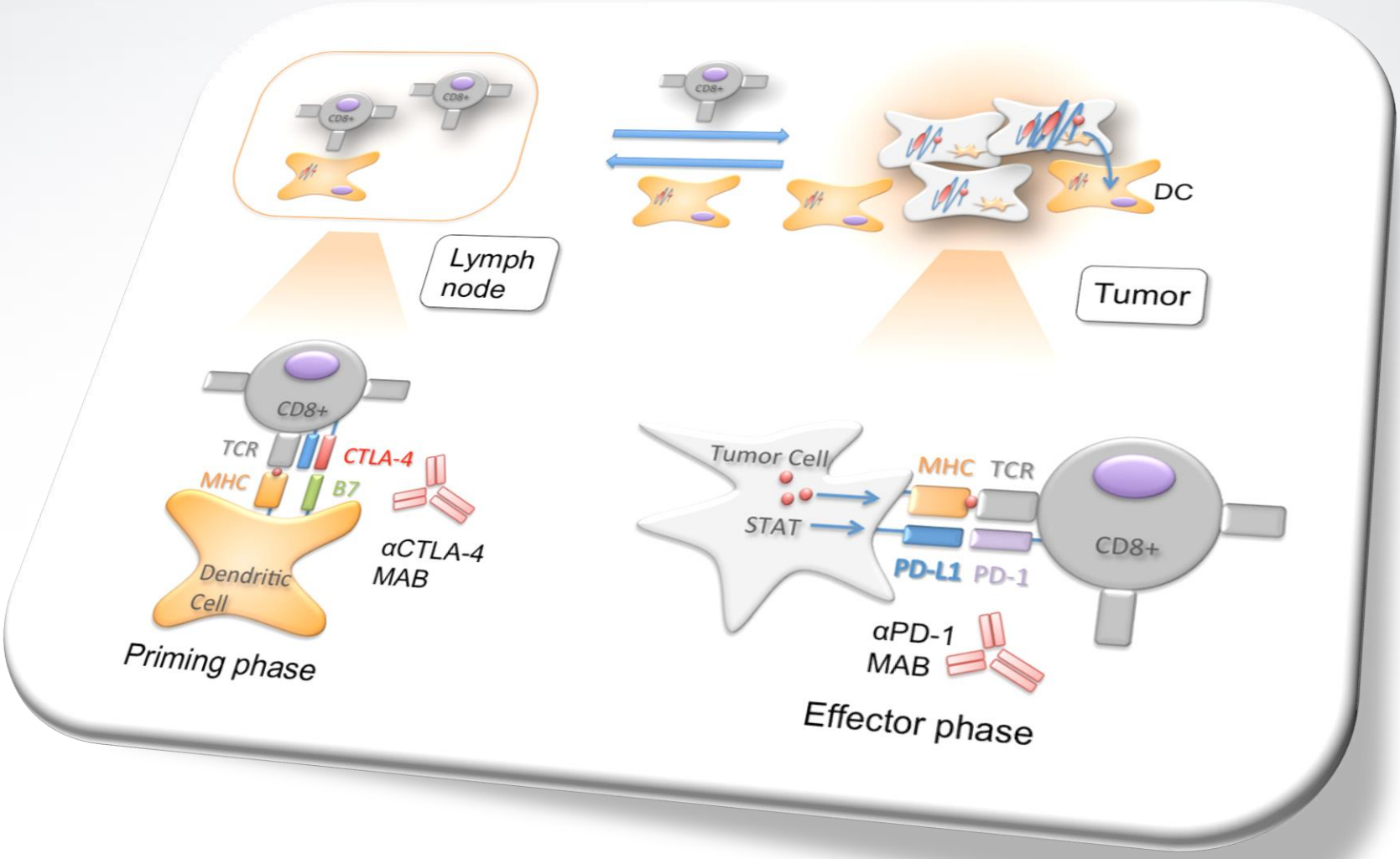
The NEW ENGLAND JOURNAL of MEDICINE

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



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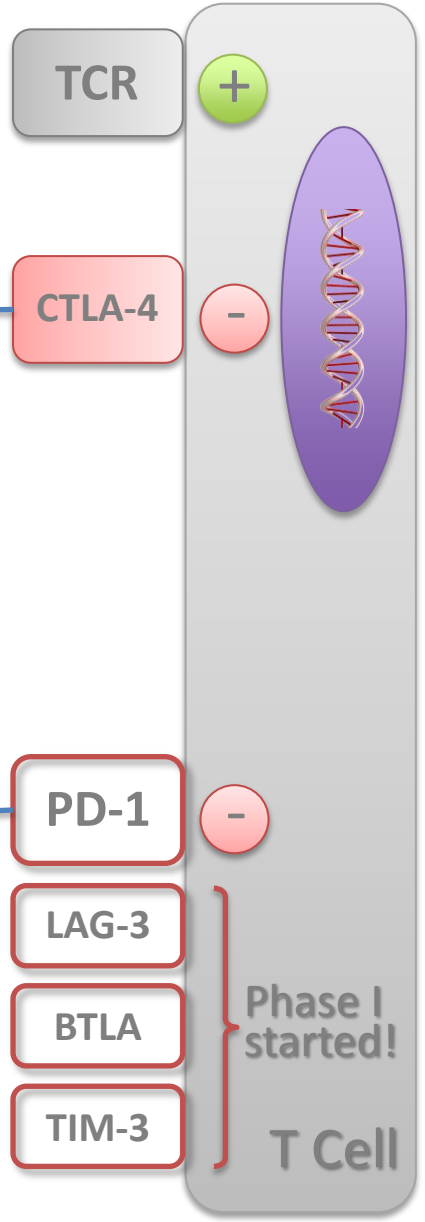
CA-209-003[5]: Phase 1
- Nivolumab, 2nd +
- RR 31%, mOS: 17
- HR OS/PFS: NR/NR

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

CA-209-037[11]: Phase 3
- Nivo / ICC, 2nd line
- RR 32%,
- HR OS/PFS: NA/NA

CA-209-066[6]: Phase 3
- Nivo / DTIC, 1st line
- RR 40%,
- HR OS/PFS: 0.42/.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;
8 Hodi *Cancer Immunol Res* 2014; 9 Puzanov, ASCO 2014; 10 Hodi, *JAMA* 2014
11 ASCO/ESMO/SMR 2014 (Time units in months unless specified, NA: Not Available, NR: Not Relevant)

Nivolumab and ipilimumab combination

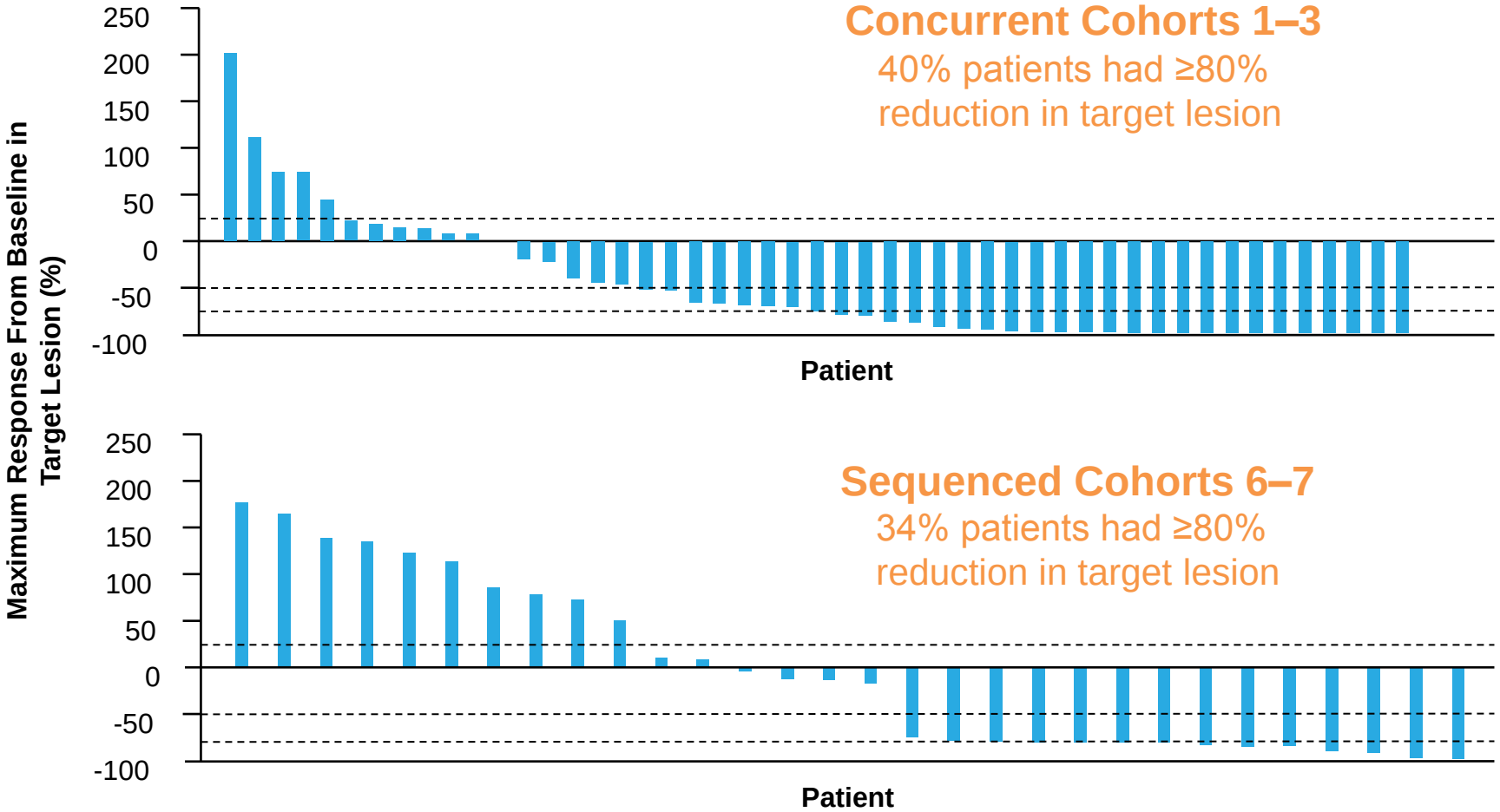
Phase I data

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)**

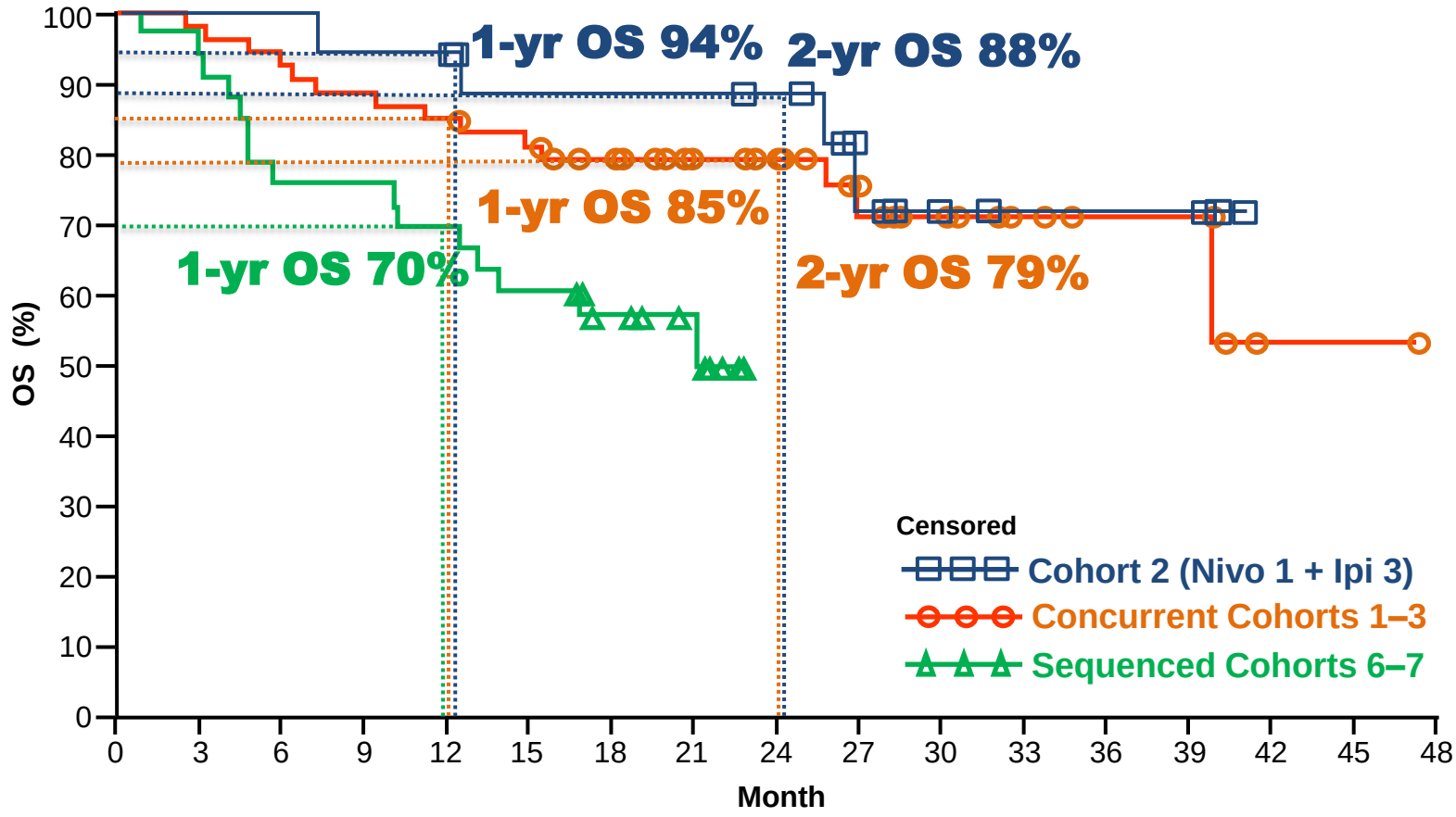
Data from ASCO, ESMO & SMR 2014

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.

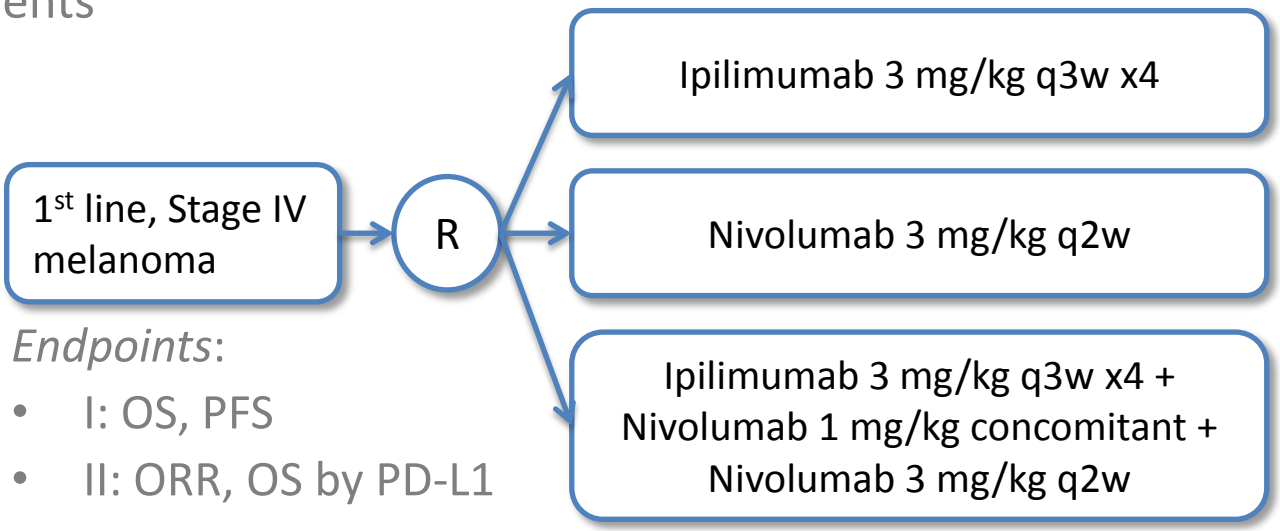
Treatment-Related AEs Reported in ≥15% of Patients

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 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

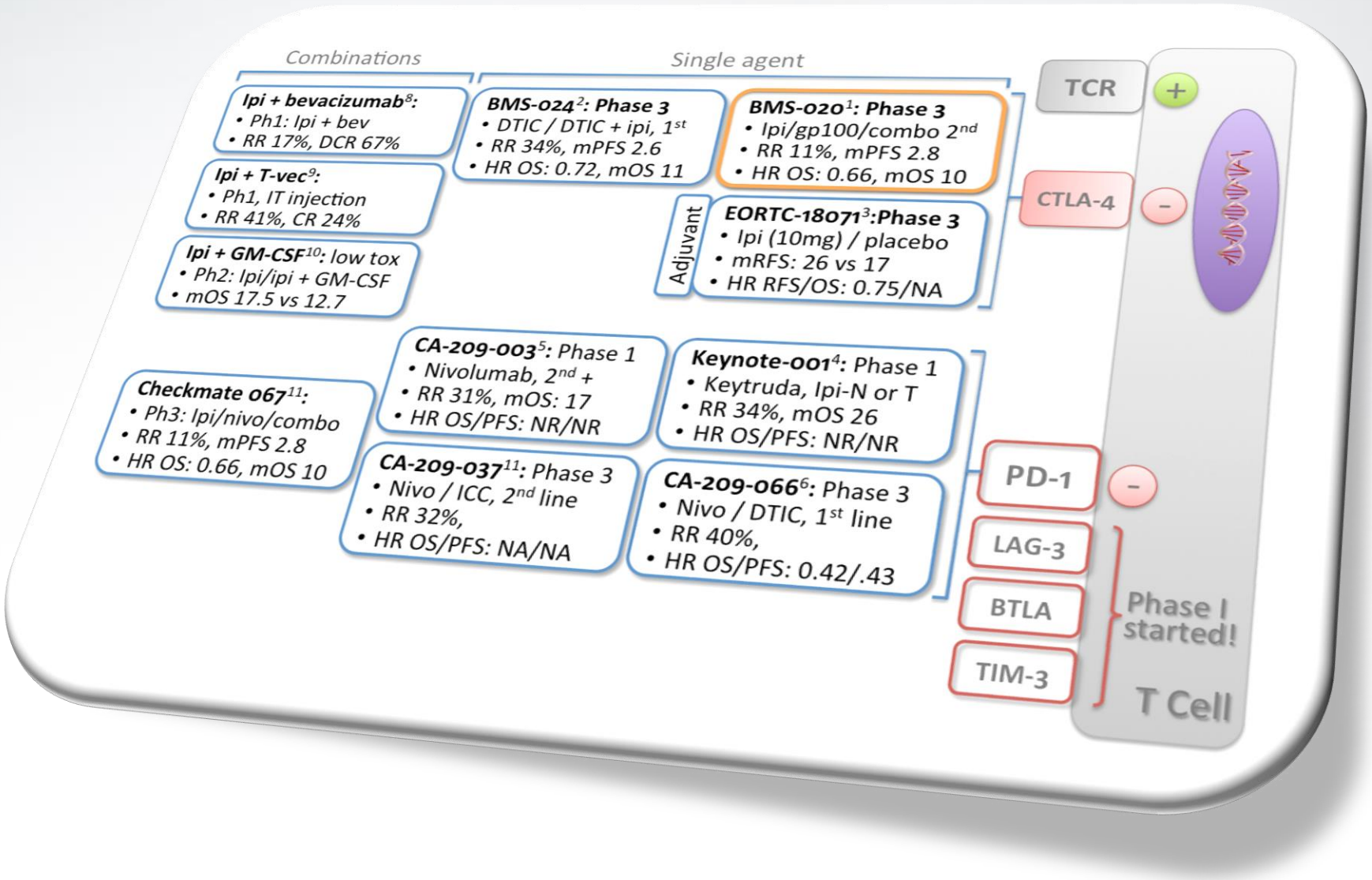


Endpoints:

- 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.

Thank you!


Combinations
Single agent
Ipi + bevacizumab[8]:
• Ph1: Ipi + bev
• RR 17%, DCR 67%
Ipi + T-vec[9]:
• Ph1, IT injection
• RR 41%, CR 24%
Ipi + GM-CSF[10]: low tox
• Ph2: Ipi/ipi + GM-CSF
• mOS 17.5 vs 12.7
BMS-024[2]: Phase 3
• DTIC / 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) / placebo
• mRFS: 26 vs 17
• HR RFS/OS: 0.75/NA
Checkmate 067[11]:
• Ph3: Ipi/nivo/combo
• RR 11%, mPFS 2.8
• HR OS: 0.66, mOS 10
CA-209-003[5]: Phase 1
• Nivolumab, 2nd +
• RR 31%, mOS: 17
• HR OS/PFS: NR/NR
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• Nivo / DTIC, 1st line
• RR 40%,
• HR OS/PFS: 0.42/.43
TCR
+
CTLA-4
-
PD-1
-
LAG-3
BTLA
TIM-3
Phase I started!
T Cell