GOOD SCIENCE
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BEST PRACTICE

ESMO SUMMIT LATIN AMERICA 2019

Practice changing studies in Melanoma

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CONFLICT OF INTEREST DISCLOSURE

Paolo A. Ascierto

Consultant/advisory role:

Bristol-Meyers Squibb, Roche-Genentech, Merck Sharp & Dohme, Novartis, Array, Merck Serono, Pierre-Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore.

Research funding:

Bristol-Meyers Squibb, Roche-Genentech, Array

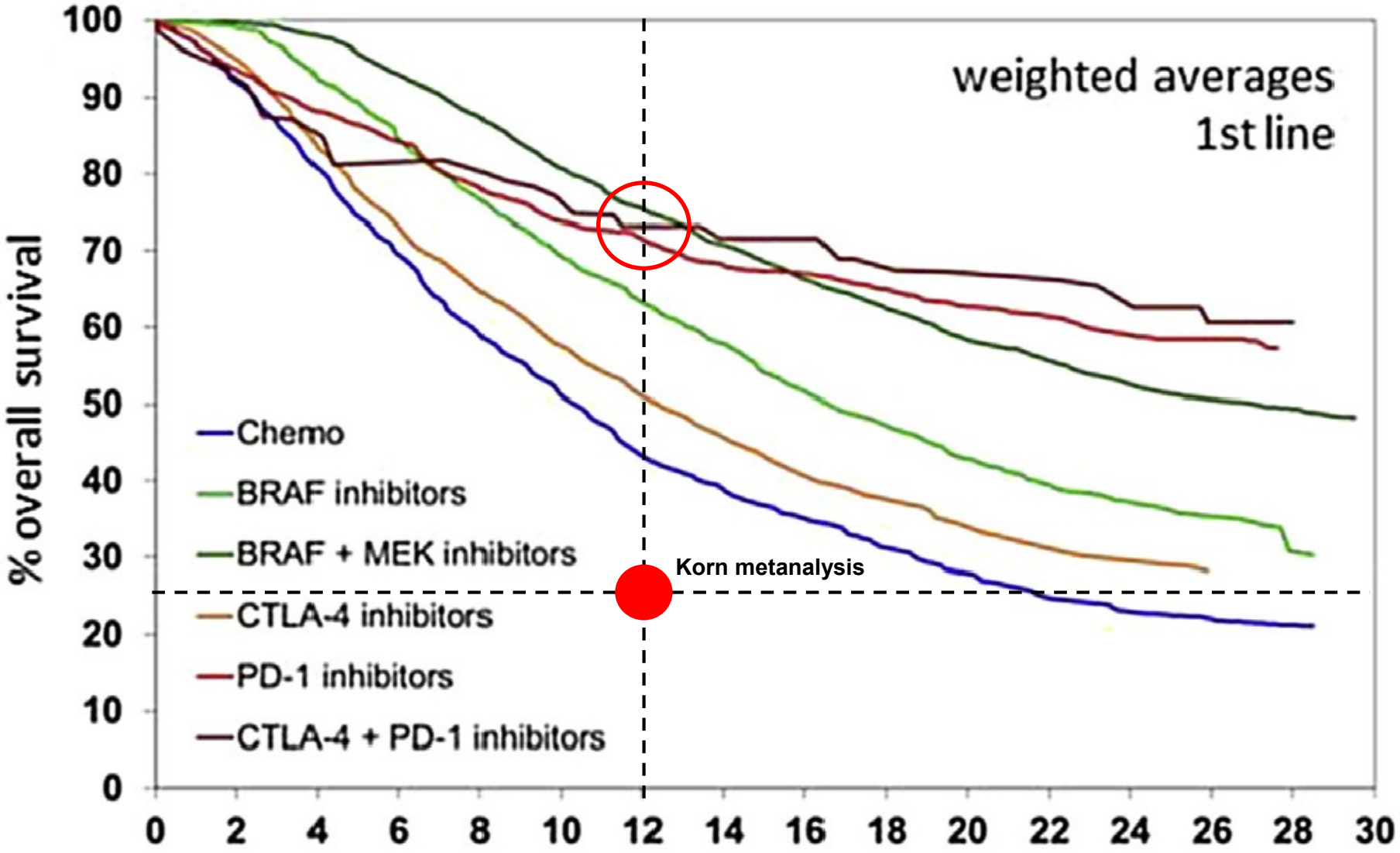
Travel support:

MSD

Non-financial interests:

President of Fondazione Melanoma Onlus, Napoli, Italy. President of Campania Society of ImmunoTherapy of Cancer (SCITO), Italy. Member of Steering Committee of Society of Melanoma Research (SMR). Member the Board of Cancer Development Drug Forum (CDDF). Member of Board of Directors for the Society of Immuno-Therapy of Cancer (SITC).

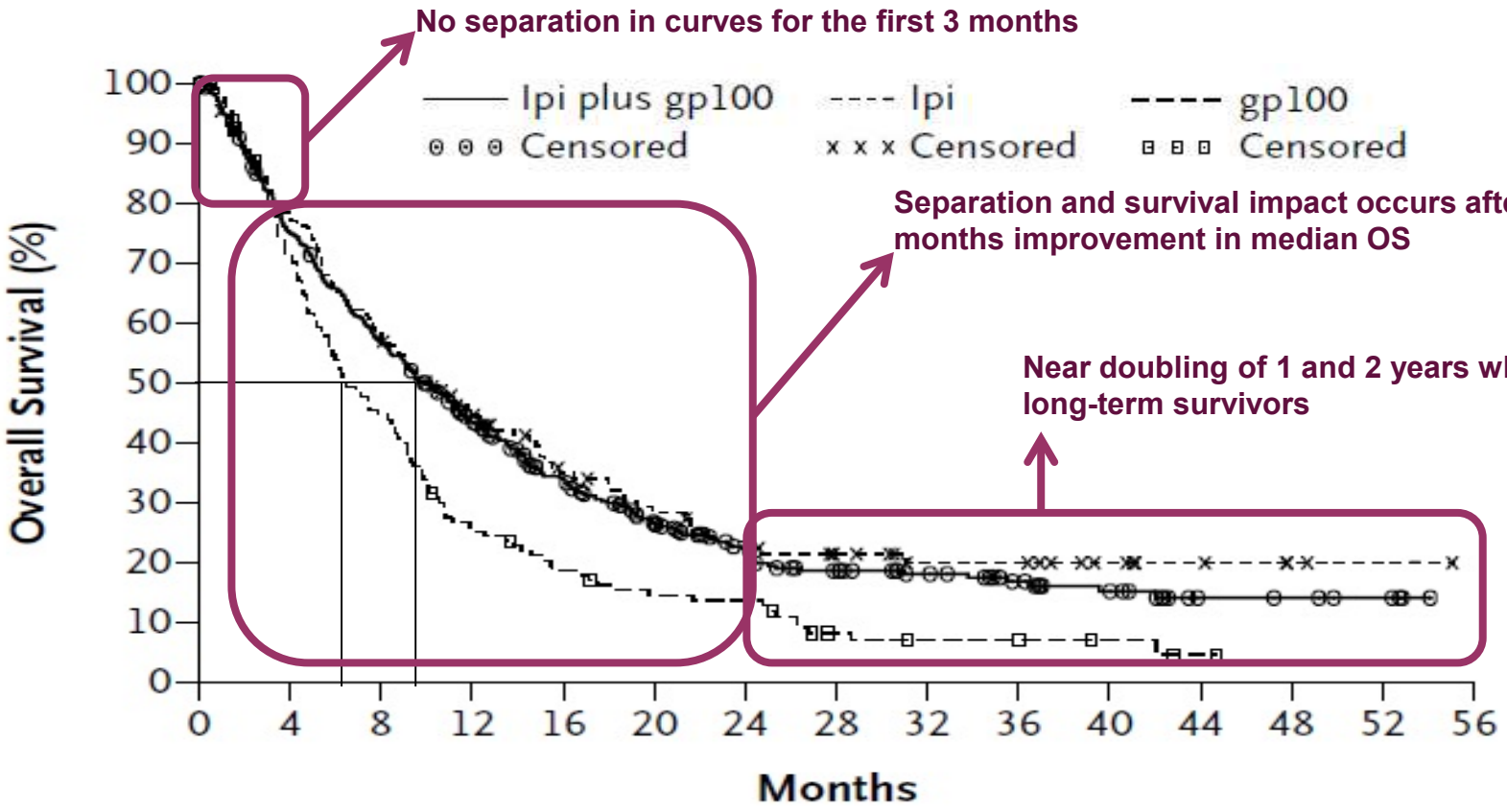
First-line therapy: Overall survival



Mean survival curves created by weighted averaging of digitised Kaplan-Meier survival curves of metastatic melanoma patients treated in selected clinical trials.
Ugurel S, Roehmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, Larkin J, Long GV, Lorigan P, McArthur GA, Ribas A, Robert C, Schadendorf D, and Garbe C:
Eur J Cancer 53: 125-134 (2016)

The MDX010-020 study: randomized phase III, double blinded, three arms study which compared ipilimumab + gp100 vs ipilimumab + placebo vs gp100 + placebo

N. 676 pretreated advanced melanoma patients were enrolled.
Randomization was 3:1:1 and the primary endpoint was OS



Median OS

ipi + gp100 = 10,0 mos
Ipi + placebo = 10,1 mos
gp100 + placebo = 6,4 mos

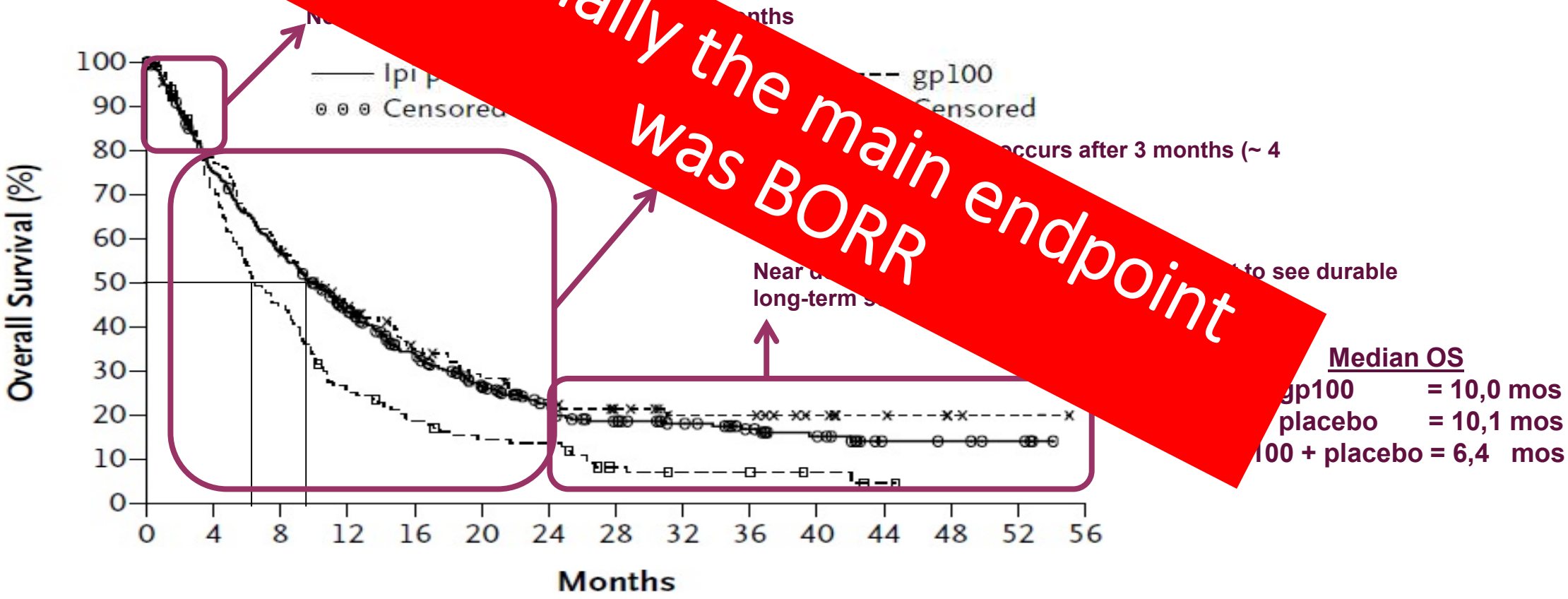
Hodi et al New Engl J Med 2010; 363:711-23

What would have happened if MDX010-020 study would have been negative ?

The MDX010-020 study: randomized phase III, double blinded, three arms study which compared ipilimumab + gp100 vs ipilimumab + placebo vs gp100 + placebo

N. advanced melanoma patients were enrolled.
1:1 and the primary endpoint was OS

Originally the main endpoint was BORR



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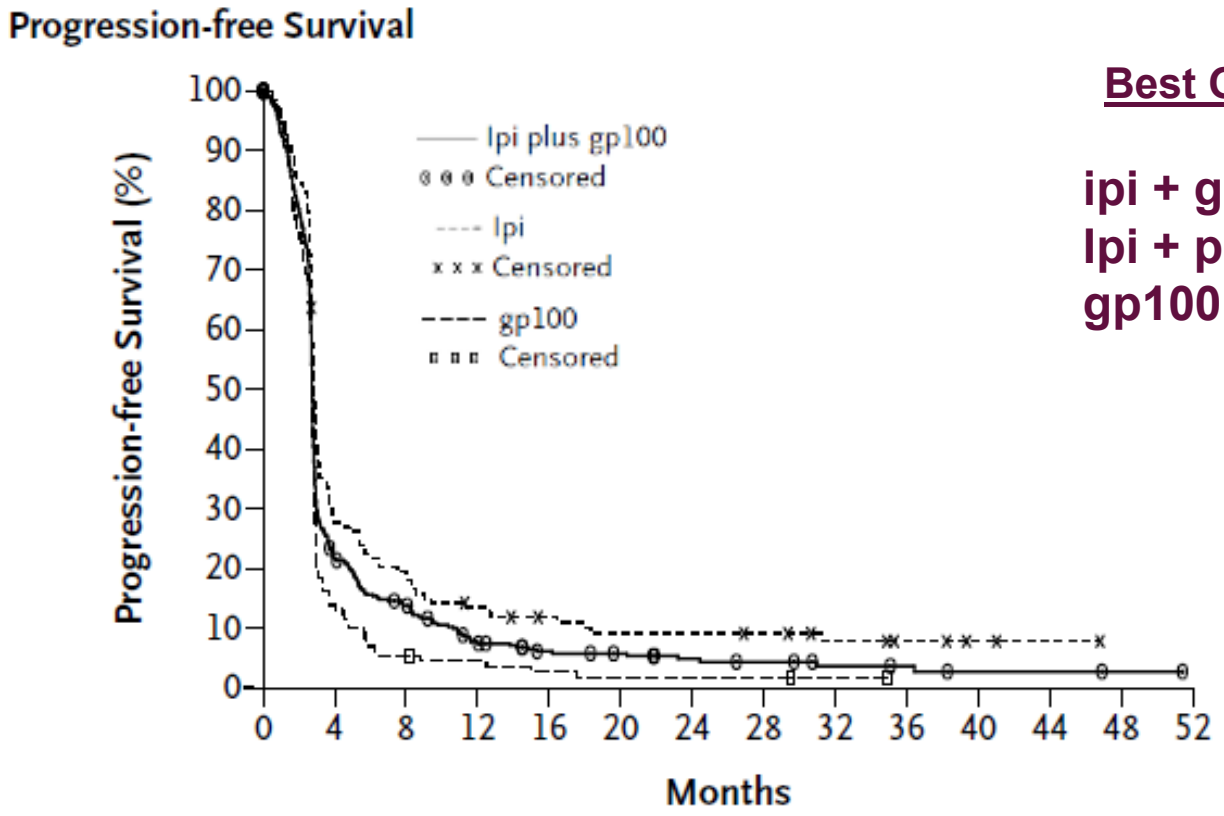
Near d to see durable
long-term s

Median OS

gp100 = 10,0 mos
placebo = 10,1 mos
100 + placebo = 6,4 mos

Hodi et al New Engl J Med 2010; 363:711-23

No effect in surrogate endpoints



No. at Risk

Ipi plus gp100	403	85	52	27	17	14	10	8	5	4	2	2	1	0
Ipi	137	37	26	17	13	10	10	9	6	4	2	1	0	0
gp100	136	18	7	5	3	2	2	2	1	0	0	0	0	0

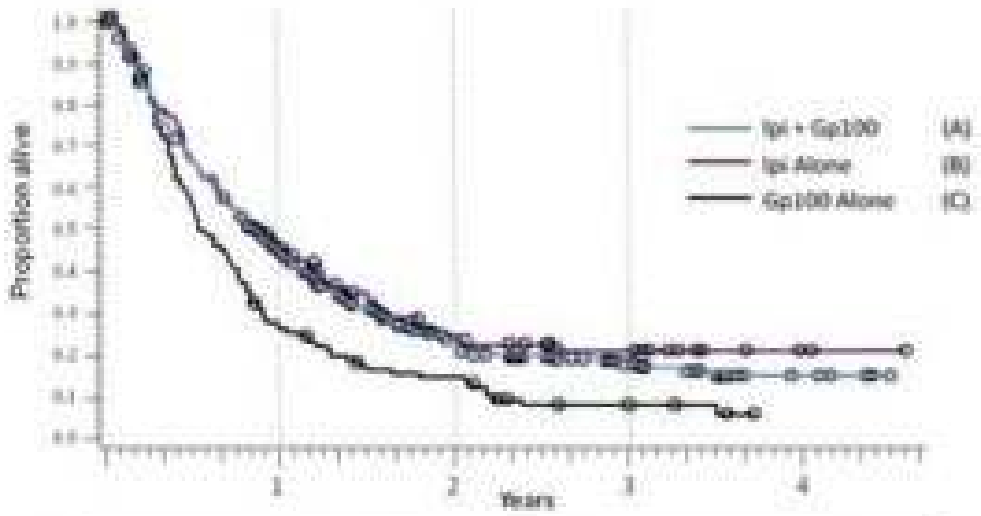
Best Overall Response Rate (BORR)

ipi + gp100 = 5,7 %
Ipi + placebo = 10,9 %
gp100 + placebo = 1,5 %

Hodi et al New Engl J Med 2010; 363:711-23

MDX010-020 study

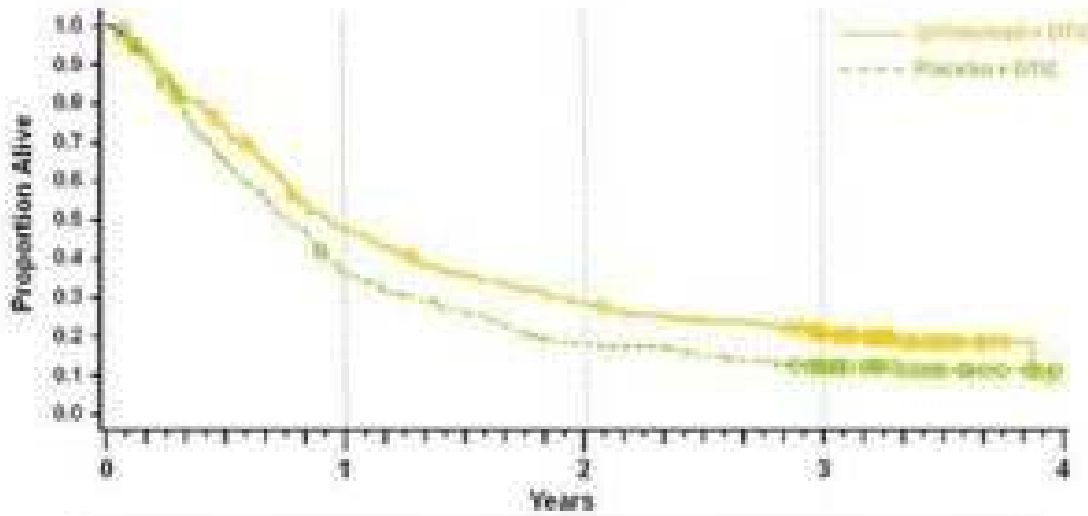
modified from Hodi et al. N Engl J Med. 2010[3]



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Ca184-024 study

modified from Robert et al. N Engl J Med. 2011[4]



Survival Rate	1 Year	2 Year	3 Year
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.5	17.9	12.2

In the field of I-O is the dosage important ?

Historical Data: Phase 2 Studies

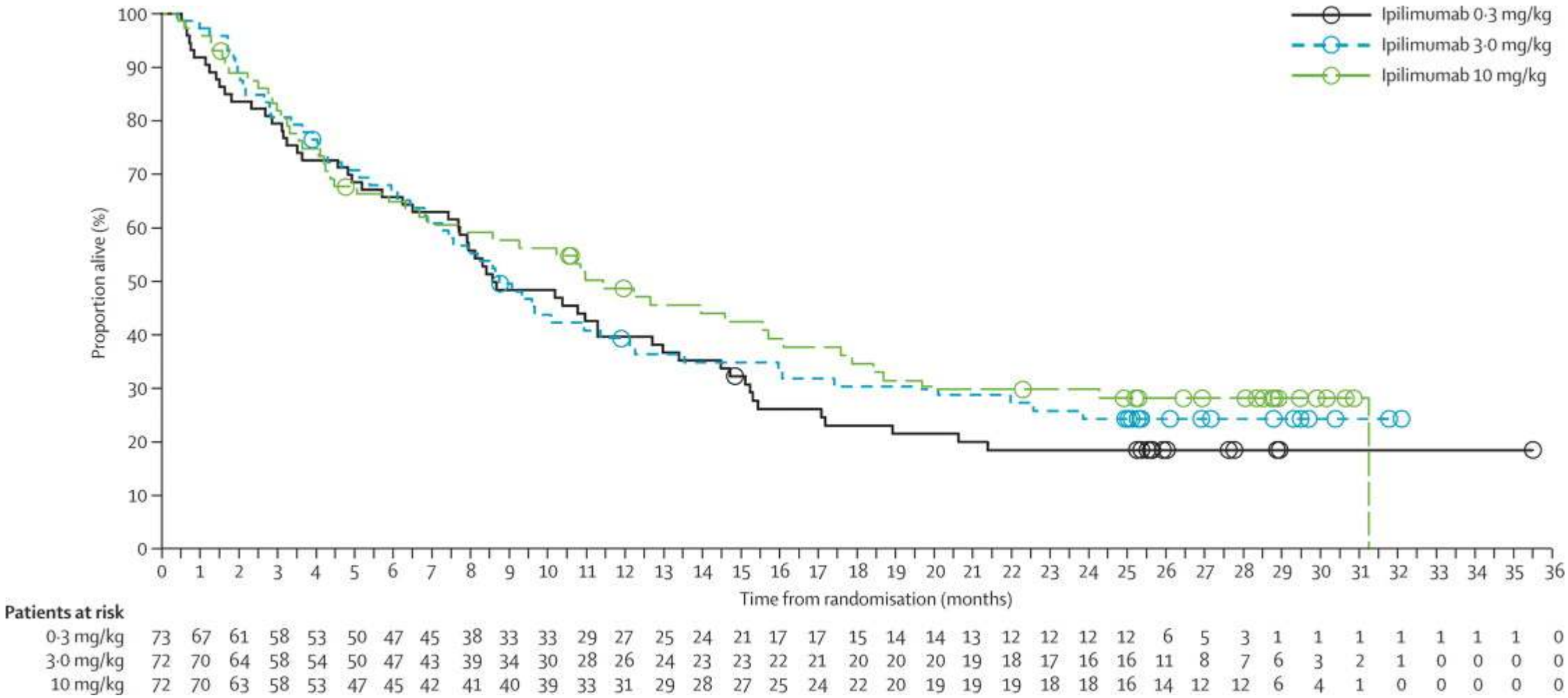
- **Dose effect**

	0.3 mg/kg N=73	3 mg/kg N=72	10 mg/kg N=72	P value (trend test)
Complete or Partial Response	0%	4.2%	11.1%	0.0015

- **Combination of ipilimumab (3 mg/kg) + DTIC**
  - **Durable objective responses**
  - **Adverse events consistent with other ipilimumab studies**

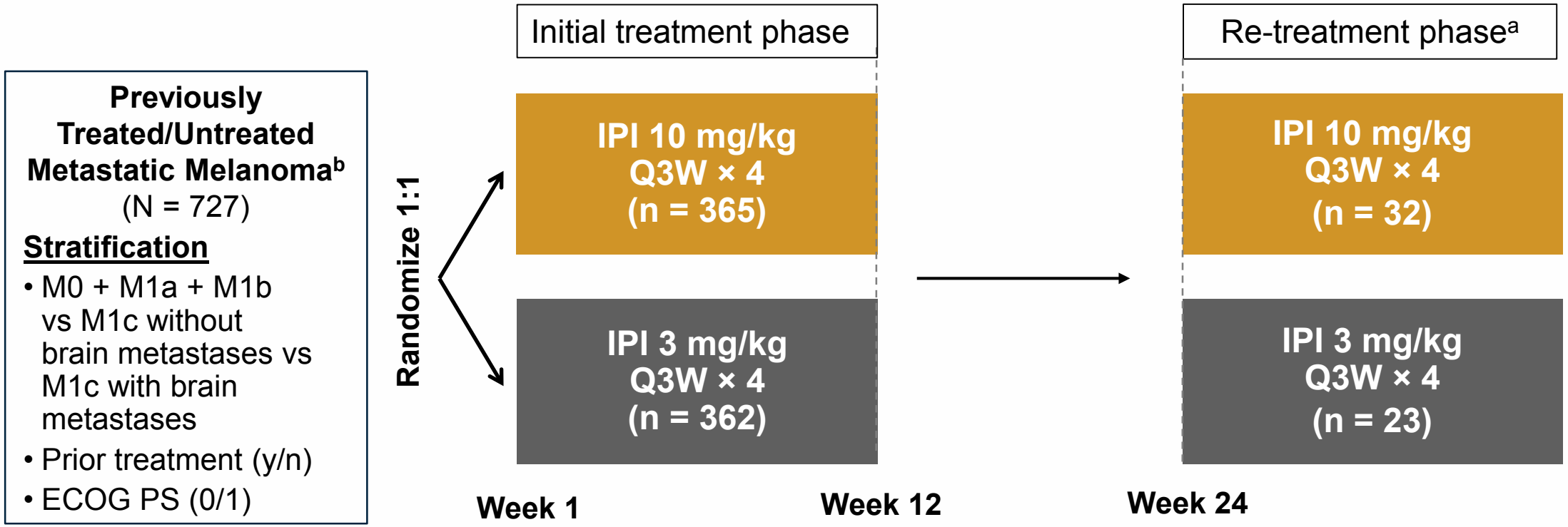
Wolchok et al . Lancet Oncol. 2010;11:155-164
Hersh et al. Invest New Drugs. 2011;29:489-498

Ipilimumab phase 2 dose-ranging study: Kaplan-Meier estimate for overall survival



Wolchok et al . Lancet Oncol. 2010;11:155-164

CA184-169: Study Design



- **Enrollment period:** March 2012 to August 2012
- No crossover allowed between treatment arms

[a]After initial response (or stable disease >3 months) and subsequent progressive disease in the absence of intolerable toxicity.

[b]Patients could not be treated with BRAF/PD-1 therapy.

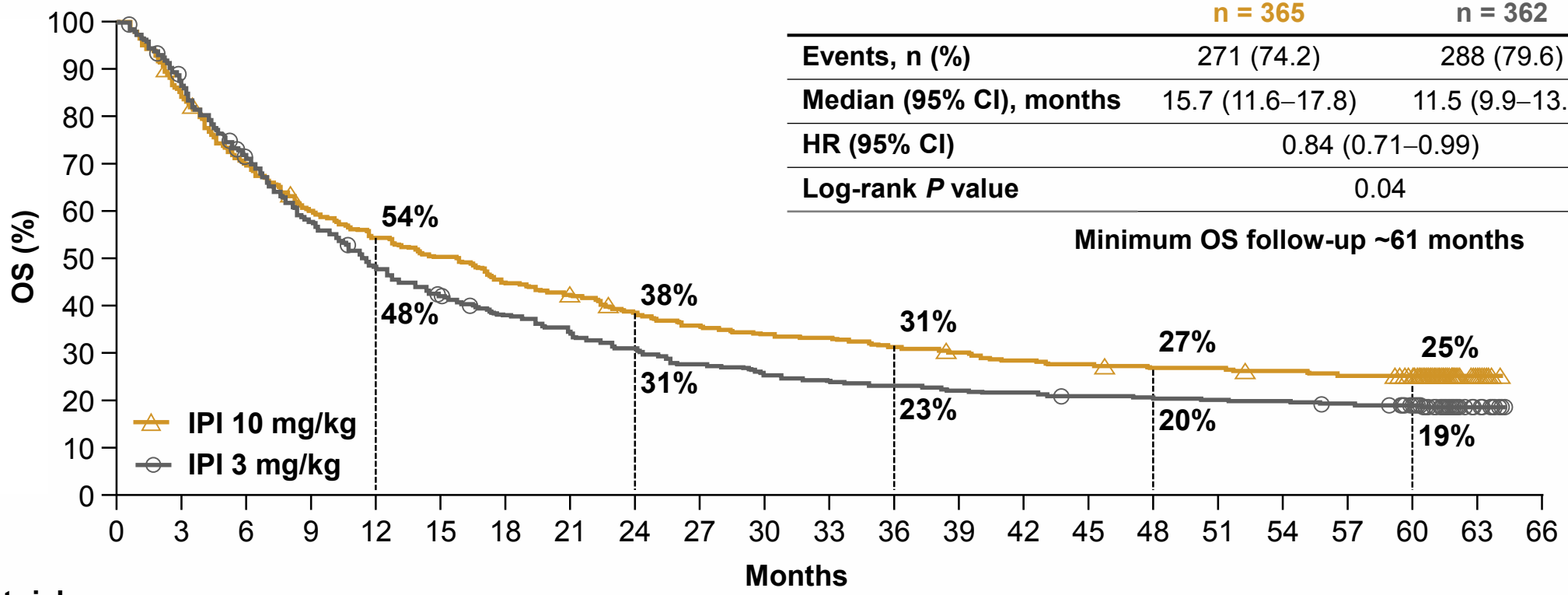
ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, ipilimumab; Q3W, every 3 weeks.

Ascierto et al. Melanoma Bridge meeting. Naples, 1 Dec 2018

OS: All Randomized Patients

	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events, n (%)	271 (74.2)	288 (79.6)
Median (95% CI), months	15.7 (11.6–17.8)	11.5 (9.9–13.3)
HR (95% CI)	0.84 (0.71–0.99)	
Log-rank *P* value	0.04	

Minimum OS follow-up ~61 months

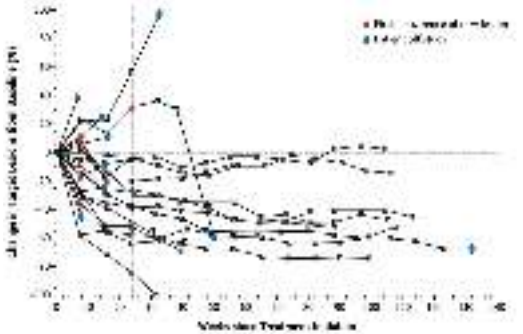


Patients at risk:

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	106	100	97	93	93	90	87	78	13	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	74	71	69	68	67	64	58	7	0

Ascierto et al. Melanoma Bridge meeting. Naples, 1 Dec 2018

Nivolumab phase 1 study



Dose of Anti–PD-1 Antibody	Objective Response†	Objective-Response Rate‡	Duration of Response§	Stable Disease ≥24 wk		Progression-free Survival Rate at 24 wk¶
	no. of patients/ total no. of patients	*% (95% CI)*	*mo*	*no. of patients/ total no. of patients*	*% (95% CI)*	*% (95% CI)*
Melanoma						
0.1 mg/kg	4/14	29 (8–58)	7.5+, 5.6+, 5.6, 5.6	1/14	7 (0.2–34)	40 (13–66)
0.3 mg/kg	3/16	19 (4–46)	3.8+, 2.1+, 1.9+	1/16	6 (0.2–30)	31 (9–54)
1.0 mg/kg	8/27	30 (14–50)	24.9+, 22.9, 20.3+, 19.3+, 18.4+, 7.6+, 5.6+, 5.3+	3/27	11 (2–29)	45 (26–65)
3.0 mg/kg	7/17	41 (18–67)‖	22.4+, 18.3+, 15.2+, 12.9, 11.1, 9.3, 9.2+	1/17	6 (0.1–29)	55 (30–80)
10.0 mg/kg	4/20	20 (6–44)	24.6+, 23.9+, 18.0+, 17.0	0/20	0	30 (9–51)
All doses	26/94	28 (19–38)		6/94	6 (2–13)	41 (30–51)

Topalian et al. NEJM 2012

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

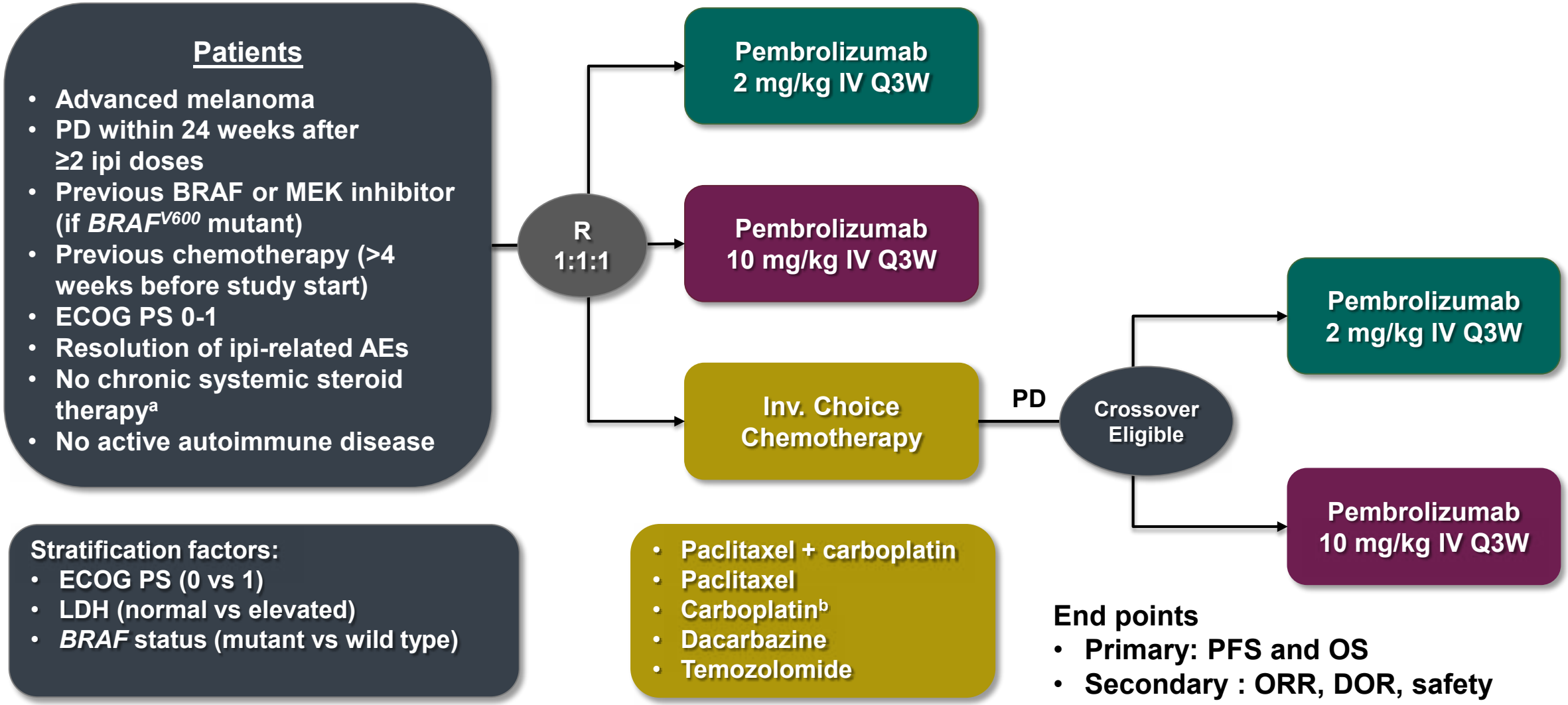
Pembrolizumab phase 1 study

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jasmine Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

Regimen and Ipilimumab Status	RECIST				Immune-Related Response	
	No. of Patients	Confirmed and Unconfirmed Objective Response	Confirmed Objective Response	Duration of Response†	No. of Patients	Confirmed Objective Response
		no. (% [95% CI])		*mo*		*no. (% [95% CI])*
10 mg/kg every 2 wk						
No prior ipilimumab	39	21 (54 [37–70])	19 (49 [32–65])‡	1.9–10.8	41	23 (56 [40–72])
Prior ipilimumab	13	8 (62 [32–86])	8 (62 [32–86])§	2.8–8.3	16	9 (56 [30–80])
Total	52	29 (56 [41–69])	27 (52 [38–66])	1.9–10.8	57	32 (56 [42–69])
10 mg/kg every 3 wk						
No prior ipilimumab	19	7 (37 [16–62])	5 (26 [9–51])	2.6–5.6	24	8 (33 [16–55])
Prior ipilimumab	26	9 (35 [17–56])	7 (27 [12–48])	2.8–8.3	32	7 (22 [9–40])
Total	45	16 (36 [22–51])	12 (27 [15–42])	2.6–8.3	56	15 (27 [16–40])
2 mg/kg every 3 wk, no prior ipilimumab	20	7 (35 [15–59])	5 (25 [9–49])¶	2.1–5.5	22	3 (14 [3–35])
Total‖	117	52 (44 [35–54])**	44 (38 [25–44])	1.9–10.8	135	50 (37 [29–45])

KEYNOTE-002 Study Design (NCT01704287)



[a]Defined as >10 mg/day prednisone or equivalent.
[b]Carboplatin monotherapy removed early in study by a protocol amendment.

Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma☆

Omid Hamid [a,*], Igor Puzanov [b,1], Reinhard Dummer [c], Jacob Schachter [d], Adil Daud [e], Dirk Schadendorf [f], Christian Blank [g], Lee D. Cranmer [h,2], Caroline Robert [i], Anna C. Pavlick [j], Rene Gonzalez [k], F. Stephen Hodi [l], Paolo A. Ascierto [m], April K.S. Salama [n], Kim A. Margolin [o], Tara C. Gangadhar [p], Ziwen Wei [q], Scot Ebbinghaus [q], Nageatte Ibrahim [q], Antoni Ribas [r]

European Journal of Cancer 50 (2014) 1607–1617

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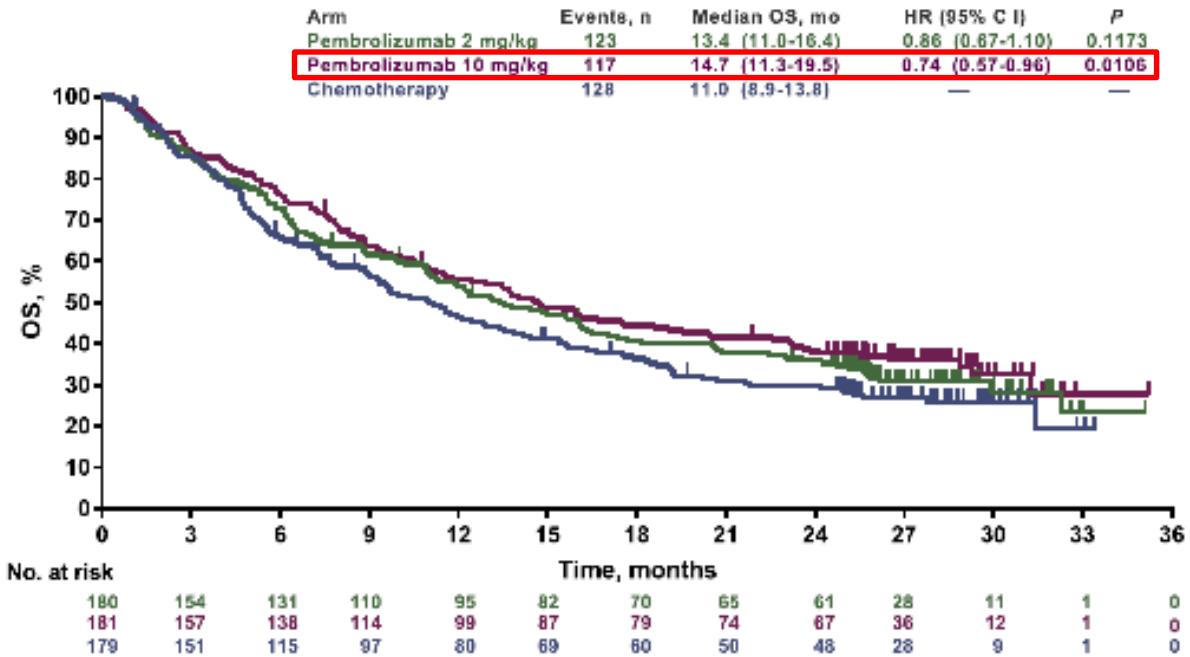
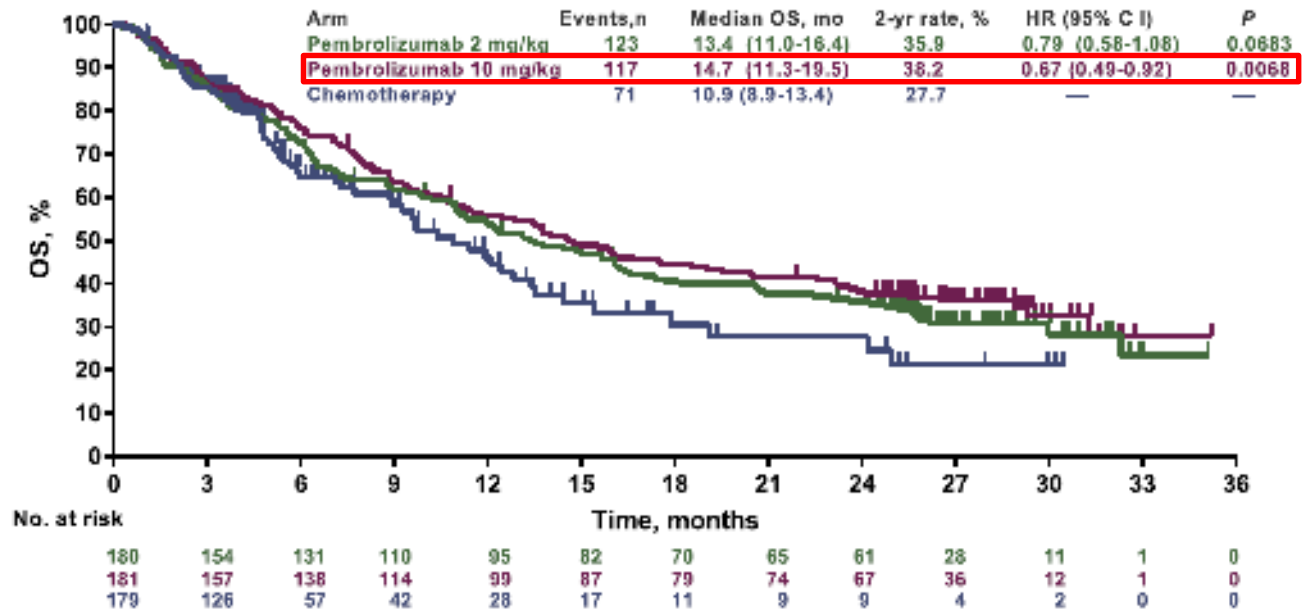


Adjusted for the cross-over



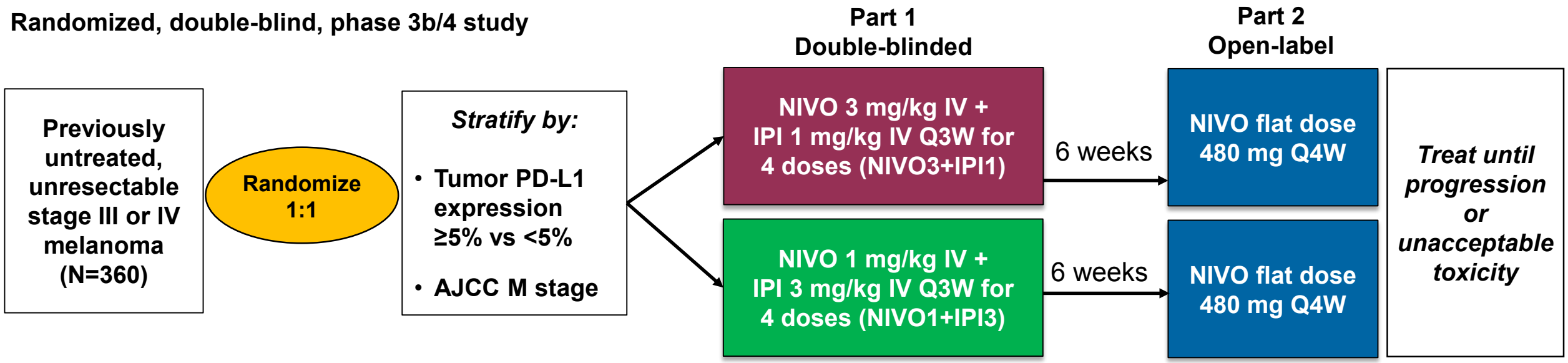
CheckMate 511: Overview & Study Design

Background

- Combined inhibition of PD-1 and CTLA-4 with nivolumab (NIVO) and ipilimumab (IPI) has demonstrated efficacy in several tumor types at different dosing schedules
- In advanced melanoma, NIVO 1 mg/kg plus IPI 3 mg/kg (NIVO1+IPI3) is the approved dose based on the CheckMate 067 trial, in which NIVO1+IPI3 and NIVO 3 mg/kg showed a higher objective response rate (ORR), longer progression-free survival (PFS), and improved overall survival (OS) vs IPI alone
- CheckMate 511 was conducted to determine if NIVO 3 mg/kg plus IPI 1 mg/kg (NIVO3+IPI1) improves the safety profile of the combination

Study Design

Randomized, double-blind, phase 3b/4 study



Endpoints

- The primary endpoint was to compare the incidence of treatment-related grade 3-5 AEs between groups
- Secondary endpoints included investigator-assessed ORR by RECIST v1.1, PFS and OS*

**Descriptive analyses; study was not designed nor powered to formally demonstrate non-inferiority of NIVO3+IPI1 to NIVO1+IPI3*

CA209-511 study: Results – Primary Endpoint

- Results presented here are from a database lock on June 1, 2018, with a minimum patient follow-up of 12 months
  - Median follow-up was ~19 months in both groups
  - 180 patients were treated in the NIVO3+IPI1 group and 178 in the NIVO1+IPI3 group
- The incidence of treatment-related grade 3-5 AEs was significantly lower in the NIVO3+IPI1 group compared with the NIVO1+IPI3 group
  - Grade 5 treatment-related AEs were reported in 1 patient (0.6%) in the NIVO3+IPI1 group (rhabdomyolysis and autoimmune myocarditis)

	NIVO3+IPI1 (N=180)	NIVO1+IPI3 (N=178)
Rate of treatment-related grade 3-5 AEs, % (n/N) (95% CI)	**33.9%** (61/180) (27.0, 41.3)	**48.3%** (86/178) (40.8, 55.9)
P value	**0.0059**	
Treatment-related AEs, %	85.6	93.8
Grade 3-4	33.3	48.3
Grade 5	0.6	0
All cause serious AEs, %	47.8	63.5
Grade 3-4	33.9	47.8
Grade 5	3.3	1.7
Treatment-related AEs leading to discontinuation, %	23.9	33.1

Includes events reported between the first dose and 30 days after the last dose of study therapy.

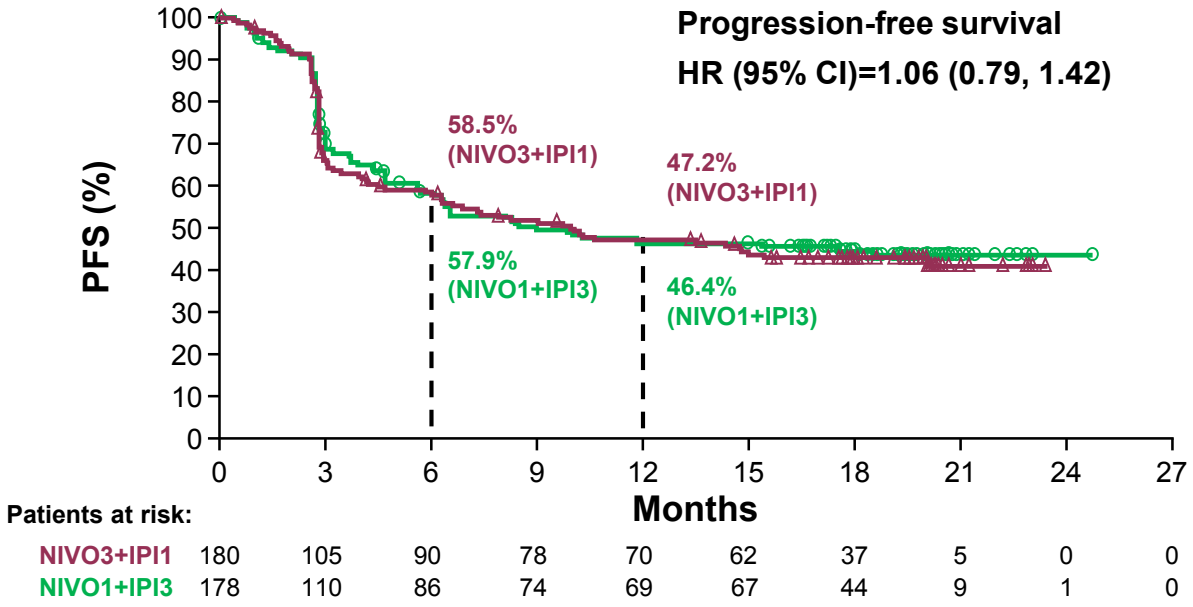
Lebbè et al ESMO 2018

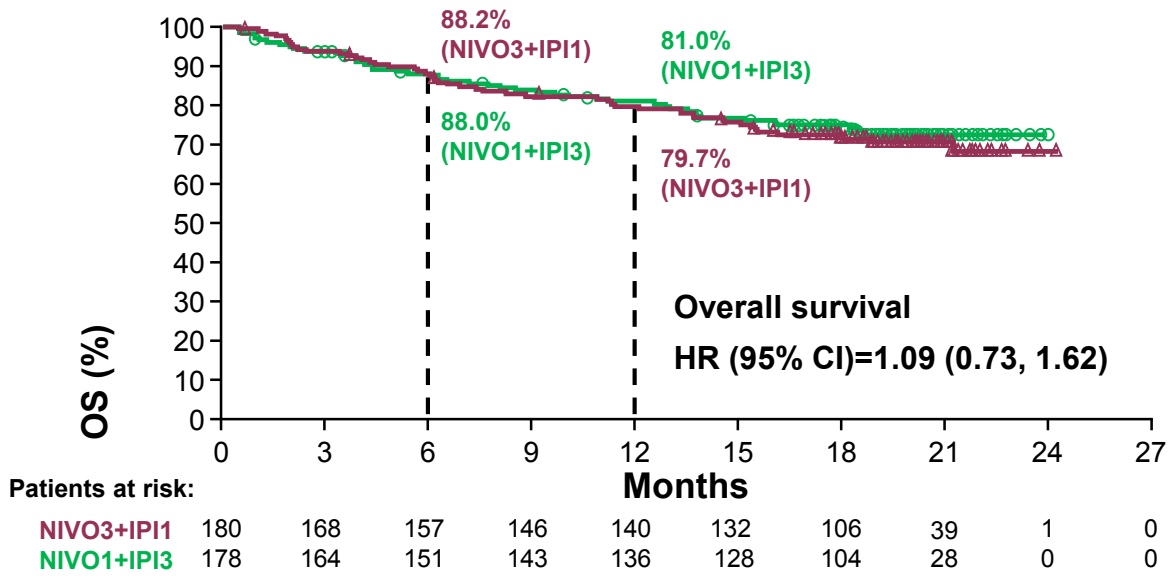
CA209-511 study: Results/Summary

Secondary efficacy endpoints (descriptive analyses)

- While ORR numerically favored NIVO1+IPI3, ORR was not significantly different between the two groups

	NIVO3+IPI1 (N=180)	NIVO1+IPI3 (N=178)
Investigator-assessed ORR, % (95% CI)	45.6 (38.1–53.1)	50.6 (43.0–58.1)
P value	0.3451	

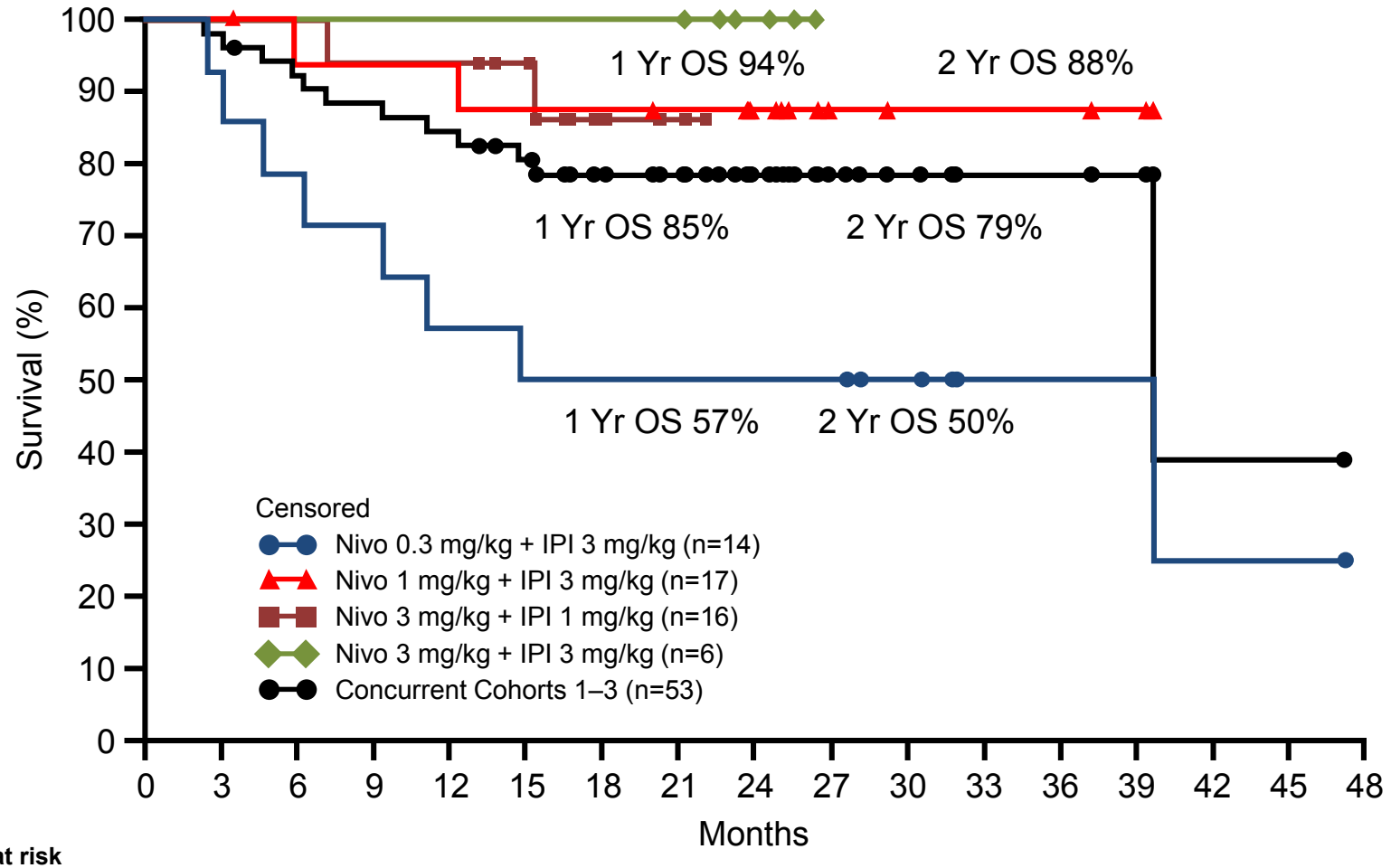




1. Hodi FS, et al. ESMO 2018 Congress. Oral Presentation (abstract LBA44).

Lebbè et al ESMO 2018

CA209-004: Overall Survival for Concurrent Therapy by Dose Cohort

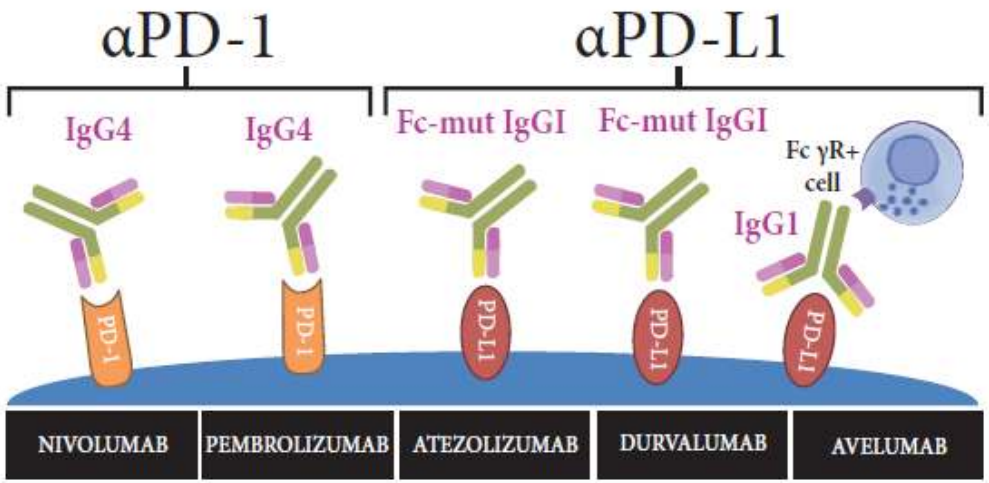


No. at risk

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

Sznol M, et al. J Clin Oncol 2014;32(suppl 5s): abstract LBA9003^

Current doses for anti-PD-1/PD-L1



	NIVOLUMAB	PEMBROLIZUMAB	ATEZOLIZUMAB	DURVALUMAB	AVELUMAB
Target	PD-1	PD-1	PD-L1	PD-L1	PD-L1
Isotype	IgG4	Ig4	Fc-mutated IgG1*	Fc-mutated IgG1*	IgGI
ADCC	No	No	No	No	Yes
Half life	27 days	25 days	27 days	17 days	6 days
Doses tested during clinical development	up to 10 mg/kg Q2W	up to 10 mg/kg Q2W	up to 20 mg/kg Q3W	up to 20 mg/kg Q3W	up to 20 mg/kg Q3W
Doses for First approvals	3mg/kg Q2W	2mg/kg Q2W	1200mg Q3W flat dose	10mg/kg Q2W	10mg/kg Q2W
Dose for Current approval extensions	240mg Q2W and 480mg Q4W flat doses	200mg Q3W flat dose			

Ascierto and Marabelle. Annals of Oncology 2018

How do immune checkpoint-targeted antibodies work? The need for improved pharmacokinetic evaluation in early phase studies

P. A. Ascierto[1*] & A. Marabelle[2,3]

[1]Unit of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, ITalic; [2]Département d'Innovation Thérapeutique et d'Essais Précoces, Gustave Roussy, Université Paris-Saclay, Villejuif; [3]INSERM U1015, Villejuif, France

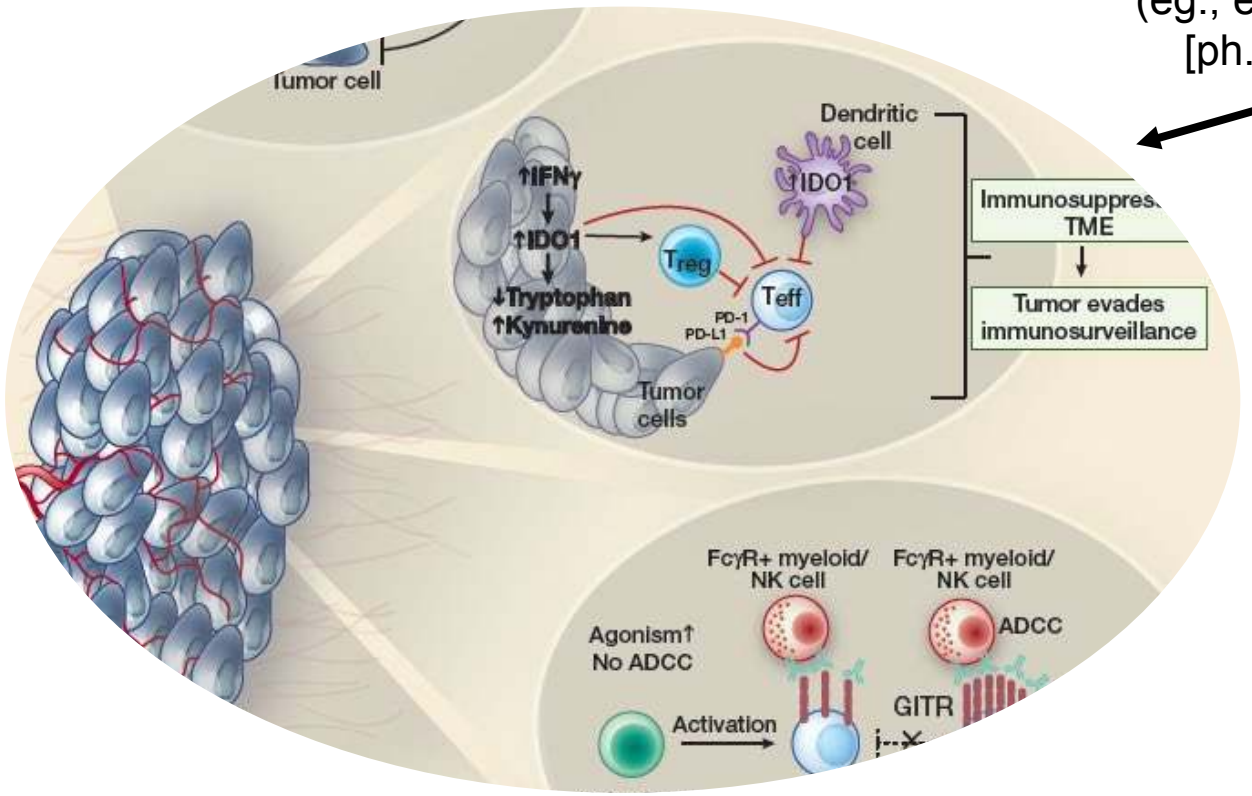
(*E-mail: p.ascierto@istitutotumori.na.it)

ANNALS OF ONCOLOGY

We need of better Phase 1 studies

New emerging pathways for future combination with anti-PD-1/PD-L1 compounds: *IDO1 inhibition*

IDO1 inhibitors
(eg., epacadostat [ph. 2/3], indoximod [ph. 2/3], BMS.986205 [ph. 2/3])



Ascierto PA & McArthur JA. *J Transl Med* 2017;15:173

Epacadostat Plus Pembrolizumab in Patients With Advanced Melanoma: Phase 1 and 2 Efficacy and Safety Results From ECHO-202/KEYNOTE-037

O. Hamid,[1] T. F. Gajewski,[2] A. E. Frankel,[3] T. M. Bauer,[4] A. J. Olszanski,[5] J. J. Luke,[2] A. S. Balmanoukian,[1] E. V. Schmidt,[6] B. Sharkey,[7] J. Maleski,[7] M. M. Jones,[7] T. C. Gangadhar[8]

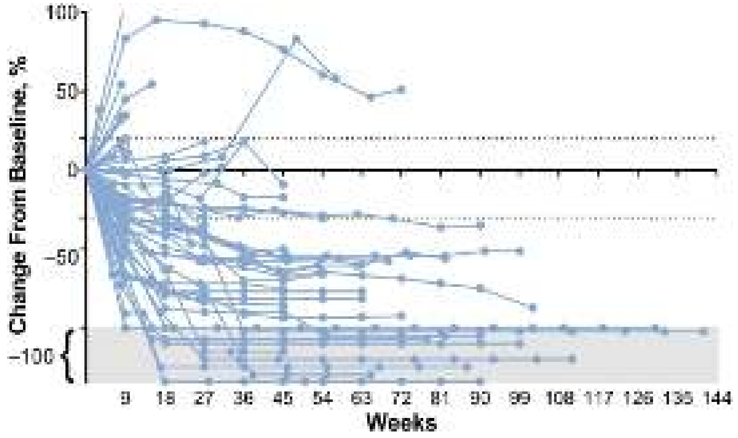
[1]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [2]University of Chicago, Chicago, IL, USA; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA*; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Fox Chase Cancer Center, Philadelphia, PA, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]Incyte Corporation, Wilmington, DE, USA; [8]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA

Presentation #1214O
Session: Melanoma and Other Skin Tumours
Presented at the ESMO Annual Meeting 2017
Madrid, Spain
September 9, 2017

Percentage Change From Baseline in Target Lesions Over Time

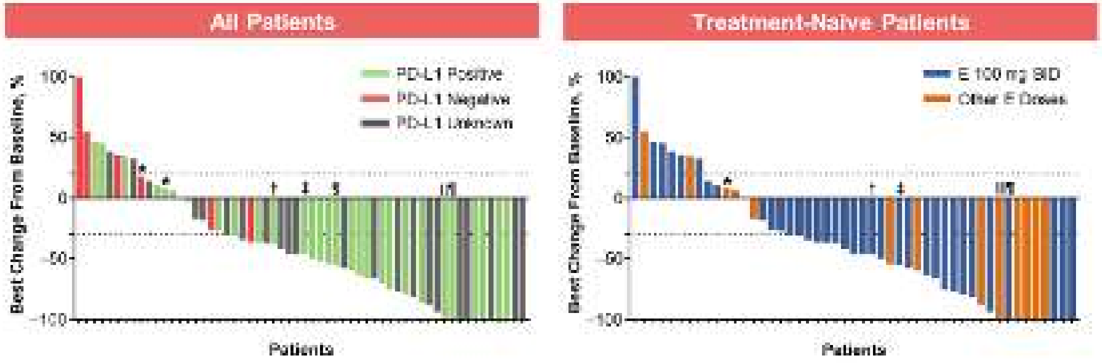
All Patients

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma



Best Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma



Conclusions

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma

- Epacadostat plus pembrolizumab demonstrated promising antitumor activity in patients with advanced melanoma

All Patients (n=63)	Treatment-Naive for Advanced Disease, All E Doses (n=53)	Treatment-Naive for Advanced Disease, E 100 mg (n=38)
• 56% ORR (14% CR) • 71% DCR • 12.4 month median PFS* • 49% landmark 18-month PFS*	• 55% ORR (13% CR) • 72% DCR • 22.8 month median PFS* • 52% landmark 18-month PFS*	• 58% ORR (8% CR) • 74% DCR • Median PFS not reached* • 55% landmark 18-month PFS*

- Epacadostat plus pembrolizumab demonstrated a favorable safety profile in these phase 1/2 melanoma patients that is consistent with previous reports;[1,2] the incidence of related grade 3/4 toxicity was 20%
- These results support the ongoing phase 3 investigation of epacadostat plus pembrolizumab in patients with advanced melanoma (ECHO-301/KEYNOTE-252; N=706, fully accrued)

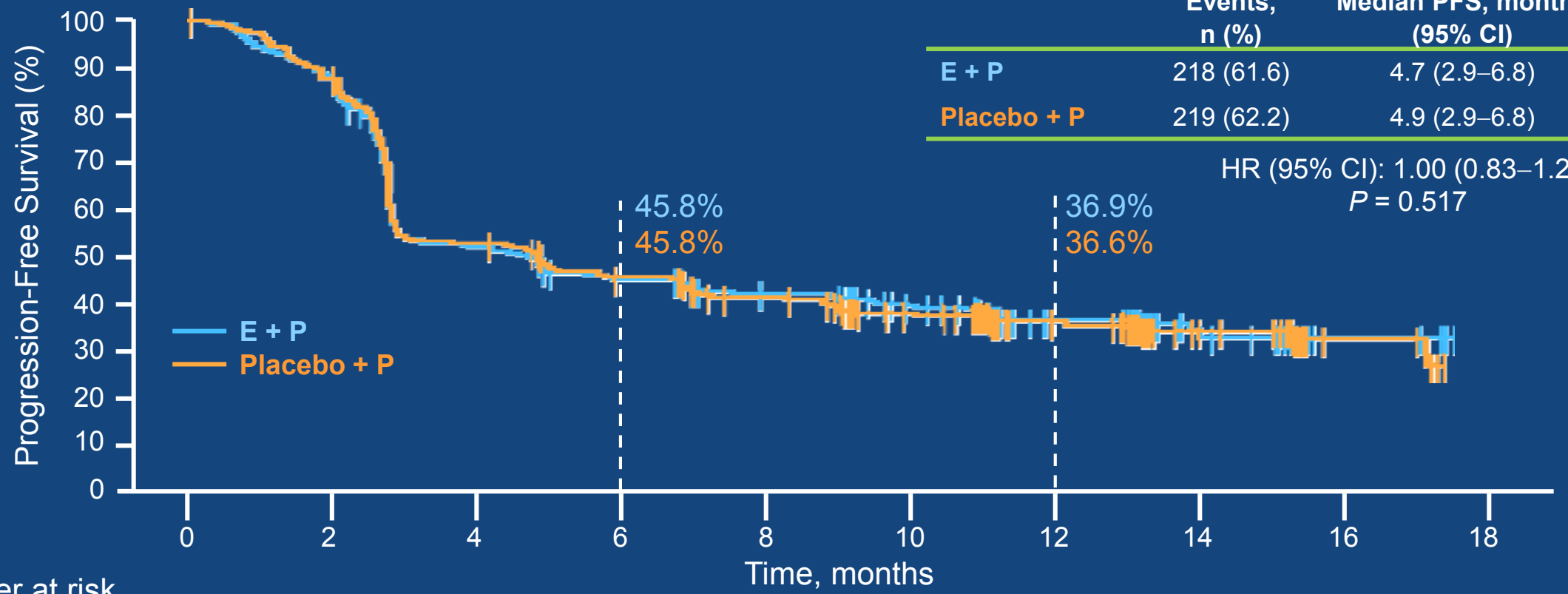
Presented by Paolo A. Ascierto at ASCO 2018

Hamid et al ESMO 2017

Progression-Free Survival (RECIST v1.1, BICR)

	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517



Number at risk

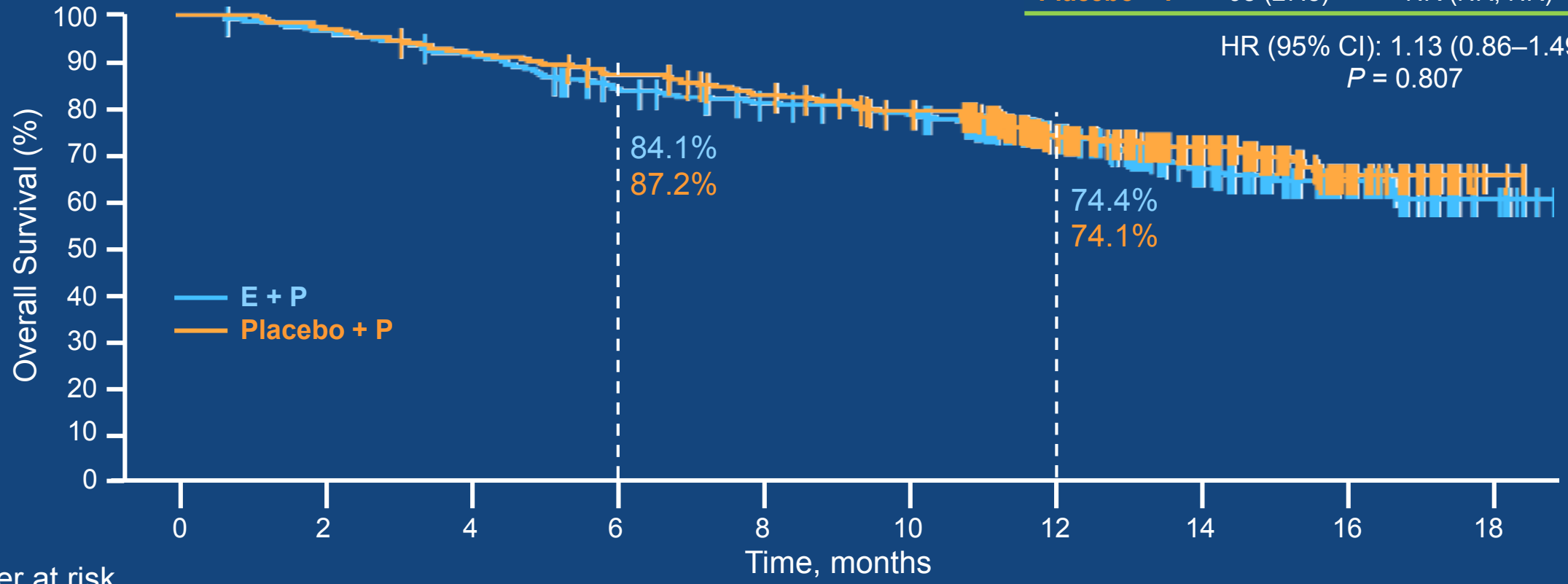
E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
PFS defined as time from randomization to disease progression or death, whichever occurred first.

Overall Survival

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

What is the role of IDO inhibition ?

Abstract 9511 (Daud A, et al): Epacadostat Plus Nivolumab for Advanced Melanoma: Updated Phase 2 Results of the ECHO-204 Study

Study Design

Data Cutoff: Oct 29, 2017

Phase 1
Dose Escalation
Epacadostat PO 25, 50, 100, or 300 mg BID
+
Nivolumab IV 3 mg/kg Q2W

- Phase 1 MTD not exceeded
- RPTD: 100 and 300 mg BID
- Phase 2 cohorts enrolled at 100 mg BID in parallel to further 300 mg BID evaluation in phase 1
- Phase 2 cohorts completed enrollment with 300 mg BID once RPTD established

Phase 2
Open-Label Cohort Expansion
Epacadostat 100 mg or 300 mg BID
+
Nivolumab 240 mg IV Q2W

Tumor cohorts
- MEL
- SCCHN
- GC
- CRC
- NSCLC
- HNSCC
- OVCA

Eligibility Criteria
- ≥1 prior treatment for advanced disease
- Known BRAF mutation status
- Prior anti-PD-1 or -PD-L1 therapy or treatment allowed if discontinued ≥12 weeks prior to enrollment
- Ocular melanoma was excluded

Baseline Patient Demographics and Disease Characteristics

Characteristic	Epacadostat Dosage: 100 mg BID (n=8)	300 mg BID (n=42)
Median (range) age, y	65.0 (54–73)	63.0 (30–86)
Men, n (%)	5 (62.5)	31 (73.8)
White, n (%)	8 (100.0)	37 (88.1)
ECOG PS 0 / 1, n (%)	6 (75.0) / 2 (25.0)	33 (78.6) / 8 (19.0)
Common sites of metastases, n (%)		
Lung	7 (87.5)	17 (40.5)
Lymph nodes	6 (75.0)	25 (59.5)
Liver	2 (25.0)	7 (16.7)
M1c / non-M1c stage, n (%)	4 (50.0) / 4 (50.0)	15 (35.7) / 26 (61.9)
Normal / elevated LDH,* n (%)	5 (62.5) / 2 (25.0)	27 (64.3) / 10 (23.8)
Treatment-naive for advanced disease, n (%)	6 (75.0)	34 (81.0)
Mutated / WT BRAF,* n (%)	3 (37.5) / 5 (62.5)	14 (33.3) / 27 (64.3)
Positive† / negative PD-L1 status,* n (%)	2 (25.0) / 3 (37.5)	15 (35.7) / 16 (38.1)
Positive† / negative IDO1 status,* n (%)	3 (37.5) / 0	18 (42.9) / 9 (21.4)

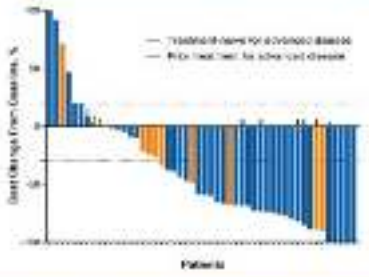
Daud A, Saleh M, Hu J, Bleeker J, Riese M, Meier R, Zhou L, Serbest G, Levitt R. Epacadostat Plus Nivolumab for Advanced Melanoma: Updated Phase 2 Results of the ECHO-204 Study. Abstract no. 9511.

ECHO-204 Advanced Melanoma: Response

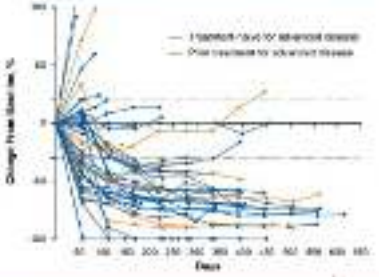
Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; RECIST v1.1)

Ongoing responses in 27/31 patients as of the October 29, 2017, data cutoff; DOR ranged from 55+ to 565+ days (median not reached)

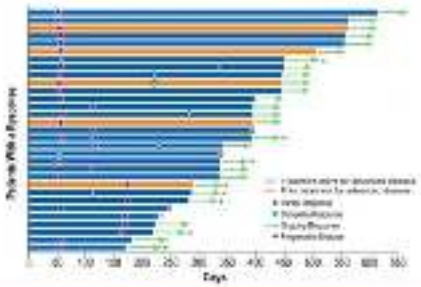
Best Percentage Change From Baseline in Target Lesions



Best Percentage Change in Target Lesions Over Time



Time To and Duration of Response

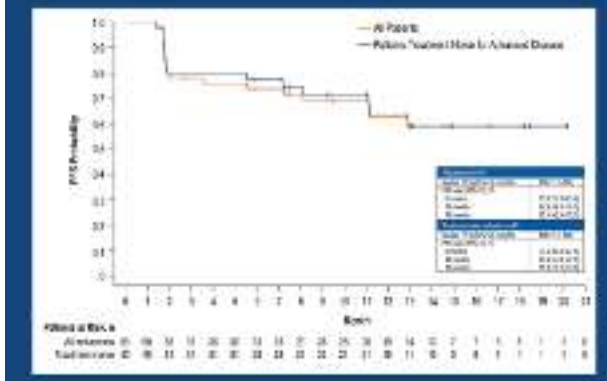


Daud A, Saleh M, Hu J, Bleeker J, Riese M, Meier R, Zhou L, Serbest G, Levitt R. Epacadostat Plus Nivolumab for Advanced Melanoma: Updated Phase 2 Results of the ECHO-204 Study. Abstract no. 9511.

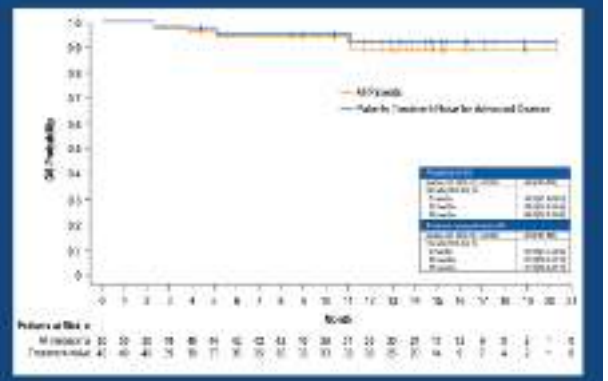
ECHO-204 Advanced Melanoma: PFS and OS

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; RECIST v1.1)

PFS (median not reached)



OS (median not reached)



Daud A, Saleh M, Hu J, Bleeker J, Riese M, Meier R, Zhou L, Serbest G, Levitt R. Epacadostat Plus Nivolumab for Advanced Melanoma: Updated Phase 2 Results of the ECHO-204 Study. Abstract no. 9511.

ECHO-204 Advanced Melanoma: TRAEs (≥15%)

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2)

- Epacadostat 100 mg BID (n=8)
  - Grade ≥3 TRAE in 1 patient (pneumonitis)
  - Temporary dose interruption in 3 patients (37.5%) due to TRAEs
  - No dose reduction, treatment discontinuation, or death events due to TRAEs
- Epacadostat 300 mg BID (n=42)
  - Grade ≥3 TRAEs in 20 patients (47.6%)
  - Temporary dose interruptions in 23 patients (54.8%) due to TRAEs
  - Temporary dose reductions in 7 patients (16.7%) due to TRAEs
  - Treatment discontinuation in 8 patients (19.0%) due to TRAEs
  - No TRAE led to death

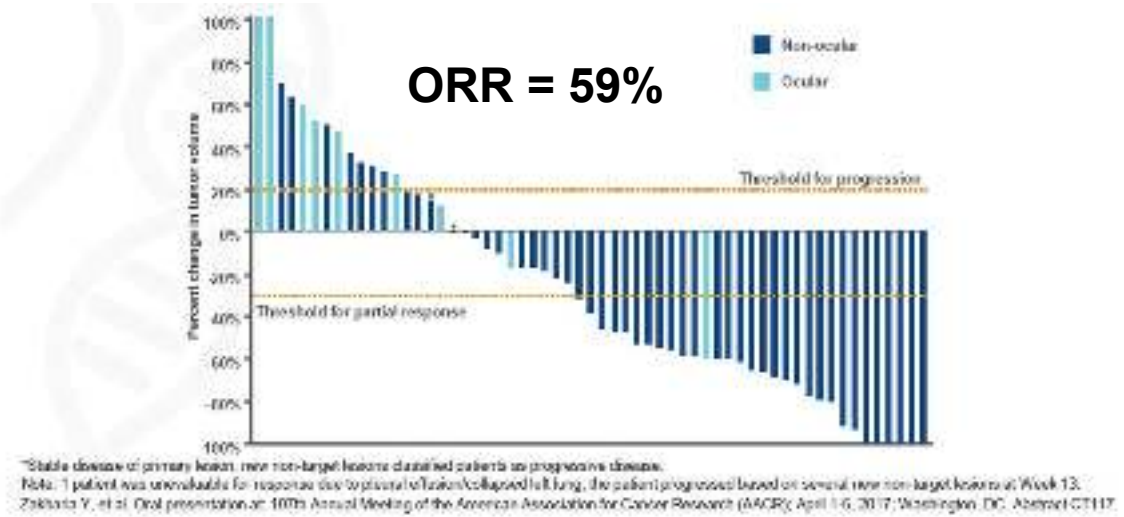
Daud A, Saleh M, Hu J, Bleeker J, Riese M, Meier R, Zhou L, Serbest G, Levitt R. Epacadostat Plus Nivolumab for Advanced Melanoma: Updated Phase 2 Results of the ECHO-204 Study. Abstract no. 9511.

Daud et al ASCO 2018

Interim Analysis of the Phase 2 Clinical Trial of the IDO Pathway Inhibitor Indoximod in Combination With Pembrolizumab for Patients With Advanced Melanoma

Yousef Zakharia,[1] Robert McWilliams,[2] Montaser Shaheen,[3] Kenneth Grossmann,[4] Joseph Drabick,[5] Mohammed Milhem,[1] Olivier Rixe,[6] Samir Khleif,[7] Ryan Ertl,[8] Eugene Kennedy,[9] David Munn,[7] Nicholas Vahanian,[7] Charles Link[9]

[1]University of Iowa, Iowa City, IA, [2]Mayo Clinic, Rochester, MN, [3]University of Arizona, Tucson, AZ, [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, [5]Penn State Cancer Institute, Hershey, PA, [6]University of New Mexico, Albuquerque, NM, [7]Georgia Cancer Center, Augusta, GA, [8]Medical Oncology, Avera, IA



*Stable disease of primary lesion, new non-target lesions classified patients as progressive disease.
Note: 1 patient was unevaluable for response due to pleural effusion/collapsed left lung; the patient progressed based on several new non-target lesions at Week 13.
Zakharia Y, et al. Oral presentation at: 108th Annual Meeting of the American Association for Cancer Research (AACR); April 1-5, 2017; Washington, DC. Abstract CT117.

Most Commonly Observed Adverse Events*

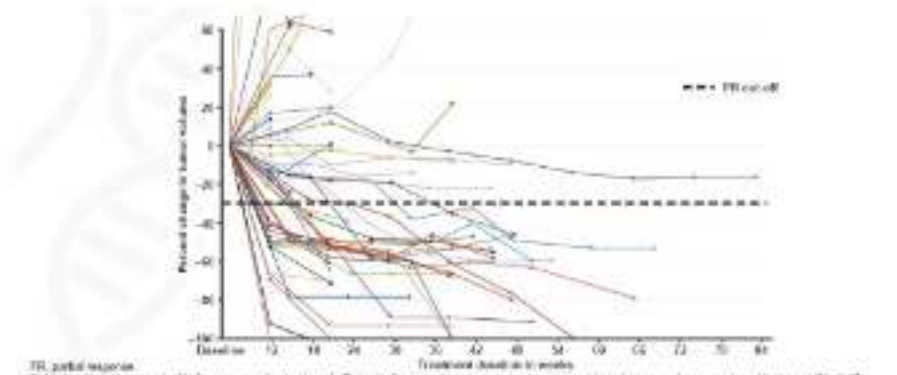
Combination Therapy Generally Well Tolerated

	Indoximod + pembrolizumab (n = 60)		
AE, n (%)†	Any grade	Grade ≥2	Grade ≥3‡
Fatigue	36 (60)	35 (58)	1 (2)
Headache	20 (33)	20 (33)	0 (0)
Nausea	19 (32)	19 (32)	0 (0)
Arthralgia	17 (28)	17 (28)	0 (0)
Diarrhea	17 (28)	16 (26)	1 (2)
Pruritus	16 (26)	16 (26)	0 (0)
Rash	14 (23)	13 (21)	1 (2)
Cough	13 (21)	13 (21)	0 (0)

AE, adverse event.
†Occurring in ≥20% of patients, regardless of attribution.
‡No grade 4 or grade 5 events were reported.
Zakharia Y, et al. Oral presentation at: 108th Annual Meeting of the American Association for Cancer Research (AACR); April 1-5, 2017; Washington, DC. Abstract CT117.

Change in Tumor Volume Over Time

Durable and Ongoing Responses

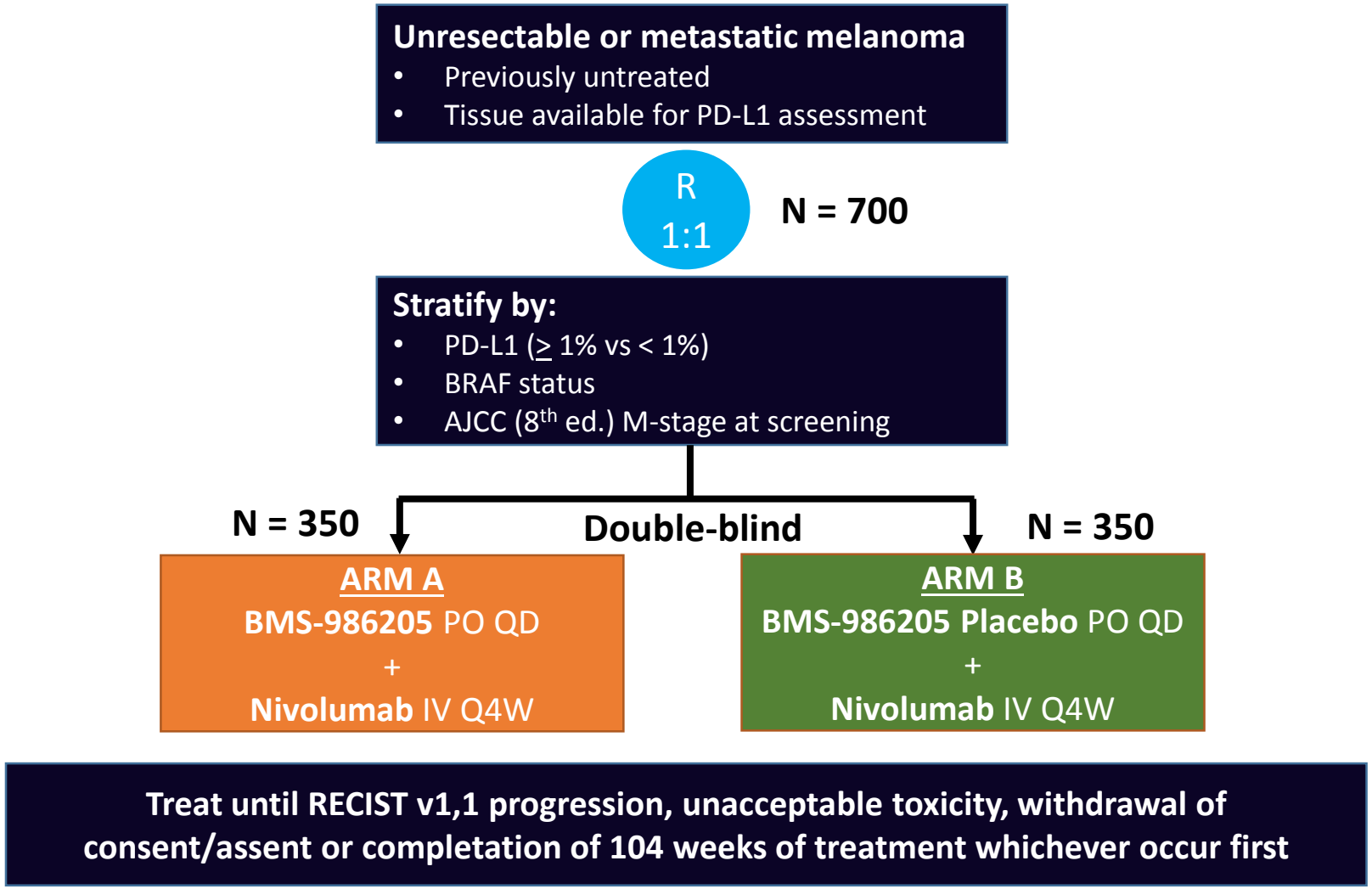


PR, partial response.
Note: 1 patient was unevaluable for response due to pleural effusion/collapsed left lung; the patient progressed based on several new non-target lesions at Week 13.
Zakharia Y, et al. Oral presentation at: 108th Annual Meeting of the American Association for Cancer Research (AACR); April 1-5, 2017; Washington, DC. Abstract CT117.

Presented by Paolo A. Ascierto at ASCO 2018

Zakharia et al AACR 2017

CA017-055: Phase 3, Randomized, Double-blind Study of BMS-986205 Combined with Nivolumab versus Nivolumab in Participants with Metastatic or Unresectable Melanoma that is Previously Untreated



Presented by Paolo A. Ascierto at ASCO 2018

Clinicaltrial.gov identifier NCT03329846

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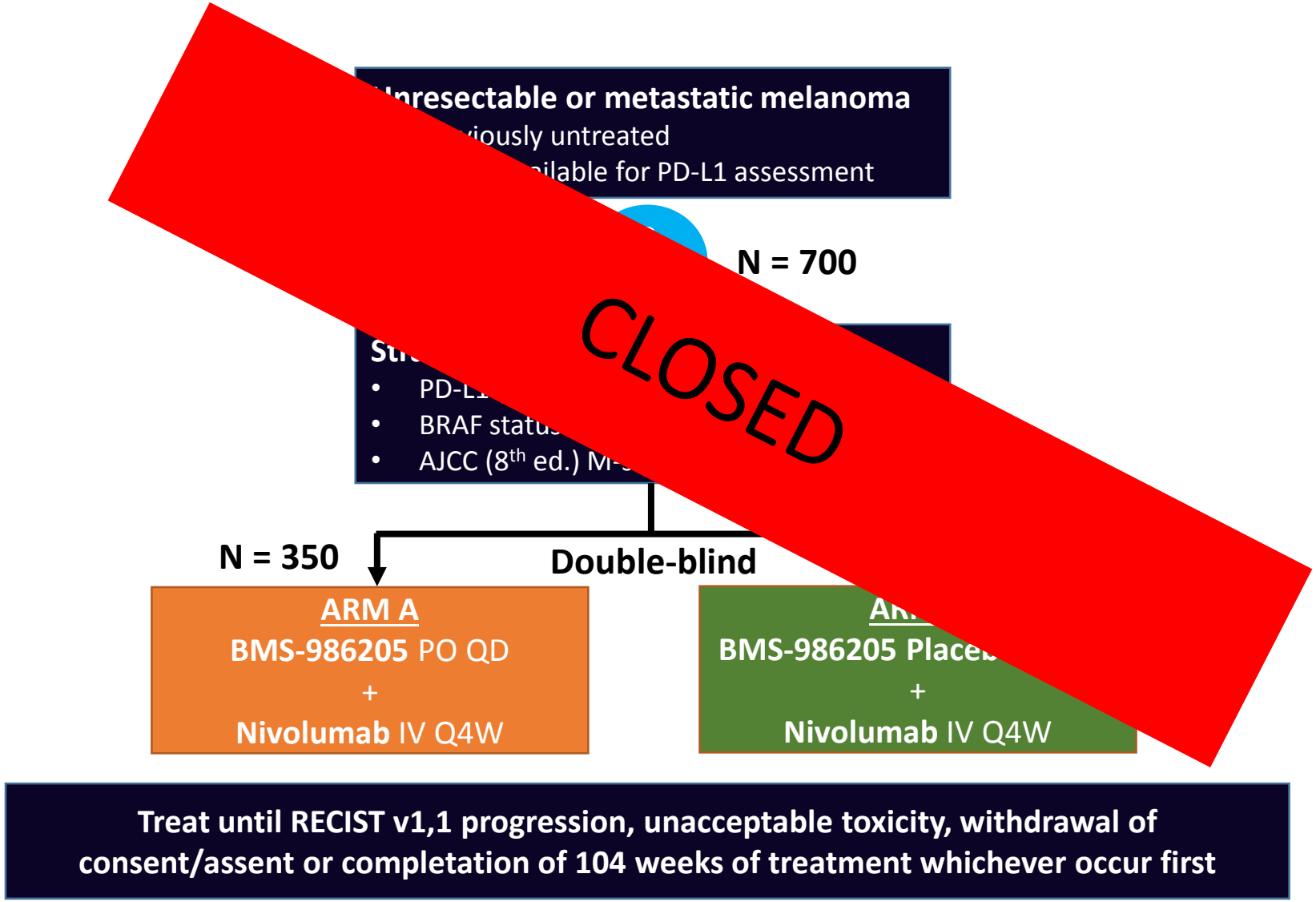


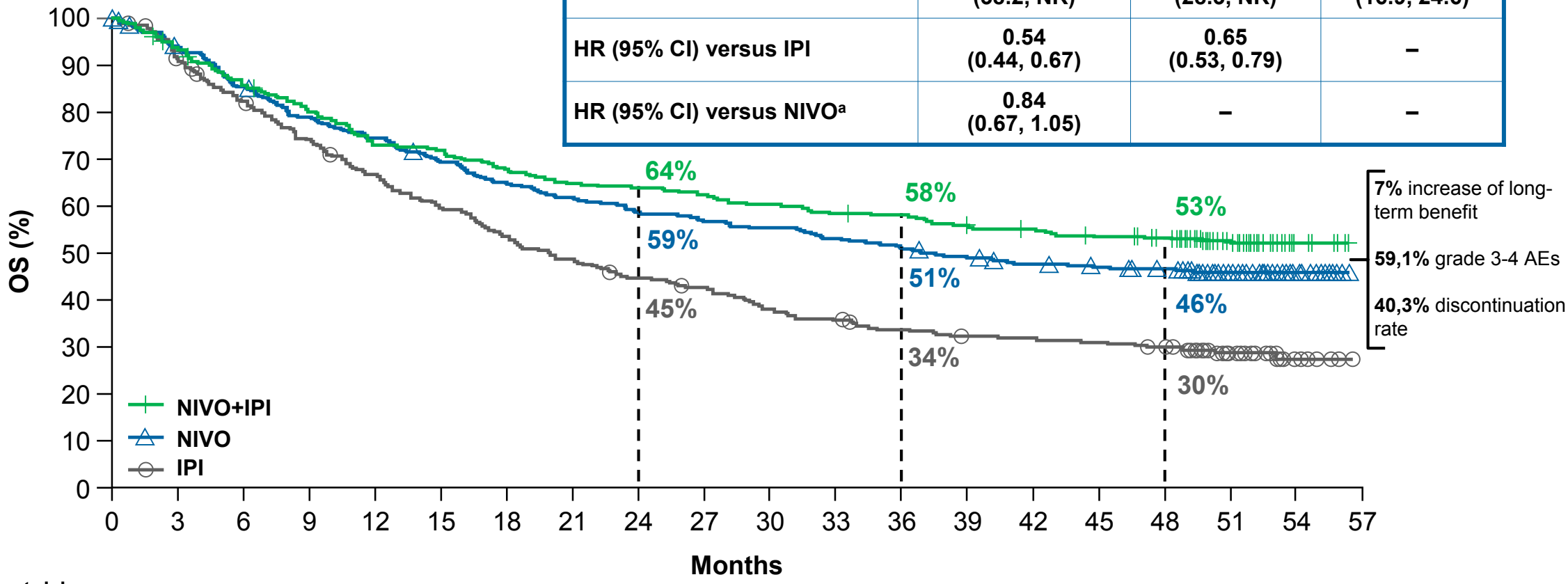
Presented by Paolo A. Ascierto at ASCO 2018

Clinicaltrial.gov identifier NCT03329846

Combination or sequencing ?

Checkmate 067: Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

Hodi et al ESMO 2018

Subsequent Therapies: All Randomized Patients

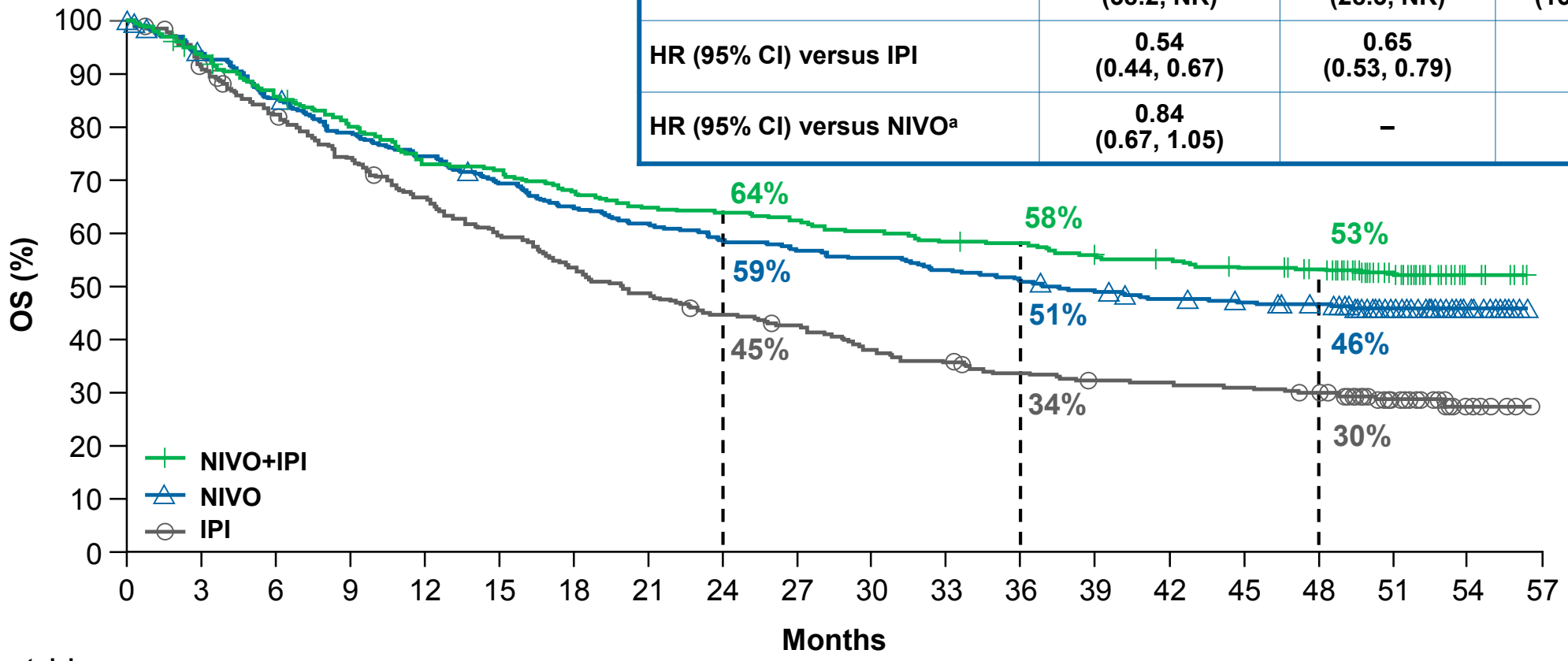
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Any subsequent therapy, n (%)[a]	**135 (43)**	**182 (58)**	**236 (75)**
Subsequent systemic therapy	104 (33)	150 (48)	206 (65)
Subsequent immunotherapy	53 (17)	103 (33)	148 (47)
Anti-PD-1 agents[b]	36 (12)	47 (15)	143 (45)
Anti-CTLA-4 agents[b]	19 (6)	91 (29)	17 (5)
Other immunotherapy	7 (2)	12 (4)	11 (4)
BRAF inhibitor[c]	42 (13)	60 (19)	72 (23)
MEK inhibitor[c]	32 (10)	43 (14)	42 (13)
Other investigational agent	8 (3)	9 (3)	15 (5)
Other	45 (14)	63 (20)	75 (24)
Subsequent radiotherapy	61 (19)	92 (29)	123 (39)
Subsequent surgery	60 (19)	69 (22)	95 (30)
Median time from randomization to subsequent systemic therapy, mo (95% CI)[d]	**NR**	**25.2 (16.0, 43.2)**	**8.1 (6.5, 8.7)**

[a]Patients may have received more than 1 subsequent therapy (eg, radiation, surgery, and systemic therapies). [b]May include patients treated with PD-1+CTLA-4 combination. [c]May include patients treated with BRAF+MEK combination. [d]Excluding patients who died and never received subsequent therapy

Hodi et al ESMO 2018

Checkmate 067: Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



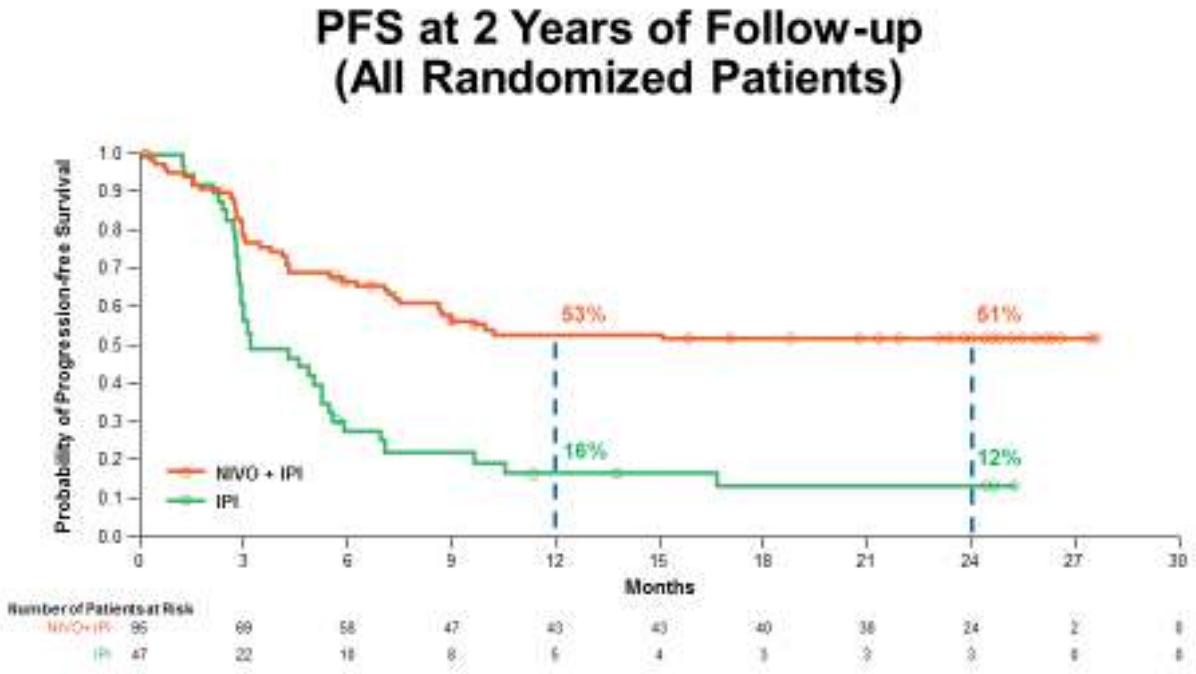
Patients at risk:

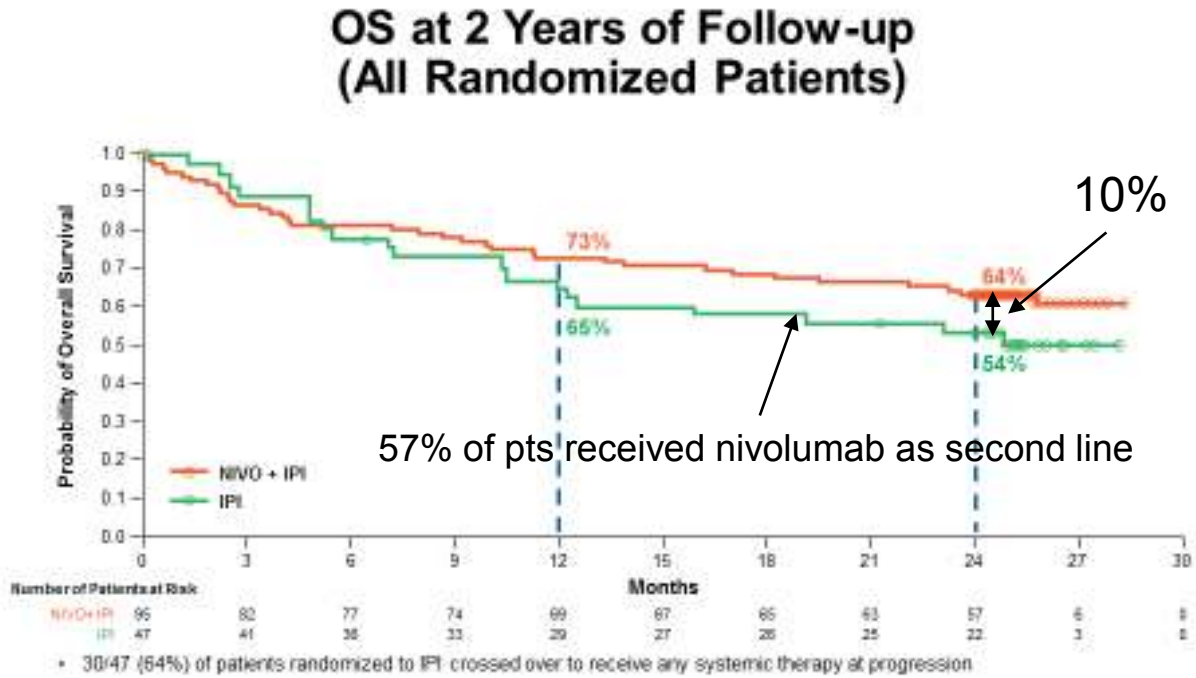
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

Hodi et al ESMO 2018

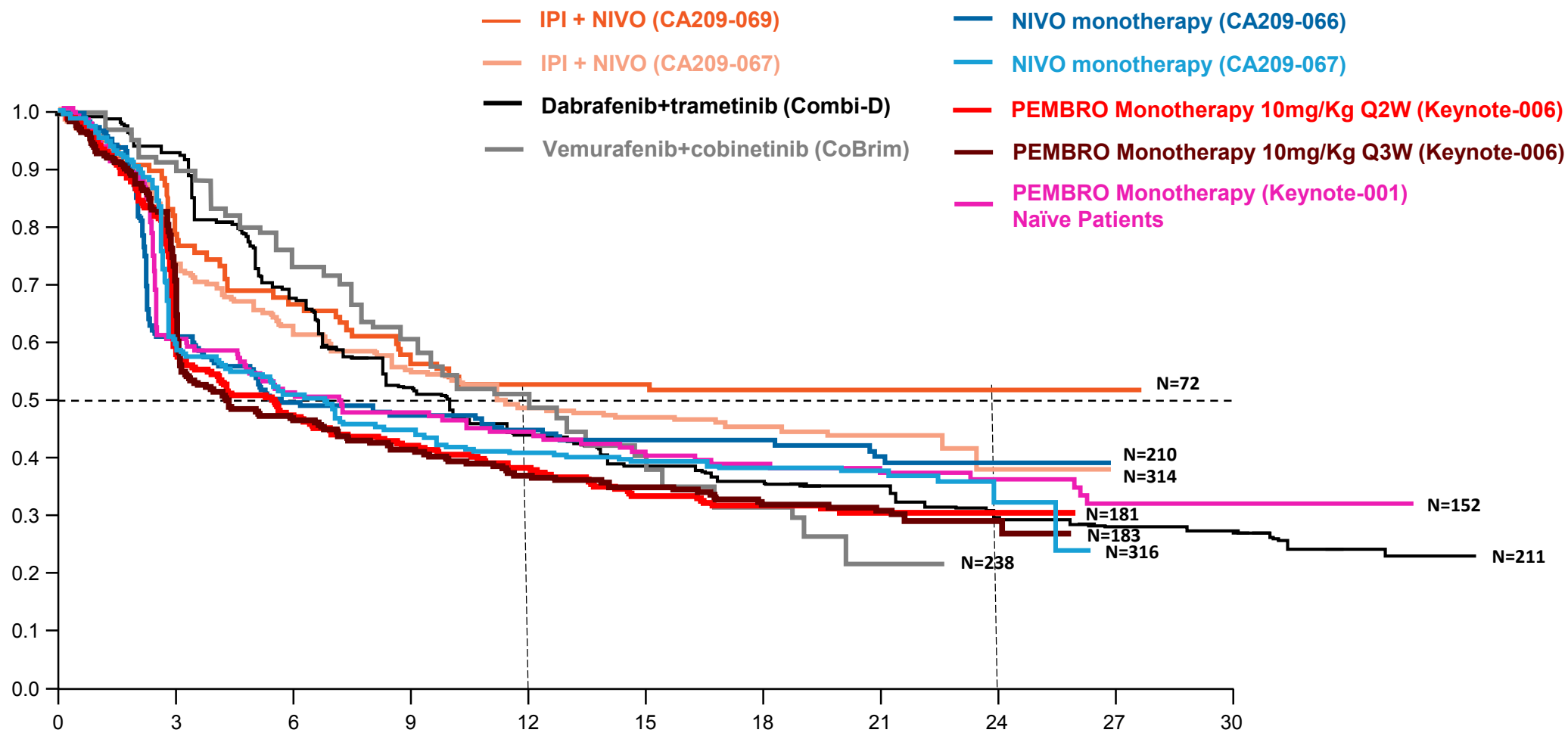
CA209-069 study: PFS and OS



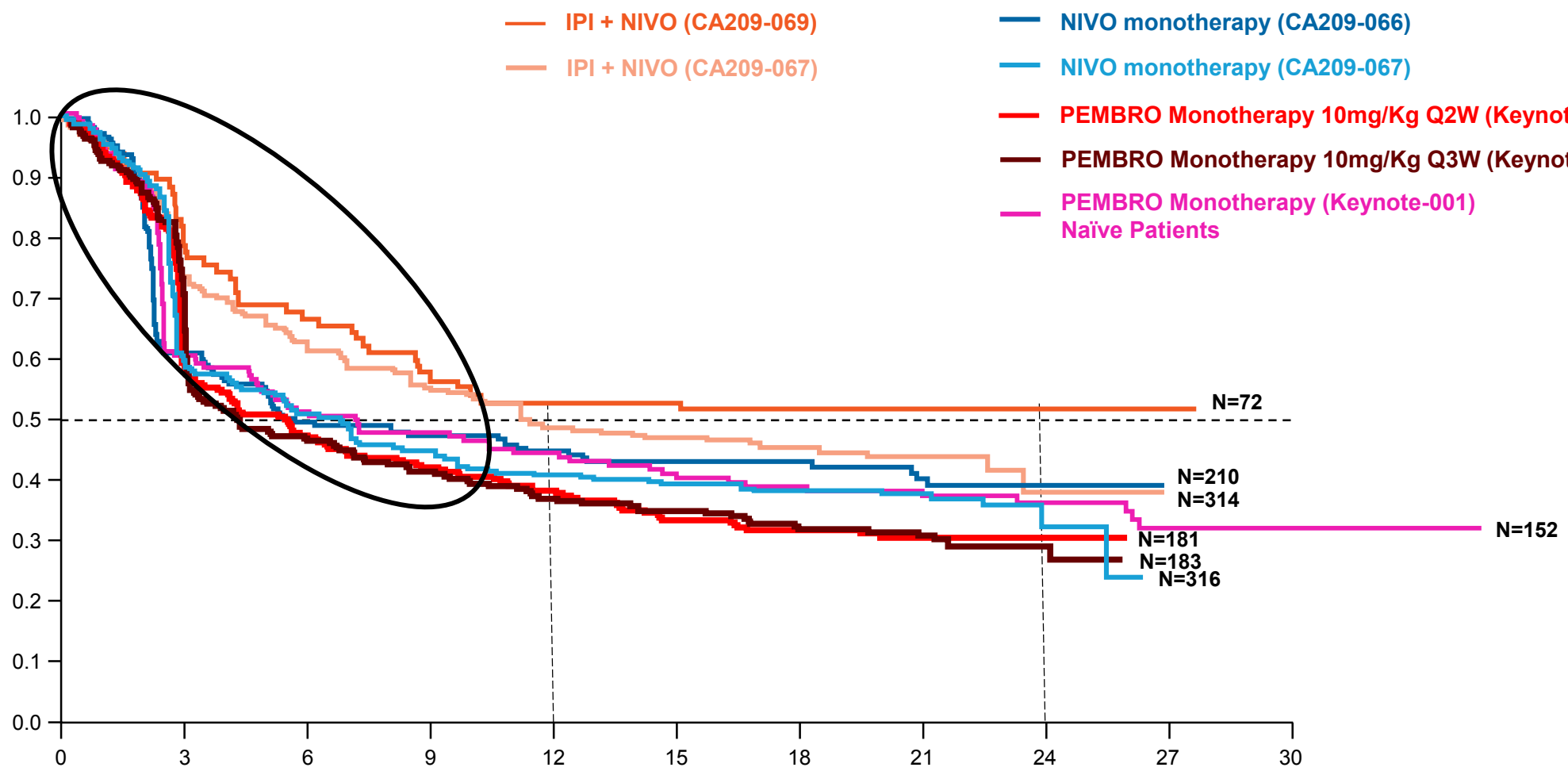


Postow et al AACR 2016
Hodi et al. Lancet Oncol. 2016 Sep 9

PFS Landmark analysis of the most important studies in advanced melanoma



PFS Landmark analysis of the most important studies in advanced melanoma



Treatment decision based on patient's characteristic

Patient history
(eg, autoimmune disease)

Organ system function,
especially cardiac function

Patient's wishes and
lifestyle factors

Mutational status

Performance status

Brain mtx

Tumor burden

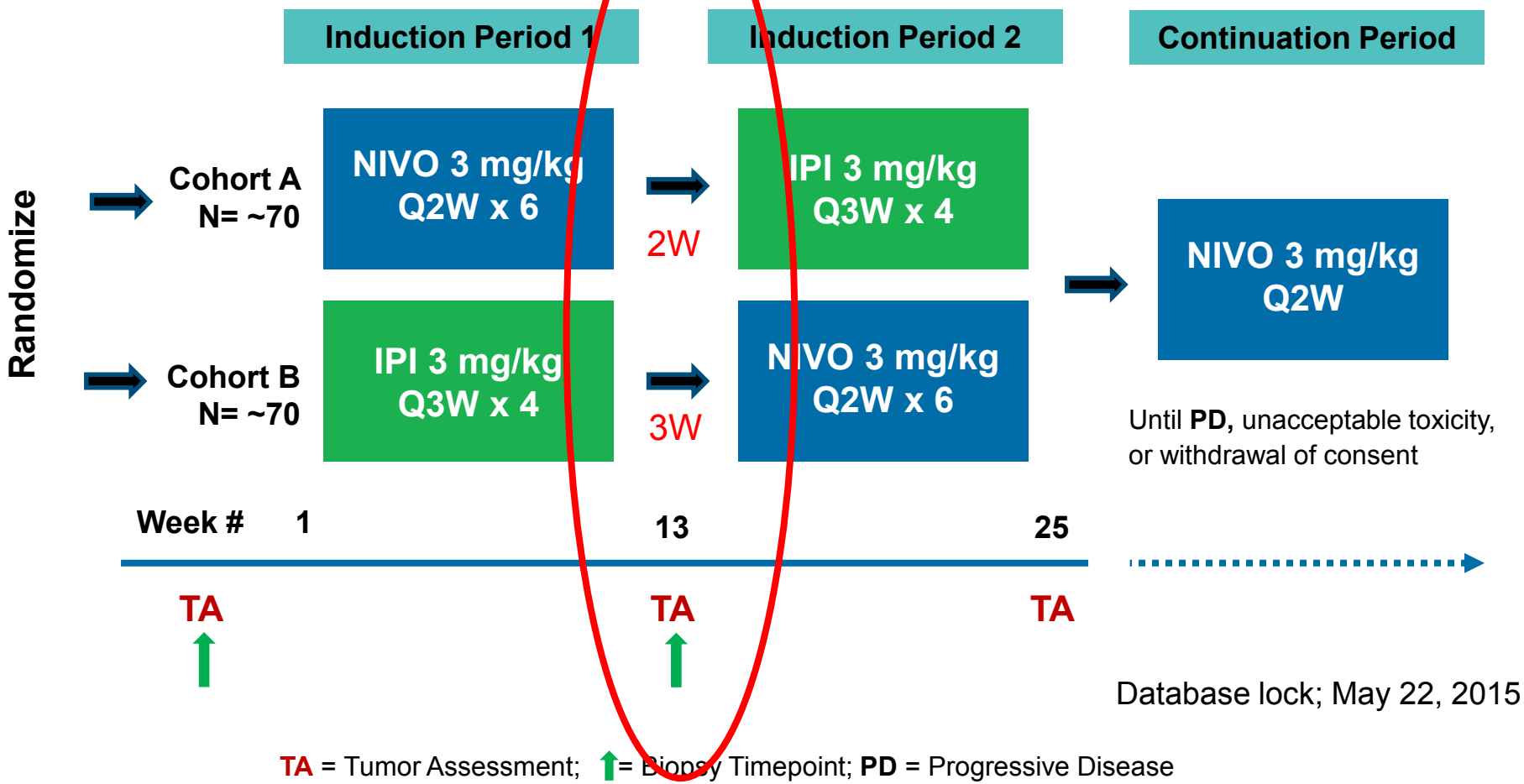
LDH level

Disease Tempo

Ascierto ESMO 2016

CheckMate 064: Study Design

Randomized, open-label, phase 2 study evaluating the safety and efficacy of two immune checkpoint inhibitors given sequentially with planned switch



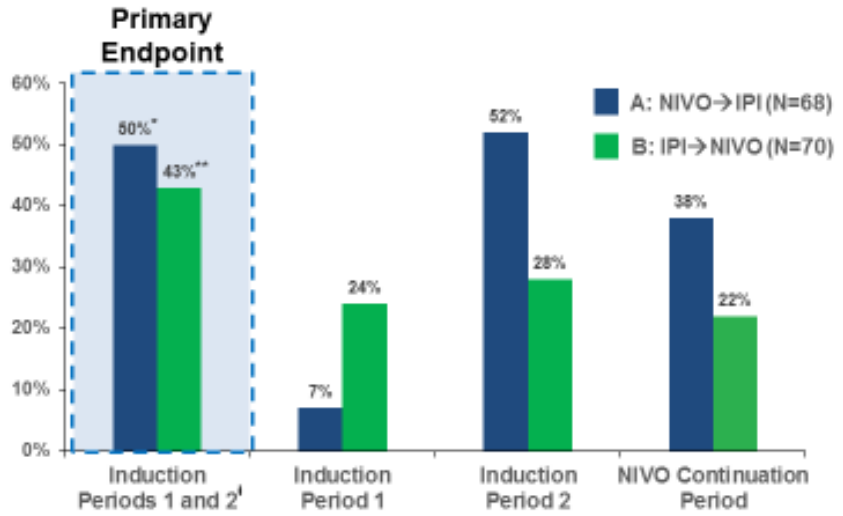
Database lock; May 22, 2015

TA = Tumor Assessment; ⬆ = Biopsy Timepoint; **PD** = Progressive Disease

Weber J et al Lancet Oncology 2016

CheckMate 064

Treatment-related Grade 3-4 AEs

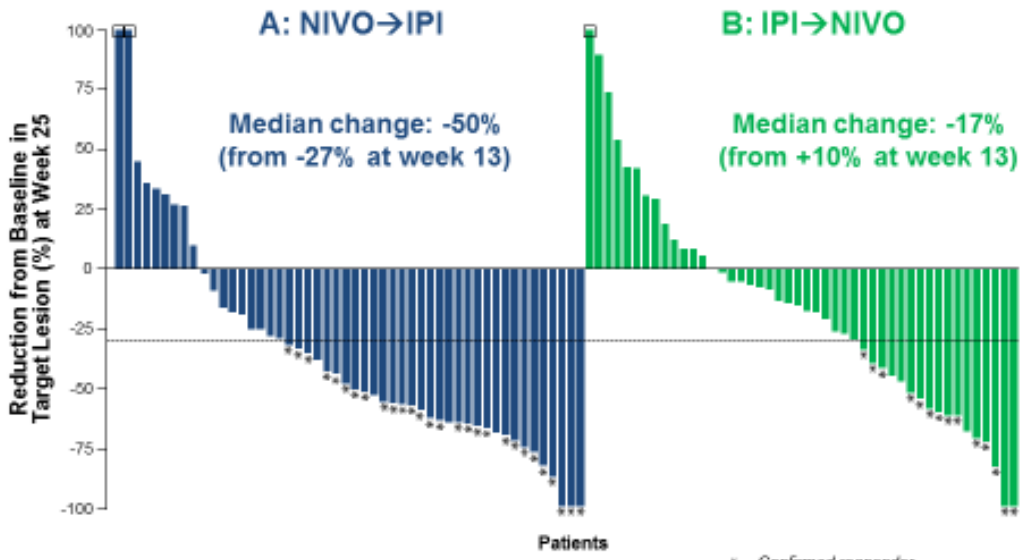


- There were no study drug-related deaths in either cohort
- Treatment-related grade 3-4 AEs leading to discontinuation Cohort A: 24%, Cohort B: 27%

* 95% CI: **37.6%–62.4%**
** 95% CI: **31.1%–55.3%**
†**AEs are counted only once for both induction periods**

9

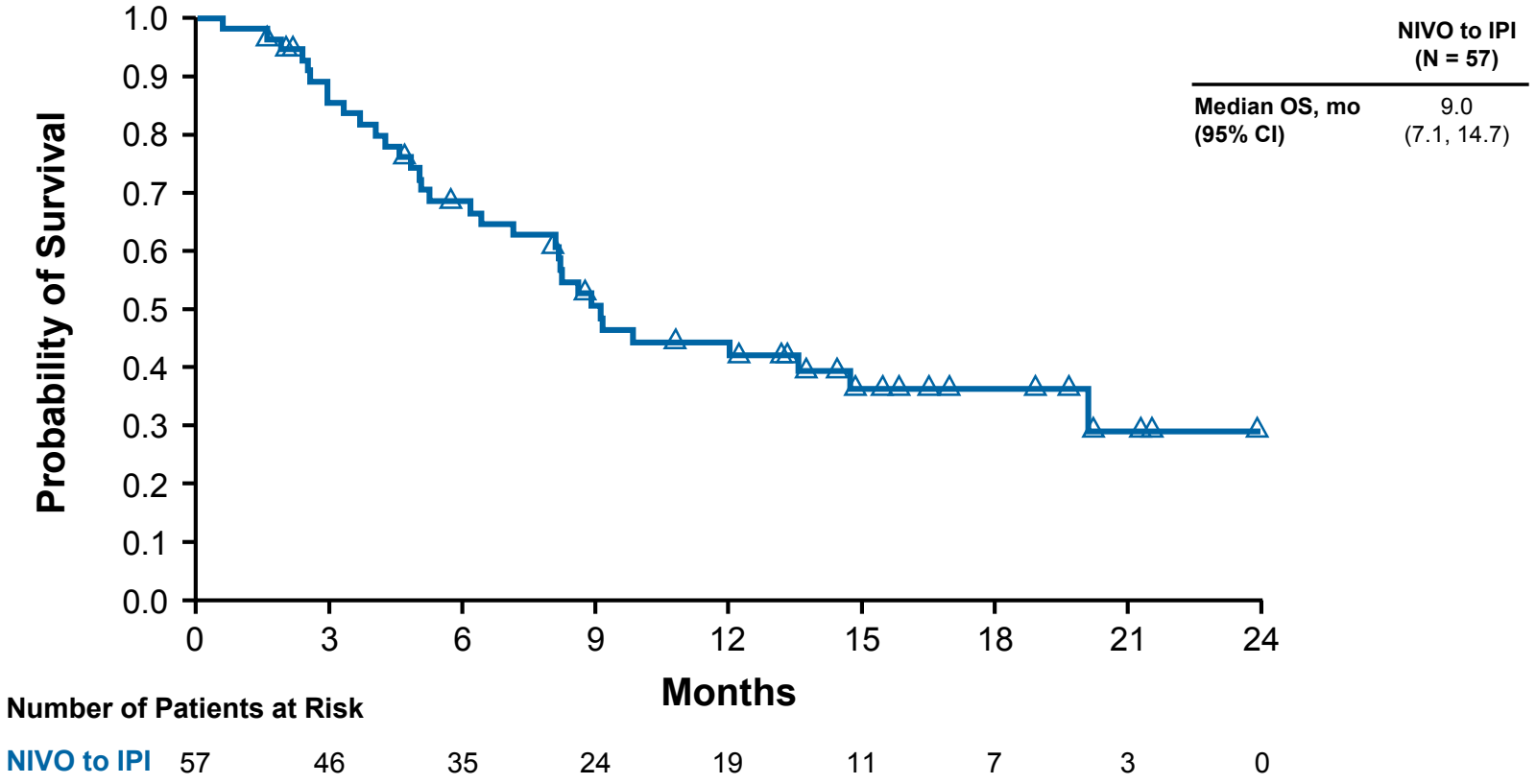
Tumor Burden Change From Baseline at Week 25



13

Hodi et al ECC 2015
Weber J et al Lancet Oncology 2016

CA209-066: additional OS since start of IPI

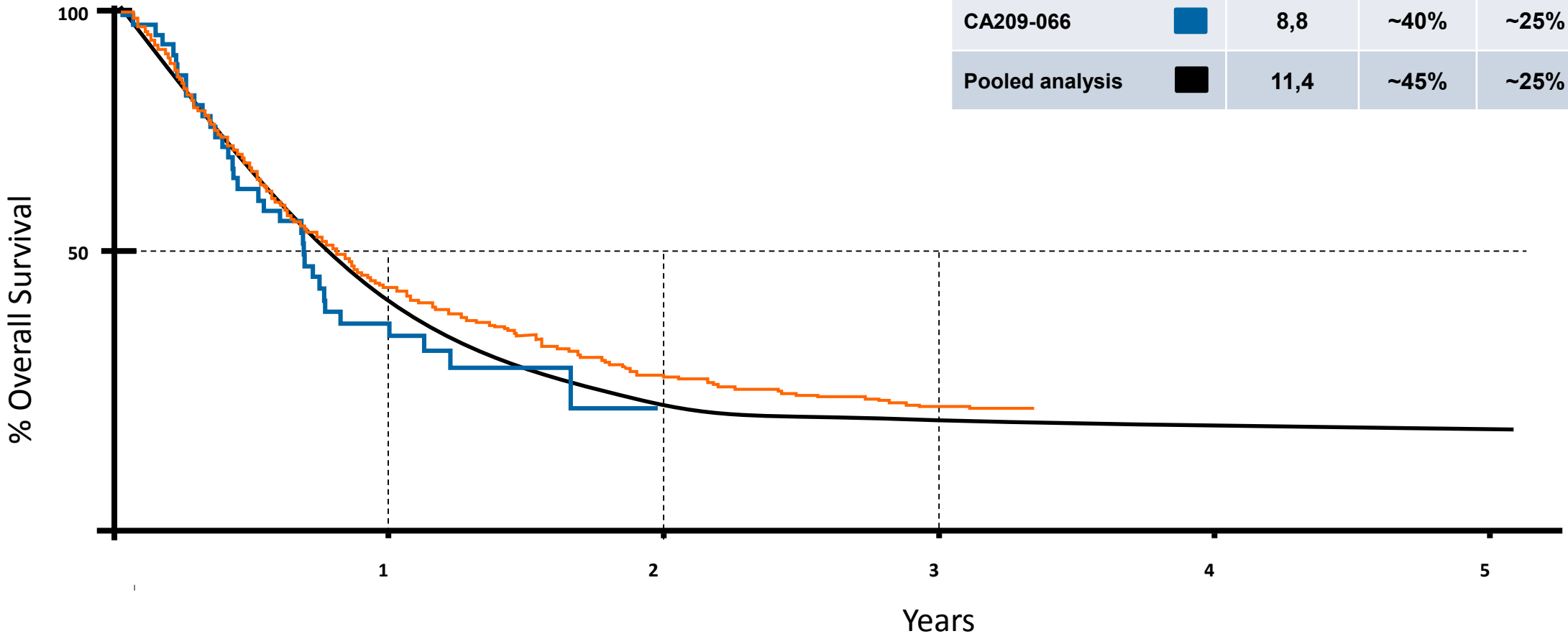


Among these patients, ORR was 8.8% (n = 5, all PR) after the start of IPI

Atkinson V et al SMR 2015

OS curves from the most important study with ipilimumab …

Study	mOS (mos)	1-yrs OS%	2-yrs OS%	3-yrs OS%
CA184-169 Ipi 3 mg/kg	11,5	48%	31%	23%
CA209-066	8,8	~40%	~25%	NA
Pooled analysis	11,4	~45%	~25%	22%



Is OS still the most important endpoint ?

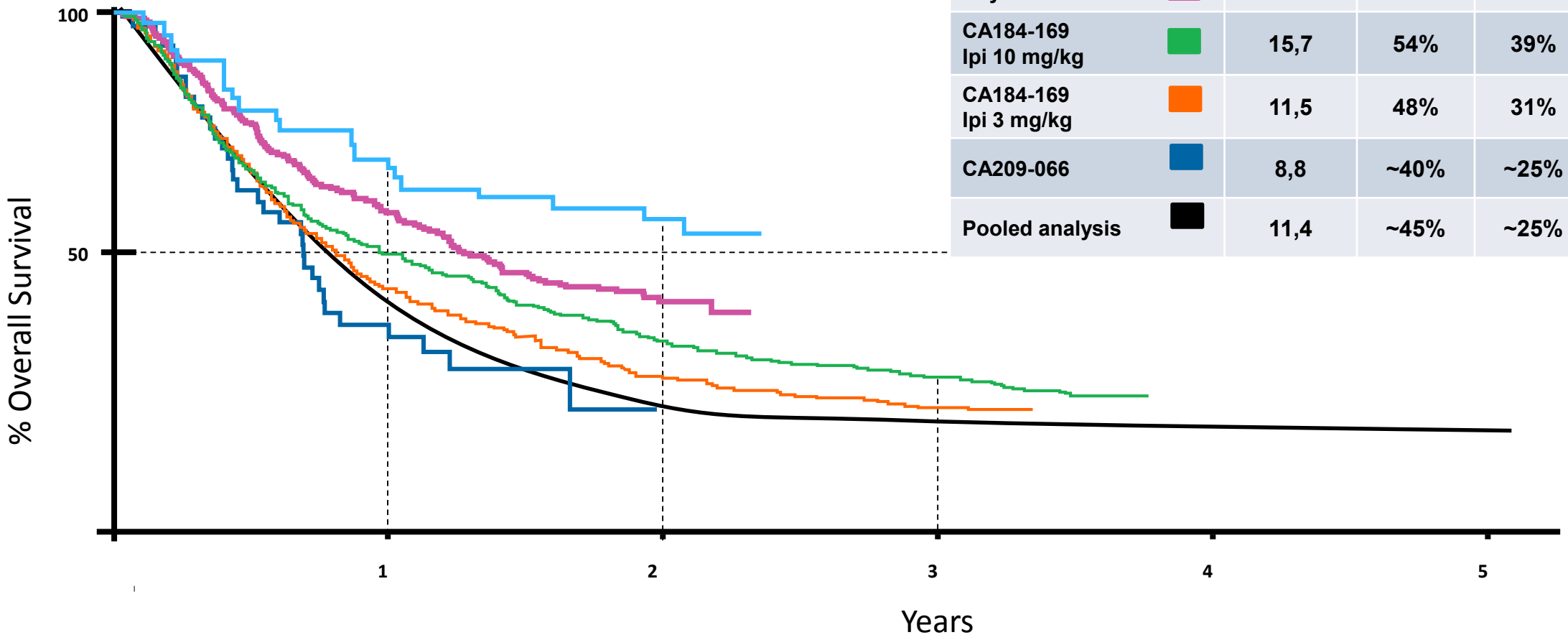
Yes, of course …. But ….

Is OS still the most important endpoint ?

Yes, of course …. But ….

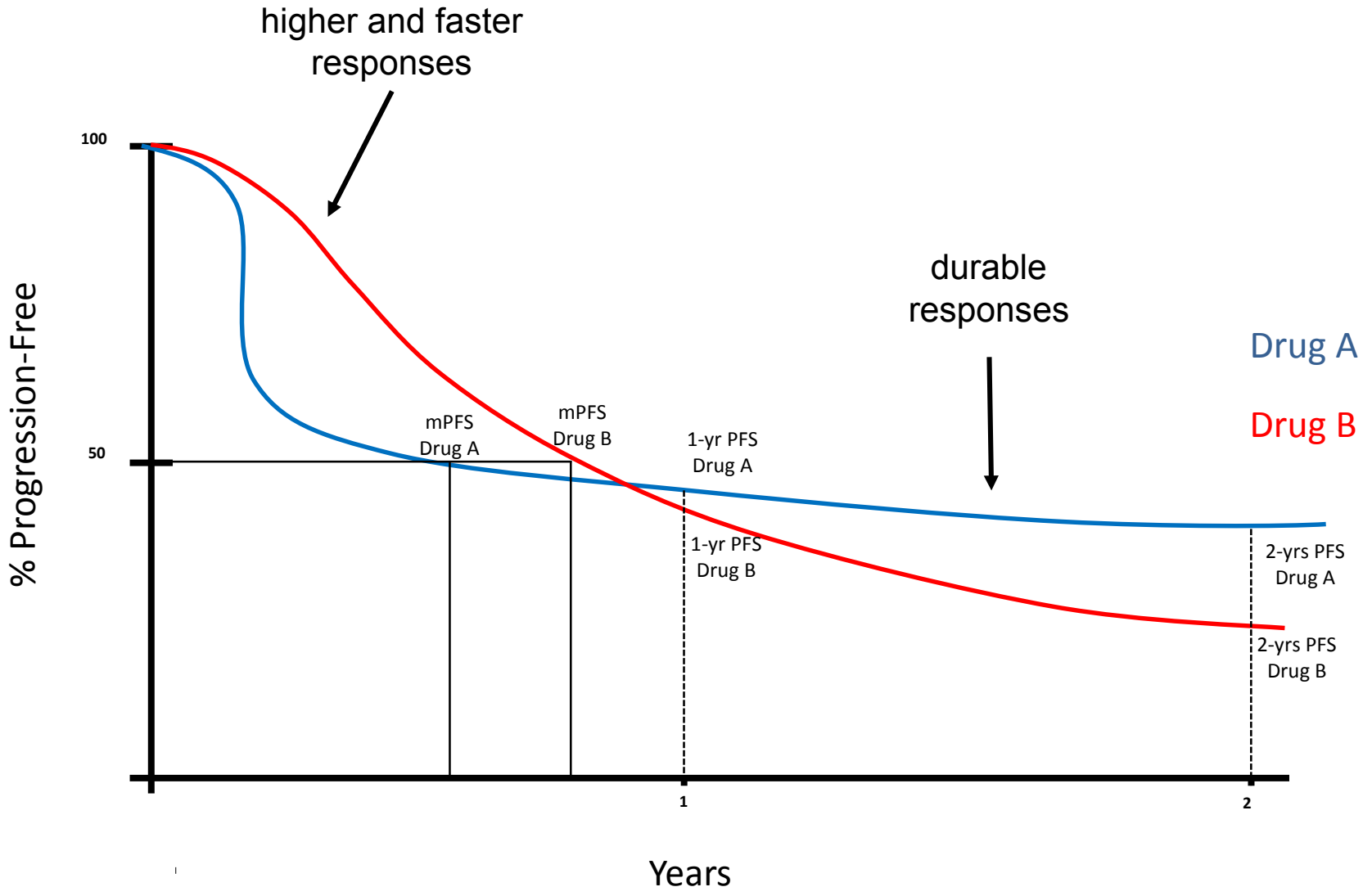
OS curves form the most important study with ipilimumab …

Study	mOS (mos)	1-yrs OS%	2-yrs OS%	3-yrs OS%
CA209-069	NR	65%	54%	NA
Keynote-006	NR	59%	43%	NA
CA184-169 Ipi 10 mg/kg	15,7	54%	39%	31%
CA184-169 Ipi 3 mg/kg	11,5	48%	31%	23%
CA209-066	8,8	~40%	~25%	NA
Pooled analysis	11,4	~45%	~25%	22%



Wolchok JD, et al. *N Engl J Med.* 2017;377(14):1345-1356. Long GV, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 9503. Ascierto PA, et al. *Lancet Oncol.* 2017;18(5):611-622. Ascierto PA, et al. *JAMA Oncol.* 2018 Oct 25 [Epub ahead of print]. Schadendorf D, et al. *J Clin Oncol.* 2015;33(17):1889-1894.

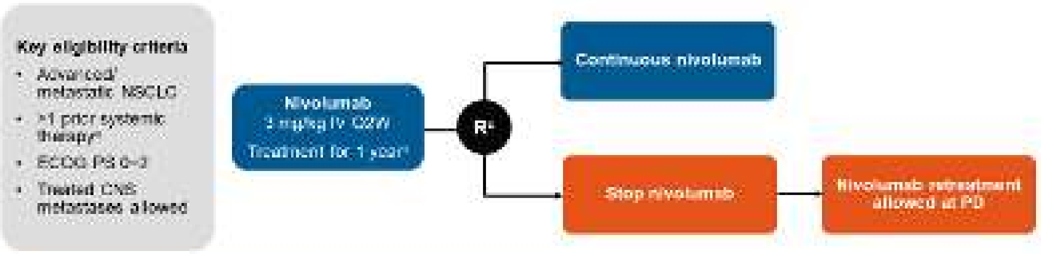
PFS curves may predict long-term benefit …



Ascierto PA & Long GV. Lancet Oncol. 2016;17:1037-1039.

What about the treatment duration?

CheckMate 153: Continuous vs 1-Year Nivolumab
Study Design



Exploratory endpoints: safety/efficacy with continuous vs 1-year treatment; efficacy, other (eg, biomarkers, PK)

- At database lock (May 15, 2017), minimum/median follow-up time post-randomization was 13.0/14.9 months

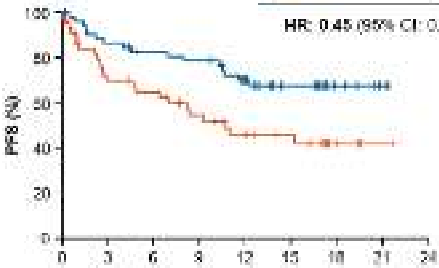
1. Hussein M, et al. Oral presentation at IASLC 16th World Conference on Lung Cancer; September 6–9, 2015; Denver, CO, USA. Abstract ORAL02.02. 2. Waterhouse D, et al. Poster presentation at ASCO Annual Meeting; June 3–7, 2016; Chicago, IL, USA. Abstract 3059.

CheckMate 153: Continuous vs 1-Year Nivolumab
PFS From Randomization by Response Status[a]

CR/PR

	Median, months (95% CI)
Continuous tx	NR (NR)
1-year tx	10.6 (4.6, NA)

HR: 0.45 (95% CI: 0.24, 0.85)

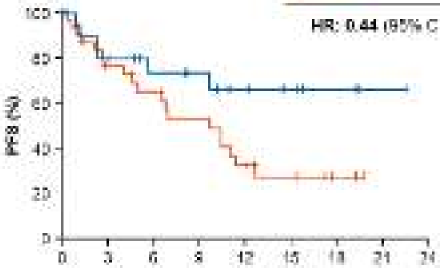


No. at risk	0	3	6	9	12	15	18	21	24
Continuous tx	53	45	41	38	29	17	7	2	0
1-year tx	49	36	28	20	14	11	3	1	0

SD

	Median, months (95% CI)
Continuous tx	NR (5.6, NA)
1-year tx	9.6 (4.5, 12.6)

HR: 0.44 (95% CI: 0.17, 1.09)



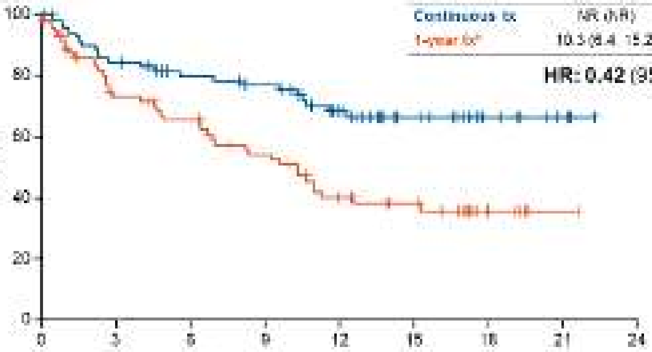
No. at risk	0	3	6	9	12	15	18	21	24
Continuous tx	23	15	12	10	7	6	5	1	0
1-year tx	38	21	17	13	7	6	2	0	0

[a]Best overall response prior to randomization; minimum/median follow-up time post-randomization, 13.0/14.9 months. NA = not available.

CheckMate 153: Continuous vs 1-Year Nivolumab
PFS From Randomization[a]

	Median, months (95% CI)	PFS rate, % 6-month	PFS rate, % 1-year
Continuous tx	NR (NR)	80	65
1-year tx	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)



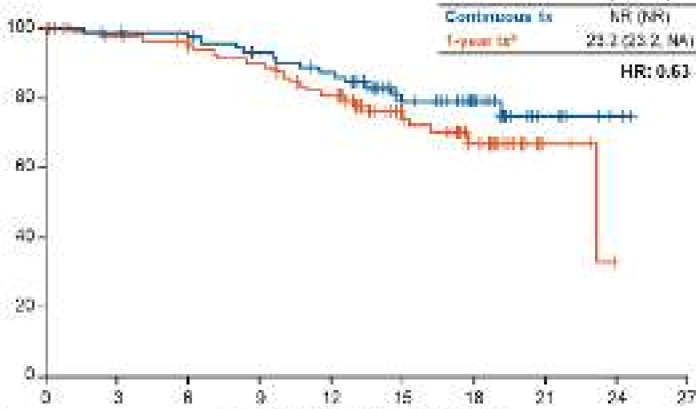
No. at risk	0	3	6	9	12	15	18	21	24
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 13.0/14.9 months. NR = not reached; tx = treatment.

CheckMate 153: Continuous vs 1-Year Nivolumab
OS From Randomization[a]

	Median, months (95% CI)	OS rate, % 6-month	OS rate, % 1-year
Continuous tx	NR (NR)	97	88
1-year tx	23.2 (23.2, NA)	95	81

HR: 0.63 (95% CI: 0.33, 1.20)

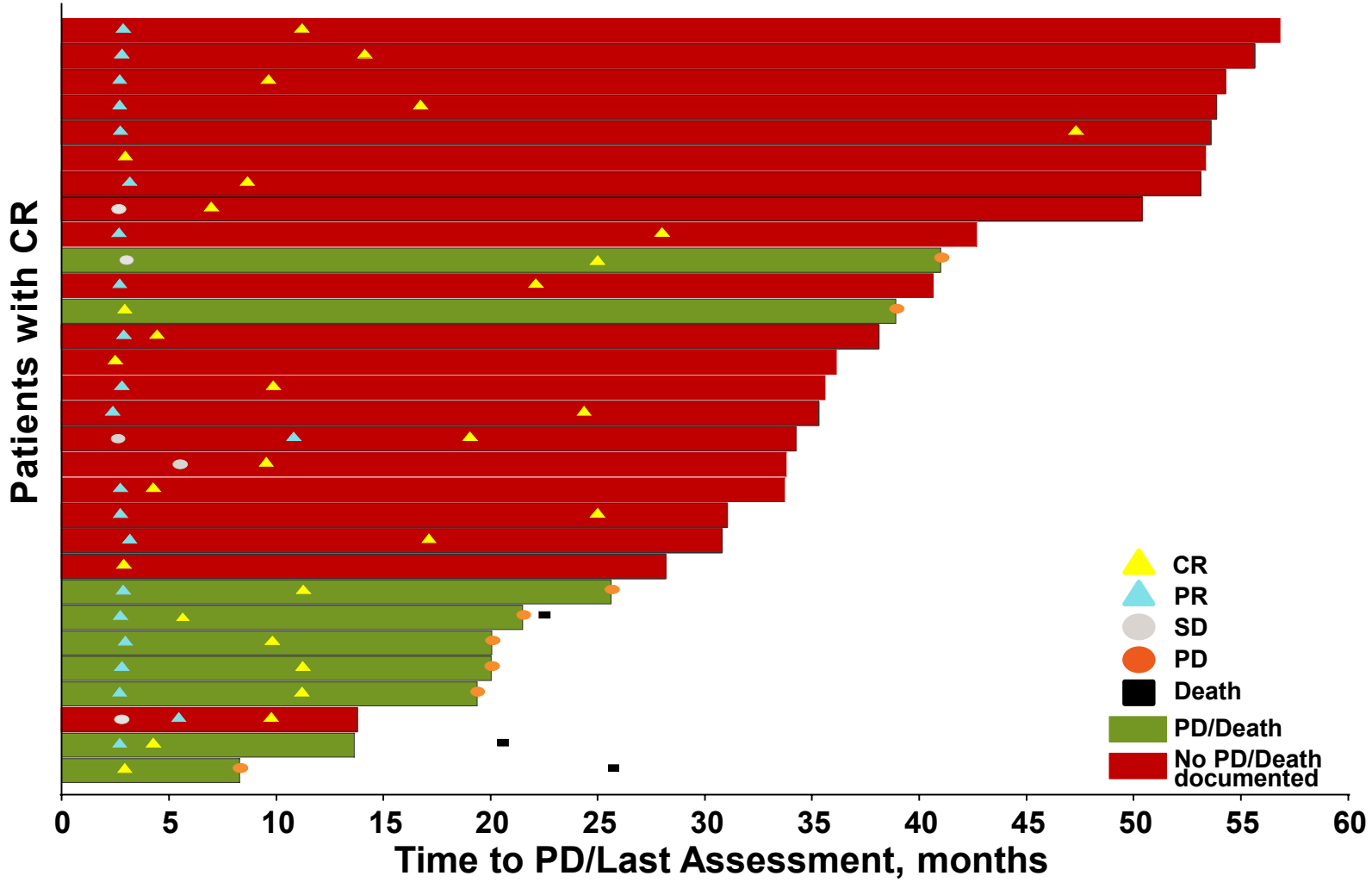


No. at risk	0	3	6	9	12	15	18	21	24	27
Continuous tx	76	74	72	67	62	41	28	7	2	0
1-year tx	87	79	74	70	61	38	23	4	0	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 13.0/14.9 months. [b]With optional retreatment allowed at PD.

Spiegel et al. ESMO 2017

Characteristics of Complete Response (RECIST v1.1, INV) to Pembrolizumab



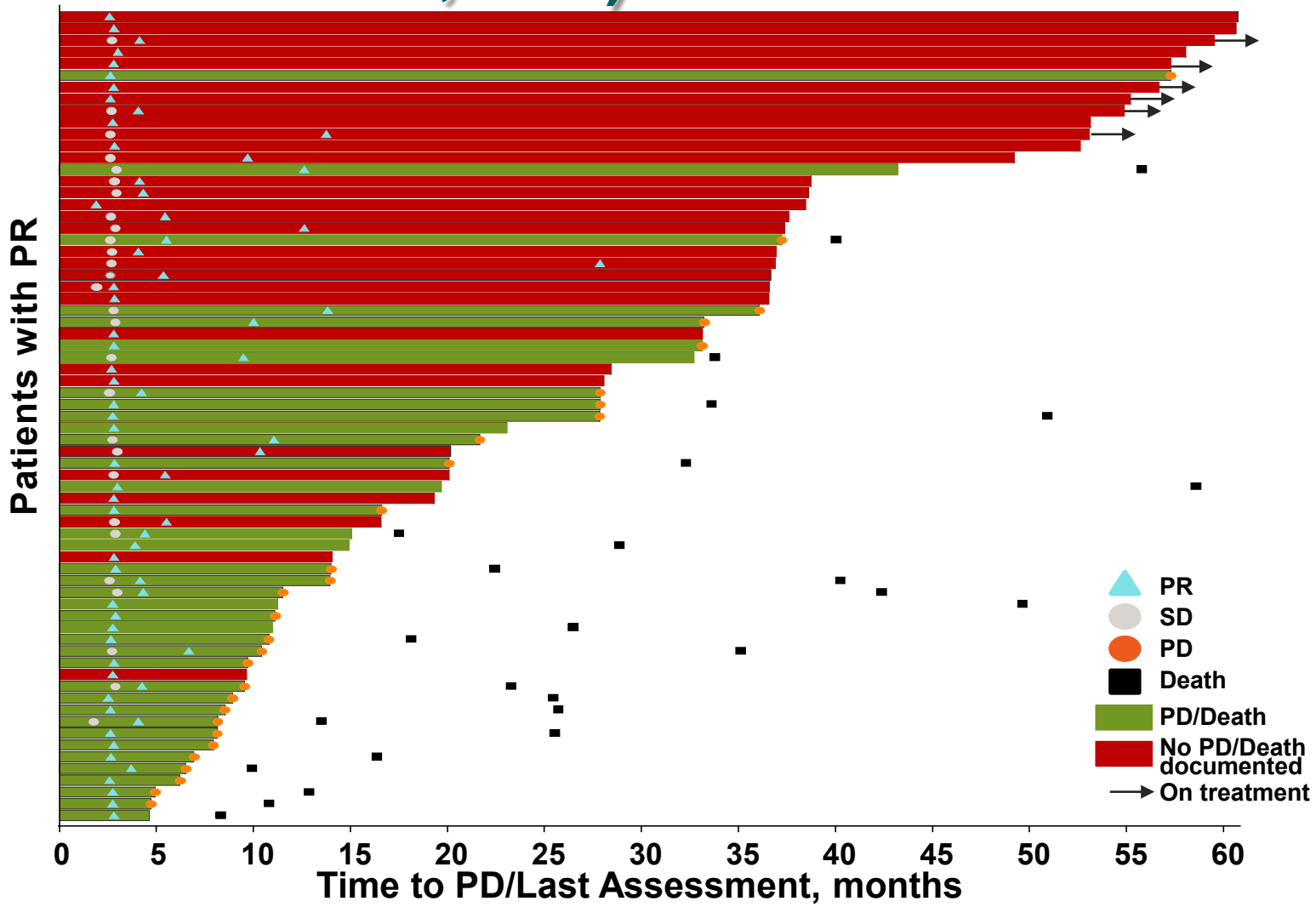
30 patients had best response of CR

- Median time to CR: 2.8 mo (range, 2.4-24.9)
- Median time from SD to CR: 6.9 mo (range, 3.9-21.9) in 5 patients
- Median time from PR to CR: 8.2 mo (1.4-44.4) in 22 patients
- Median duration of CR: not reached (range, 5.5 to 53.9+)

Data cutoff: 30 May 2018.
Of 22 patients without progression, 16 discontinued because of an AE (n = 3) or patient/physician decision (n = 13)..

Ribas et al SMR 2018

Characteristics of Partial Response (RECIST v1.1, INV) to Pembrolizumab



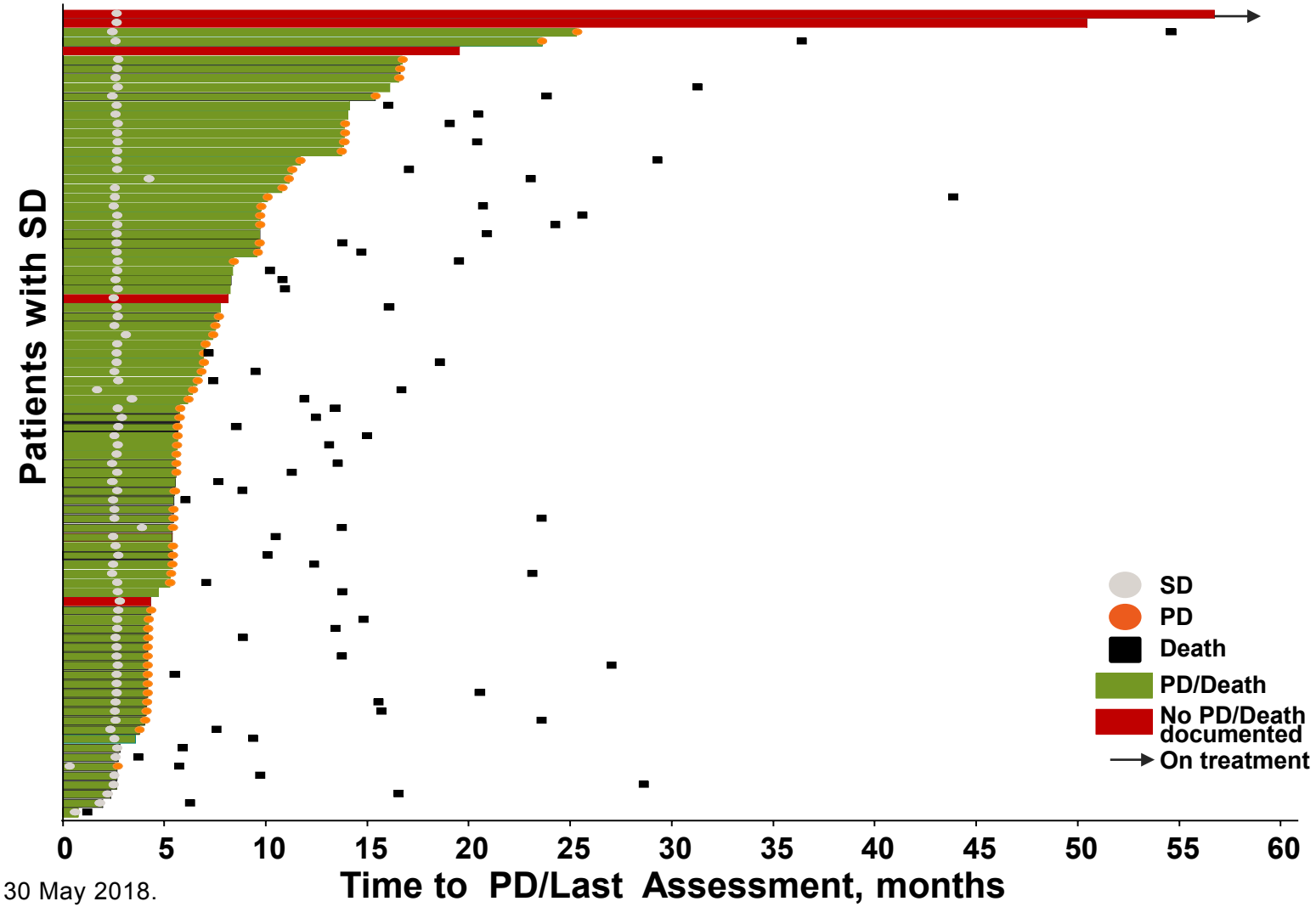
69 patients had best response of PR

- Median time to PR: 2.9 mo (range, 1.9-27.9)
- Median time from SD to PR: 2.7 mo (range, 0.9-25.2) in 28 patients
- Median duration of PR: 54.7 mo (range, 1.9+ to 58.2+)

Data cutoff: 30 May 2018.
Of 40 patients without progression, 31 discontinued because of an AE (n = 15) or physician/patient decision (n = 16)..

Ribas et al SMR 2018

Characteristics of Stable Disease to Pembrolizumab



88 patients had best response of SD

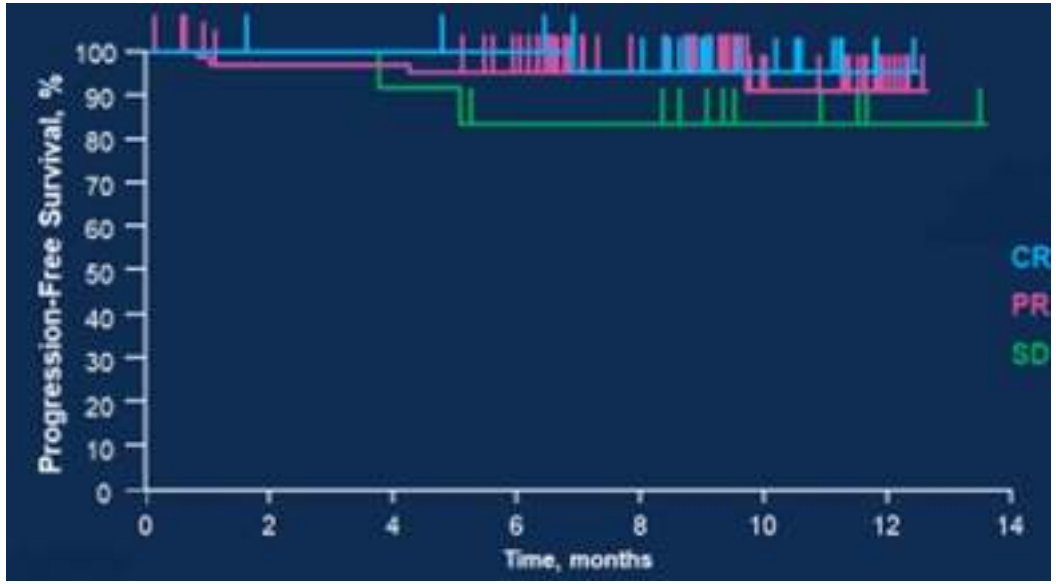
- Median duration of SD: 7.8 mo (range, 0.8+ to 56.7+)

Ribas et al SMR 2018

Data cutoff: 30 May 2018.

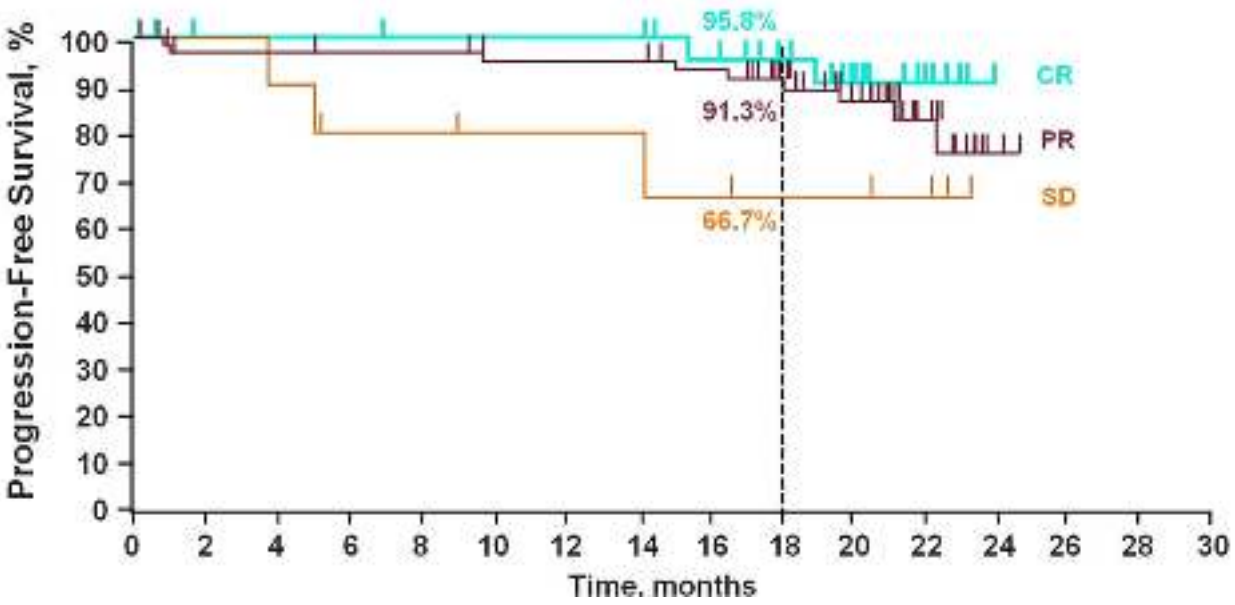
Duration of SD is from randomization to progression. Of 25 patients without progression, 24 discontinued because of an AE (n = 11) or patient/physician decision (n = 13).

Keynote 006: PFS in Patients Who Completed Protocol-Specified Time on Pembrolizumab



Median follow-up after ≥94 weeks pembro:

9.7 months



Median follow-up after ≥94 weeks pembro:

20.3 (0.03-24.8) months

Long et al ASCO 2018
Robert et al. ASCO 2017

MY PERSONAL CONCLUSIONS

- The right endpoint is crucial when we design clinical trial
- Dosage may be important even in the field of I-O.
- We need of better pharmacokinetic and biomarkers studies in phase 1 trials.
- Combination or sequencing? The question is still open
- Duration of treatment still debated (CR for sure, PR may be, not for SD) … it depends also by the possibility to treat patients with a re-challange.

Thank you!

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