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Sacro Cuore - Don Calabria
Ospedale Classificato e Presidio Ospedaliero Accreditato
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IRCCS
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Cancer Care Center
Negrar di Valpolicella

Incontri di aggiornamento del Dipartimento Oncologico

Responsabile Scientifico:
DOTT.SSA STEFANIA GORI

Martedì 18 giugno 2019

Immunoterapia nel melanoma

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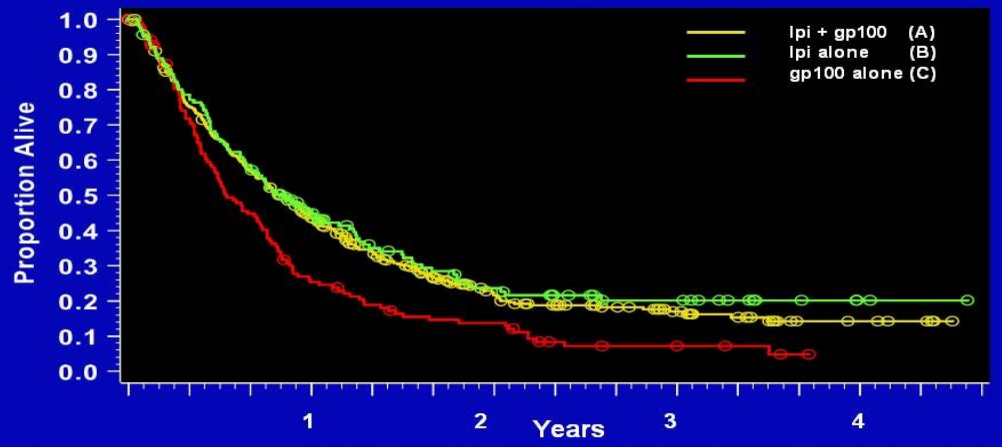
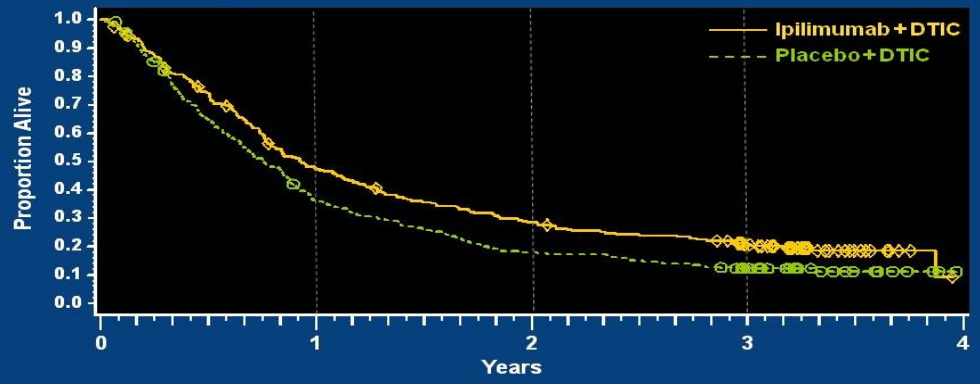
Kaplan-Meier Analysis of Survival



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

18

Study 024: Overall Survival



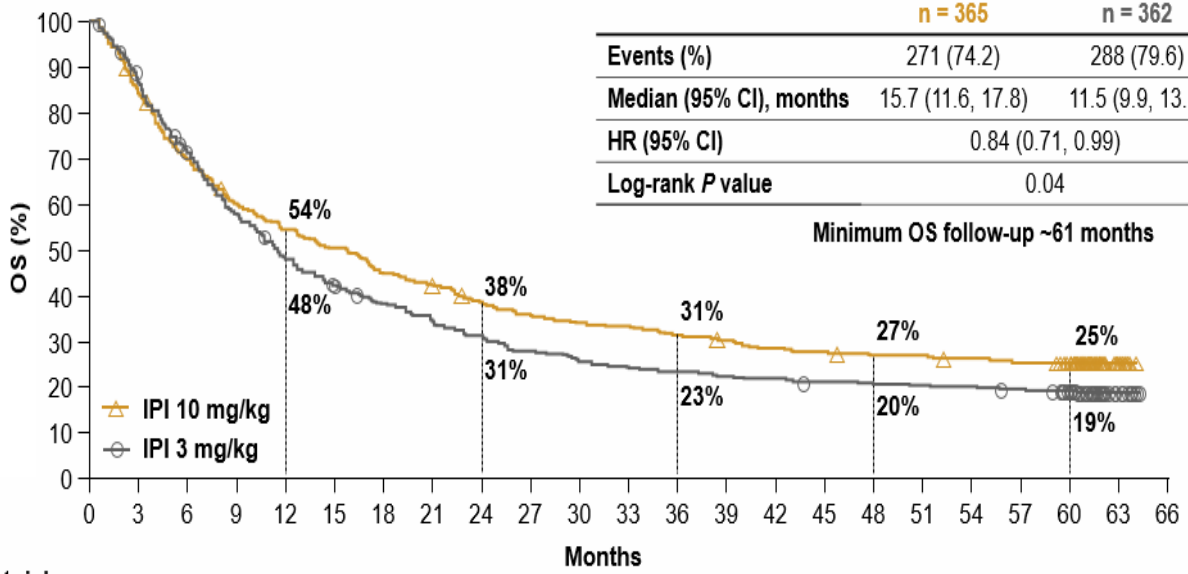
Estimated Survival Rate	1 Year	2 Year	3 Year*
Ipilimumab+DTIC n=250	47.3	28.5	20.8
Placebo+DTIC n=252	36.3	17.9	12.2

*3-year survival was a post-hoc analysis

PRESENTED AT: ASCO Annual '11 Meeting

16

OS: All Randomized Patients



	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	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

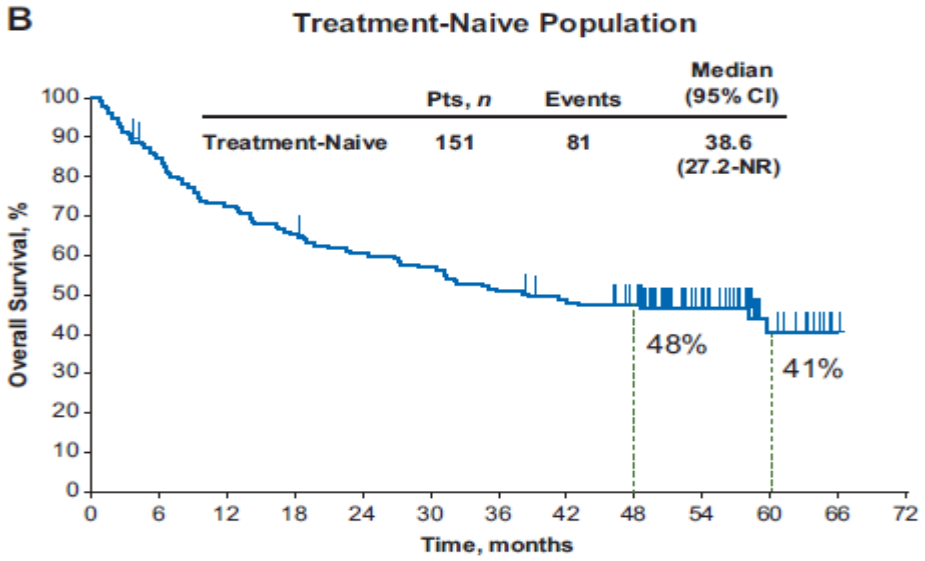
Hodi FS et at. NEJM 2010

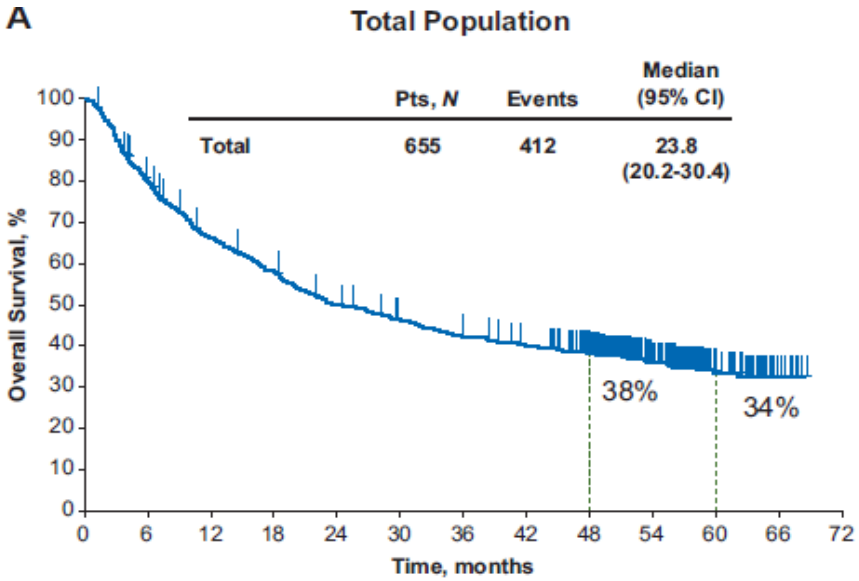
Robert C et al. NEJM 2011

Ascierto P. et al. Lancet Oncol 2017, updated 2018

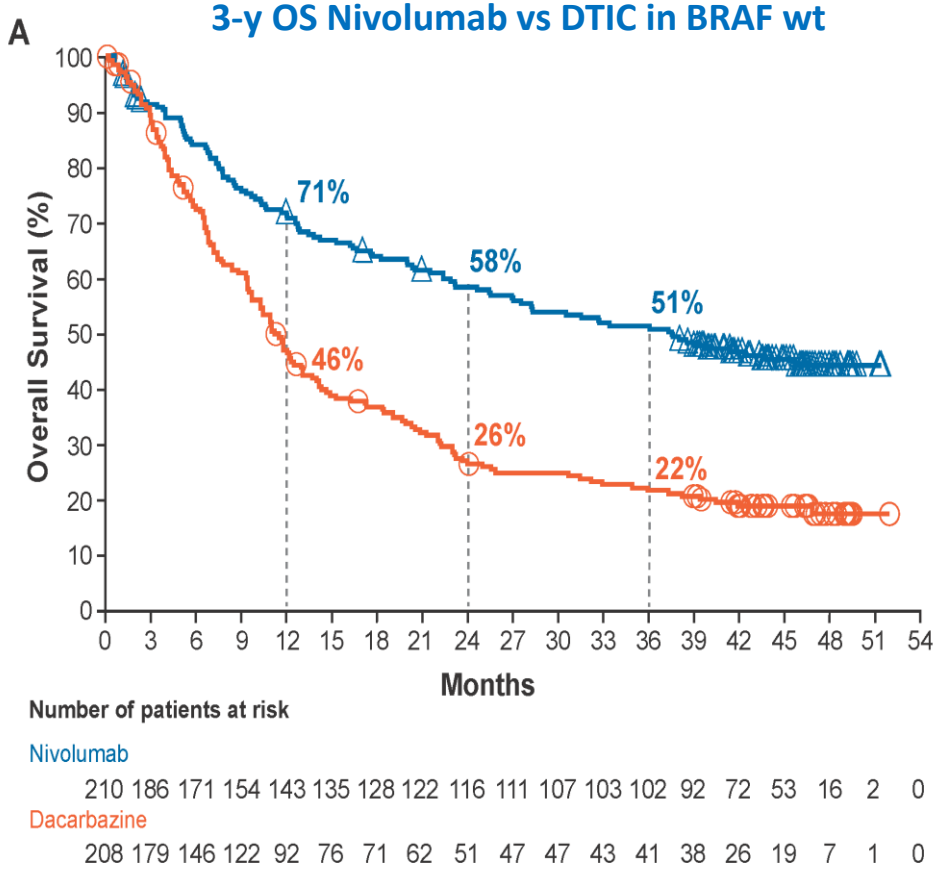
Anti PD-1: better activity and efficacy in untreated patients

5-y OS Pembrolizumab KEYNOTE-001





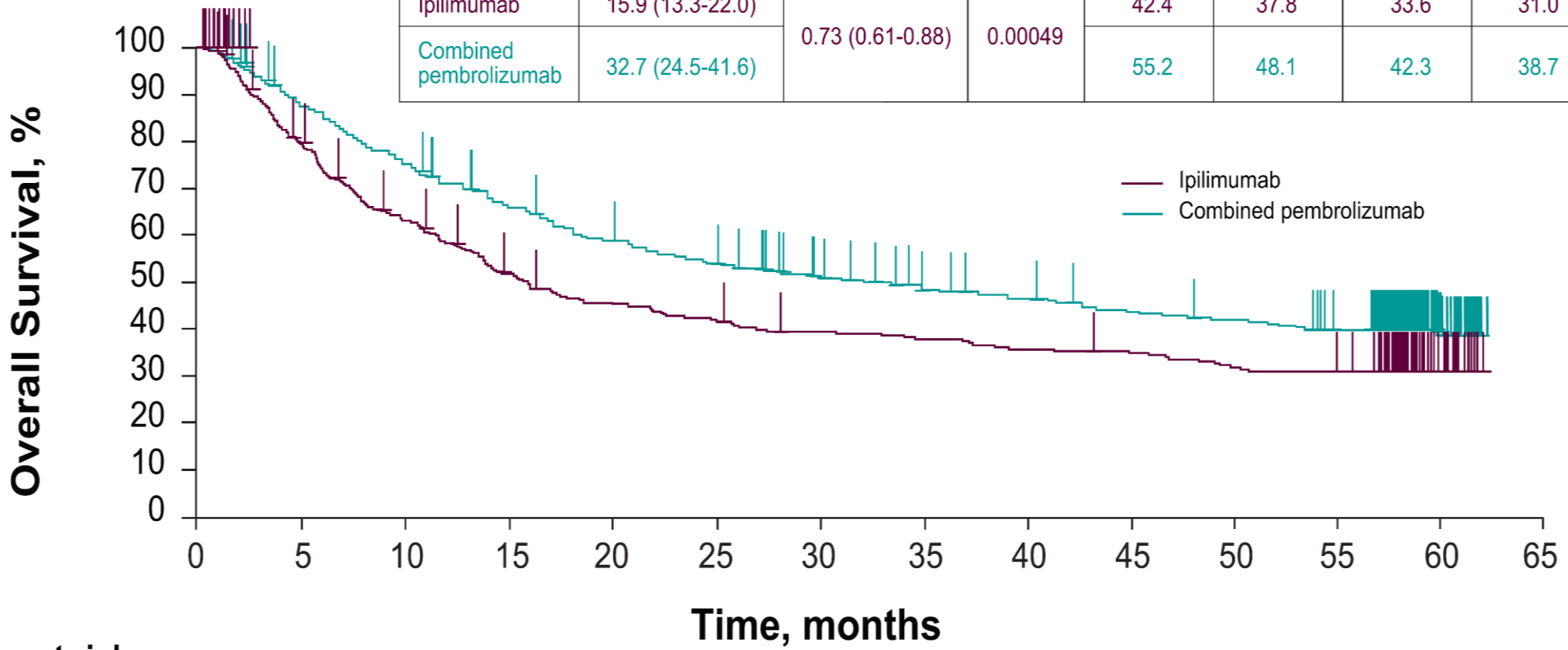
3-y OS Nivolumab vs DTIC in BRAF wt



O'Hamid et al Ann Oncol 1-7,2019
P.Ascierto et al JAMA Oncol 187-194,2019

Keynote-006: KM Estimates of OS in the Total Study Population

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	15.9 (13.3-22.0)	0.73 (0.61-0.88)	0.00049	42.4	37.8	33.6	31.0
Combined pembrolizumab	32.7 (24.5-41.6)			55.2	48.1	42.3	38.7

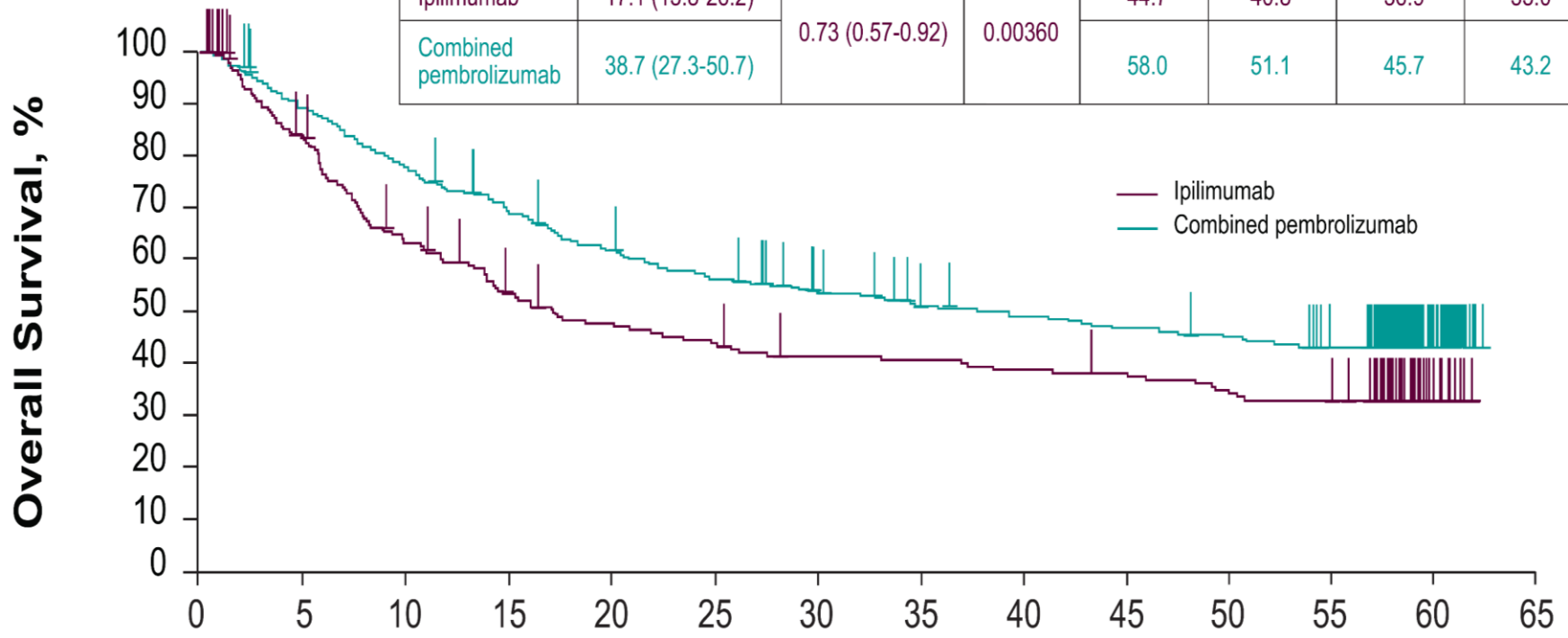


No. at risk														
Ipilimumab	277	202	158	127	111	102	94	90	85	83	75	72	19	0
Combined pembrolizumab	556	481	416	357	317	289	264	245	233	217	208	194	47	0

Robert KN006 AACR 2019

Keynote-006: KM Estimates of OS in Patients Receiving First-Line Treatment

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2

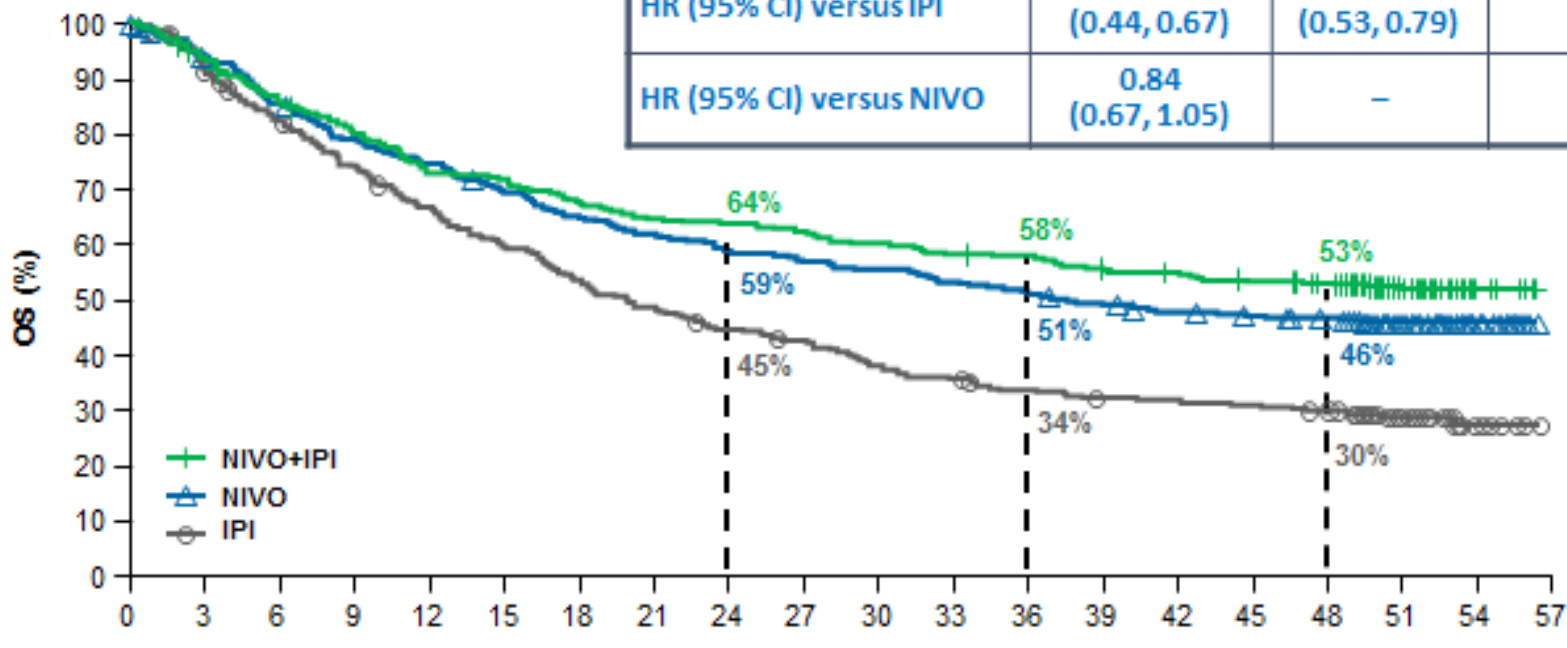


No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

Robert KN006 AACR 2019

Overall Survival checkmate 067

	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	0.84 (0.67, 1.05)	–	–



Patients at risk:

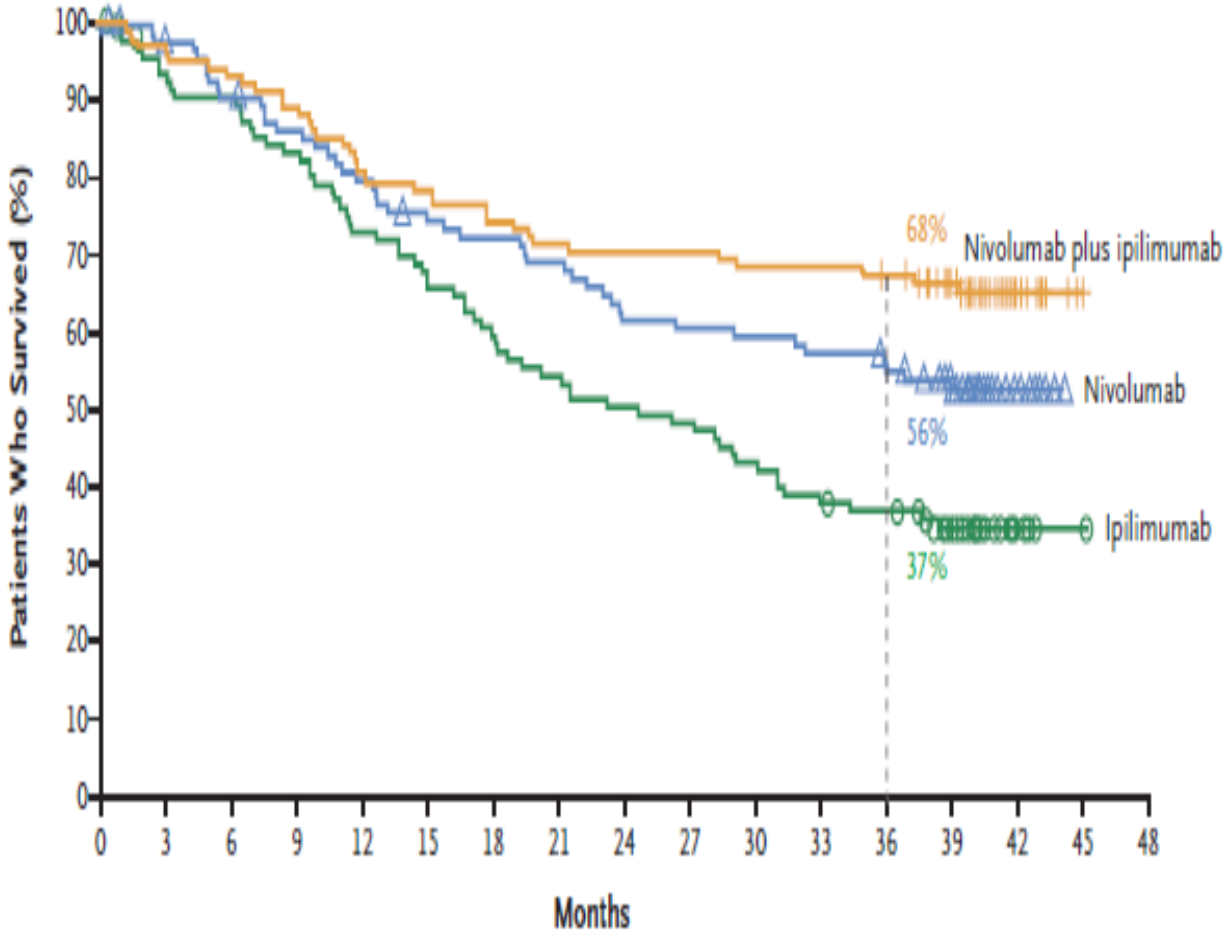
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

*Descriptive analysis

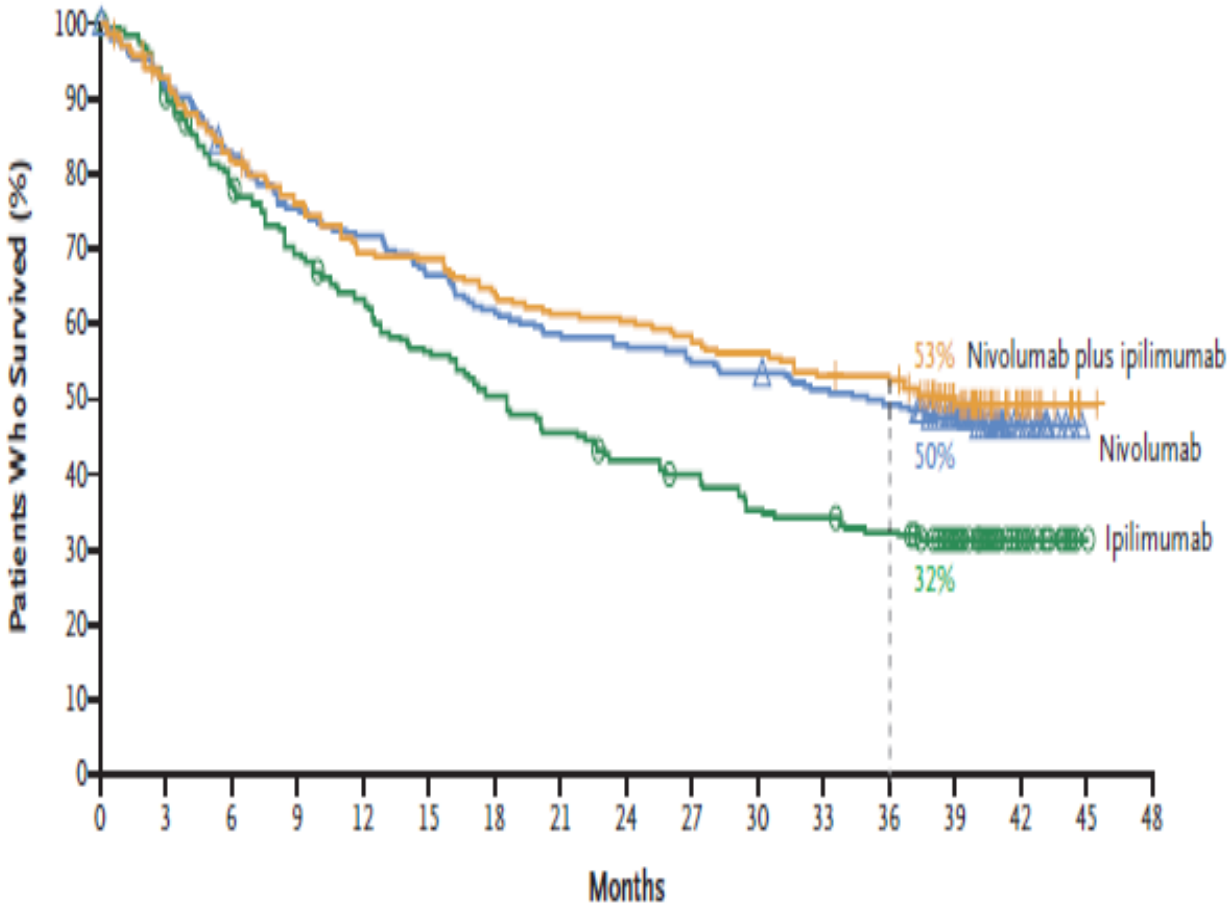
Wolchock JD et al. NEJM 2017
Hodi FS et al. Lancet Oncol 2018

OVERALL SURVIVAL WITH COMBINATION IN BRAF MUTATED PATIENTS (CHECKMATE 067)

OVERALL SURVIVAL IN PATIENTS BEARING BRAF MUTATIONS

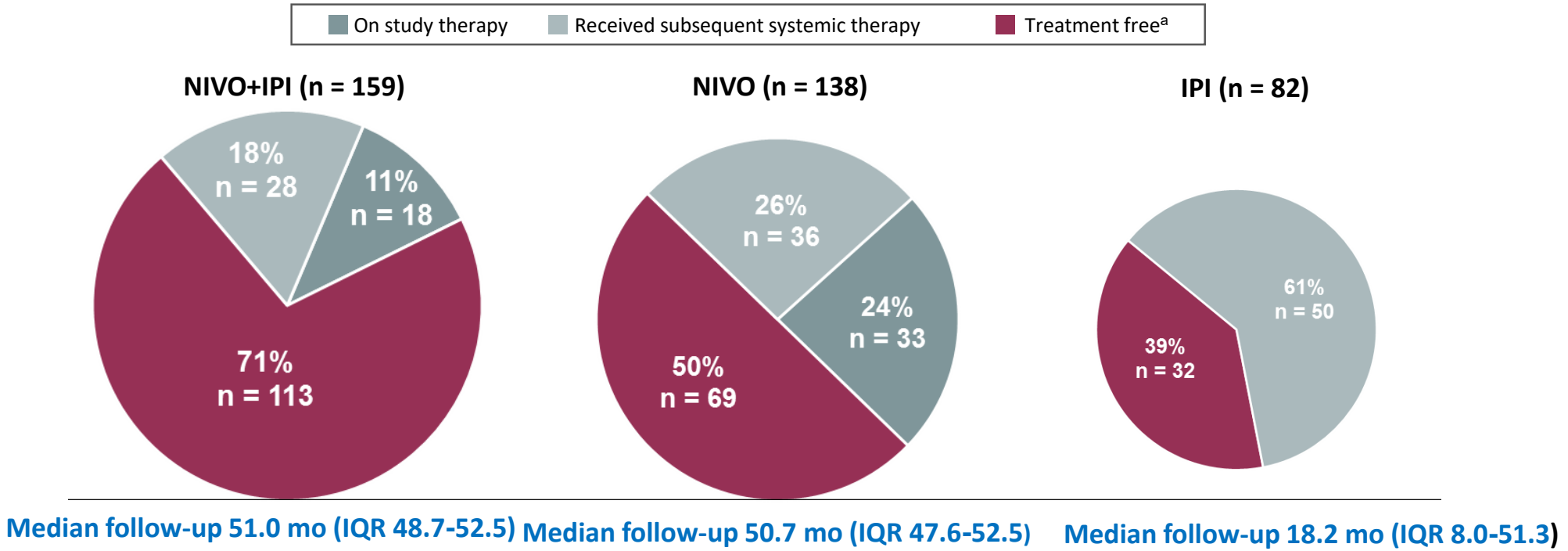


OVERALL SURVIVAL IN BRAF WILD TYPE PATIENTS



Wolchok J.D. et al. *NEJM* 2017

Patients Alive at 4 Years Checkmate 067

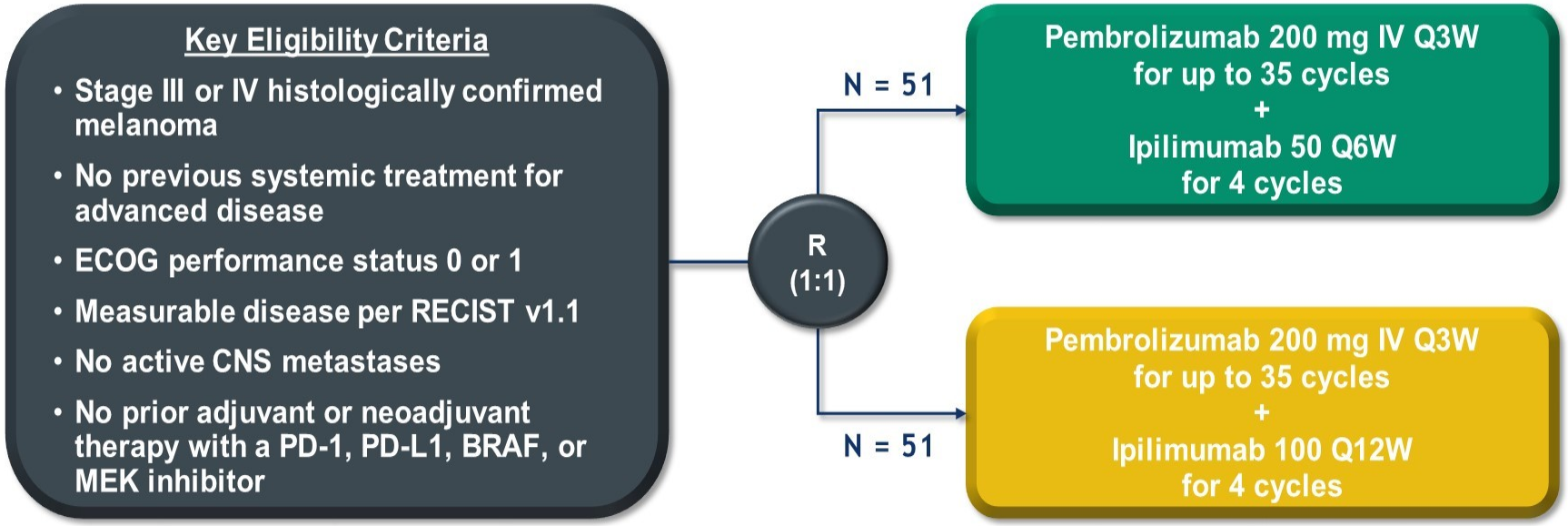


Median follow-up 51.0 mo (IQR 48.7-52.5) Median follow-up 50.7 mo (IQR 47.6-52.5) Median follow-up 18.2 mo (IQR 8.0-51.3)

- **At the 3-year follow-up, 67% of patients (114/170) in the NIVO+IPI group were treatment free**

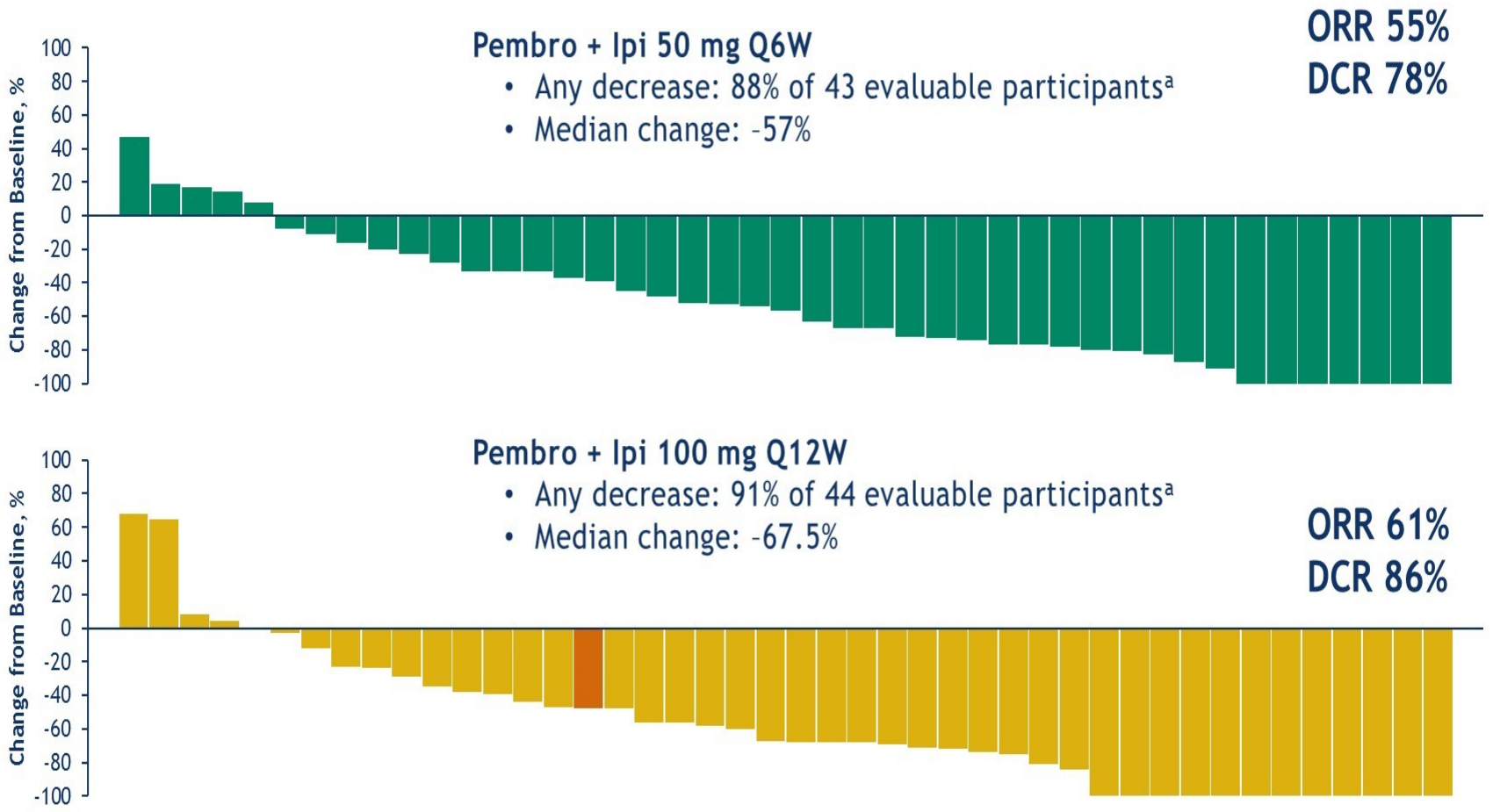
[a]Off study treatment for any reason and never received subsequent systemic therapy

Long et al – Pembrolizumab + ipilimumab



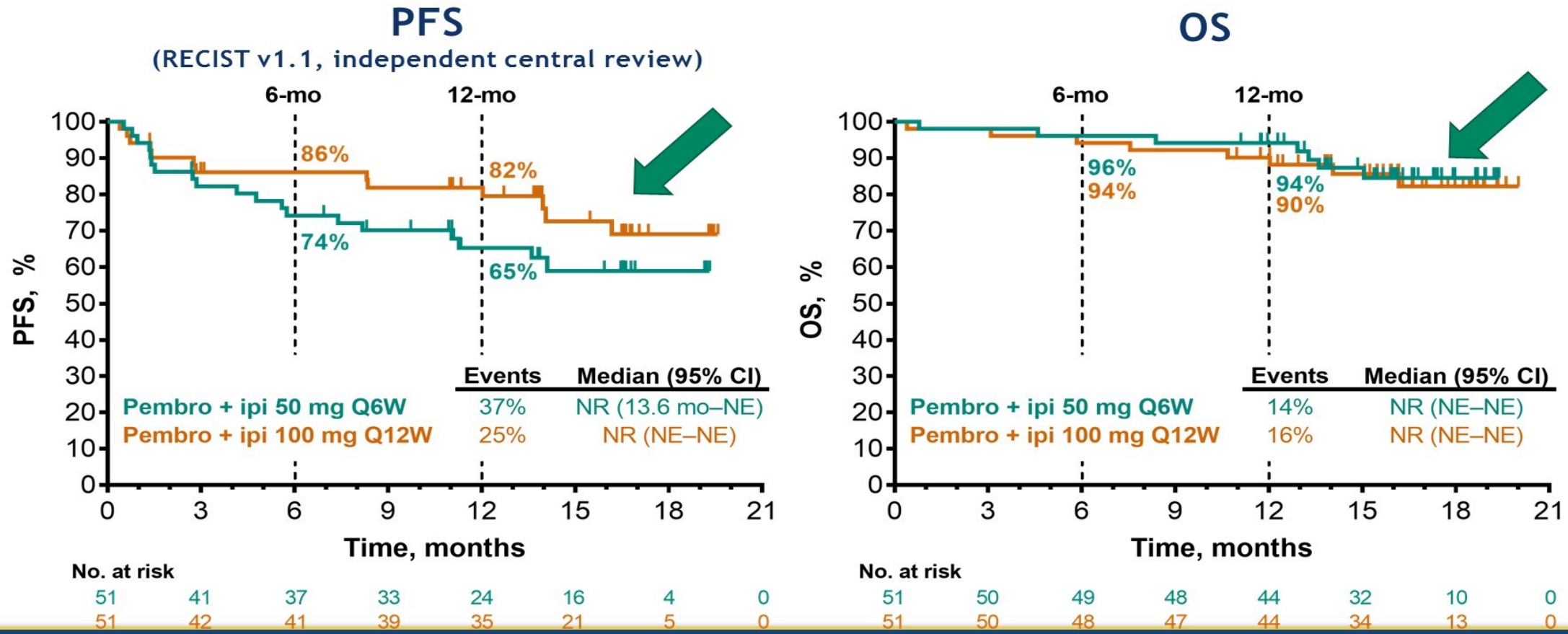
- **Primary end points:** grade 3-5 treatment-related AE rate and ORR[a]
- **Secondary end points:** PFS,[a] DOR,[a] OS

Change from Baseline in Target Lesions
(RECIST v1.1, Independent Central Review)

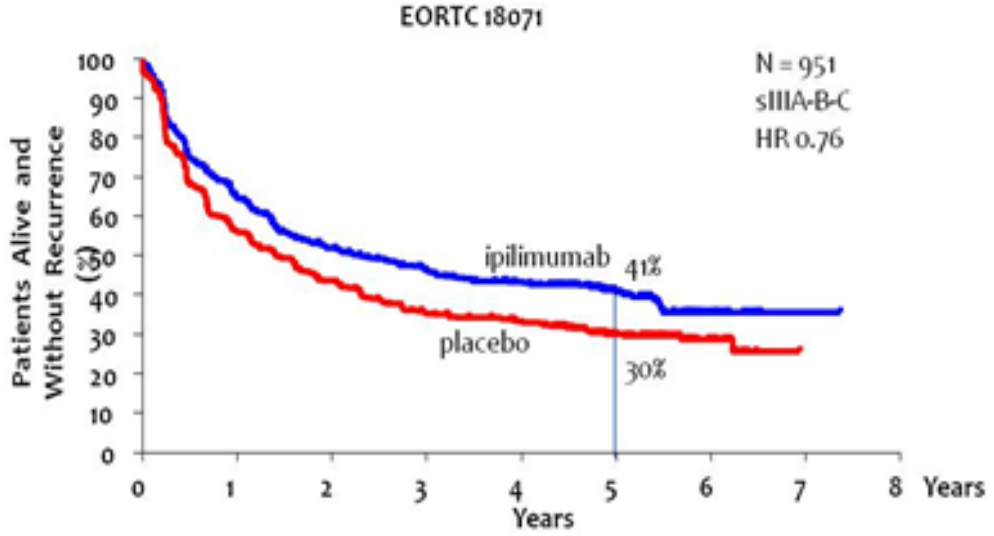


Presented By Douglas Johnson at 2019 ASCO Annual Meeting

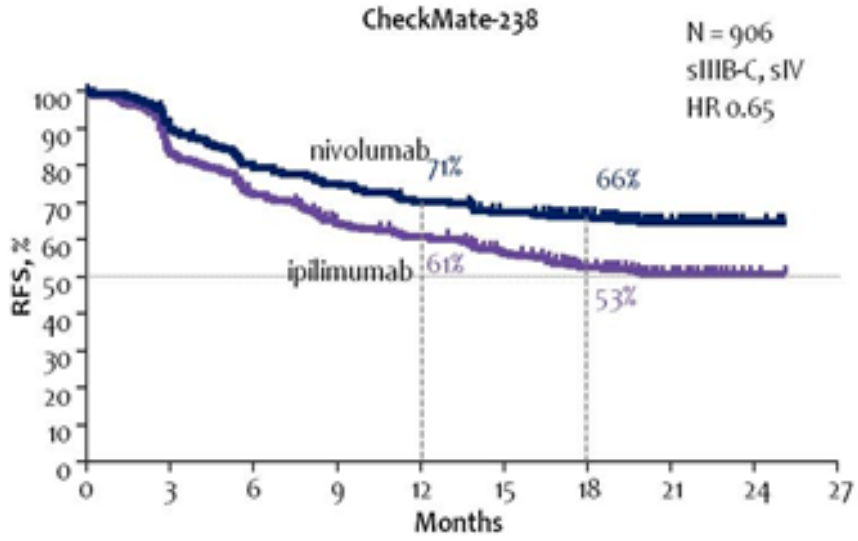
Kaplan-Meier Survival Estimate



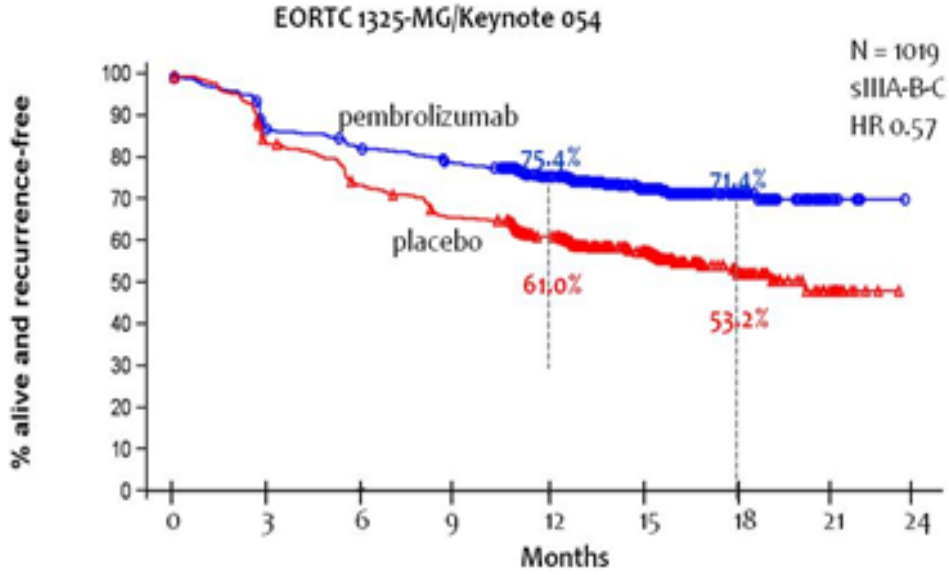
Adjuvant immunotherapy in melanoma



Eggermont *et al.* NEJM 2016



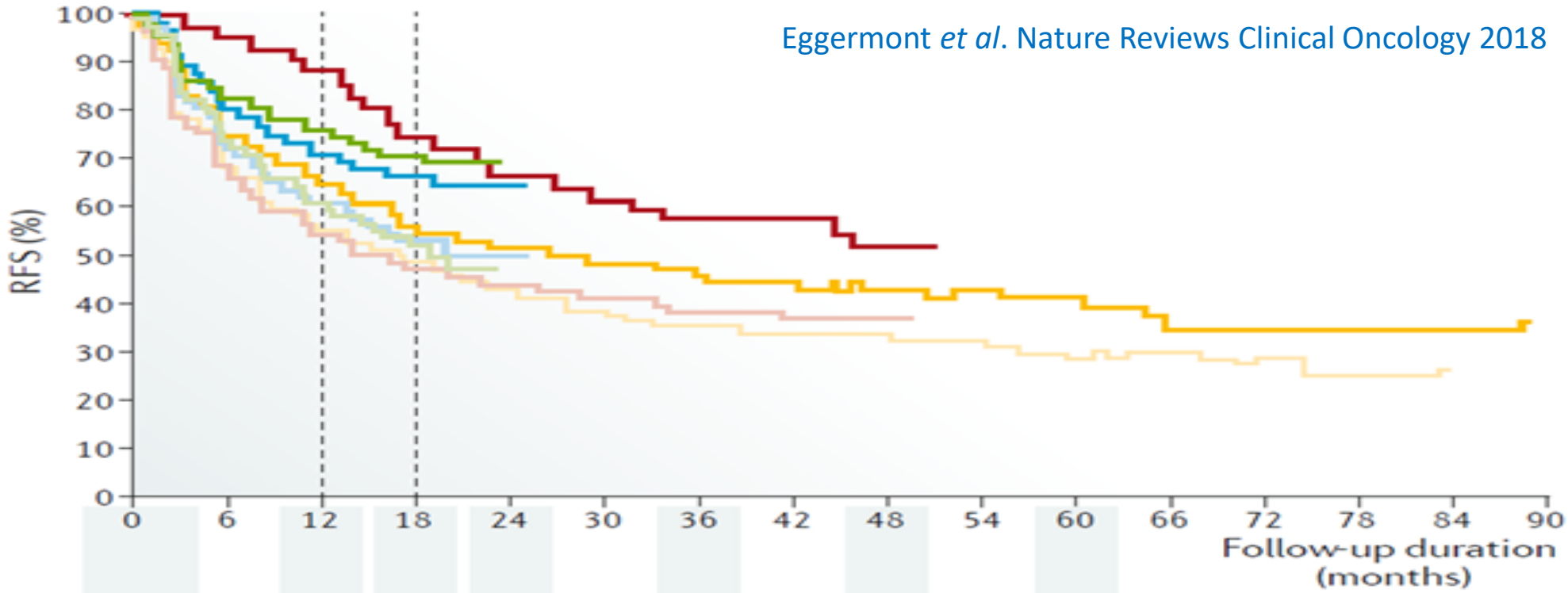
Weber *et al.* NEJM 2017



Eggermont *et al.* AACR 2018

KM-curves of estimated RFS in adjuvant trials for melanoma

Eggermont *et al*. Nature Reviews Clinical Oncology 2018



Placebo (EORTC 18071)	100%	56%	49%	–	–	–	30%	HR 0.76, 95% CI 0.64–0.89
Ipilimumab (EORTC 18071)	100%	65%	57%	–	–	–	41%	
Placebo (COMBI-AD)	100%	56%	49%	44%	39%	–	–	HR 0.47, 95% CI 0.39–0.58
Dabrafenib + trametinib (COMBI-AD)	100%	88%	73%	67%	58%	–	–	
Ipilimumab (CheckMate 238)	100%	61%	53%	–	–	–	–	HR 0.65, 97.6% CI 0.51–0.83
Nivolumab (CheckMate 238)	100%	71%	66%	–	–	–	–	
Placebo (KEYNOTE-054)	100%	61%	53%	–	–	–	–	HR 0.57, 98.4% CI 0.43–0.74
Pembrolizumab (KEYNOTE-054)	100%	75%	71%	–	–	–	–	

Modern melanoma NST trials

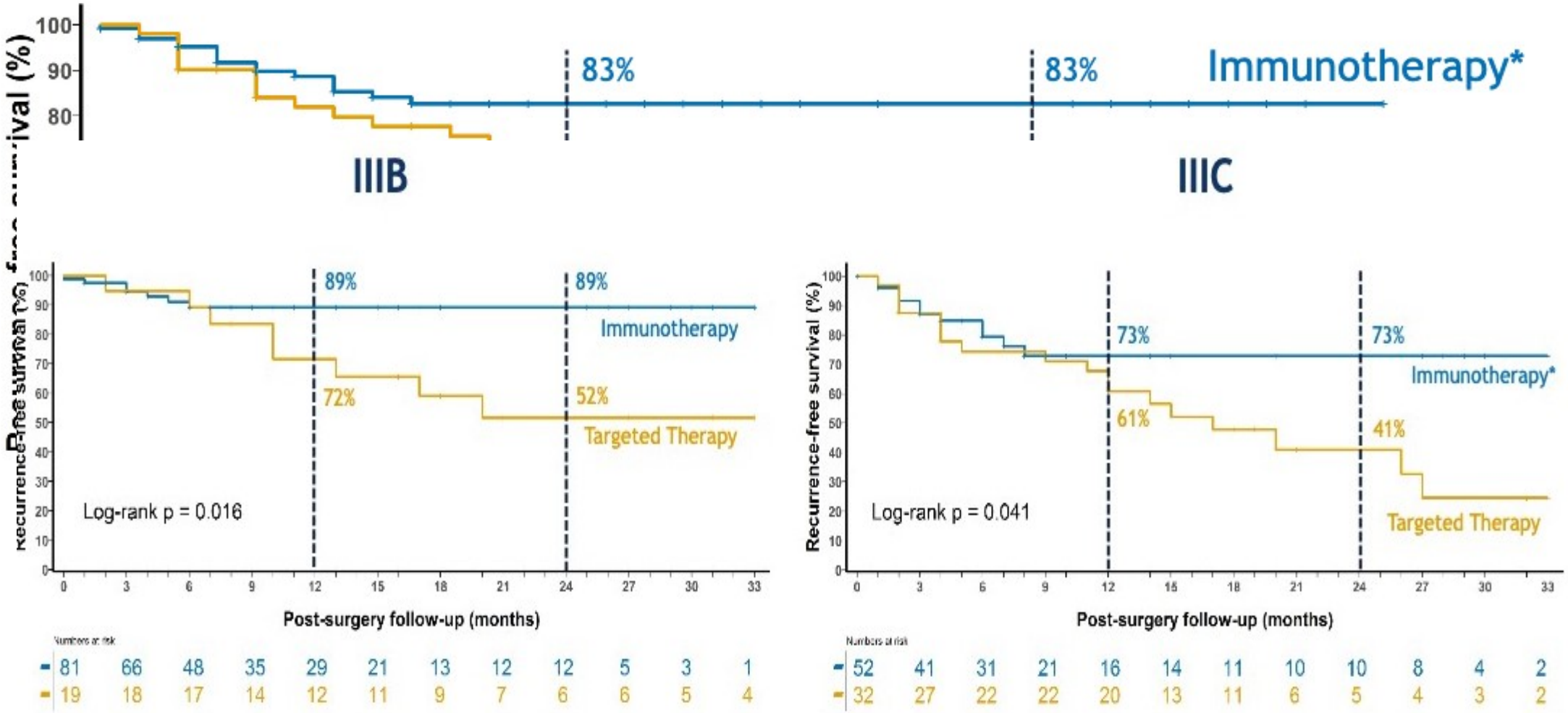
Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	Dab/Tram	21	58	19.7	18.6
Long Lancet Oncol 2019*	Dab/Tram	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019*	Ipi+nivo	86	57^	NR	8.3

* In press

^arm B = I1N3

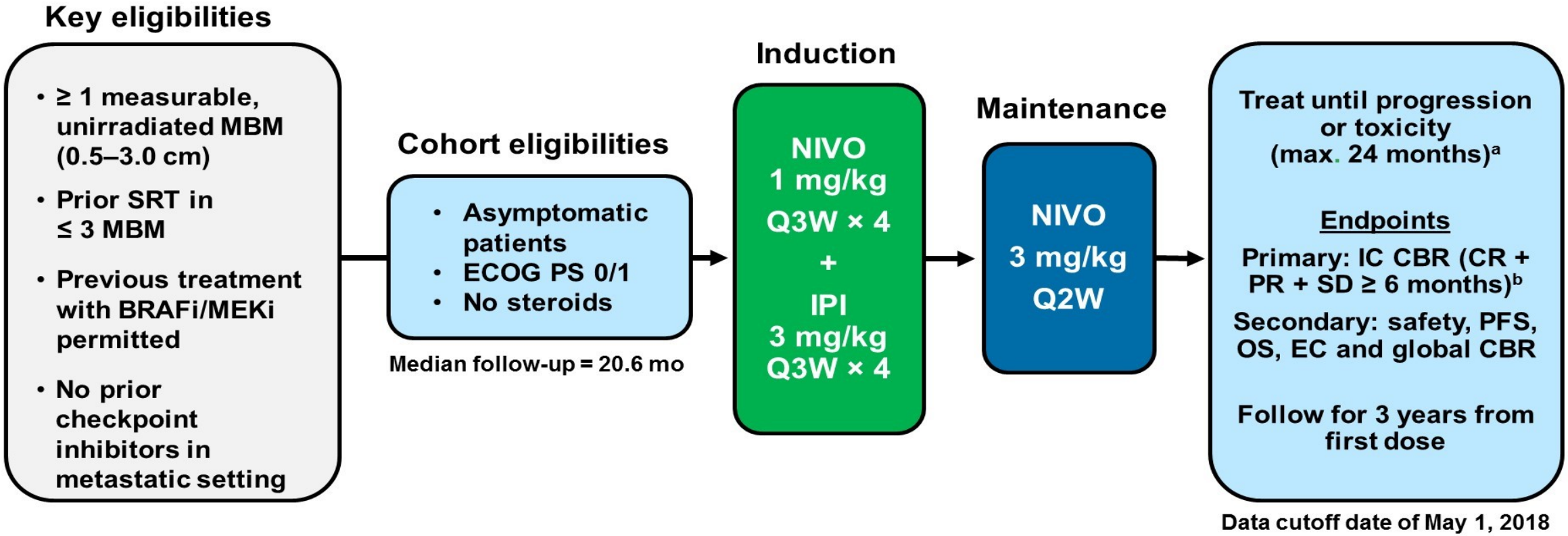
AM.Menzies et al ASCO 2019

RFS by drug class



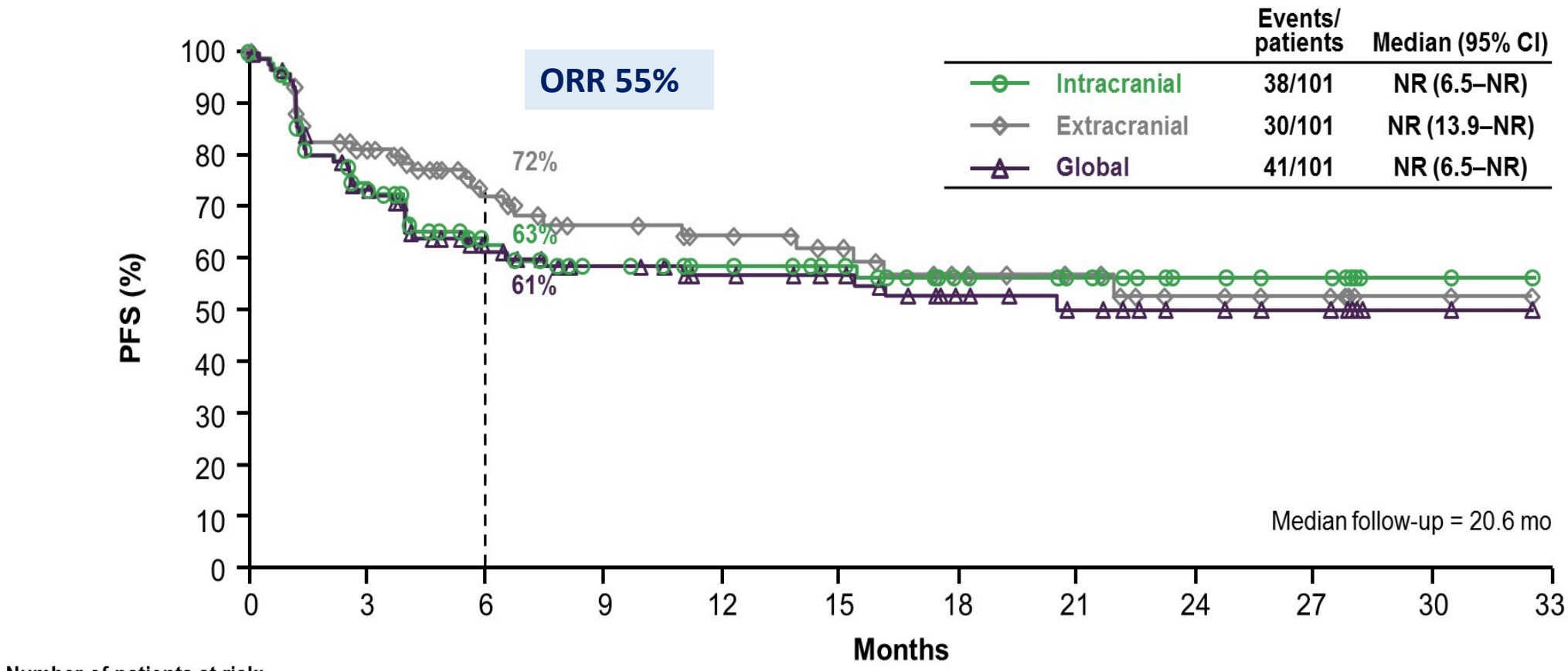
AM.Menzies et al ASCO 2019

CheckMate 204 Study Design

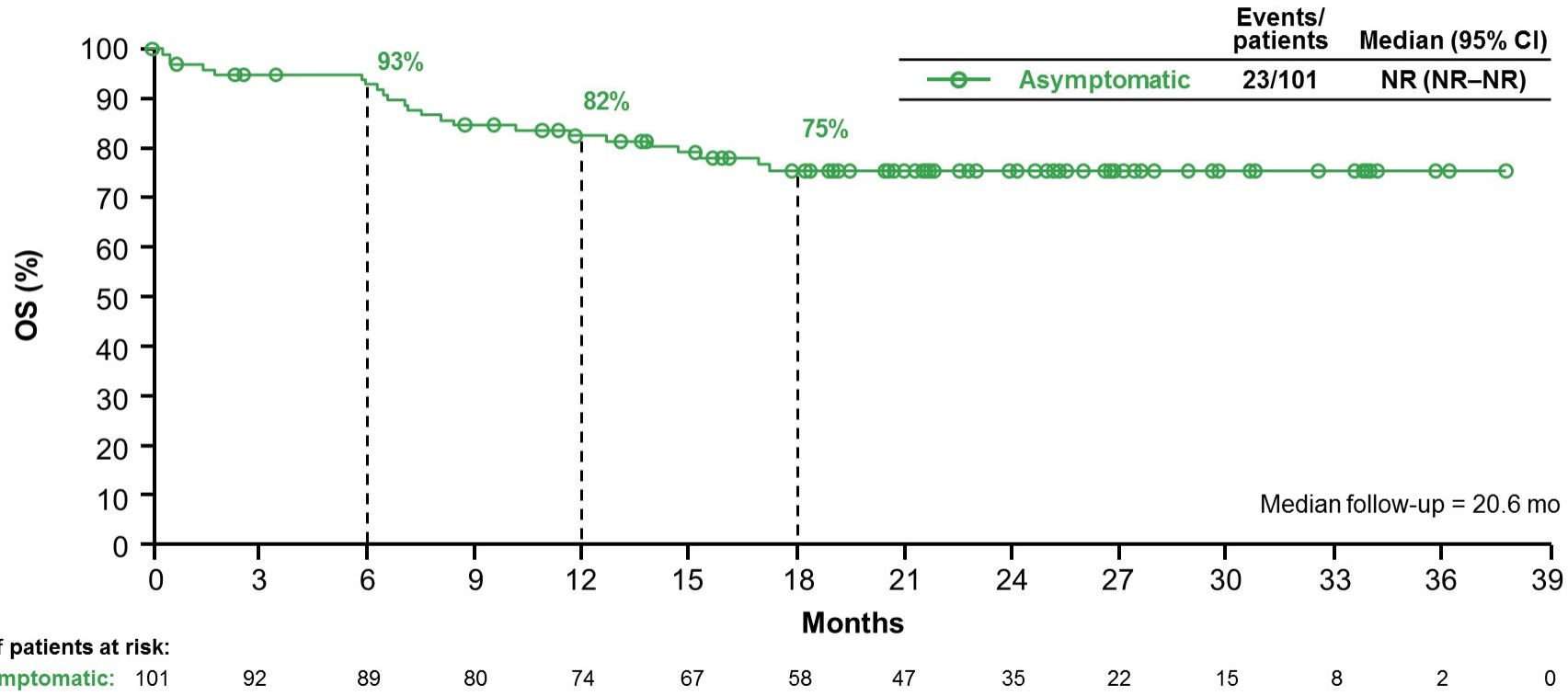


CBR, clinical benefit rate; CR, complete response; EC, extracranial; IC, intracranial; MBM, melanoma brain metastases; PR, partial disease; SD, stable disease; SRT, stereotactic radiosurgery.
[a]Patients with grade 3–4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved and all patients who discontinued proceeded to follow-up;
[b]Using modified RECIST v1.1.

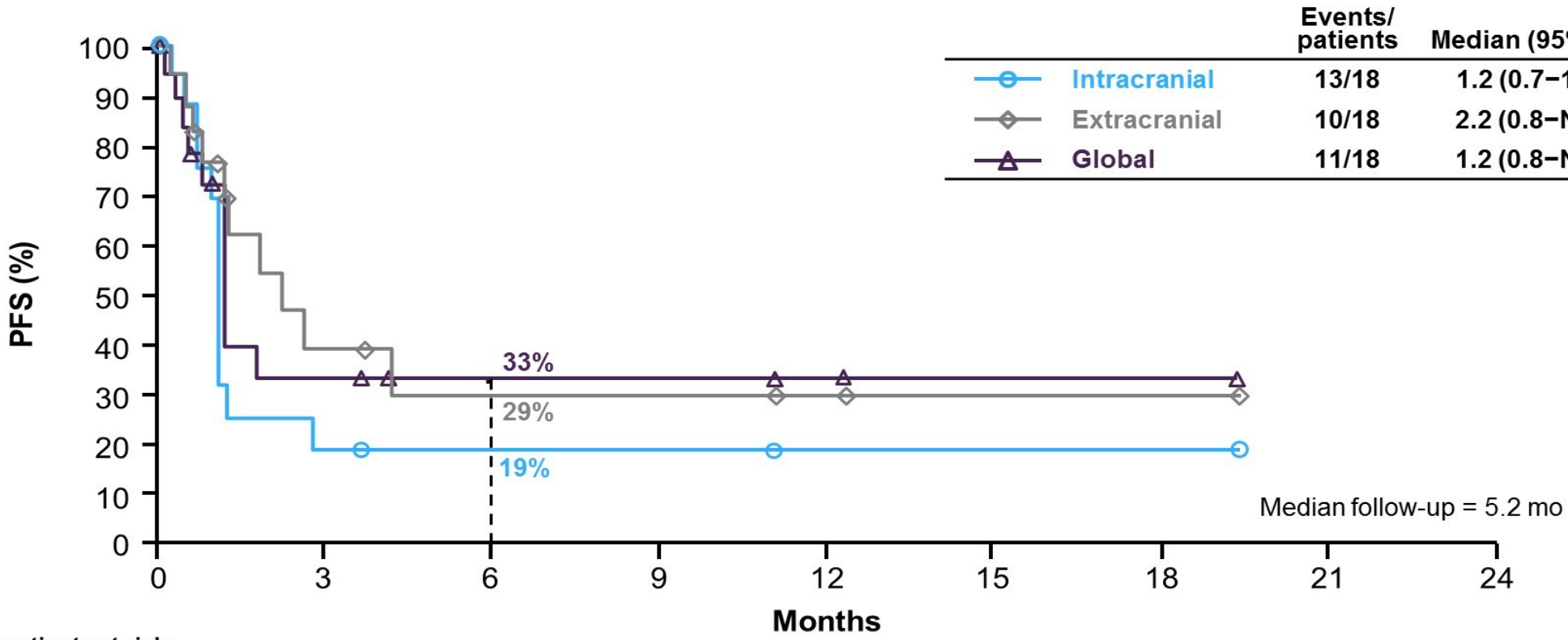
Progression-Free Survival – Asymptomatic Patients



Overall Survival – Asymptomatic Patients



Progression-Free Survival – Symptomatic Patients



	Events/ patients	Median (95% CI)
Intracranial	13/18	1.2 (0.7–1.3)
Extracranial	10/18	2.2 (0.8–NR)
Global	11/18	1.2 (0.8–NR)

Number of patients at risk:									
Intracranial:	18	3	2	2	1	1	1	0	0
Extracranial:	18	5	3	3	2	1	1	0	0
Global:	18	5	3	3	2	1	1	0	0

Depth of Response and Survival in Advanced or Metastatic Melanoma

Methods – Selection

- Randomized trial data in marketing applications to FDA between 2011 and 2018 evaluating drugs in patients with previously untreated advanced or metastatic melanoma
  - Excluded trials of intralesional therapies
- 10 randomized trials identified
  - Included 4826 patients who had not received prior therapy for metastatic disease
    - Excluded 102 patients who were not treated
    - Excluded 446 patients with incomplete assessments
- 4278 evaluable patients

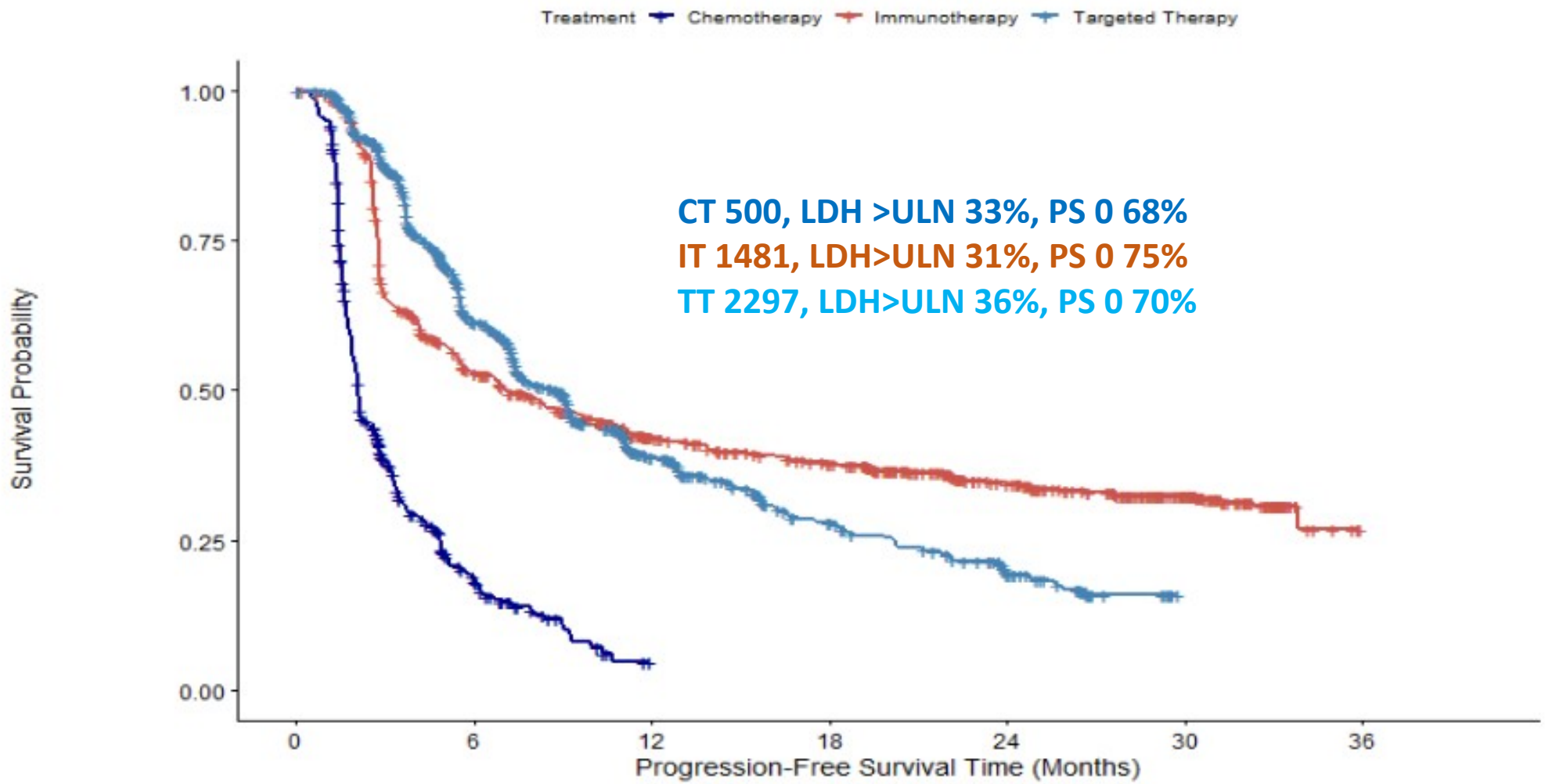
C.Osgood et al ASCO 2019

Depth of Response and Survival in Advanced or Metastatic Melanoma

C.Osgood et al ASCO 2019

Progression-Free Survival by Treatment Type

FDA

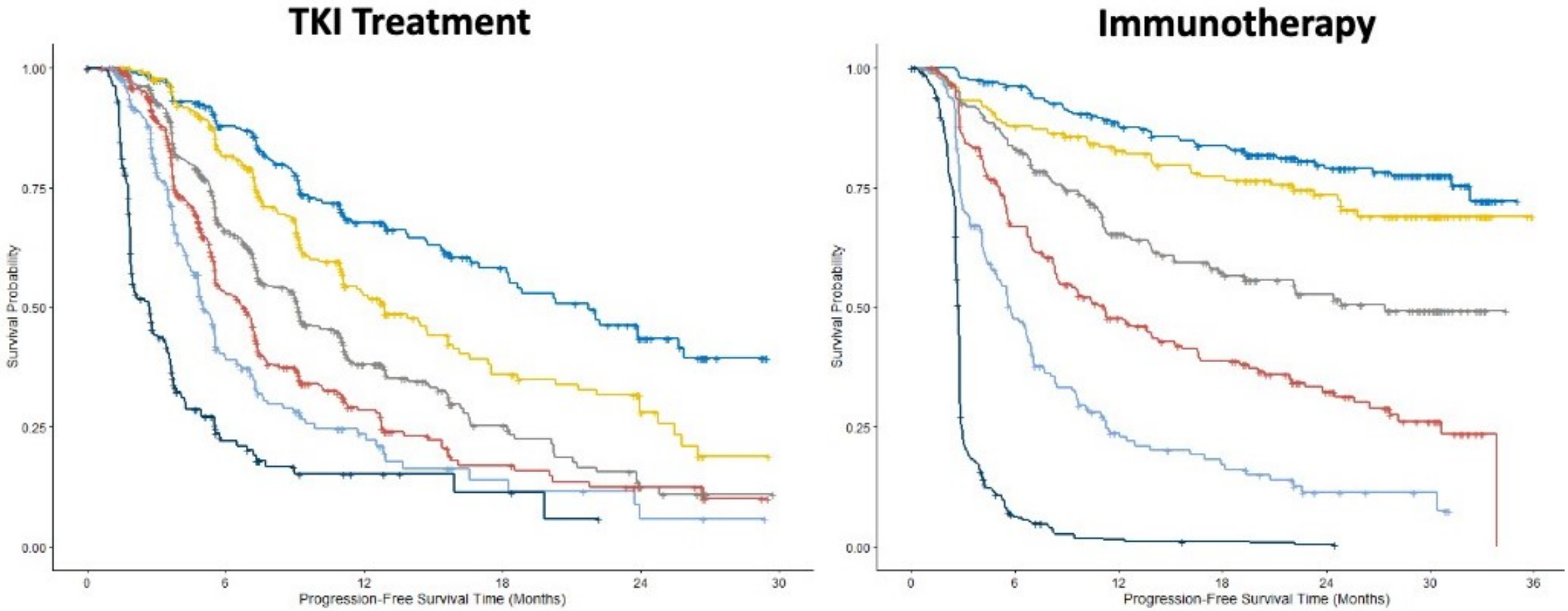


CT 500, LDH >ULN 33%, PS 0 68%

IT 1481, LDH>ULN 31%, PS 0 75%

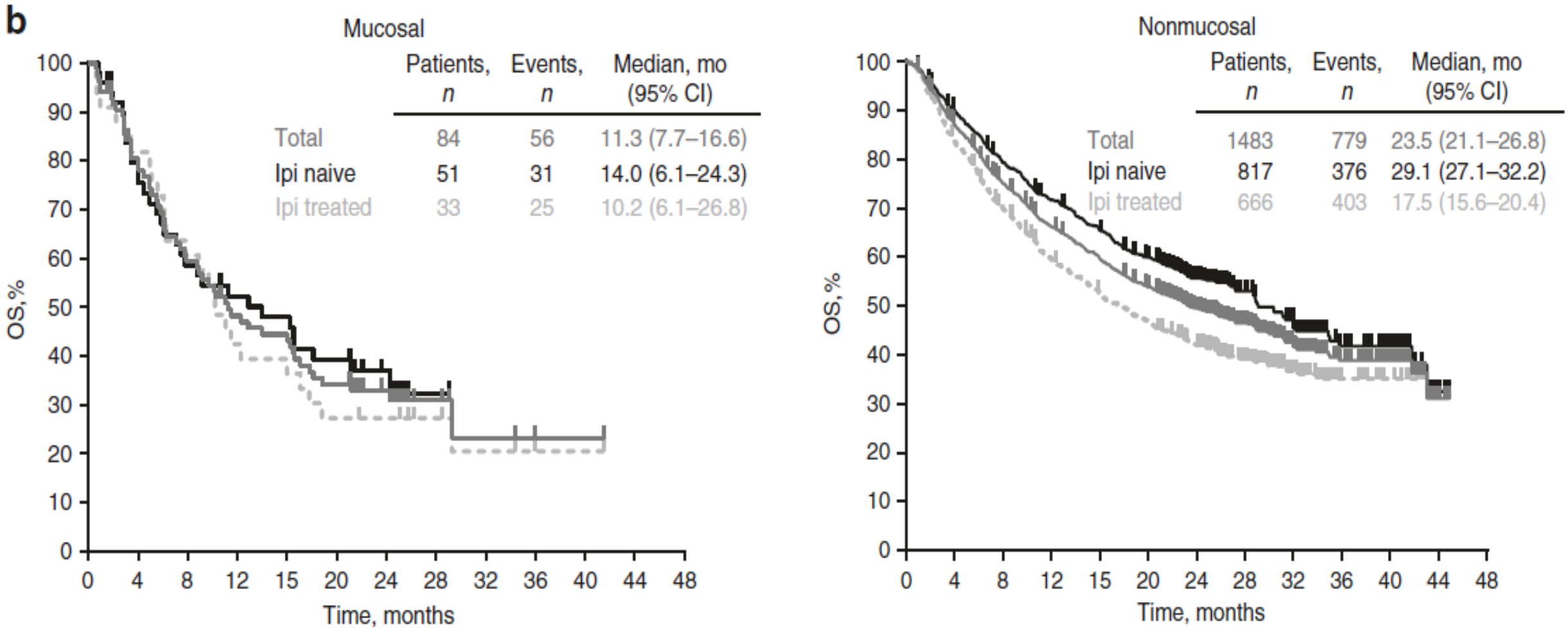
TT 2297, LDH>ULN 36%, PS 0 70%

Progression Free Survival by Reduction Category



C.Osgood et al ASCO 2019

Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006

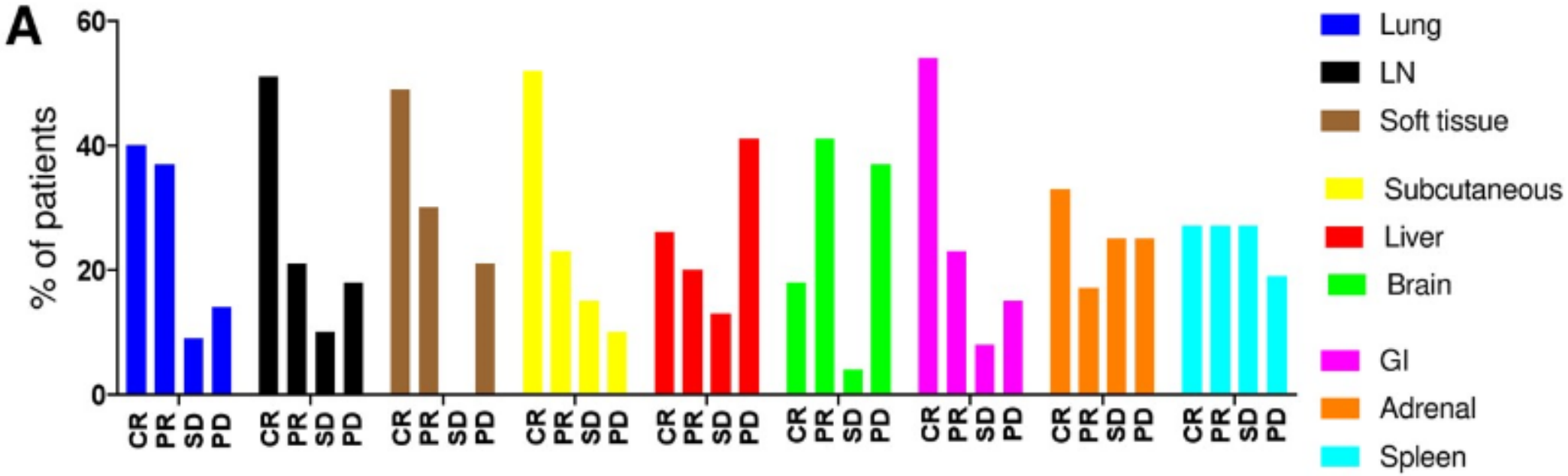


O.Hamid et al. BJC, 2019

Distinct patterns of response and toxicity by sites of metastases in patients treated with ipilimumab combined with PD-1 antibodies

Ines Pires da Silva[1,2], Serigne Lo[1], Maria Gonzalez[1], Alexander Guminski[1,3], Georgina V. Long[1,2,3], Alexander M. Menzies[1,2,3]
[1]Melanoma Institute Australia, Sydney, Australia; [2]University of Sydney, Sydney, Australia; [3]Royal North Shore and Mater Hospitals, Sydney, Australia

RESPONSE PER DISEASE SITE



ASCO 2018

Distinct patterns of response and toxicity by sites of metastases in patients treated with ipilimumab combined with PD-1 antibodies

Ines Pires da Silva[1,2], Serigne Lo[1], Maria Gonzalez[1], Alexander Guminski[1,3], Georgina V. Long[1,2,3], Alexander M. Menzies[1,2,3]
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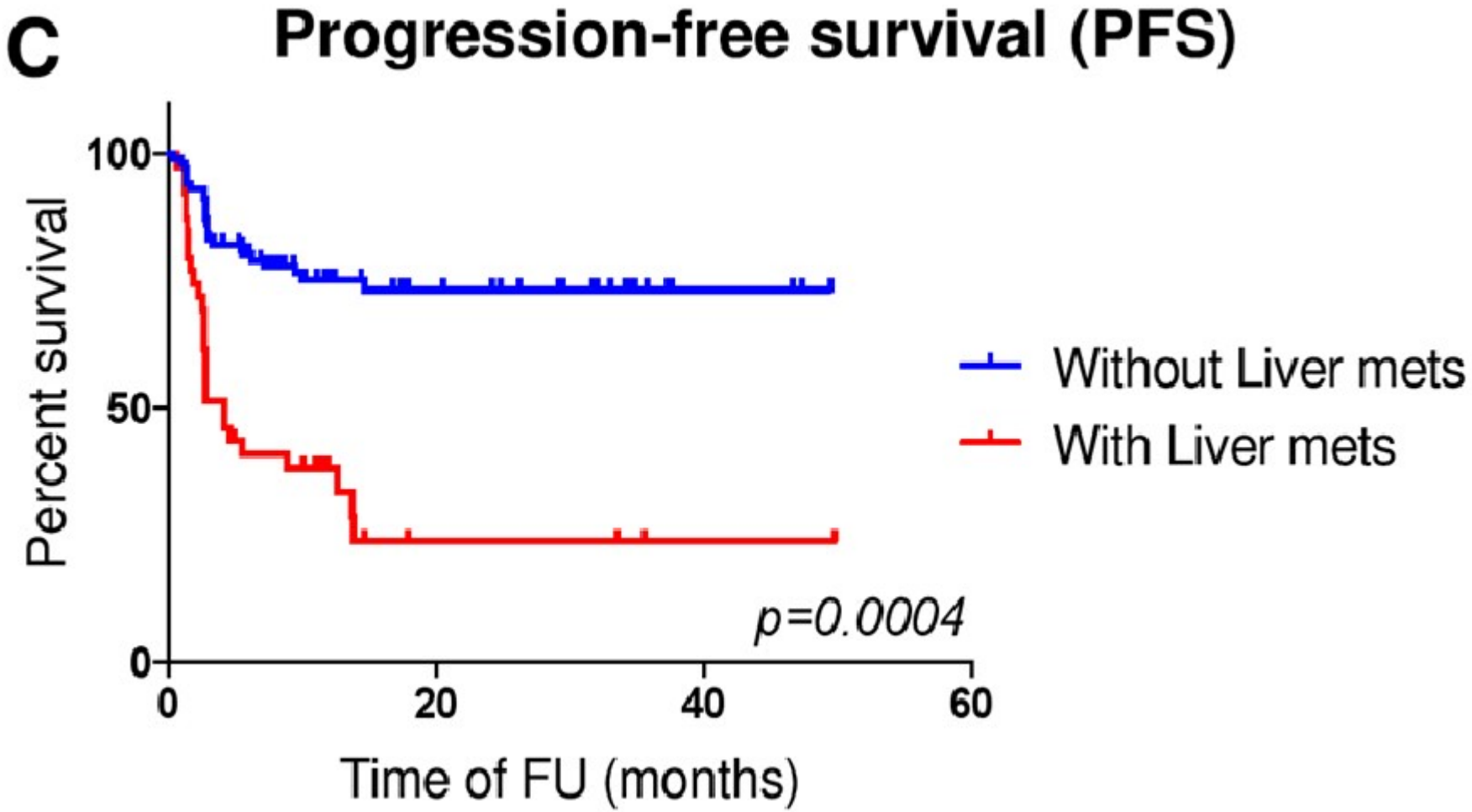
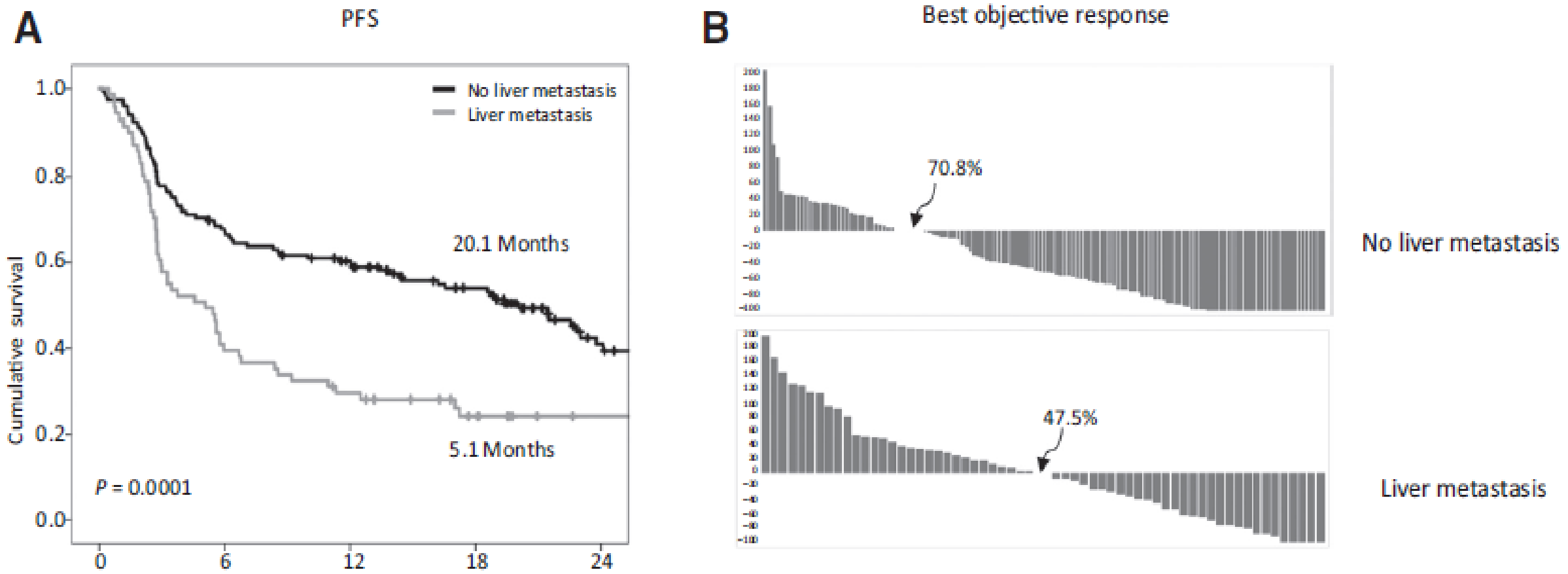


ASCO 2018

Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC

Paul C. Tumeh[1], Matthew D. Hellmann[2], Omid Hamid[3]

Cancer Immunology Research
2017



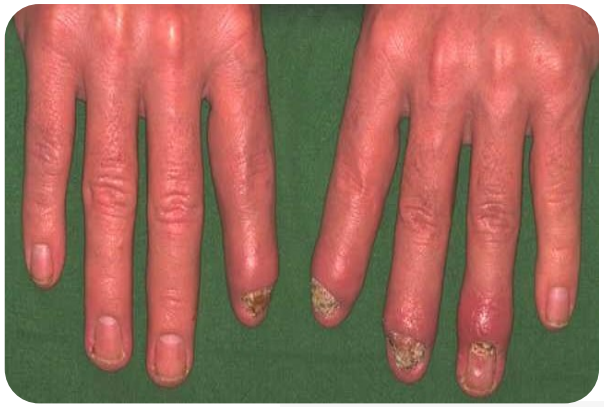
Melanoma cohort 223 pts treated with pembrolizumab

Impact of clinicopathological characteristics on survival in patients treated with ICI for metastatic melanoma (1598 pts CRT)

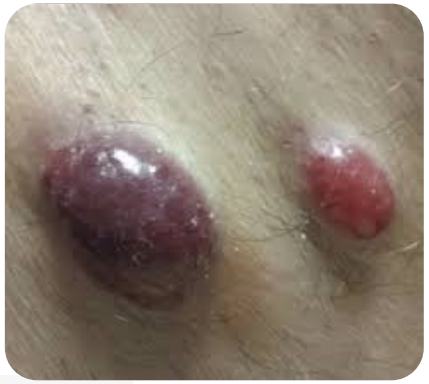
Characteristic	Overall survival HR	95% CI
female	0.84	0.69 -1.01
male	0.60	0.42-0.84
< 65 y-old	0.74	0.55-1.01
> 65 y-old	0.59	0.55-1.01
ECOG PS 0	0.64	0.38-1.06
ECOG PS1	0.75	0.60-0.94
M0/M1a/M1b	0.63	0.46-0.87
M1c	0.69	0.54-0.88
LDH <ULN	0.63	0.43-0.86
LDH>UNL	0.70	0.50-0.94

Bin Zhao et al. in press

The T cell Tug-of-war



PD1
CTLA4
TIM3
LAG3



Activation

TCR
CD28
ICOS
OX40
GITR
CD40L
CD137

Tolerance

Tumors with the higher frequency of responses to PD1-/PD-L1 Blockade

- Hodking' Lymphoma (PD-L1,PD-L2 overexpression/gene amplification)
- Merkel cell carcinoma (MCPyV Ags, and UV mutations)
- Cancers with MSI (high TML)
- Desmoplastic Melanoma (UV mutations)

2018 Nobel Prize in Medicine report

Key takeaway

- The relationship between tumor and host is complex and dynamic

- The hierarchy of prognostic factors is complex

- Some factors are fundamental:
  - immunogenic ags
  - specific CTL maturation and tumor circulation
  - HLA expression