The Ever-Evolving World of Melanoma Treatment

Jeffrey Sosman, MD

Adjuvant Therapy of Stage III Melanoma

Overview of key adjuvant checkpoint blockade trials

Combo Phase III

Checkmate 915: Phase III, 900 pts
- Ipi 1 + nivo vs nivo
- Population: stage IIIB – D[c], IV
- Endpoint: RFS
- Accrual completed
- Results expected in 12/2020

SWOG S1404: Phase III, 1378 pts
- Ipi 10 vs. pembro vs. HD IFN-α
- Population: stage IIIA (N2a) – C, IV
- Endpoint: OS/RFS in PD-L1+
- Accrual completed
- Results expected in 05/2020

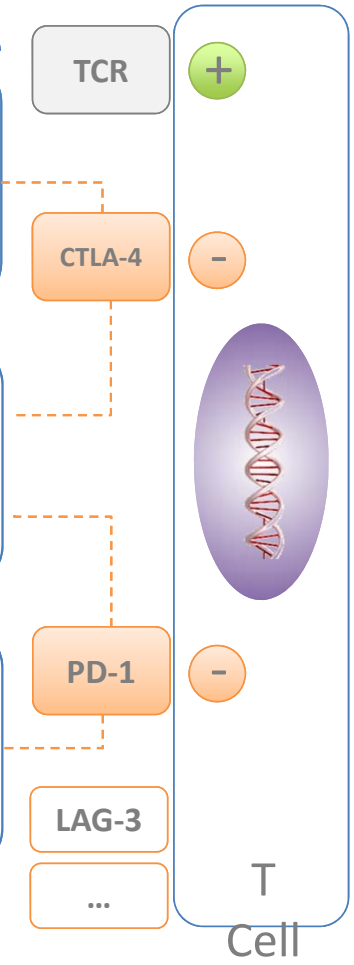
Checkmate-238[2]: Phase III, 800 pts
- Ipi 10 mg/kg vs nivo 3 mg/kg
- Population: stage III B-C, IV NED
- Endpoint: I, RFS; II, OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.65/NA

EORTC 1325[3,b]: Phase III, 1019 pts
- Pembro 200 mg vs placebo
- Population: stage III A[a]-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.57/NA

Single Agent Phase III

ECOG-1609[4]: Phase III, 1673 pts
- Ipi 10 vs ipi 3 vs HD INF-α2b
- Population: stage III B-C, IV M1a-b
- Endpoint: I, RFS & OS; II, QoL
- Adult accrual completed
- HR RFS/OS: 1.0[4]/NA

EORTC-18071[1]: Phase III, 951 pts
- Ipi 10 mg/kg vs placebo
- Population: stage III A[a]-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: 28 vs 17 / 87 vs NR
- HR RFS/OS: 0.75/0.72



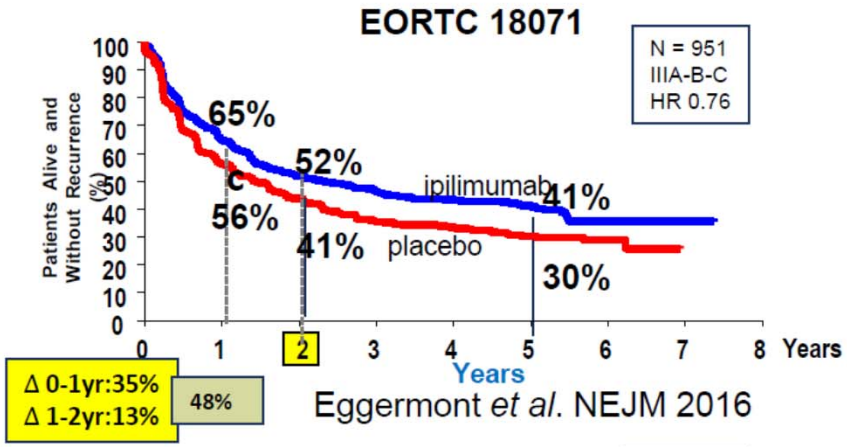
[1]Eggermont, *NEJM* 2016; [2]Weber, *NEJM* 2017; [3]Eggermont *NEJM* 2018; [4]Tarhini, ASCO 2017;Time in months, NA: Not Available, NR: Not Reached. [a] Excluding LN mets. < 1mm and in transit metastasis w/o nodal disease; [b] also Keynote-054; [c]AJCC

Comparison of stage subgroup eligibility criteria

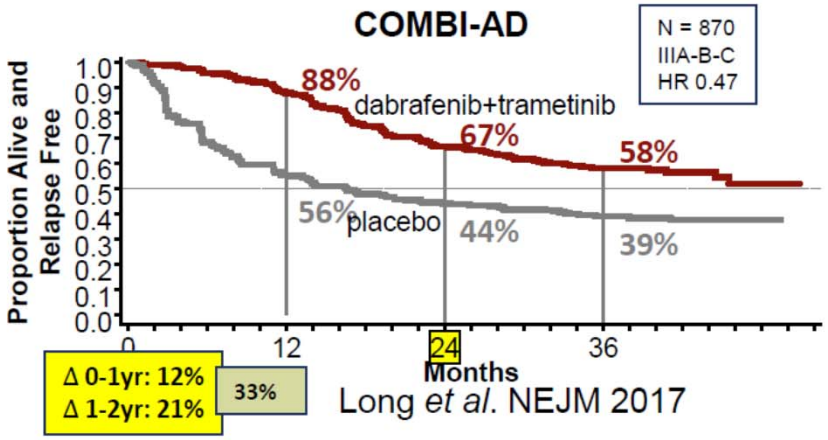
			Stage - AJCC 7th Edition (All patients NED)				
	Study	**Design**	**IIC**	**IIIA**	**IIIB**	**IIIC**	**IV**
EMA/FDA NA/11.15	EORTC 18071	Ipilimumab 10 versus placebo		✓ SN > 1mm	✓	✓ no in transit mets	
EMA/FDA 12.18/02.19	EORTC 1325	Pembrolizumab versus placebo		✓ SN > 1mm	✓	✓ no in transit mets	
	Checkmate 238	Ipilimumab 10 versus nivolumab			✓	✓	✓
EMA/FDA 07.18/12.17	ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b			✓	✓	✓ M1a-b
EMA/FDA 08.18/04.18	BRIM-8	Vemurafenib versus placebo	✓	✓ SN > 1mm	✓	✓	
	COMBI-AD	Dabrafenib + trametinib versus placebo		✓ SN > 1mm	✓	✓	

AJCC, American Joint Committee on Cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD INF-α2b, high-dose interferon-α2b; NED, no evidence of disease; SN sentinel node.

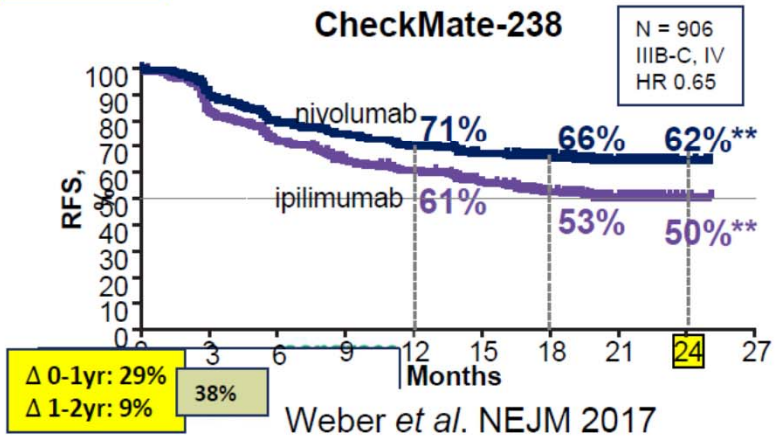
Key efficacy landmarks in the adjuvant setting of melanoma



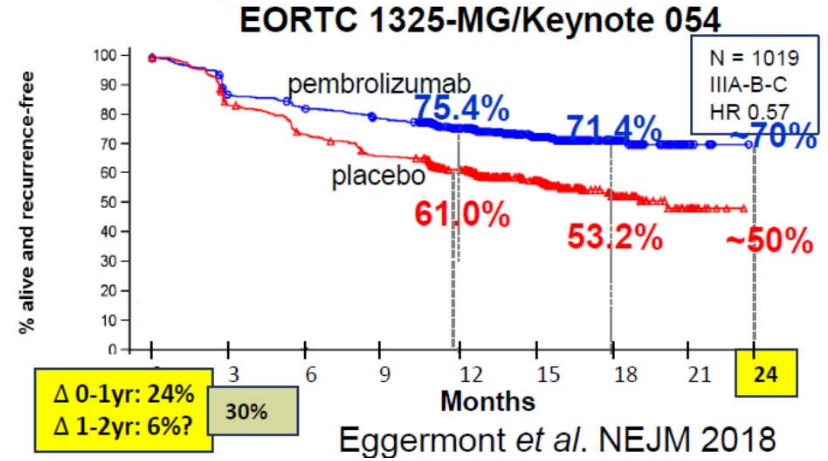
Eggermont *et al*. NEJM 2016



Long *et al*. NEJM 2017



Weber *et al*. NEJM 2017



Eggermont *et al*. NEJM 2018

Overview of PFS outcome per stage subgroup:

			Stage - AJCC 7th Edition (All patients NED)				
	Study	**Design**	**IIC**	**IIIA**	**IIIB**	**IIIC**	**IV**
EMA/FDA NA/11.15	EORTC 18071[1]	Ipilimumab 10 mg versus placebo		SN > 1mm, HR 0.98	HR 0.75	HR 1.00, 1-3 n HR 0.48, ≥ 4 n	
EMA/FDA 12.18/02.19	EORTC 1325[2]	Pembrolizumab versus placebo		SN > 1mm, HR 0.38	HR 0.58	HR 0.58	
	Checkmate 238[3]	Ipilimumab 10 versus nivolumab			HR 0.68	HR 0.68	HR 0.66 M1a/b, *HR 0.78 M1c*[2]
EMA/FDA 07.18/12.17	ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b			HR NA	HR NA	M1a-b, HR NA
EMA/FDA 08.18/04.18	BRIM-8[4]	Vemurafenib versus placebo	HR 0.0-NE	SN > 1mm, HR 0.52	HR 0.63	HR 0.8	
	COMBI-AD[5]	Dabrafenib + trametinib versus placebo		SN > 1mm, HR 0.44	HR 0.50	HR 0.45	

BARCELONA 2019 ESMO congress

Data not randomized head to head, should not be compared directly;

[1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM*

Adjuvant in melanoma: important data are still missing!

			Efficacy data		
	Study	**Design**	**HR RFS**	**HR DMFS**	**HR OS**
EMA/FDA NA/11.15	EORTC 18071[1]	Ipilimumab 10 mg versus placebo	0.76	0.76	0.72
EMA/FDA 12.18/02.19	EORTC 1325[2]	Pembrolizumab versus placebo	0.57	*0.53*[6]	NA
	Checkmate 238[3]	Ipilimumab 10 versus nivolumab	0.65	*0.73*[7]	NA
EMA/FDA 07.18/12.17	ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b	1.0	NA	NA
	BRIM-8[4]	Vemurafenib versus placebo	0.54 (IIC-IIIB) 0.8 (IIIC)	NA	NA
EMA/FDA 08.18/04.18	COMBI-AD[5]	Dabrafenib + trametinib versus placebo	0.47	0.51	0.57

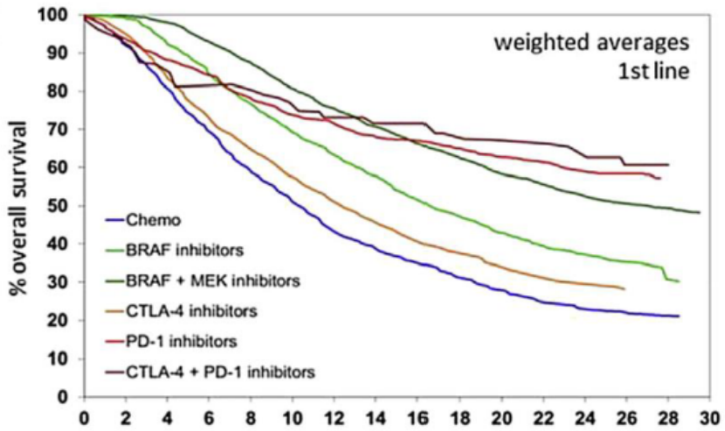
Stage III patients from these trials were required to have complete lymph node dissection!

How do we integrate those results in a post MSLT-2/ DeCOG[8,9] trial era?

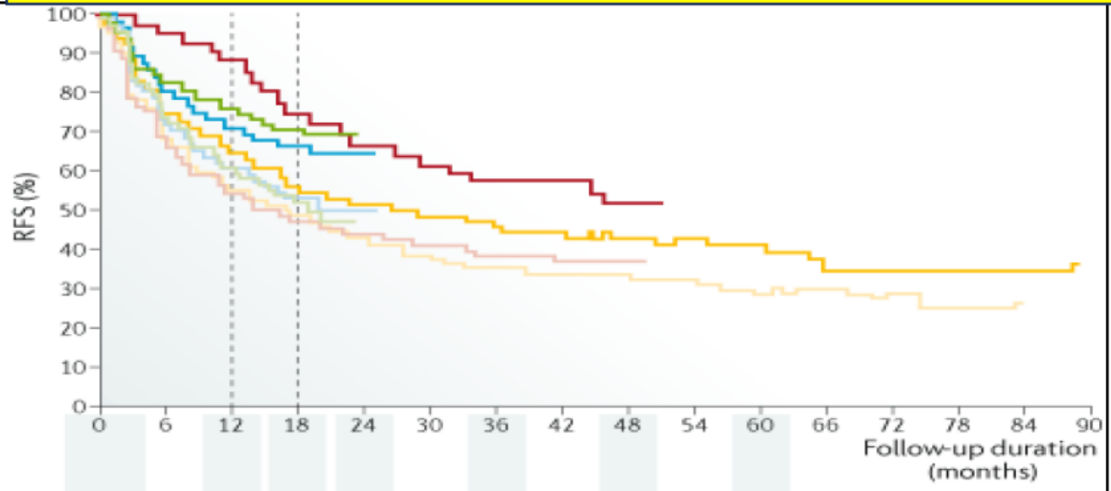
[1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM* 2017; [4]Maio, Lancet Oncol 2018; [5]Long, *NEJM* 2017;
[6]Preliminary, Eggermont, AACR 2018; [7]Exploratory; [8]Faries, NEJM 2017; [9]Leiter, Lancet 2016; Time in months;

Data not randomised head to head, should not be compared directly
DMFS, distant metastasis-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD INF-α2b, high-dose interferon-α2b; NA, not available

Ugurel S et al. Eur J Cancer 2017



Eggermont A, Robert C, & Ribas A *Nat Rev Clin Oncol* 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%	–	–	–	–	

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

BARCELONA 2019 ESMO congress

Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III/IV Melanoma: 3-Year Efficacy and Biomarker Results From the Phase 3 CheckMate 238 Trial

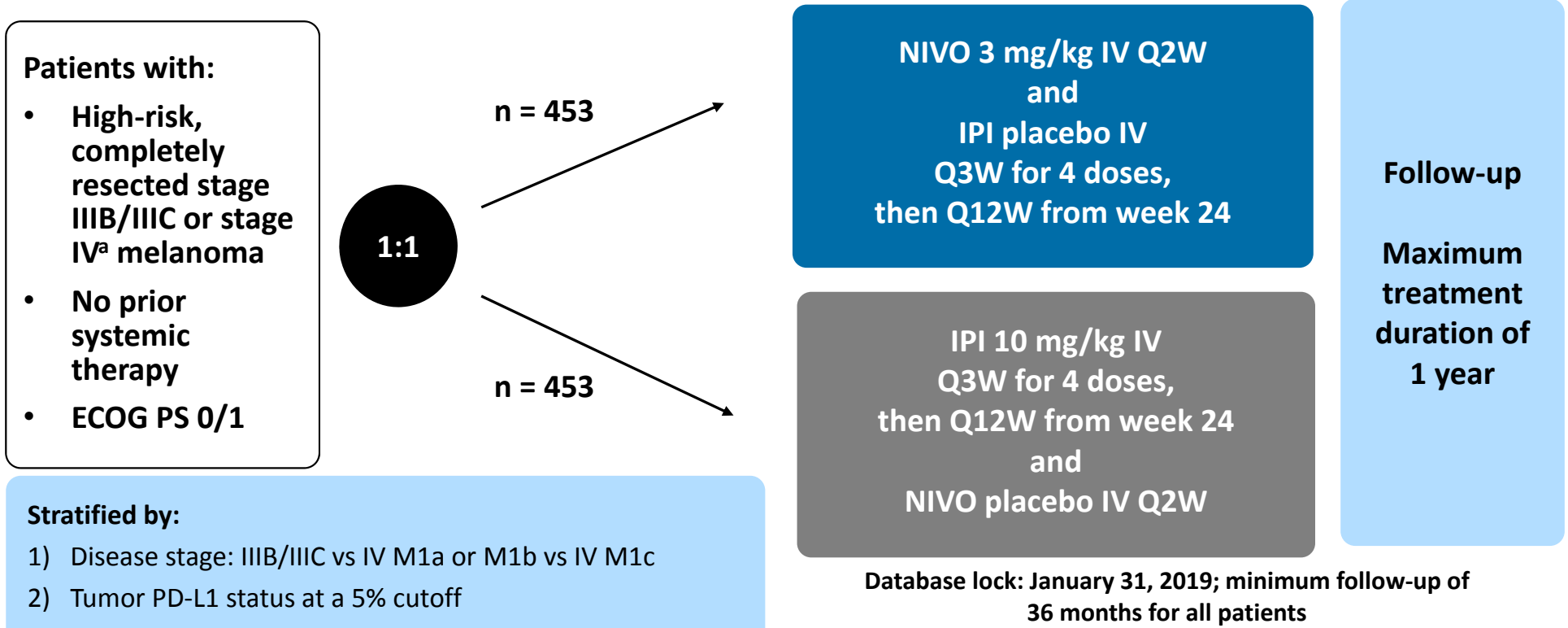
Jeffrey Weber,[1] Michele Del Vecchio,[2] Mario Mandala,[3] Helen Gogas,[4] Ana M. Arance,[5] Stéphane Dalle,[6] C. Lance Cowey,[7] Michael Schenker,[8] Jean-Jacques Grob,[9] Vanna Chiarion-Sileni,[10] Iván Márquez-Rodas,[11] Marcus Butler,[12] Michele Maio,[13] Hao Tang,[14] Abdel Saci,[14] Veerle de Pril,[14] Maurice Lobo,[14] James Larkin,[15]* Paolo A. Ascierto[16]*

[1]NYU Perlmutter Cancer Center, New York, NY, USA; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Papa Giovanni XIII Hospital, Bergamo, Italy; [4]National and Kapodistrian University of Athens, Athens, Greece; [5]Hospital Clínic de Barcelona, Barcelona, Spain; [6]Hospices Civils de Lyon, Pierre Bénite, France; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [8]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [9]Hôpital de la Timone, Marseille, France; [10]Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; [11]General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [14]Bristol-Myers Squibb, Princeton, NJ, USA; [15]The Royal Marsden NHS Foundation Trust, London, UK; [16]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

*Contributed equally.

Abstract Number 2801

CheckMate 238: Study Design



Database lock: January 31, 2019; minimum follow-up of 36 months for all patients

- Primary endpoint: RFS

NCT02388906.[a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

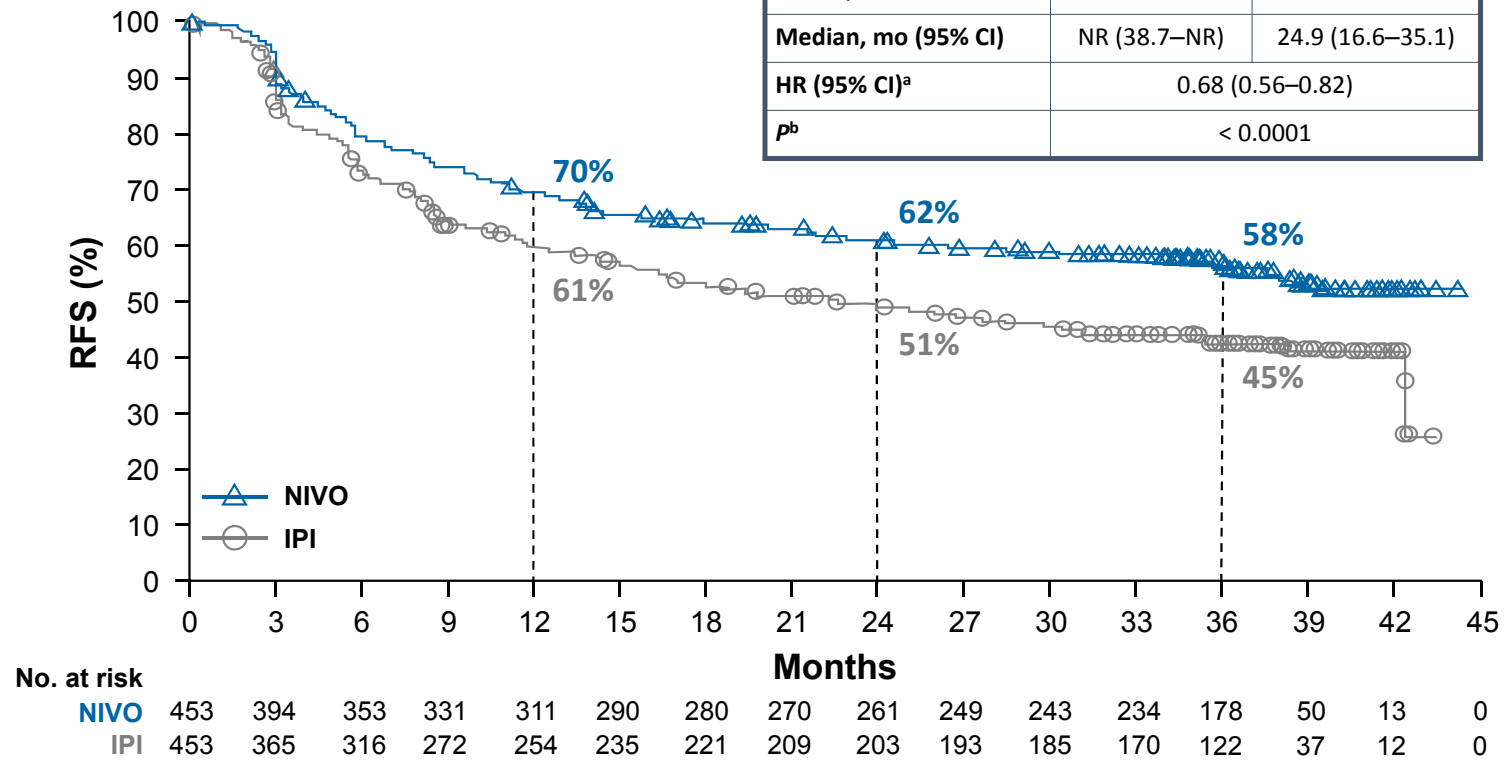
Baseline Patient Characteristics

	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
Tumor PD-L1 expression ≥ 5%,[a] %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91
Melanoma subtype, %		
Cutaneous	86	83
Mucosal	4	3
Acral	4	4

[a]PD-L1 IHC 28-8 pharmDx assay. LDH, lactate dehydrogenase; ULN, upper limit of normal.

Primary Endpoint: RFS in All Patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	188	239
Median, mo (95% CI)	NR (38.7–NR)	24.9 (16.6–35.1)
HR (95% CI)[a]	0.68 (0.56–0.82)	
***P*[b]**	< 0.0001	

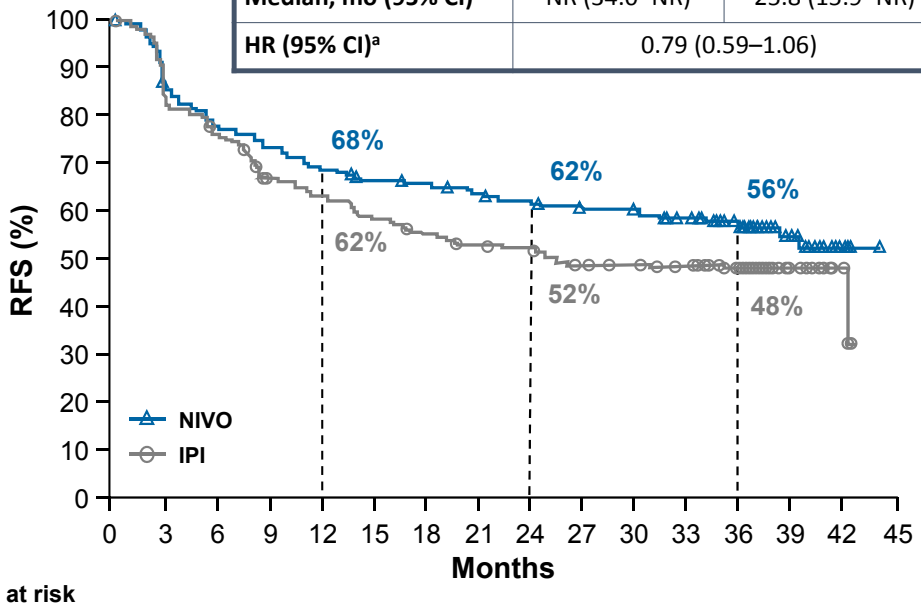


[a]Stratified; [b]Log-rank test. NR, not yet reached.

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

	NIVO (n = 187)	IPI (n = 194)
Events, n	82	98
Median, mo (95% CI)	NR (34.0–NR)	25.8 (15.9–NR)
HR (95% CI)[a]	0.79 (0.59–1.06)	

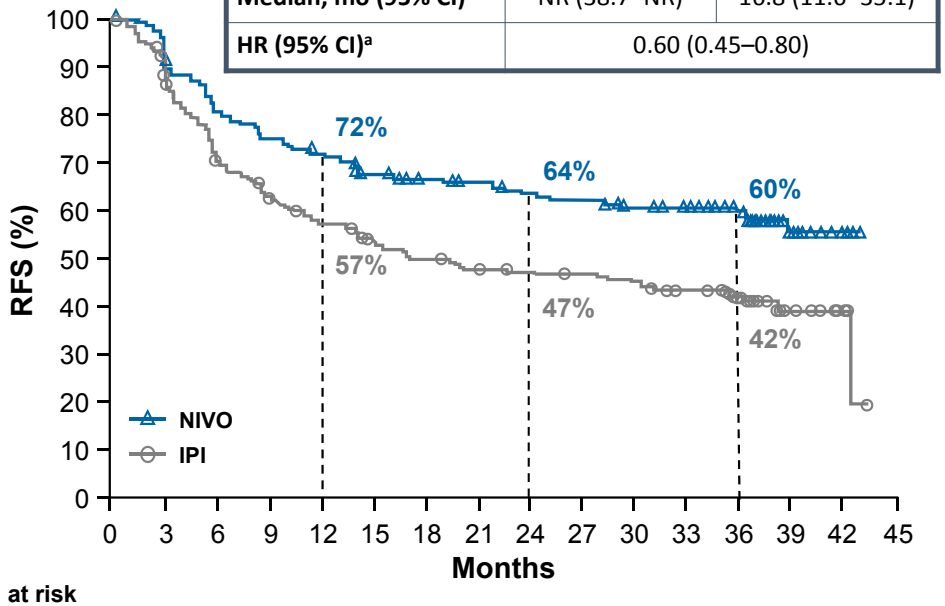


No. at risk

NIVO	187	157	142	135	126	120	118	113	109	103	102	96	76	26	8	0
IPI	194	156	143	119	113	105	98	93	91	84	82	78	62	19	5	0

BRAF Wild-type

	NIVO (n = 197)	IPI (n = 212)
Events, n	79	117
Median, mo (95% CI)	NR (38.7–NR)	16.8 (11.6–35.1)
HR (95% CI)[a]	0.60 (0.45–0.80)	



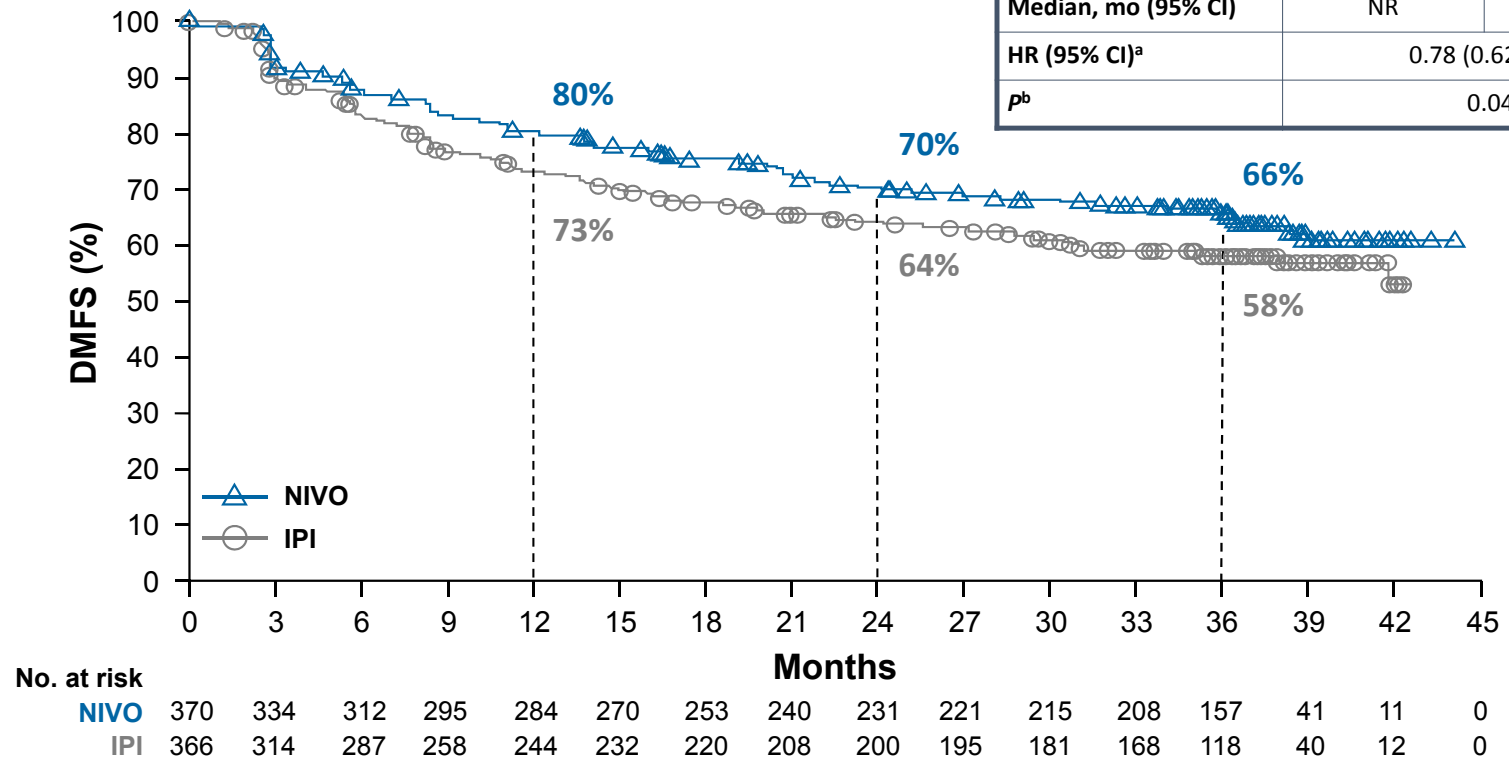
No. at risk

NIVO	197	172	154	144	137	126	119	116	111	108	103	100	75	18	3	0
IPI	212	172	139	122	111	100	94	88	86	84	81	75	49	14	6	0

[a]Unstratified.

Exploratory Endpoint: DMFS in Stage III Disease

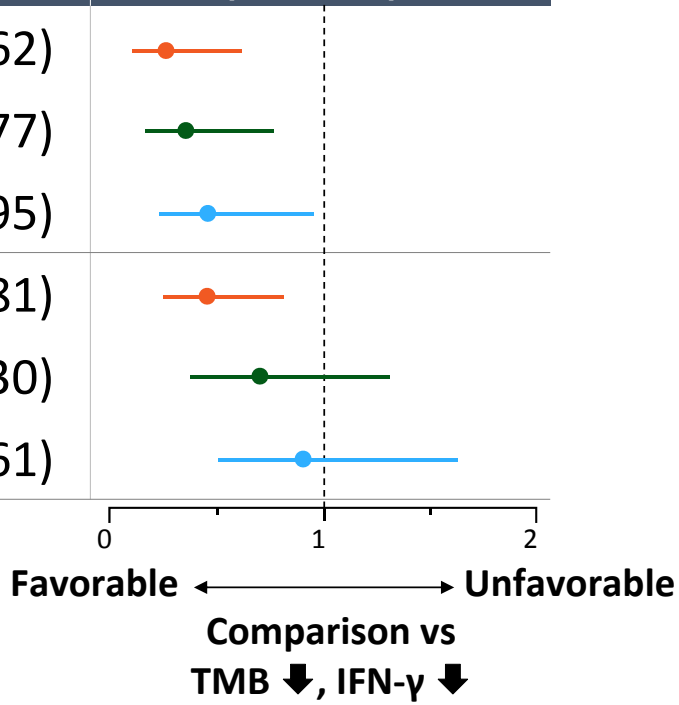
	NIVO (n = 370)	IPI (n = 366)
Events, n	126	144
Median, mo (95% CI)	NR	NR (41.8–NR)
HR (95% CI)[a]	0.78 (0.62–0.99)	
P[b]	0.044	



[a]Stratified; [b]Log-rank test.

Higher TMB and Tumor IFN-γ Expression Levels Correlate With Improved RFS With Both NIVO and IPI

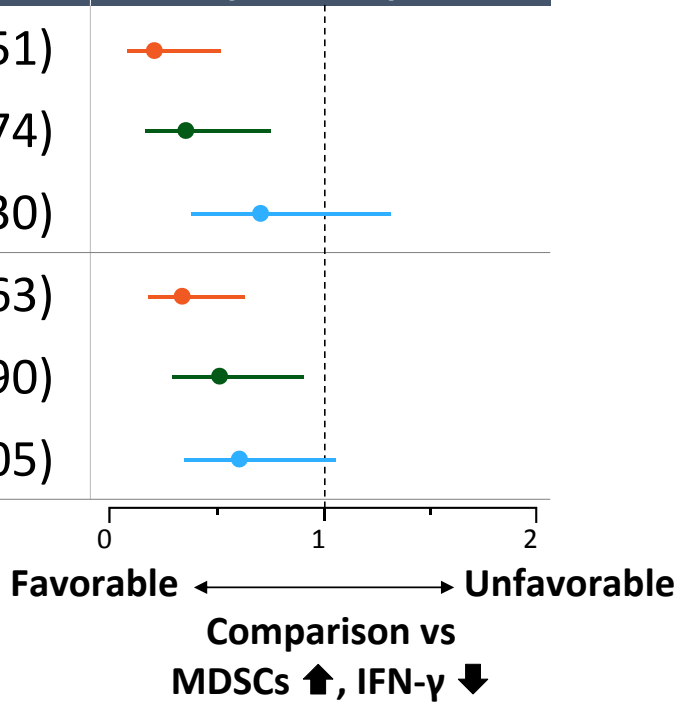
Treatment	TMB	IFN-γ	Unstratified HR (95% CI)[a]
NIVO	↑	↑	0.26 (0.11–0.62)
	↓	↑	0.35 (0.16–0.77)
	↑	↓	0.46 (0.22–0.95)
IPI	↑	↑	0.45 (0.25–0.81)
	↓	↑	0.70 (0.37–1.30)
	↑	↓	0.90 (0.50–1.61)



[a]Comparison vs TMB ↓, IFN-γ ↓.
↑, high biomarker level; ↓, low biomarker level.

Low MDSC Levels and High IFN-γ Expression May Correlate With Improved RFS With Both NIVO and IPI

Treatment	MDSCs	IFN-γ	Unstratified HR (95% CI)[a]
NIVO	↓	↑	0.20 (0.08–0.51)
	↑	↑	0.35 (0.16–0.74)
	↓	↓	0.70 (0.38–1.30)
IPI	↓	↑	0.33 (0.18–0.63)
	↑	↑	0.51 (0.29–0.90)
	↓	↓	0.60 (0.34–1.05)



[a]Comparison vs MDSCs ↑, IFN-γ ↓.
↑, high biomarker level; ↓, low biomarker level.

Summary

- Long-term (36-month) follow-up in CheckMate 238 demonstrated superior RFS with NIVO vs the active comparator IPI in patients with resected stage III/IV melanoma (HR = 0.68; 95% CI, 0.56–0.82; $P < 0.0001$)
  - NIVO continued to demonstrate a RFS benefit across most prespecified subgroups tested
  - These data further support the use of NIVO in resected stage III/IV melanoma
- Biomarker analyses demonstrated that high levels of TMB and tumor inflammation biomarkers and lower levels of peripheral suppressive immune cells, as well as combinations of these biomarkers, correlated with improved RFS with NIVO and IPI

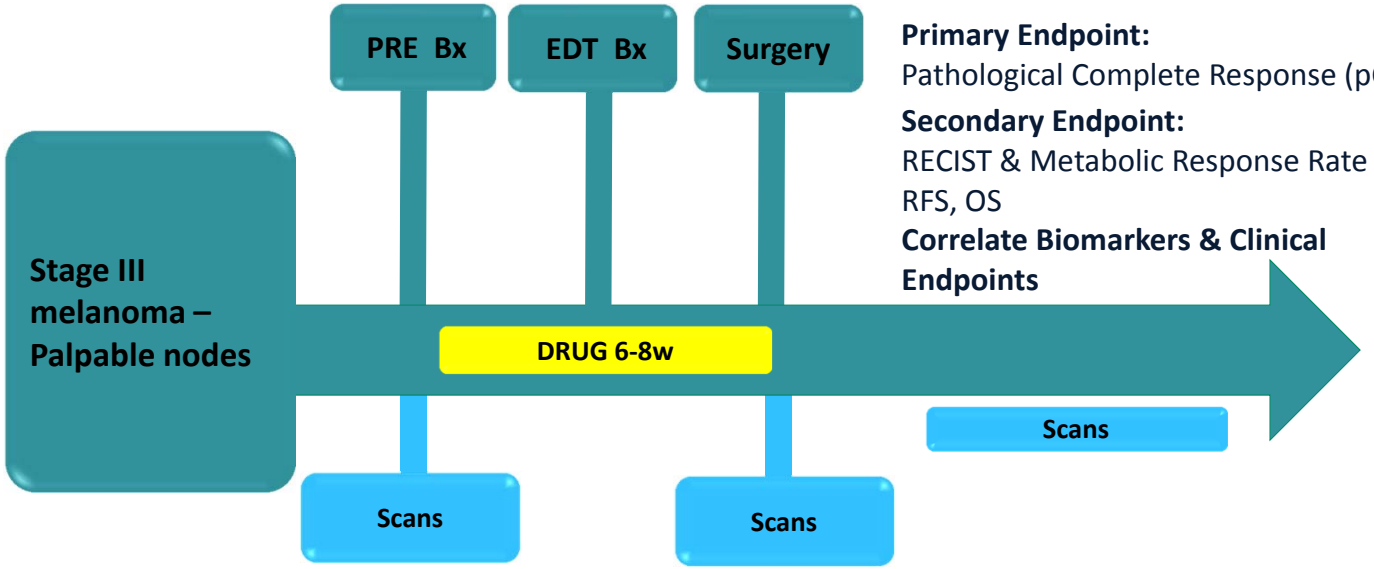
Neoadjuvant Therapy of High Risk Regional Melanoma

Melanoma needs neoadjuvant systemic therapy (NST)

- Survival remains poor even with adjuvant therapy
- Surgery can be morbid
- No current biomarkers to guide prognosis
- Need to better understand mechanisms of response and resistance

Neoadjuvant model is well suited for melanoma

- Prototype tumour for IO drug development
- Accessible tissue
- Rapid results



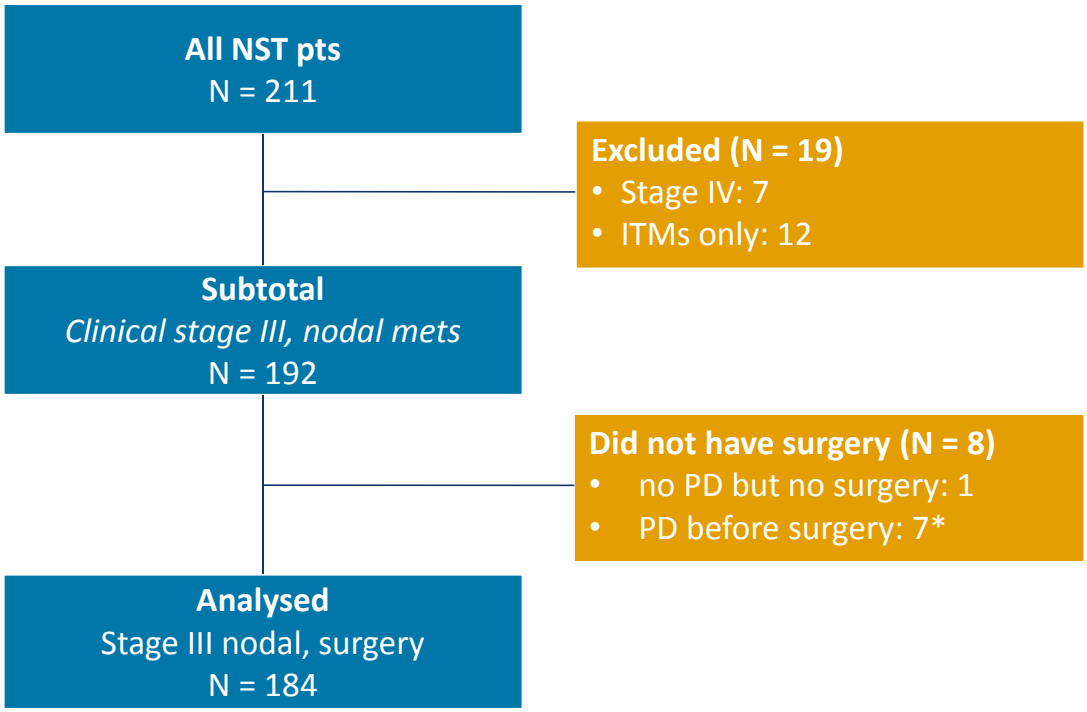
Slide adapted from Georgina Long

Modern melanoma NST trials

Trial	Population	Regimen	N
NCT02231775 Amaria et al Lancet Oncol 2018	Clincial stage III, resectable IV BRAF V600E/K	Dab/Tram x8w – surgery – Dab/Tram x44w	21
NCT01972347 Long et al Lancet Oncol 2019*	Clinical stage III BRAF V600 E/K	Dab/Tram x12w – surgery – Dab/Tram x40w	35
NCT02437279 Blank et al Nat Med 2018	Clinical stage III	I3N1 x2 – surgery – I3N1 x2	10
NCT02519322 Amaria et al Nat Med 2018	Clinical stage III, resectable IV	A: Nivo x4 – surgery – Nivo x13 B: I3N1 x3 – surgery – Nivo x13	A: 12 B: 11
NCT02434354 Huang et al Nat Med 2019	Clinical stage III, resectable IV	Pembro x1 – surgery – Pembro x17	30
NCT02977052 Rozeman et al Lancet Oncol 2019*	Clinical stage III	A: I3N1 x2 – surgery B: I1N3 x2 – surgery C: Ipi x2 – Nivo x2 – surgery	A: 30 B: 30 C: 26

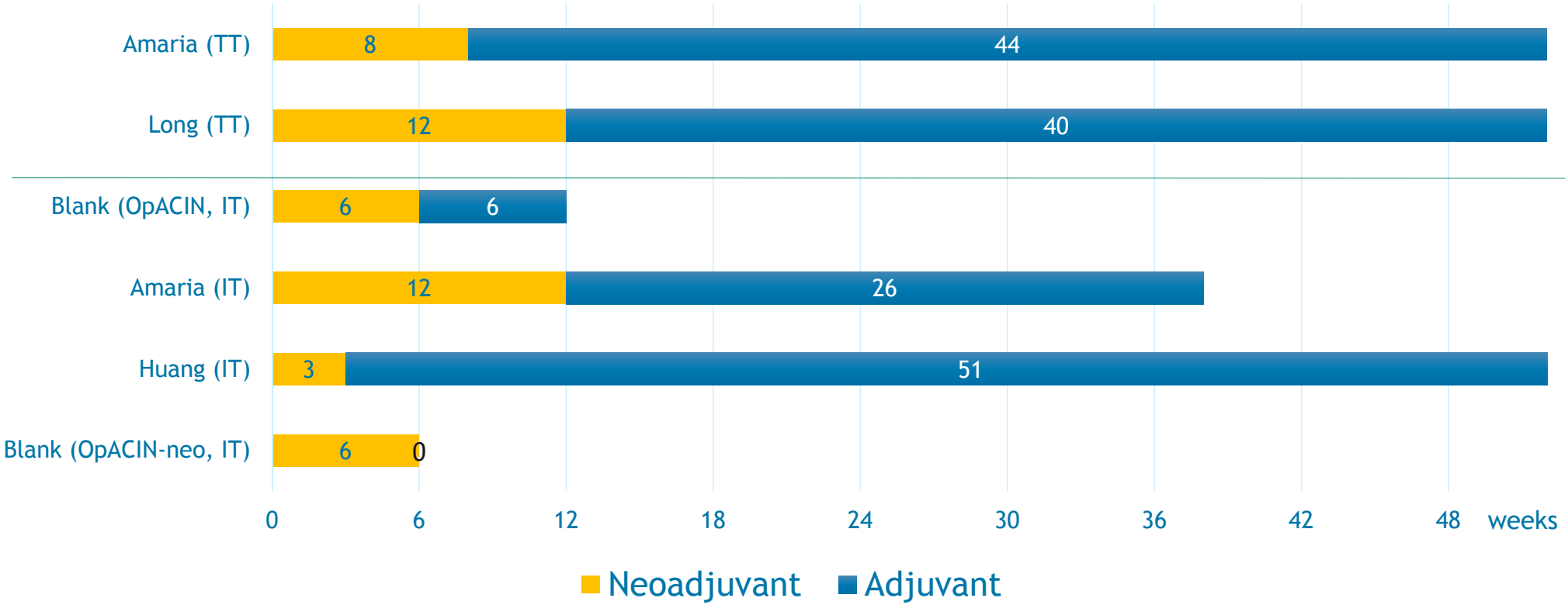
* In press

Results



*3.6% progressed prior to surgery, all on immunotherapy (7/140, 5%)

Modern melanoma NST trials



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

Modern melanoma NST trials

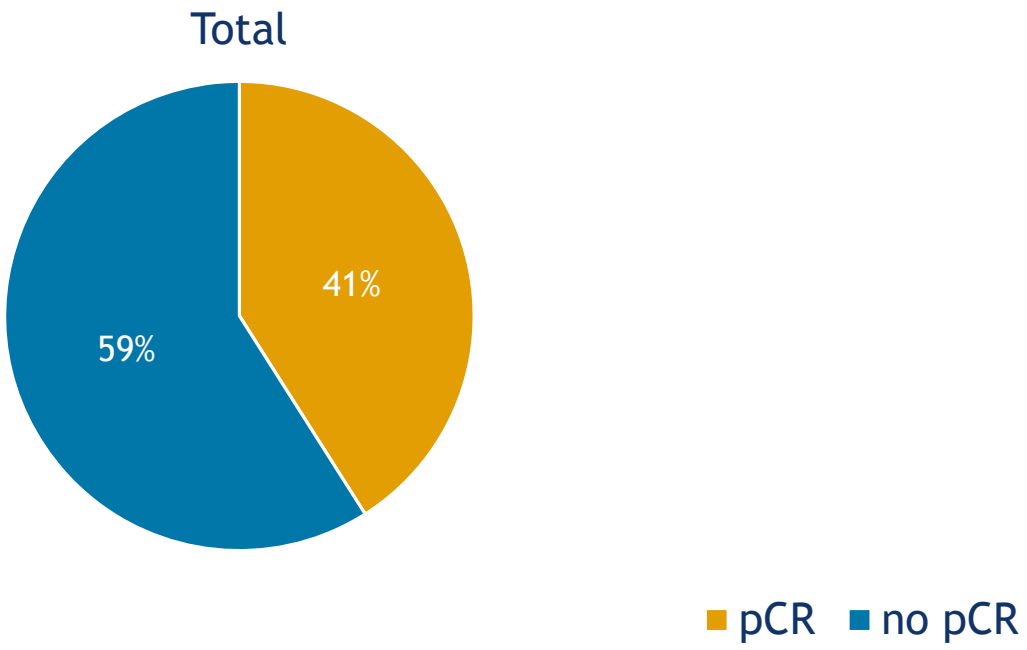
- Trials show early promise
- To improve outcomes more rapidly and advance the field, we need early markers that correlate with survival
- In several cancers, neoadjuvant response (pCR) correlates with survival and is a path to regulatory approval
- **Whether pCR correlates with survival in melanoma is unknown**

Results – Patient Characteristics

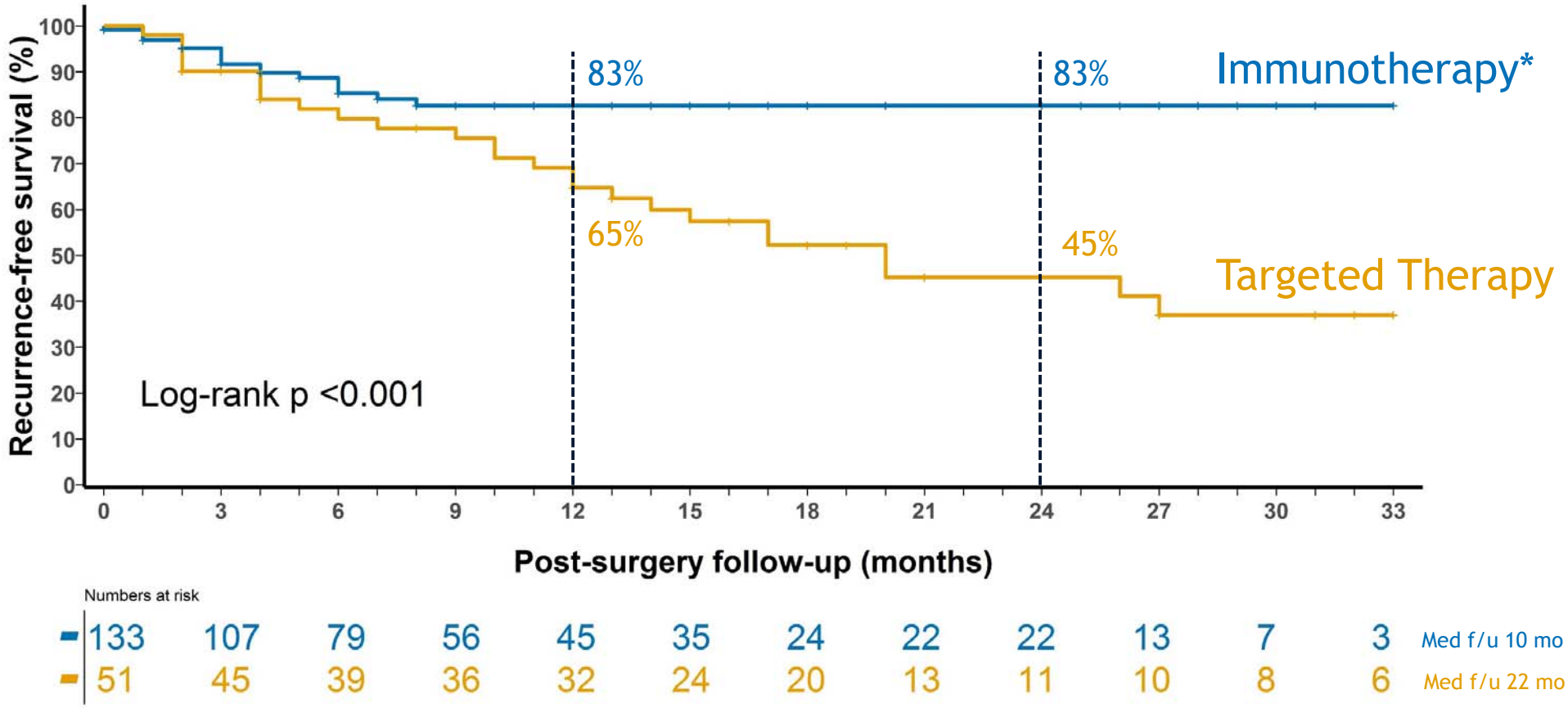
	Total N=184
Median age (range) (yrs)	57 (18-87)
AJCC v7 clinical stage at baseline	
IIIB	100 (54.3%)
IIIC	84 (45.7%)
Disease sites*	
neck	31 (16.8%)
axilla	78 (42.4%)
groin	63 (34.2%)
multiple basins	12 (6.5%)
Med. time to surgery (weeks, range)	7 (2-217)
Med. F/U post-op (months, 95% CIs)	13 (12–16)

*1 pt epitrochlear node
*2 pts nodes + ITMs

Results – pCR rates



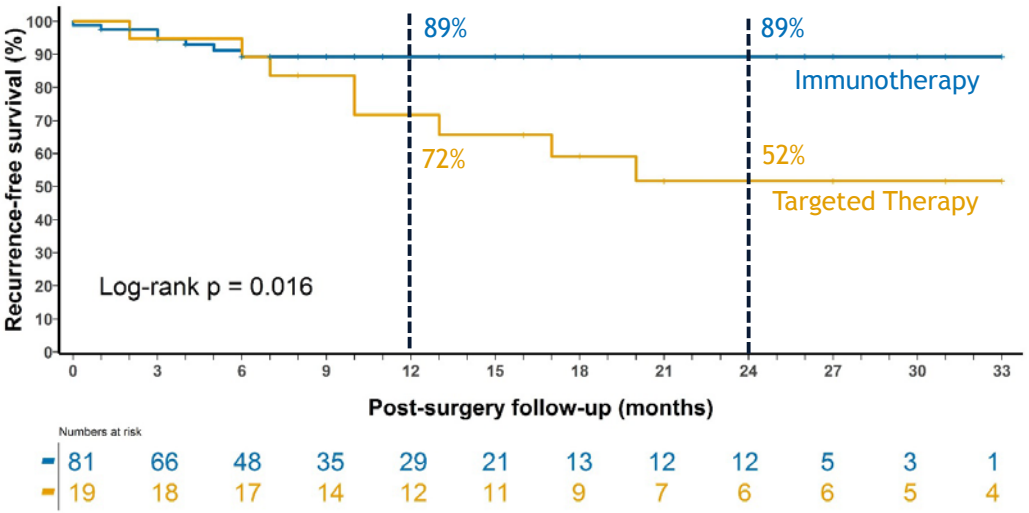
RFS by drug class



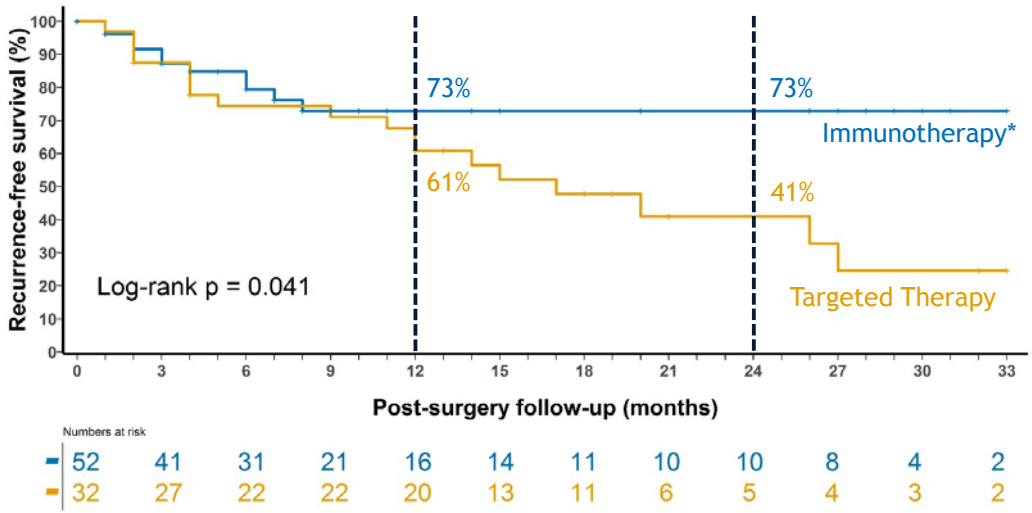
* 1 pt died from toxicity without recurrence, censored at time of death

RFS by stage and drug

IIIB

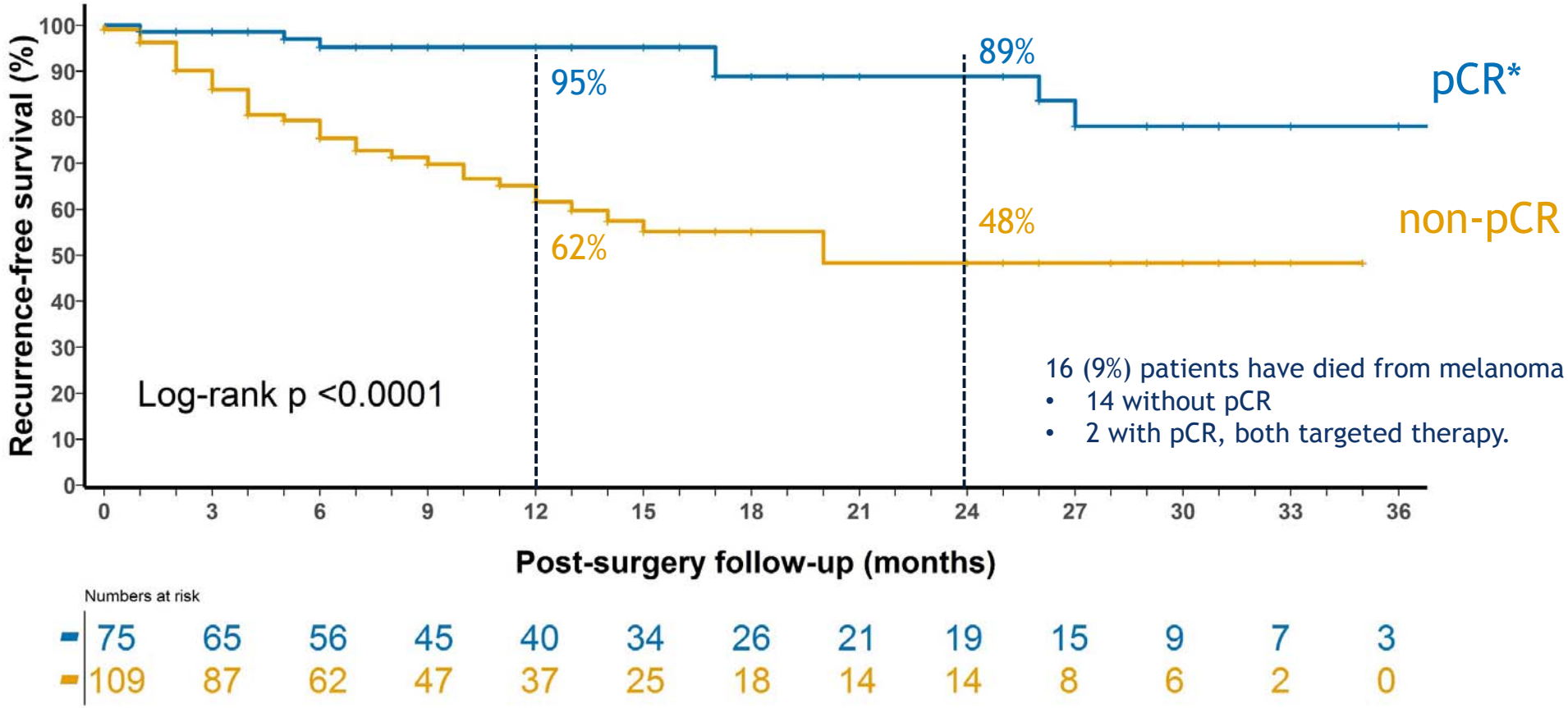


IIIC



* 1 pt died from toxicity without recurrence, censored at time of death

RFS by pathological response

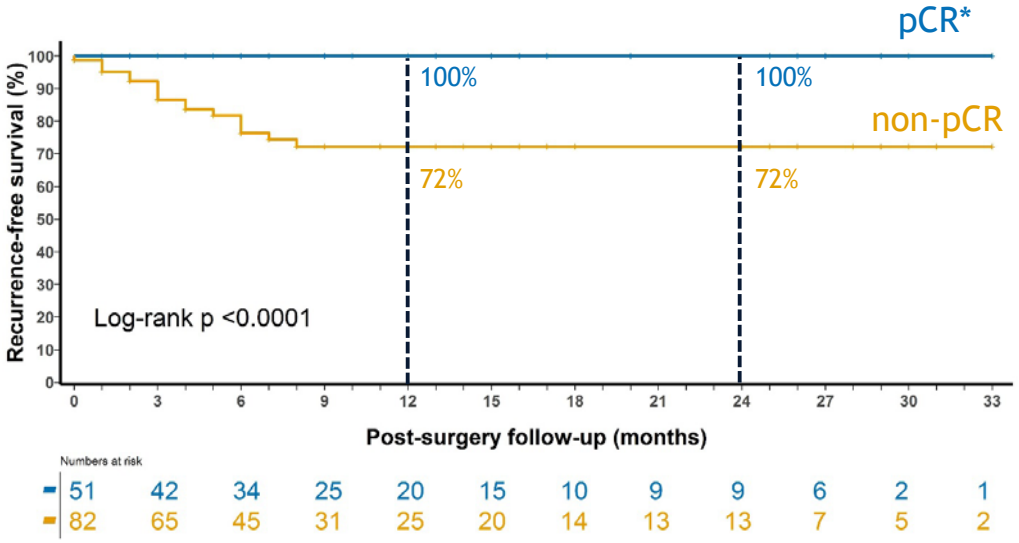


16 (9%) patients have died from melanoma
- 14 without pCR
- 2 with pCR, both targeted therapy.

* 1 pt died from toxicity without recurrence, censored at time of death

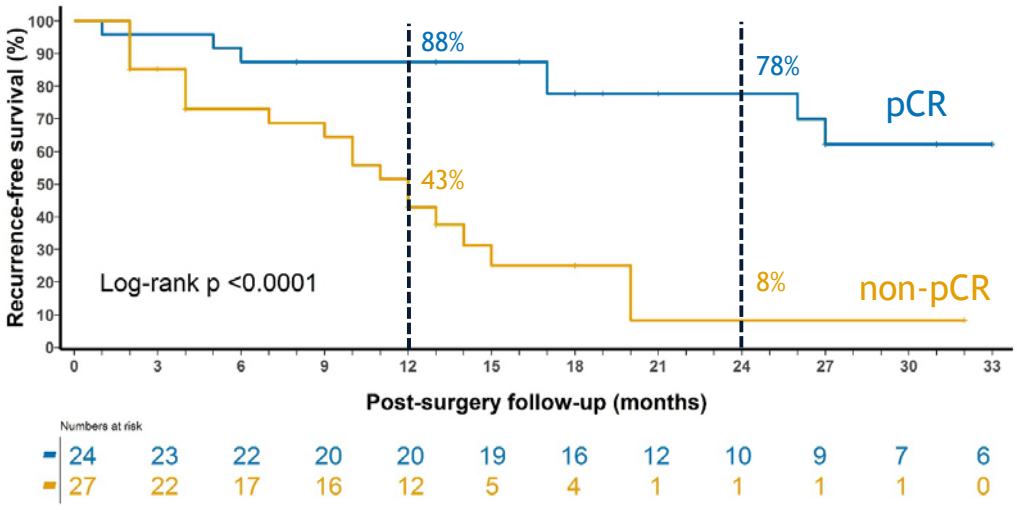
RFS by pathological response and drug

Immunotherapy



Med f/u 10 mo

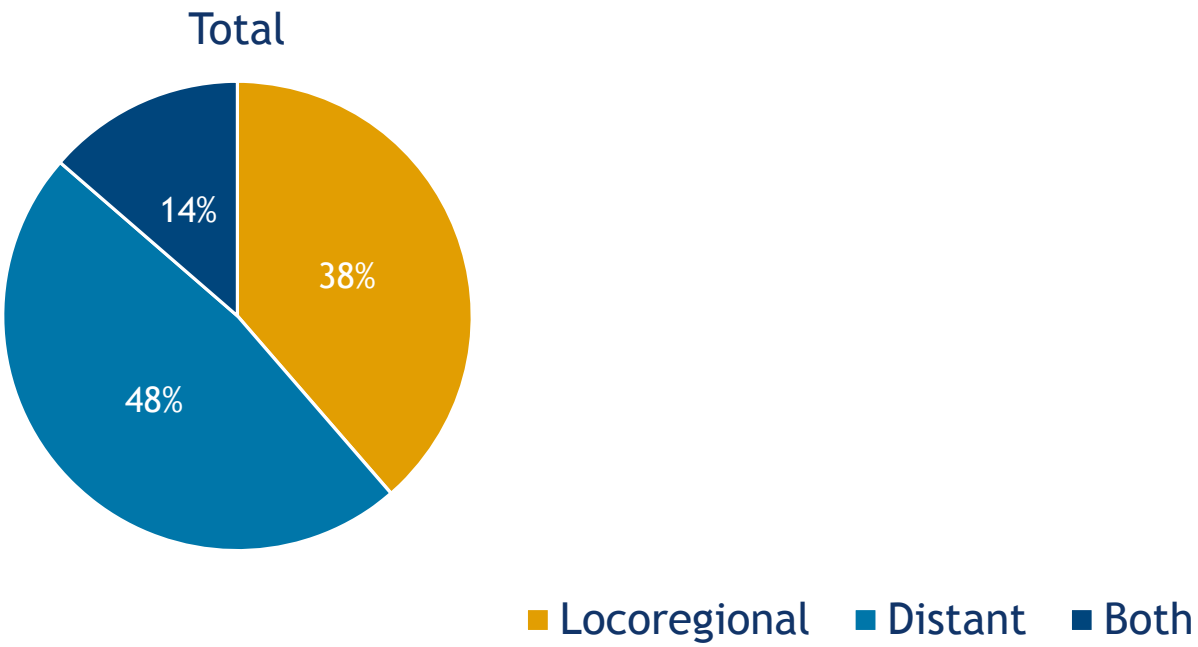
Targeted Therapy



Med f/u 22 mo

* 1 pt died from toxicity without recurrence, censored at time of death

Results – Pattern of recurrence



Conclusions

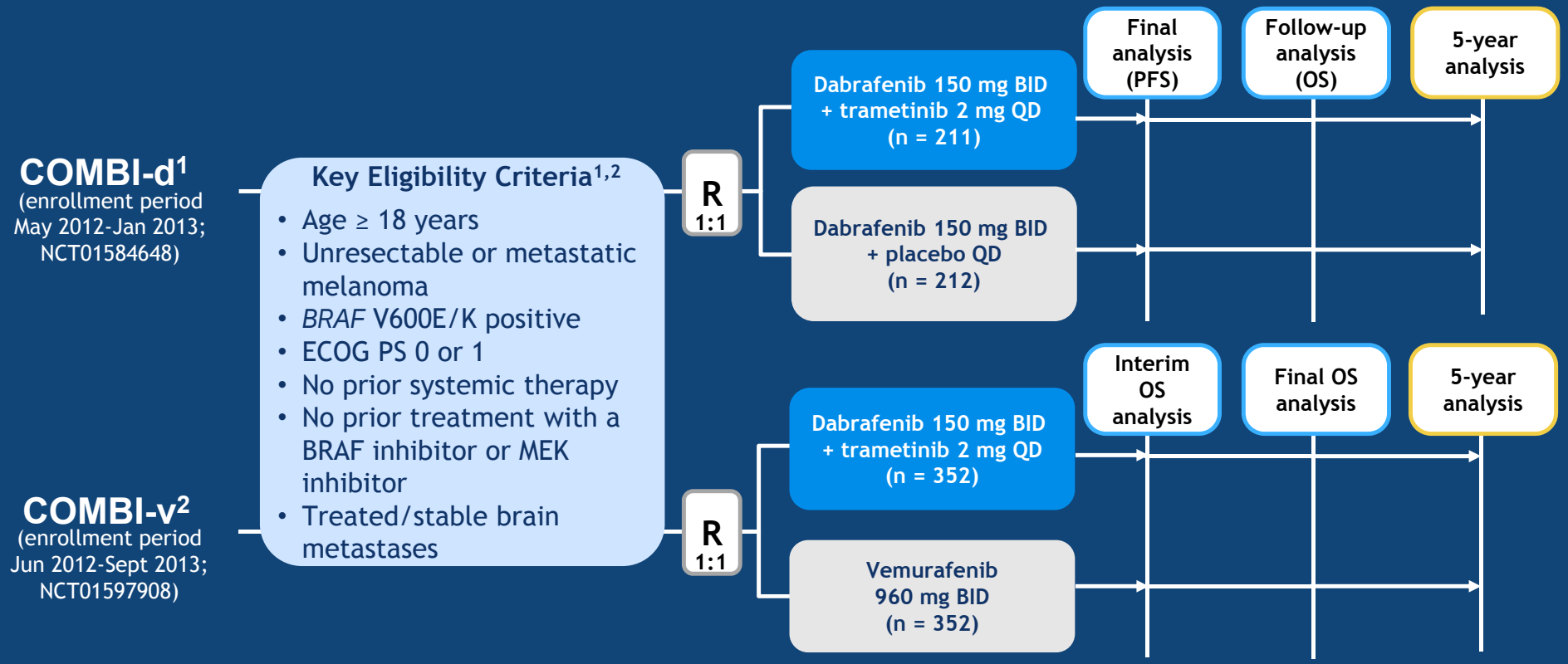
- Neoadjuvant immunotherapy and targeted therapy
  - active regimens in resectable stage III melanoma
  - associated with high pCR rate
- The ability to achieve pCR correlates with improved RFS
  - New benchmark for rapid drug development and regulatory approval
- No patient with pCR from immunotherapy has recurred to date.

Treatment of Advanced Disease Melanoma

Five-Year Analysis of Dabrafenib Plus Trametinib in Patients with *BRAF* V600–Mutant Unresectable or Metastatic Melanoma

Paul Nathan, Caroline Robert, Jean-Jacques Grob, Daniil Stroyakovskiy, Boguslawa Karaszewska, Axel Hauschild, Eugeny Levchenko, Vanna Chiarion Sileni, Jacob Schachter, Claus Garbe, Igor Bondarenko, Michael A. Davies, Antoni Ribas, Keith Flaherty, Paul Burgess, Monique Tan, Eduard Gasal, Dirk Schadendorf, Georgina V. Long

COMBI-d and COMBI-v: Study Designs



BID, twice daily; QD, once daily; R, randomized.

1. Long GV, et al. *N Engl J Med*. 2014;371:1877-1888; 2. Robert C, et al. *N Engl J Med*. 2015;372:30-39.

Baseline Characteristics

	Pooled COMBI-d/v (n = 563)
Median age (range), years	55 (18-91)
Male/female, n (%)	319 (57)/244 (43)
M stage (AJCC 7), n (%)[a]	
M0	19 (3)
M1a	75 (13)
M1b	105 (19)
M1c	363 (64)
ECOG PS, n (%)[a]	
0/≥ 1	403 (72)/155 (28)
Baseline LDH level, n (%)[a]	
Normal	365 (65)
> ULN	194 (34)
≥ 2 × ULN	64 (11)
No. of organ sites, n (%)[a]	
< 3	287 (51)
≥ 3	275 (49)
Sum of lesion diameters, median, mm	57.0

AJCC 7, American Joint Committee on Cancer, 7th edition.

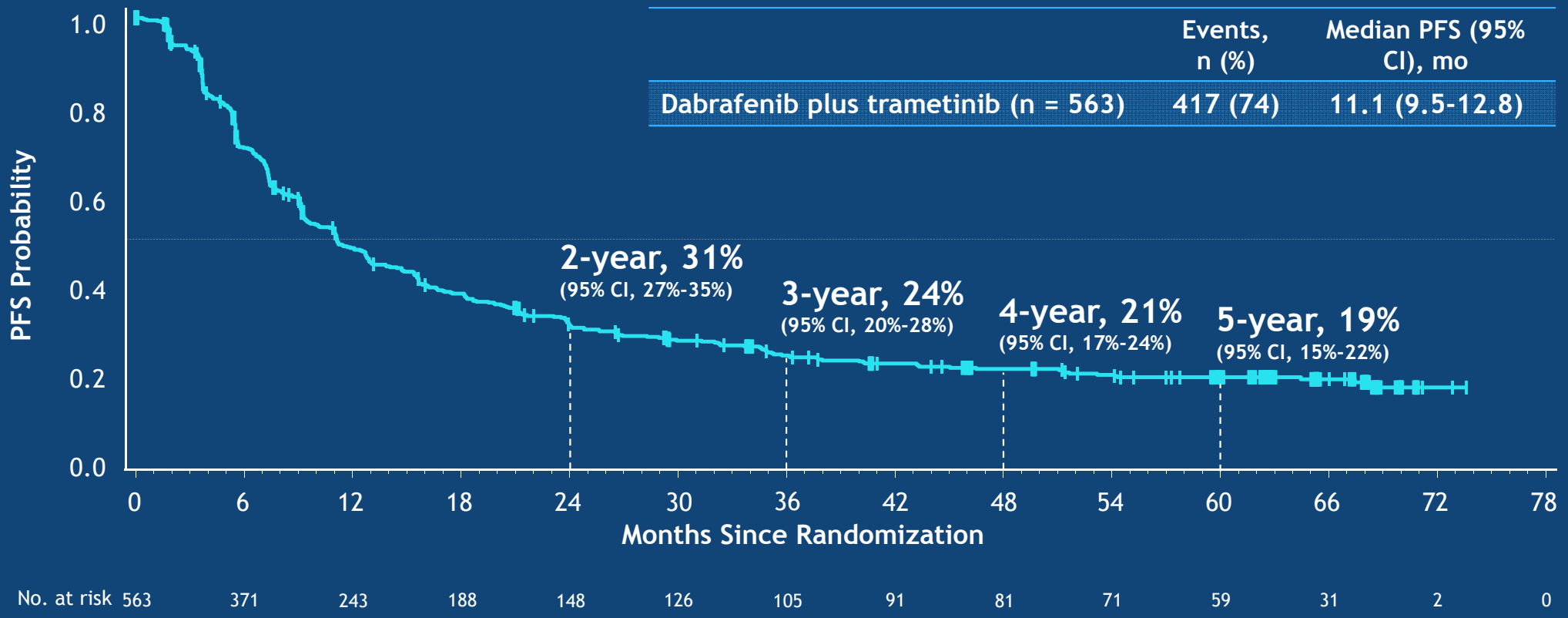
[a] Data on site of disease and number of disease sites were missing for 1 patient each. ECOG PS was missing for 5 patients, and baseline LDH level was missing for 4 patients.

Best Overall RECIST Response

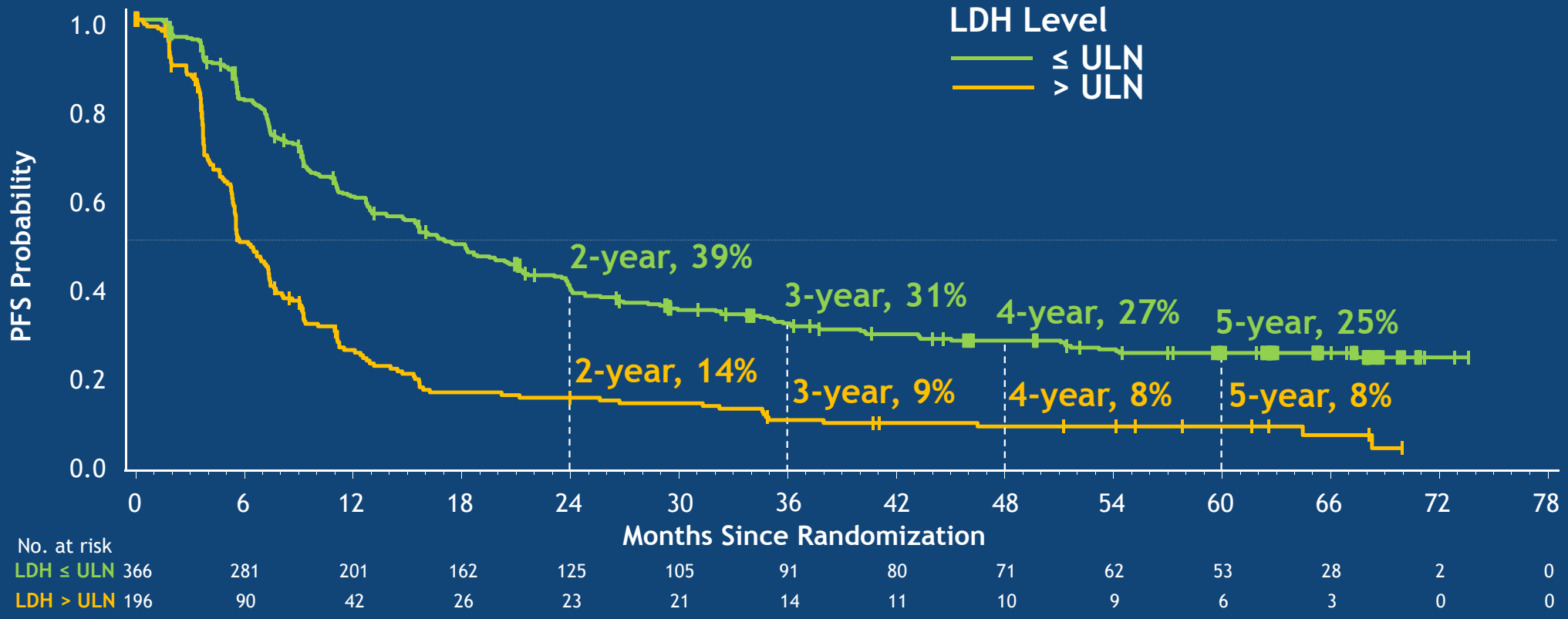
	Pooled COMBI-d/v n = 561[a]
Best overall response, n (%)	
Complete response	109 **(19)**
Partial Response	274 **(49)**
Stable disease	130 **(23)**
Progressive disease	31 **(6)**
Not evaluable	17 **(3)**
Objective response rate, n (%) [95% CI]	383 **(68)** [64-72]

RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Two patients are excluded from the table because they had no measurable disease at baseline.

Dabrafenib Plus Trametinib: 5-Year PFS

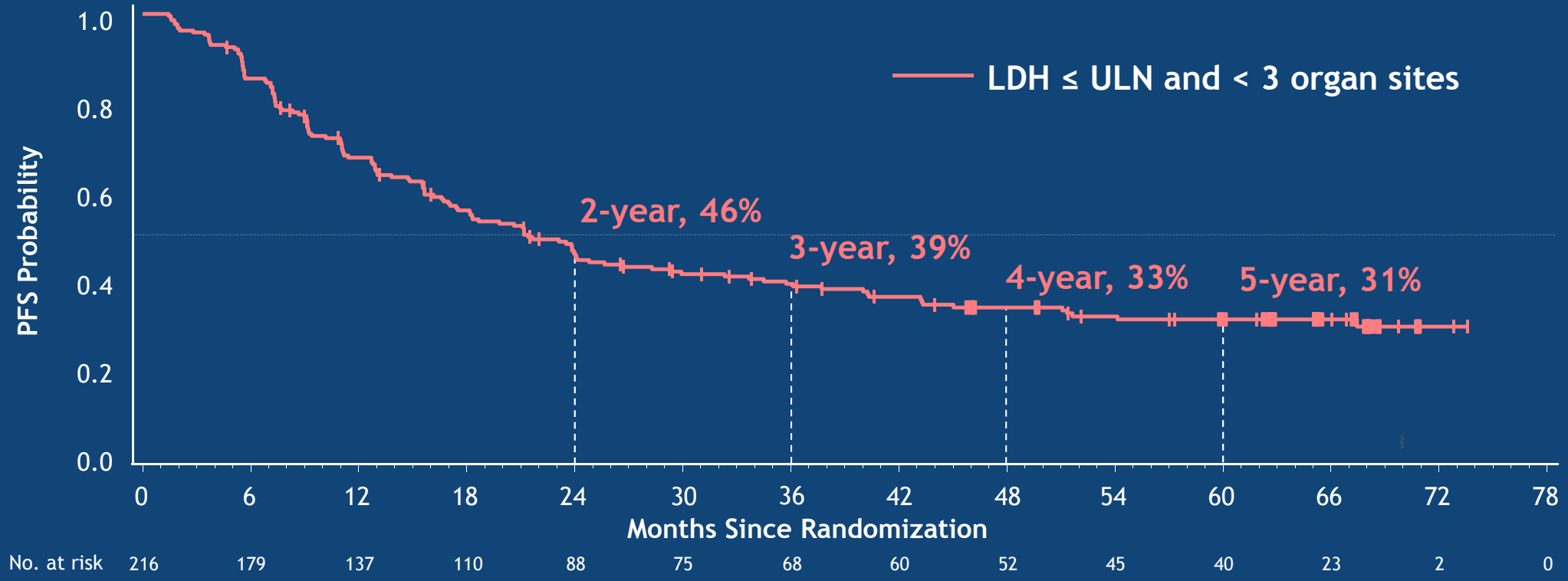


Dabrafenib Plus Trametinib: PFS by Baseline LDH Level

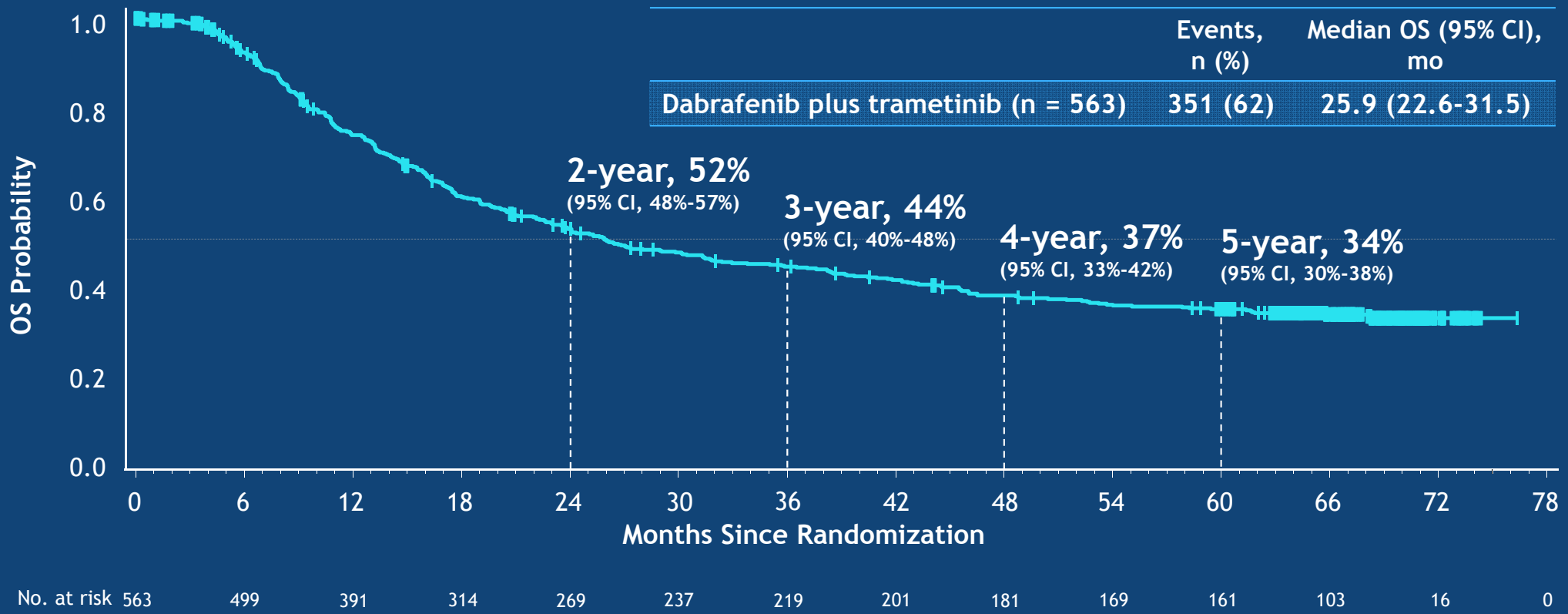


No. at risk													
LDH ≤ ULN	366	281	201	162	125	105	91	80	71	62	53	28	2	0
LDH > ULN	196	90	42	26	23	21	14	11	10	9	6	3	0	0

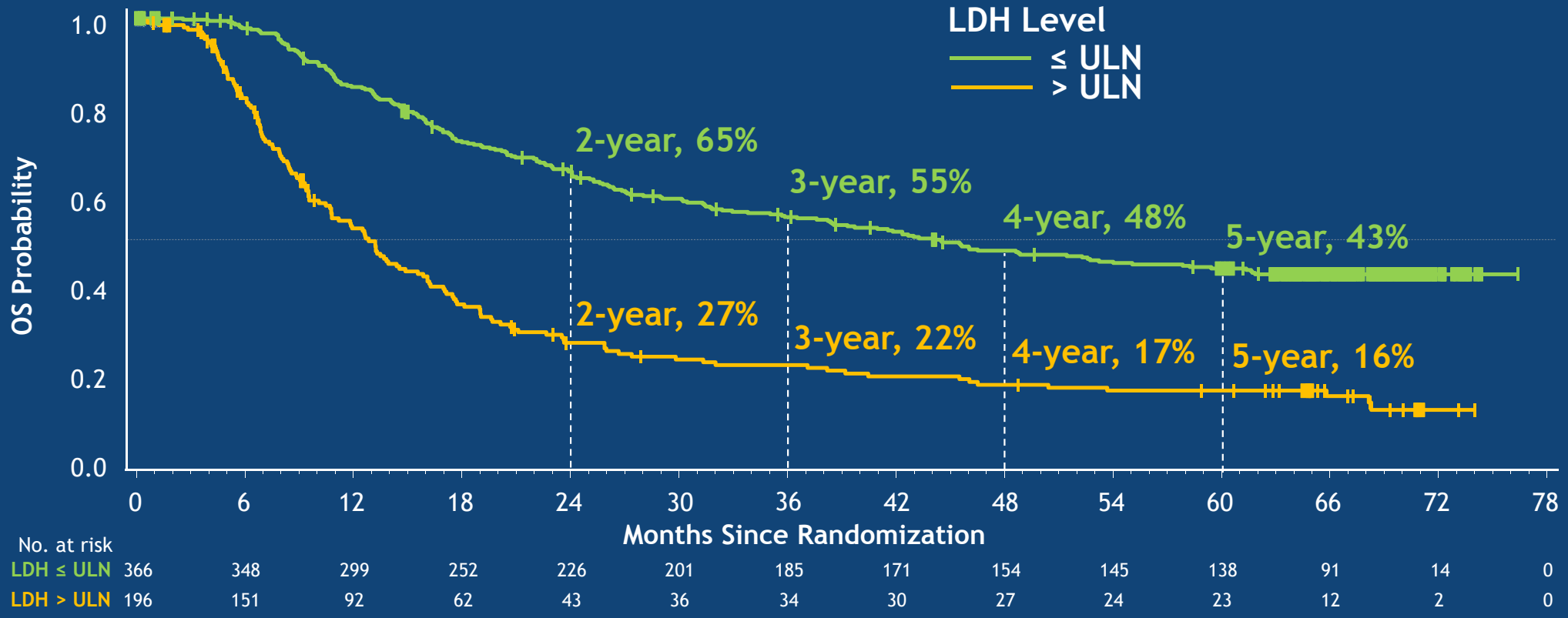
Dabrafenib Plus Trametinib: PFS in Patients With Normal LDH and < 3 Organ Sites



Dabrafenib Plus Trametinib: 5-Year OS

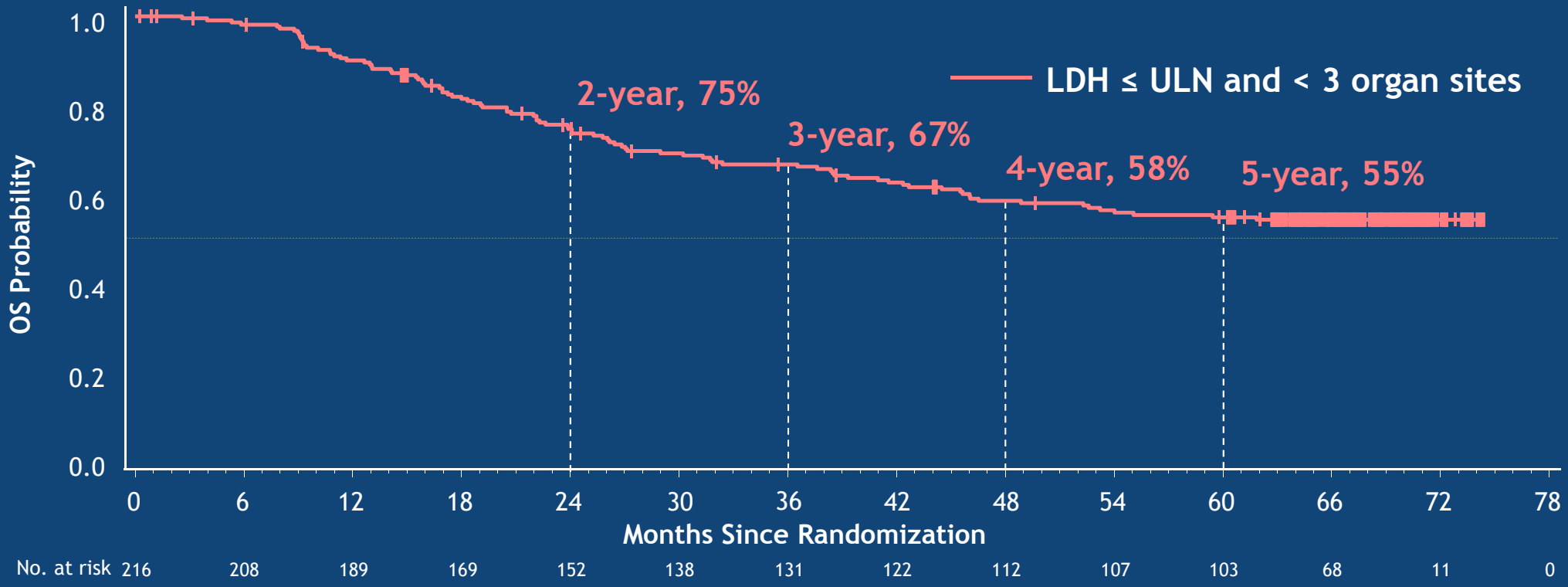


Dabrafenib Plus Trametinib: OS by Baseline LDH Level



No. at risk													
LDH ≤ ULN	366	348	299	252	226	201	185	171	154	145	138	91	14	0
LDH > ULN	196	151	92	62	43	36	34	30	27	24	23	12	2	0

Dabrafenib Plus Trametinib: OS in Patients With Normal LDH and < 3 Organ Sites

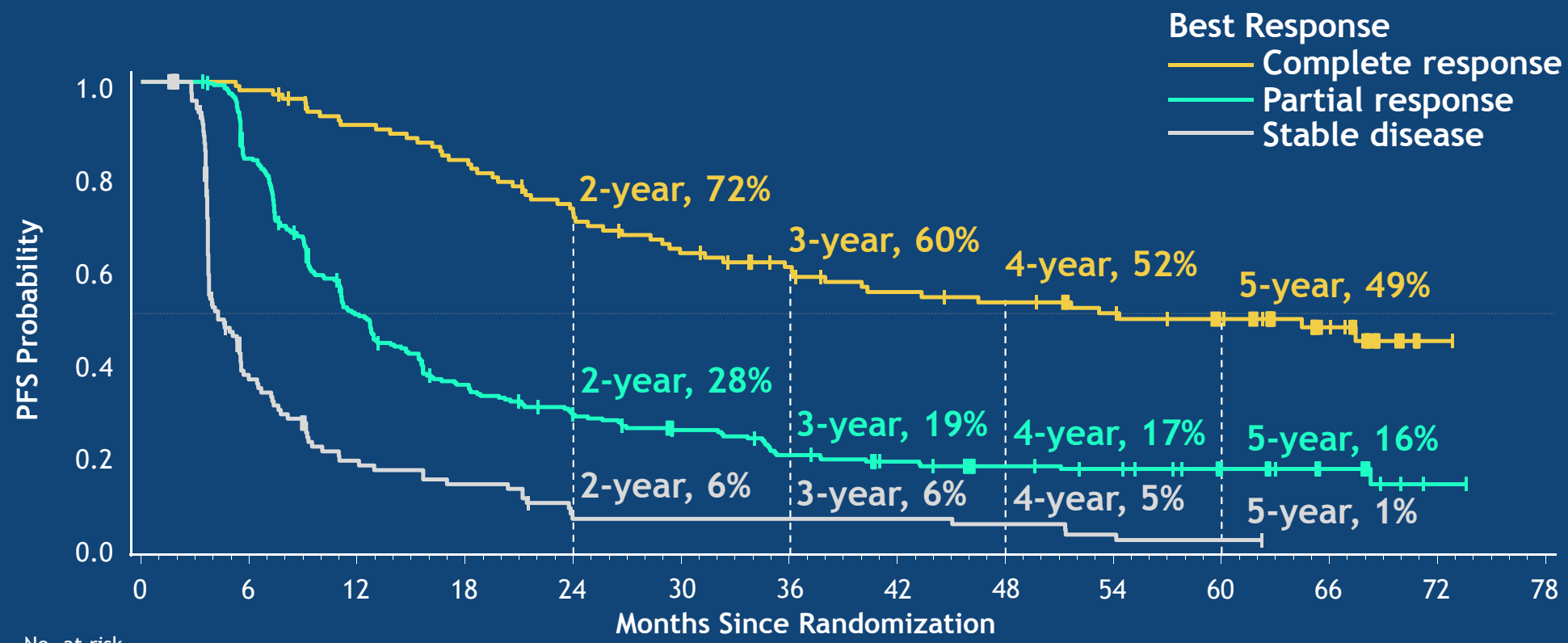


Best Overall RECIST Response

	Pooled COMBI-d/v n = 561[a]
Best overall response, n (%)	
Complete response	109 **(19)**
Partial Response	274 **(49)**
Stable disease	130 **(23)**
Progressive disease	31 **(6)**
Not evaluable	17 **(3)**
Objective response rate, n (%) [95% CI]	383 **(68)** [64-72]

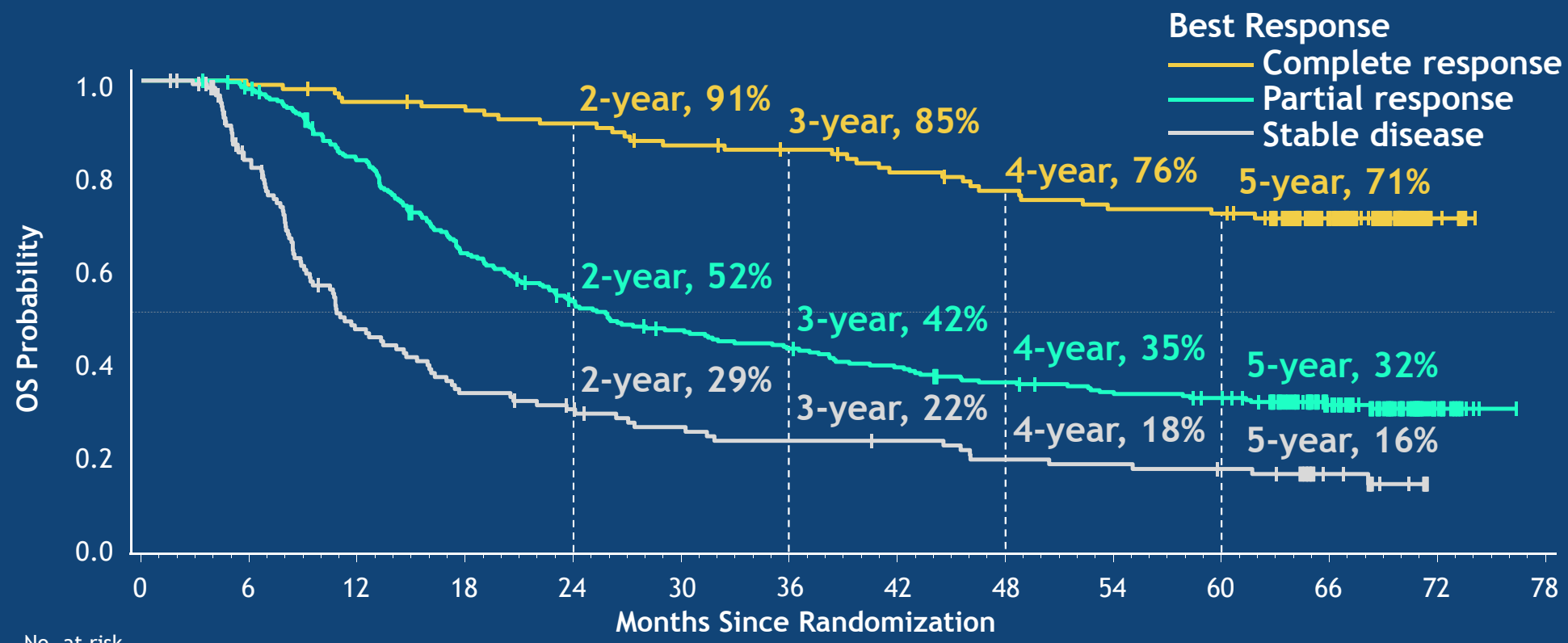
RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Two patients are excluded from the table because they had no measurable disease at baseline.

Dabrafenib Plus Trametinib: PFS by Best Response



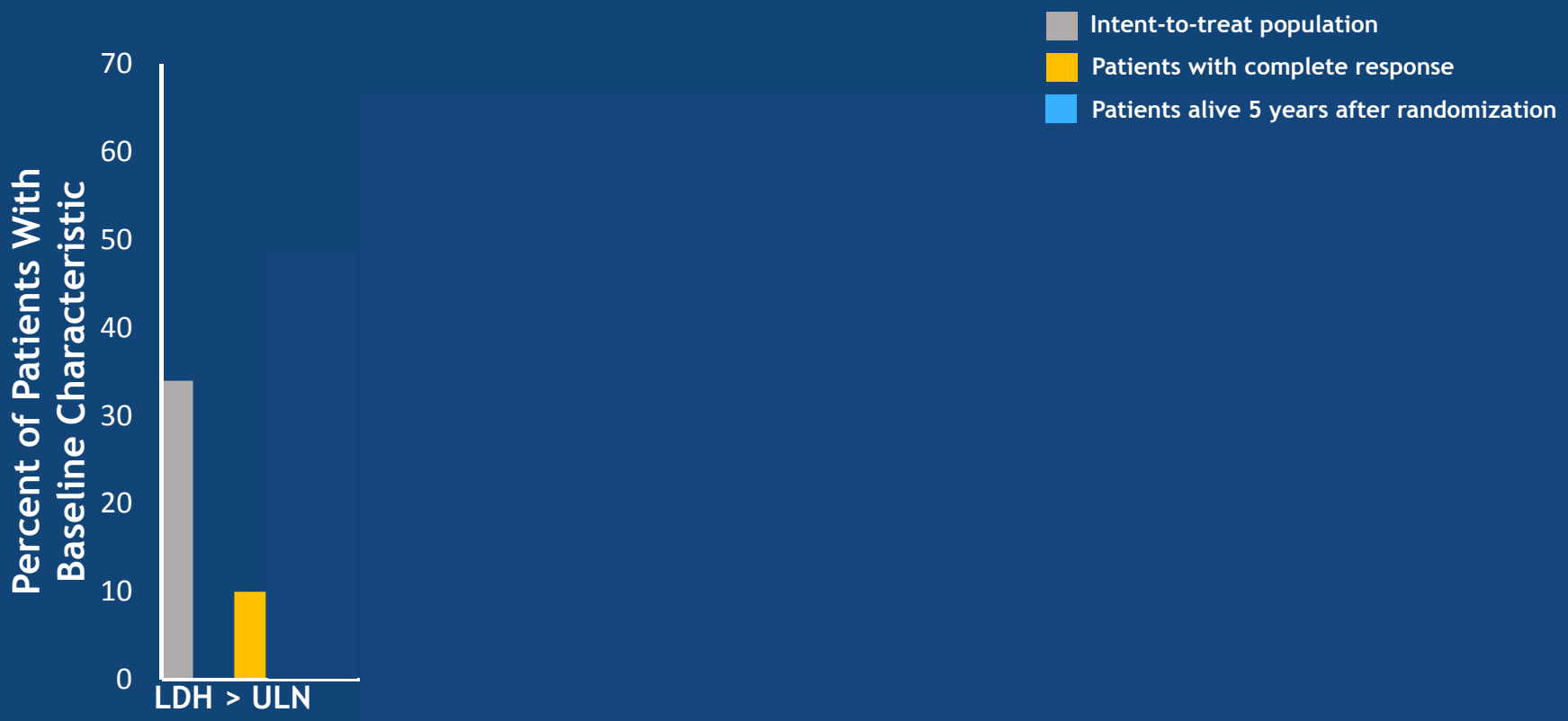
No. at risk													
Complete response	109	107	96	88	75	65	57	50	47	42	37	20	1	0
Partial response	274	224	129	87	68	56	43	36	30	27	21	11	1	0
Stable disease	130	38	18	13	5	5	5	5	4	2	1	0	0	0

Dabrafenib Plus Trametinib: OS by Best Response



No. at risk													
Complete response	109	108	103	101	97	91	88	82	77	73	72	48	4	0
Partial response	274	266	220	165	134	116	106	95	85	78	73	46	11	0
Stable disease	130	99	54	38	32	26	23	22	18	17	15	8	0	0

Proportion of Patients Who Attained CR or Were Alive at 5 Years According to Baseline Characteristics



Summary

- This is the largest data set and longest follow-up in previously untreated patients with *BRAF* V600–mutant unresectable or metastatic melanoma treated with BRAF plus MEK inhibitors
- Dabrafenib plus trametinib led to 5-year disease control in approximately one-fifth of patients and 5-year survival in approximately one-third
- Complete response appears to strongly predict long-term benefit
- Lower baseline tumor burden and less-aggressive tumor biology were associated with prolonged PFS and OS
- These results suggest that first-line treatment with dabrafenib plus trametinib provides long-term survival benefit in a sizeable cohort of patients

Treatment of Advanced Disease Melanoma

BARCELONA 2019 ESMO congress

Five-Year Survival Outcomes of the CheckMate 067 Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma

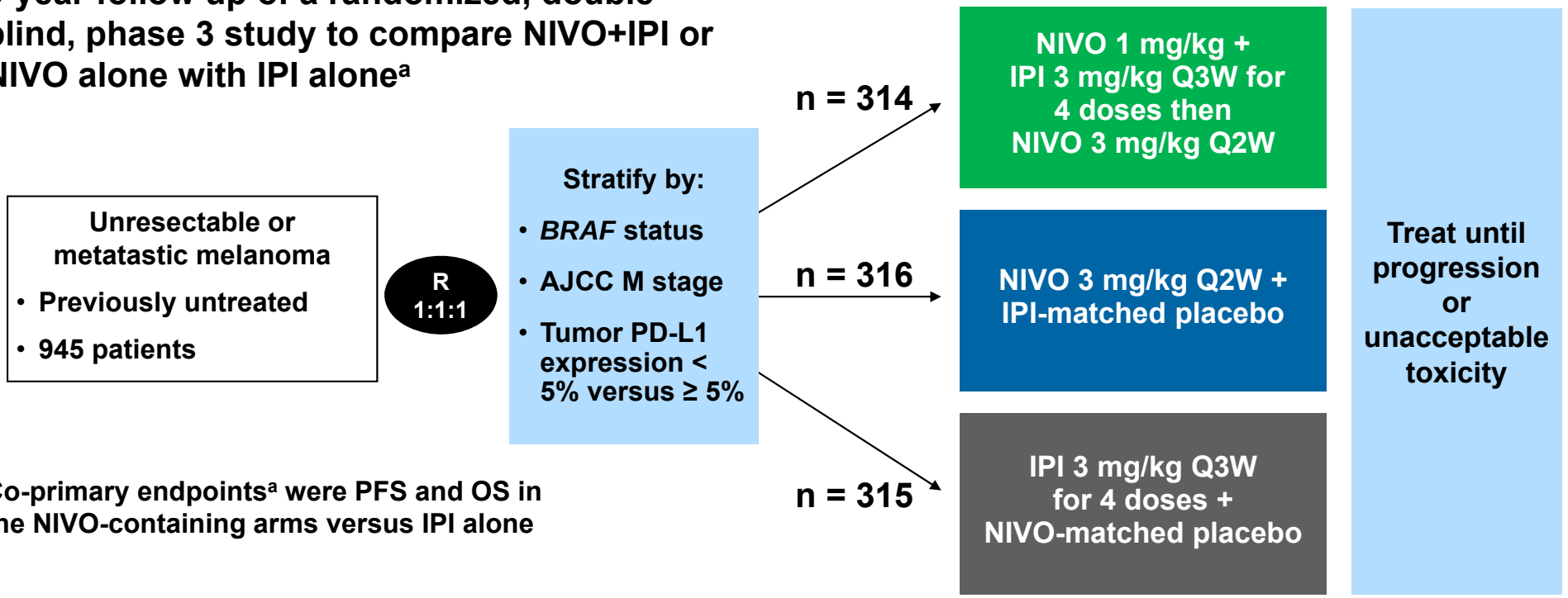
James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier F. Ferrucci,[11] Michael Smylie,[12] David Hogg,[13] Andrew Hill,[14] Ivan Márquez-Rodas,[15] John Haanen,[16] Jasmine I. Rizzo,[17] Agnes Balogh,[17] Andriy Moshyk,[17] F. Stephen Hodi,[18*] Jedd Wolchok[19*]

[1]The Royal Marsden NHS Foundation Trust, London, UK; [2]Oncology Institute of Veneto IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Aurora, CO, USA; [4]Aix-Marseille University, APHM Hospital, Marseille, France; [5]Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland; [6]University of Michigan, Ann Arbor, MI, USA; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [8]Department of Dermatology, University of Essen, Essen, Germany; & German Cancer Consortium, Heidelberg, Germany; [9]The College of Medicine, Swansea University, Swansea, UK; [10]Universitäts Spital, Zurich, Switzerland; [11]European Institute of Oncology, Milan, Italy; [12]Cross Cancer Institute, Alberta, Canada; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Tasman Oncology Research, QLD, Australia; [15]General University Hospital Gregorio Marañon, Madrid, Spain; [16]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [17]Bristol-Myers Squibb, Princeton, NJ; USA, [18]Dana-Farber Cancer Institute, Boston, MA; USA, [19]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA
*Contributed equally.

Abstract Number 2545

CheckMate 067: Study Design

5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone with IPI alone[a]



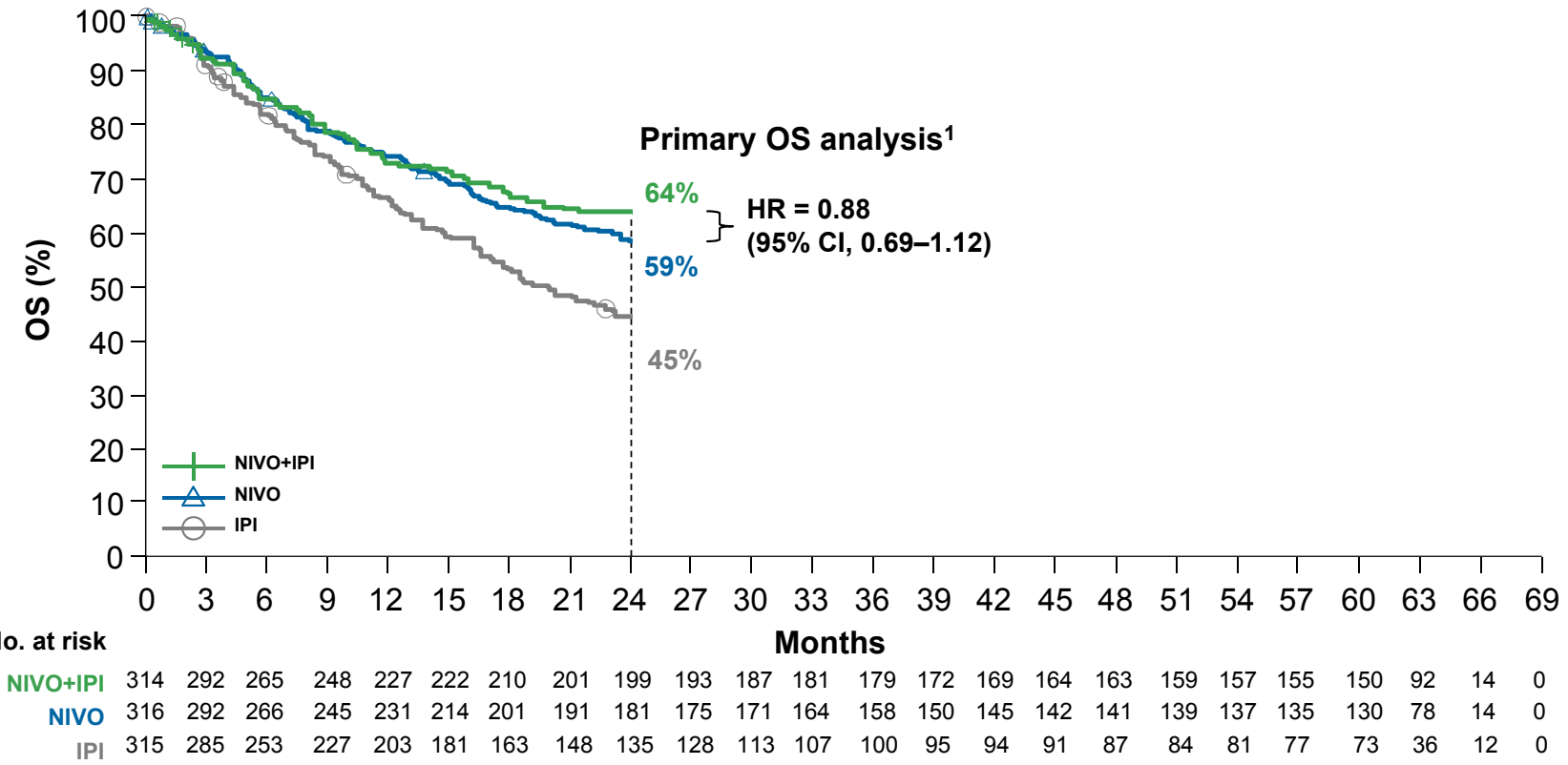
Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

Database lock: July 2, 2019; minimum follow-up of 60 months for all patients

NCT01844505

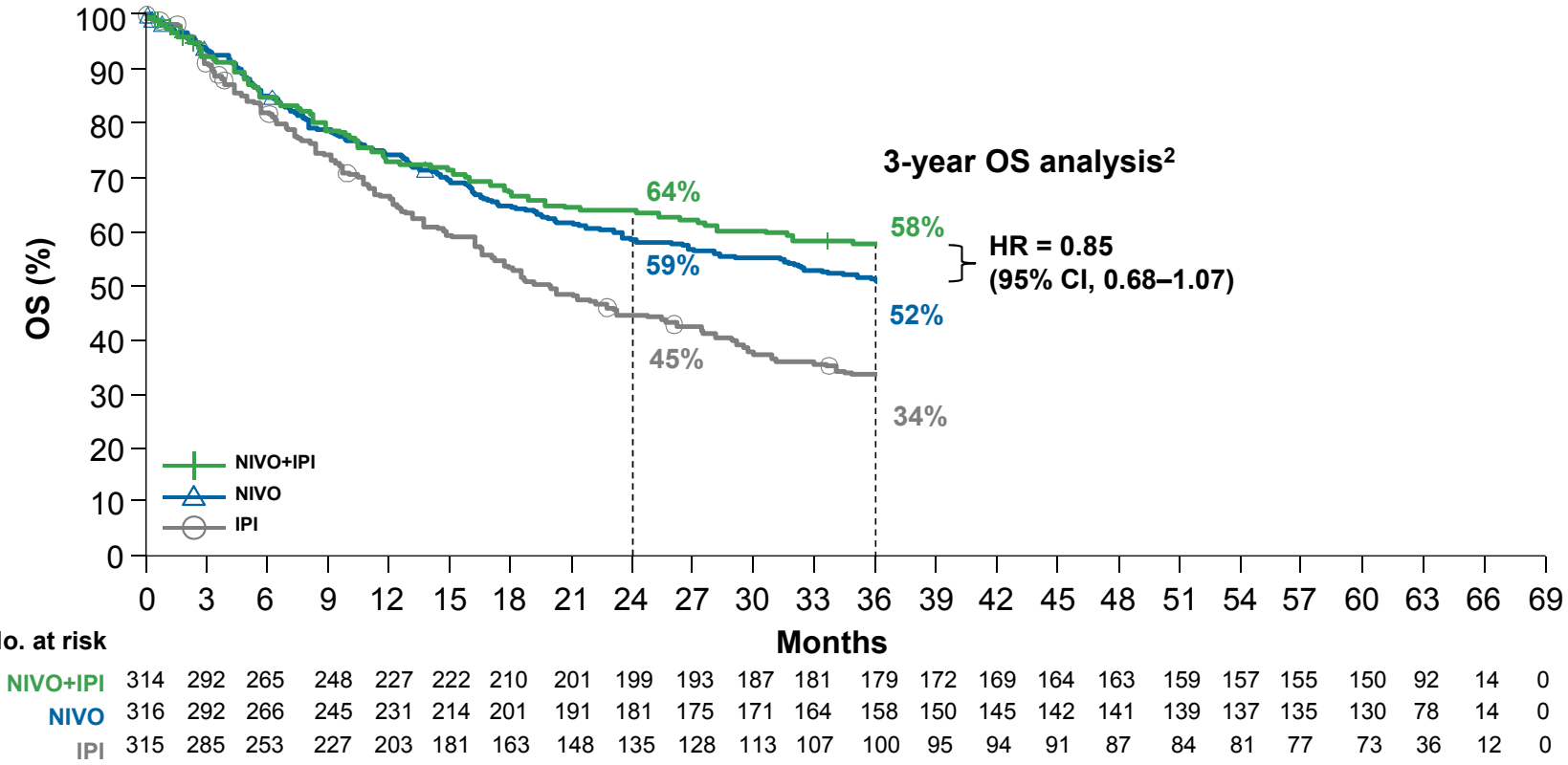
[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Overall Survival



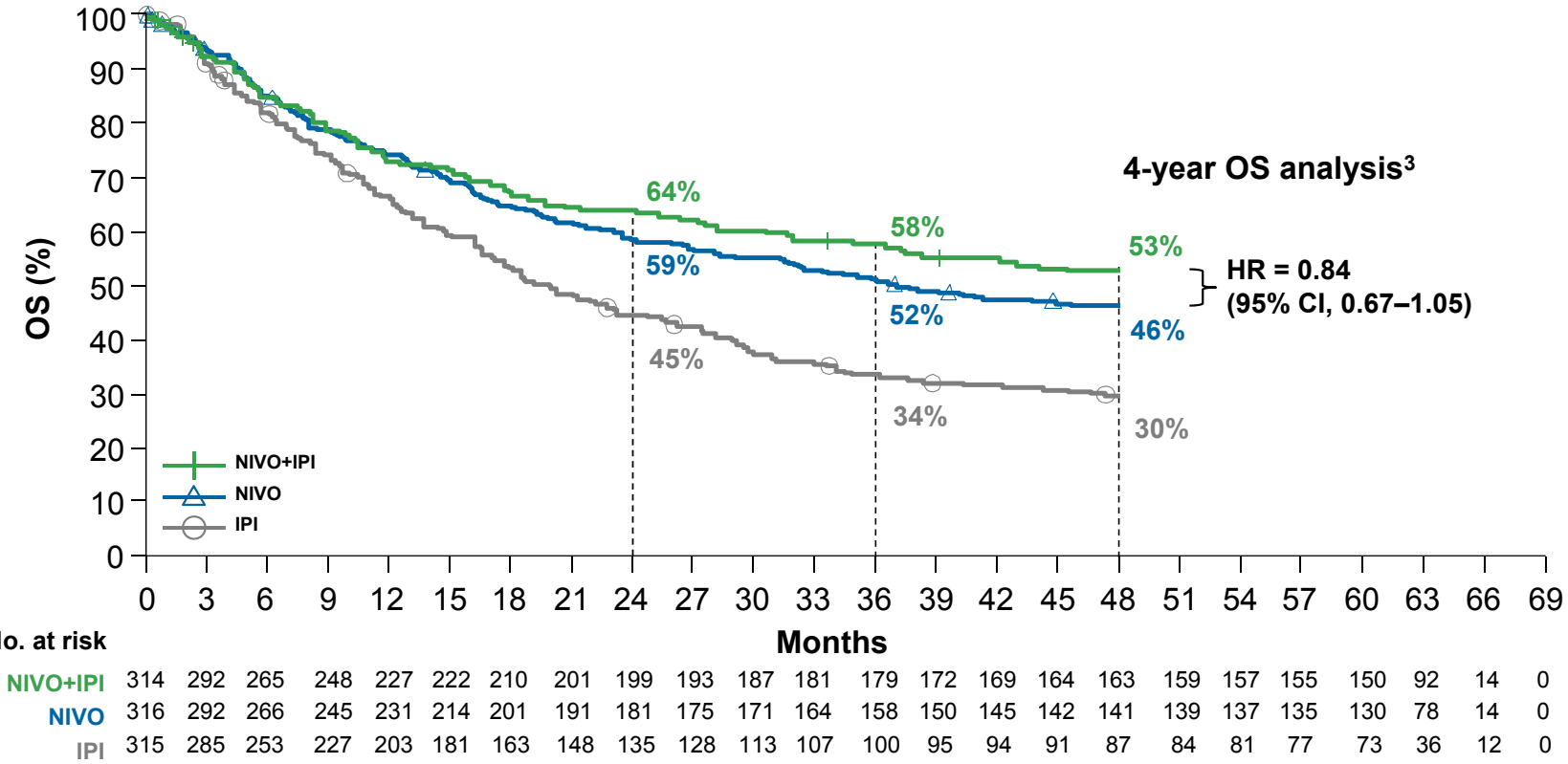
[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075.

Overall Survival



[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075;
2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356.

Overall Survival

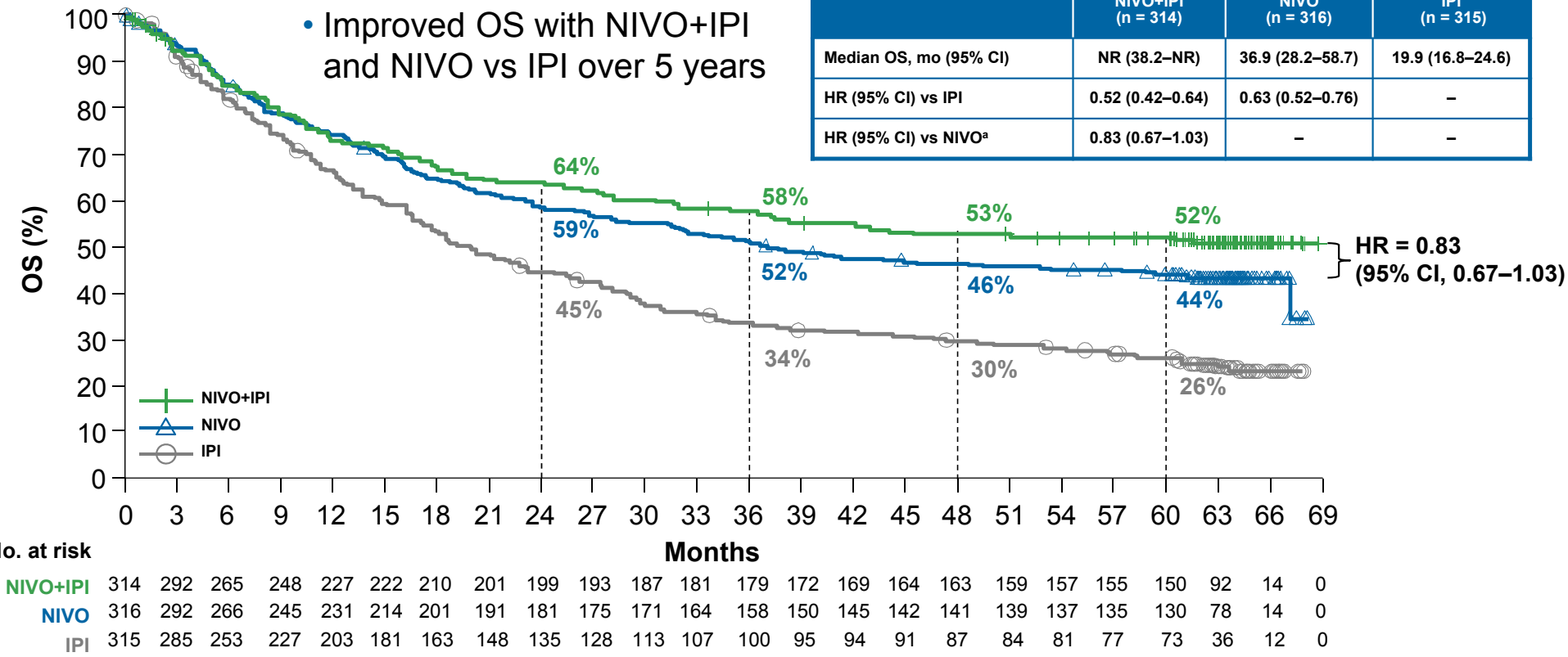


[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 3. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



No. at risk

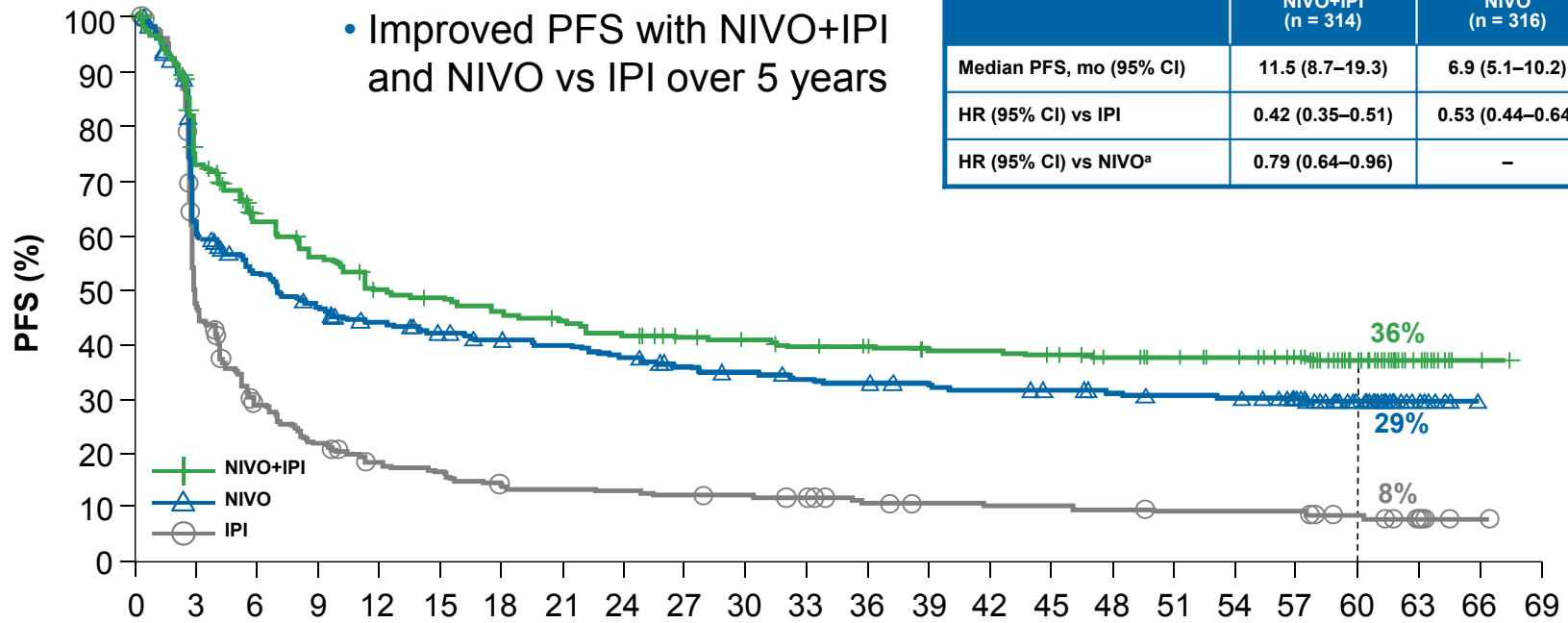
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Progression-Free Survival

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	–	–



No. at risk																								
NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

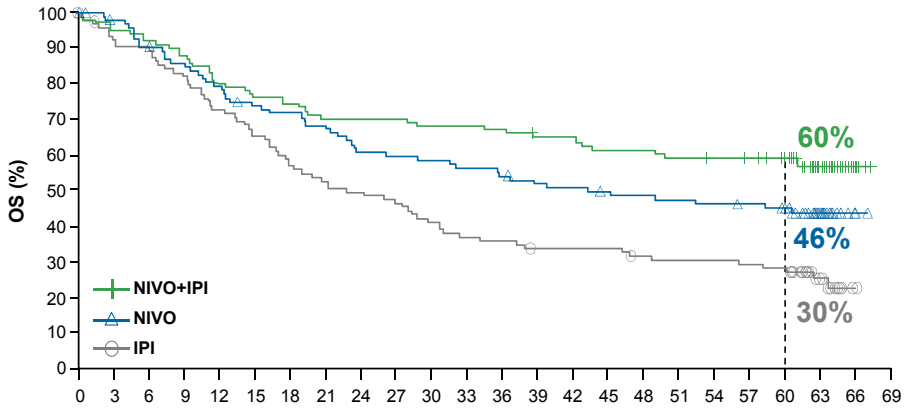
[a]Descriptive analysis.

OS in Patients With *BRAF*-Mutant and Wild-Type Tumors

- Improved OS and PFS with NIVO+IPI and NIVO vs IPI regardless of *BRAF* mutation status

BRAF Mutant

	NIVO+IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median, mo (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs IPI	0.44 (0.30–0.64)	0.63 (0.44–0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46–1.05)	–	–



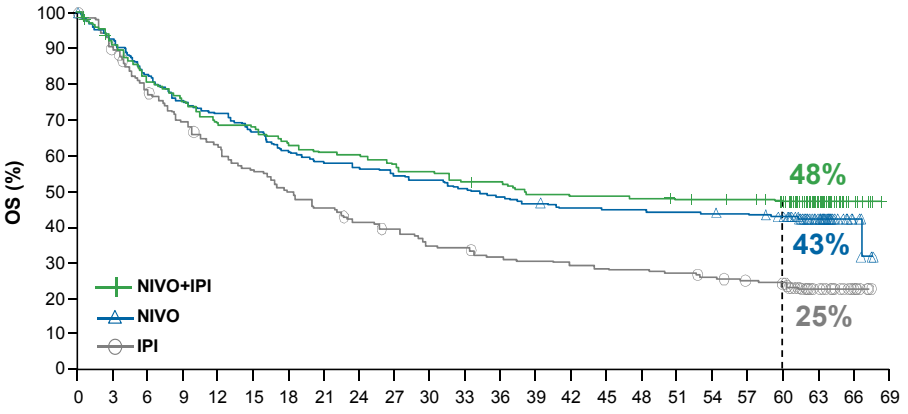
No at risk

NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	59	57	37	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	41	40	27	4	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	13	2	0

- 5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

BRAF Wild-Type

	NIVO+IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1–59.2)	18.5 (14.1–22.7)
HR (95% CI) vs IPI	0.57 (0.45–0.73)	0.64 (0.50–0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69–1.15)	–	–



No. at risk

NIVO+IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	97	96	93	55	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	94	90	51	10	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	46	23	10	0

- 5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

[a]Descriptive analysis.

Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NR[a]**	**NR (50.4–NR)**	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

- While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]
  - 19%, 21%, and 22% for NIVO+IPI
  - 16%, 18%, and 19% for NIVO
  - 5%, 5%, and 6% for IPI

[a]Although a median was reported at the previous analysis, that estimate was immature and greater than the minimum study follow-up. ITT, intention to treat.

1. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Subsequent Therapies: All Randomized Patients

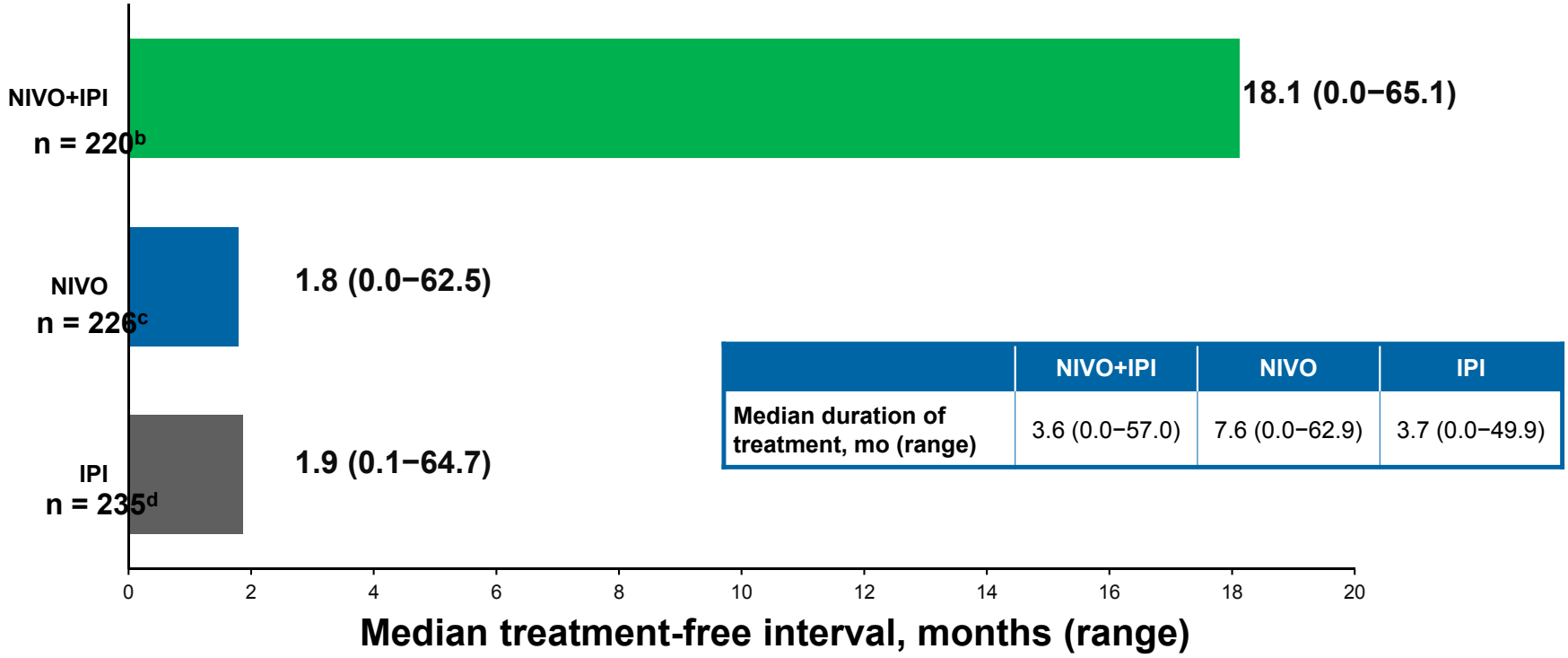
- Less than half (46%) of patients treated with NIVO+IPI received any subsequent therapy

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Any subsequent therapy, n (%)[a]	**143 (46)**	**185 (59)**	**237 (75)**
Subsequent systemic therapy	109 (35)	152 (48)	207 (66)
Subsequent immunotherapy	55 (18)	105 (33)	149 (47)
Anti–PD-1 agents[b]	39 (12)	49 (16)	144 (46)
Anti-CTLA4 agents[b]	21 (7)	91 (29)	16 (5)
BRAF inhibitor[c,d]	43 (14)	60 (19)	72 (23)
MEK/NRAS inhibitor[c]	33 (11)	43 (14)	42 (13)
Subsequent radiotherapy, n (%)	66 (21)	93 (29)	126 (40)
Subsequent surgery, n (%)	65 (21)	72 (23)	94 (30)
Median time from randomization to subsequent systemic therapy, months (95% CI)[e]	**NR (59.6–NR)**	**25.2 (16.0–43.2)**	**8.0 (6.5–8.7)**

[a]Patients may have received > 1 subsequent therapy; [b]May include patients treated with anti–PD-1+CTLA-4 combination; [c]May include patients treated with BRAF+MEK inhibitor combination; [d]Of *BRAF*-mutant patients, 40% NIVO+IPI, 56% NIVO, and 71% IPI received BRAF inhibitor; [e]Excluding patients who died and never received subsequent therapy.

Longer Treatment-Free Interval With NIVO+IPI in Patients Who Discontinued Study Therapy[a]

Population analyzed: patients who (1) were alive or (2) who died following subsequent systemic therapy

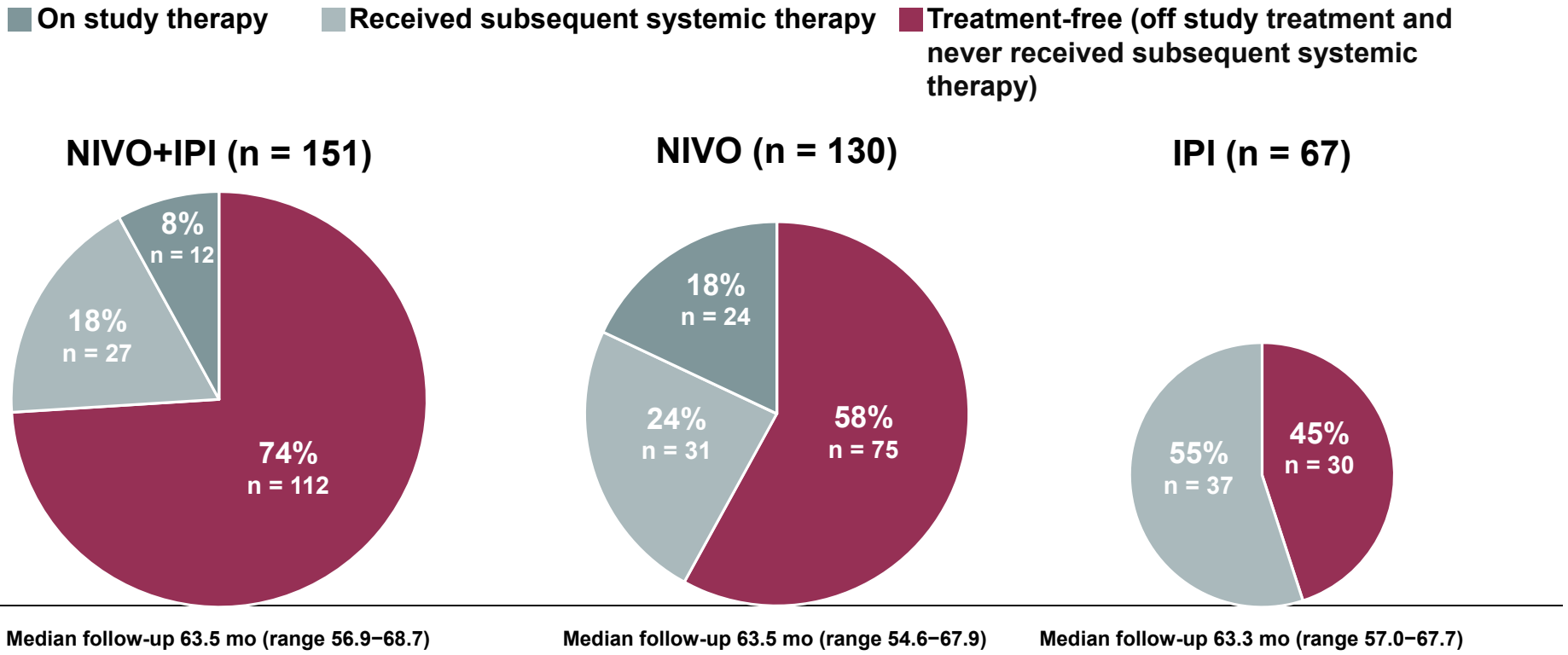


	NIVO+IPI	NIVO	IPI
Median duration of treatment, mo (range)	3.6 (0.0−57.0)	7.6 (0.0−62.9)	3.7 (0.0−49.9)

[a]Post-hoc analysis;
[b]93 patients excluded: 12 on study treatment, 53 had died without receiving subsequent systemic therapy, and 28 were no longer in follow-up and never received subsequent therapy;
[c]87 patients excluded: 24 on study treatment, 45 had died without receiving subsequent systemic therapy, and 18 were no longer in follow-up and never received subsequent therapy;

Higher Proportion of Patients Alive and Treatment-Free at 5 Years With NIVO+IPI[a]

Population analyzed: patients who were alive and followed on study



[a]Post-hoc analysis.

Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

Summary

- At 5 years, median overall survival was not yet reached for NIVO 1 mg/kg + IPI 3 mg/kg (5-year rate, 52%), representing the only treatment for metastatic melanoma for which median overall survival is > 60 months
  - Durable, sustained clinical benefit was achieved with first-line NIVO+IPI or NIVO alone in patients with advanced melanoma across clinically relevant subgroups, including *BRAF* mutation status
    - Median overall survival for patients with *BRAF* mutations was not yet reached for NIVO+IPI, 45.5 months for NIVO, and 24.6 months for IPI
    - No new safety signals or additional treatment-related deaths were observed
  - Separation of survival curves indicate continued benefit for NIVO+IPI over NIVO
  - Treatment with NIVO+IPI led to a higher chance of being alive and treatment free compared with monotherapy, with no loss of quality of life

BRAF/MEK inhibitor combination therapy

Results of clinical studies

BRAFi monotherapy

Dabrafenib

PFS HR 0.37 *vs* DTIC[1]

Vemurafenib

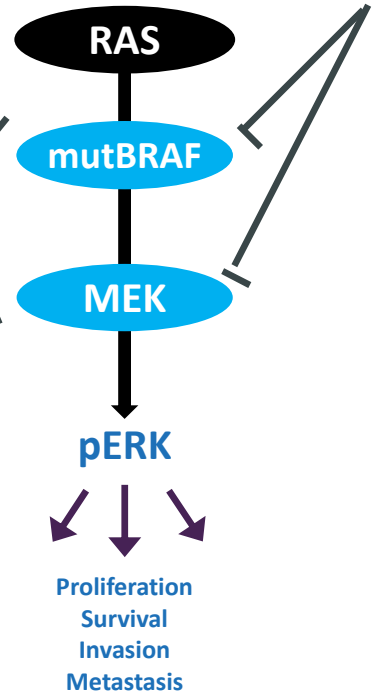
PFS HR 0.38 *vs* DTIC[2]

Hyperproliferative skin AEs (cuSCC/KA)[1,2]

MEKi monotherapy

Trametinib

PFS HR 0.45 *vs* chemotherapy[3]



BRAFi + MEKi combination therapy

Dabrafenib + trametinib

PFS HR 0.67 *vs* dabrafenib[4]

OS HR 0.71 *vs* dabrafenib[4]

PFS HR 0.56 *vs* vemurafenib[5]

OS HR 0.69 *vs* vemurafenib[5]

Vemurafenib + cobimetinib

PFS HR 0.51 *vs* vemurafenib[6]

OS HR 0.70 *vs* vemurafenib

Encorafenib + binimetinib

PFS HR 0.54 *vs* vemurafenib7

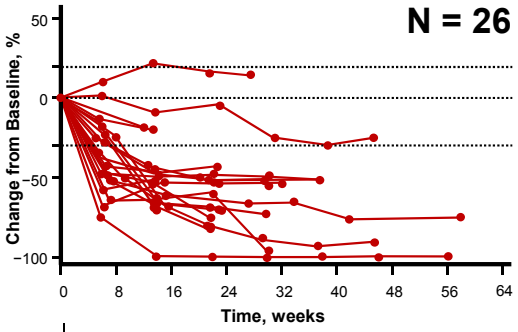
OS HR 0.61 *vs* vemurafenib

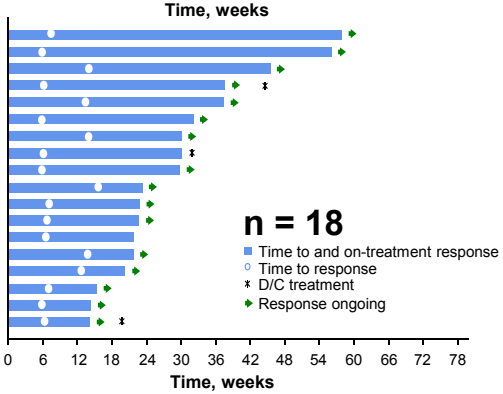
Less skin AEs with BRAFi + MEKi *vs* BRAFi[4–7]

1. Hauschild A, *et al.* Poster presented at ASCO 2013; Abstract 9013;
2. McArthur GA, *et al. Lancet Oncol* 2014;15:323–32;
3. Flaherty KT, *et al. N Engl J Med* 2012;367:107–14;
4. Long GV, *et al. Lancet* 2015;386:444–51;
5. Robert C, *et al. N Engl J Med* 2015;372:30–9;
6. Larkin J, *et al. N Engl J Med* 2014;371:1867–76.
2.7. Dummer et al. Lancet Oncol 2018

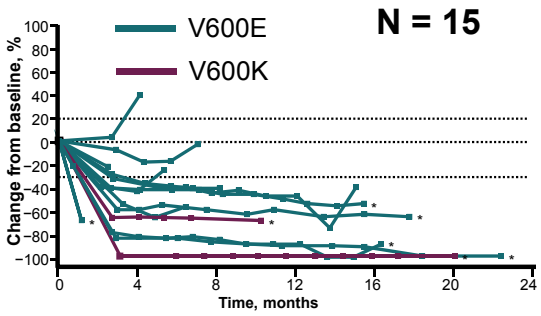
Clinical Trials Combining BRAFi + MEKi + Anti–PD-1/L1

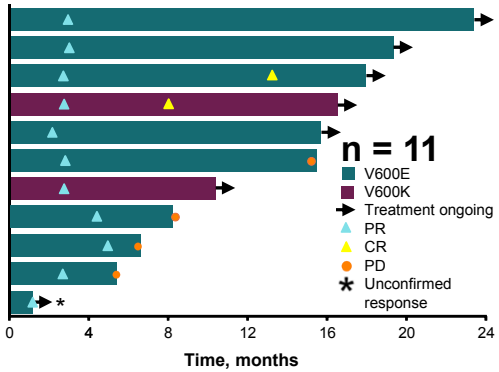
Dabrafenib + Trametinib + Durvalumab[1]



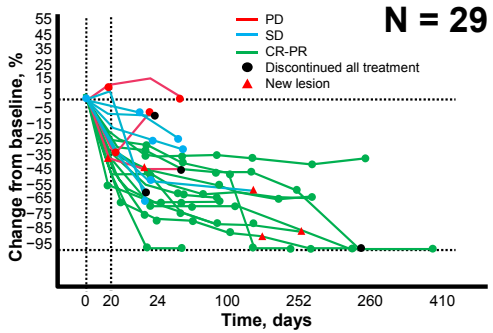


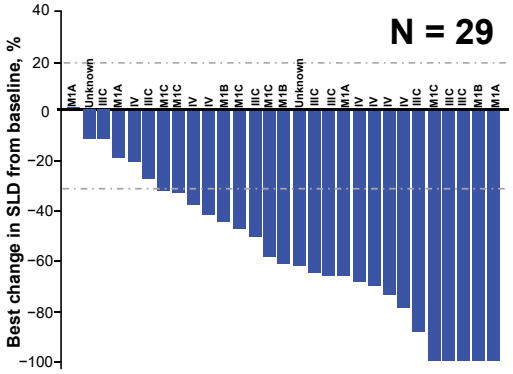
Dabrafenib + Trametinib + Pembrolizumab[2,3]



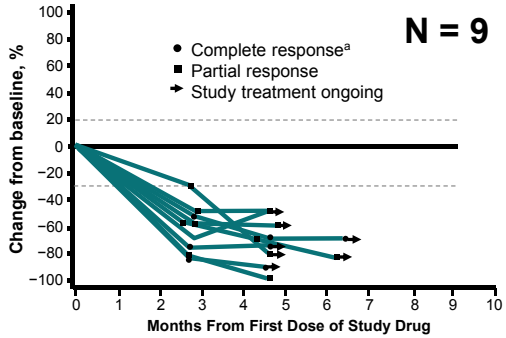


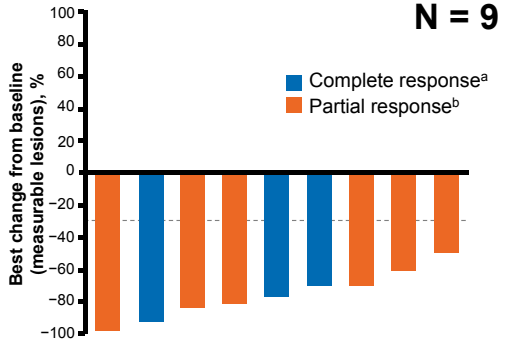
Vemurafenib + Cobimetinib + Atezolizumab[4]





Dabrafenib + Trametinib + Spartalizumab[5]

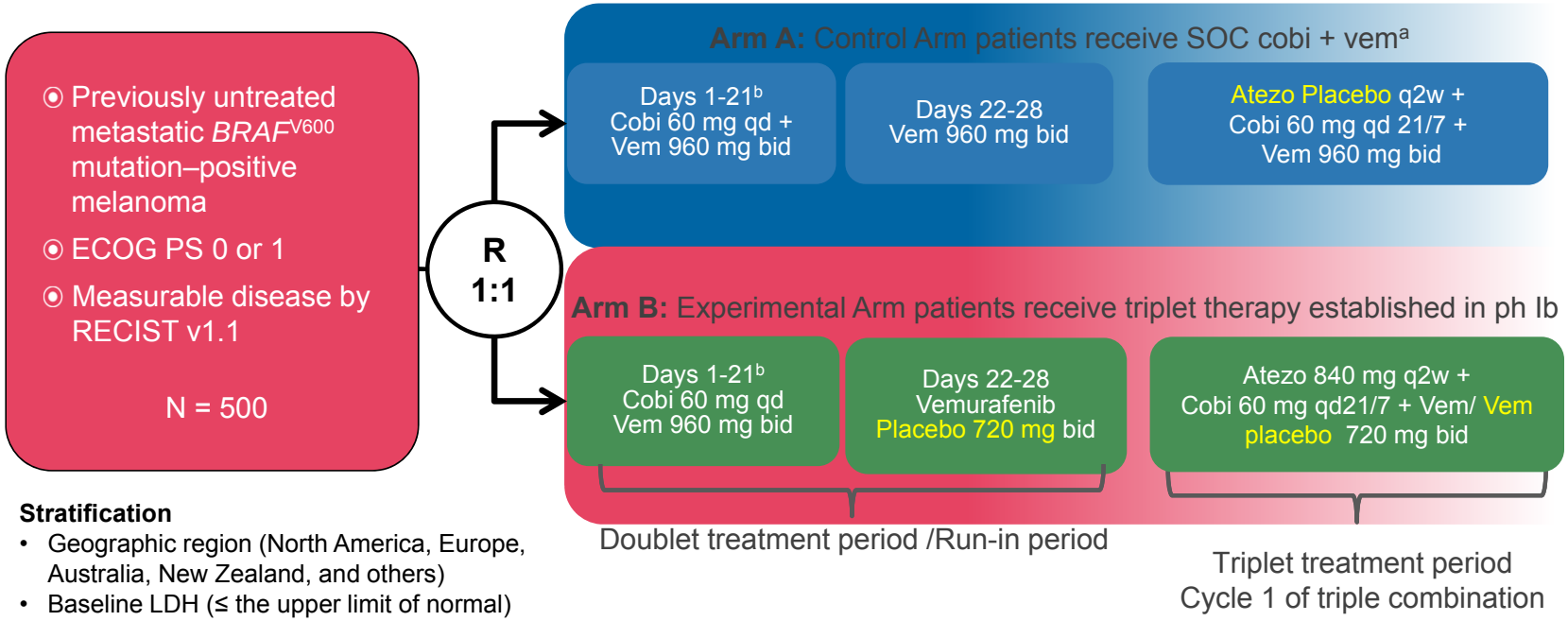




BRAFi, BRAF inhibitor; CR, complete response; D/C, discontinued; MEKi, MEK inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of lesion diameters. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change in non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change in all target lesions and (b) non-CR/non-PD response for nontarget lesions.

1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

IMspire150 (TRILOGY) Phase III Study of Atezo + Cobi + Vem in *BRAF*^{V600}mut Melanoma (NCT02908672): Study Design



Stratification

- Geographic region (North America, Europe, Australia, New Zealand, and others)
- Baseline LDH (≤ the upper limit of normal)

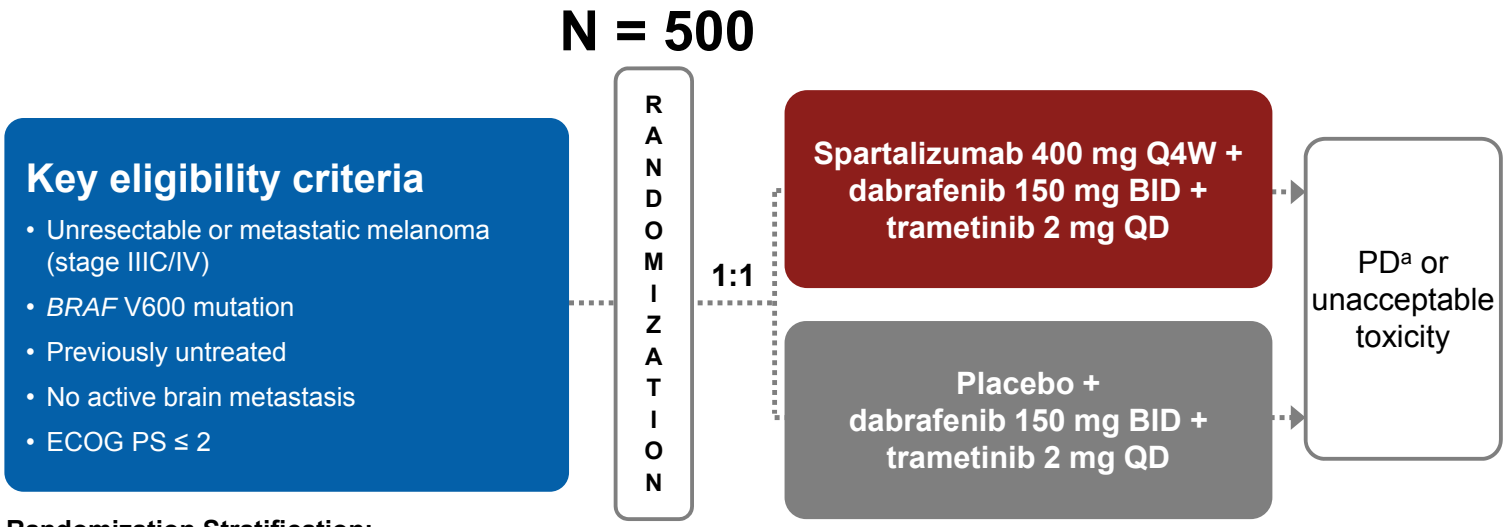
[a]The preferred treatment for *BRAF*^{V600} mutation–positive metastatic melanoma is combination targeted therapy: dabrafenib + trametinib or cobimetinib + vemurafenib (NCCN & ESMO guidelines)

[b]Cobi and vem will be dosed at the approved dose and schedule during the doublet treatment period.

Abbreviations: IRF, independent review facility; LDH, lactate dehydrogenase; R, randomized.

Reference: https://clinicaltrials.gov/ct2/show/NCT02908672. Accessed July 2017.

COMBI-i Part 3: Randomized, Double Blind, Placebo Controlled

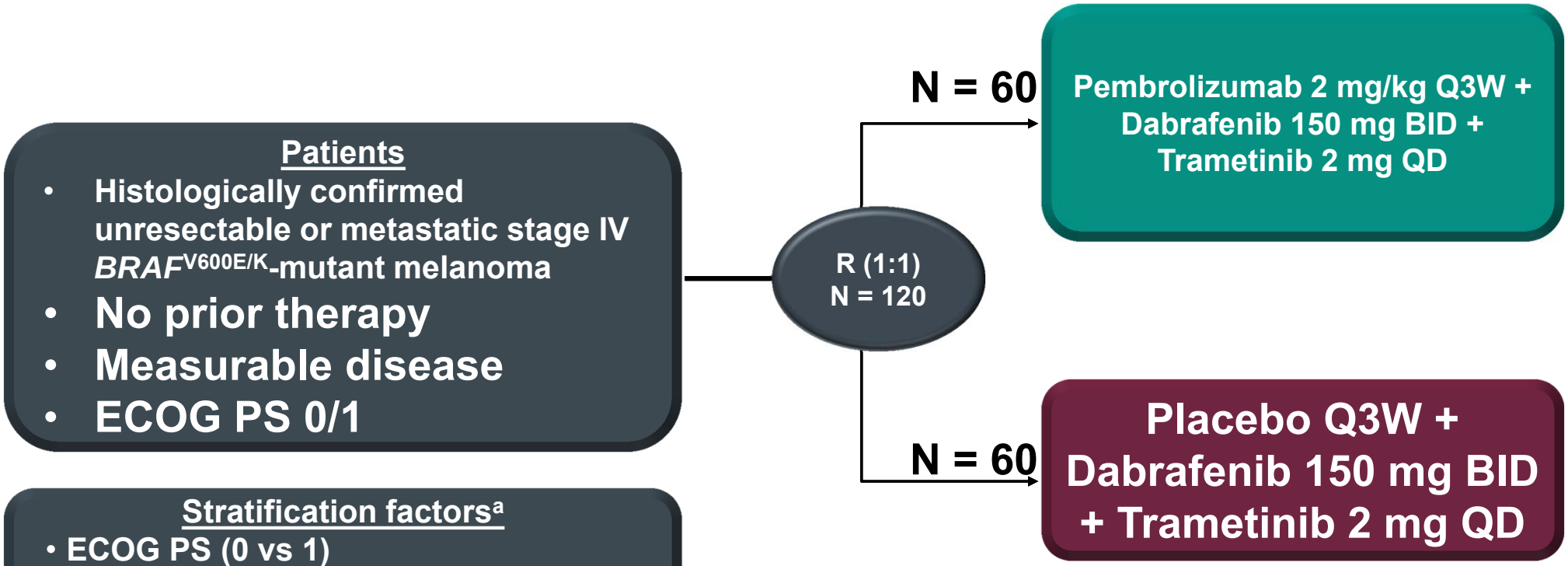


Primary endpoint: PFS[RECIST v1.1]

Secondary endpoints: OS, ORR, DOR, DCR, safety, PRO, PK

PRO, patient-reported outcomes; ULN, upper limit of normal.

KEYNOTE-022 Part 3 Study Design (NCT02130466)



- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Assessments and Statistical Considerations

Assessments

- Response: investigator review per RECIST v1.1
- AEs per NCI CTCAE v4.0 until 30 days after study end (serious AEs, 90 days)

Analysis populations

- Efficacy: all randomly assigned patients
- Safety: all patients who received ≥1 dose of study drug
- Power of PFS analysis: 80% to reject null hypothesis at 1-sided type 1 error of 0.025 with ~74 PFS events,[a] assuming HR of 0.50; observed HR ≤0.62 for statistical significance

- **Median follow-up:**
  - Pembrolizumab + D + T arm: 9.6 months (range, 2.7-19.6 months)
  - D + T arm: 9.8 months (range, 3.2-23.4 months)

[a]The data base was locked at 72 PFS events because the power of the study with 72 PFS events was identical to that with 74 PFS events.

Baseline Characteristics

	Pembro + D + T N = 60	Placebo + D + T N = 60
Age, median (range), y	54 (18-82)	58 (21-83)
Male, n (%)	33 (55)	36 (60)
ECOG PS, n (%)		
0	48 (80)	48 (80)
1	12 (20)	12 (20)
LDH, n (%)		
≤1.1 × ULN	33 (55)	34 (57)
>1.1 × ULN	27 (45)	26 (43)
BRAF mutation, n (%)		
V600E	52 (87)	49 (82)
V600K	8 (13)	11 (18)
PD-L1 status,[a] n (%)		
Positive	47 (78)	44 (73)
Negative/missing	10 (17)/3 (5)	12 (20)/4 (7)

[a]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).

Data cutoff: Feb 15, 2018.

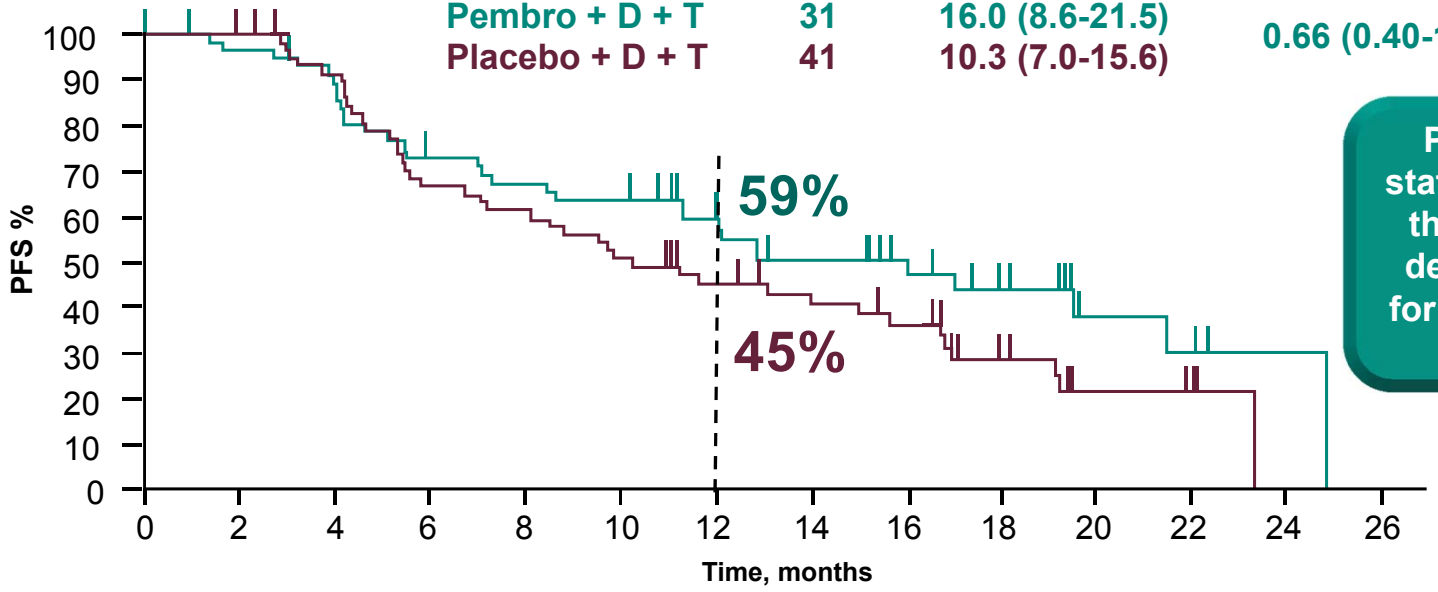
Baseline Characteristics (cont)

	Pembro + D + T N = 60	Placebo + D + T N = 60
Stage at entry, n (%)		
IIIB	1 (2)	1 (2)
IIIC	0 (0)	2 (3)
IV	59 (98)	57 (95)
Metastatic stage, n (%)		
M1a	2 (3)	10 (17)
M1b	8 (13)	9 (15)
M1c	49 (82)	38 (63)
No brain metastases, n (%)	59 (98)	59 (98)
No prior radiation, n (%)	51 (85)	54 (90)
Prior therapy, n (%)		
Adjuvant	8 (13)	5 (8)
Neoadjuvant	1 (2)	1 (2)
No prior therapy	51 (85)	54 (90)

Data cutoff: Feb 15, 2018.

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, *P* ≤ 0.025)

No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.

[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

[c]One-sided *P* value based on stratified log-rank test.

Data cutoff: Feb 15, 2018.

Best Overall Response (investigator review[a], RECIST v1.1)

	Pembro + D + T, n (%) N = 60	Placebo + D + T, n (%) N = 60	Difference in rate[b] % (95% CI)[b]	*P* Value[c]
ORR	38 (63.3)	43 (71.7)	–7.9 (–24.2 to 8.9)	0.3549
CR	11 (18.3)	8 (13.3)	5.4 (–8.2 to 18.8)	0.4229
PR	27 (45.0)	35 (58.3)	–13.2 (–30.4 to 4.7)	0.1477
DCR	51 (85.0)	56 (93.3)	–7.9 (–20.1 to 3.5)	0.1624
SD	13 (21.7)	13 (21.7)	0 (–14.9 to 15.0)	—
PD	5 (8.3)	3 (5.0)	3.0 (-7.0 to 13.6)	—
Nonevaluable	2 (3.3)	0	3.4 (–2.7 to 11.7)	—
No assessment	2 (3.3)	1 (1.7)	1.5 (–6.0 to 9.6)	—

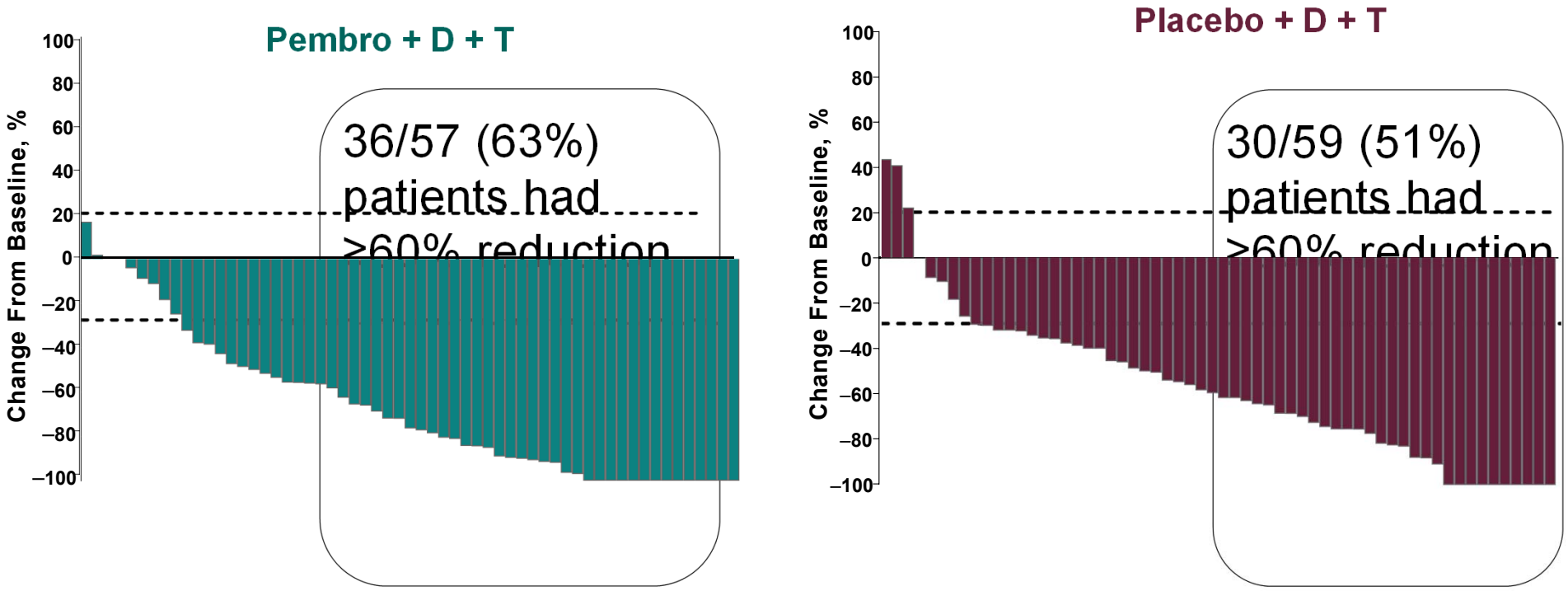
[a]Responses are based on investigator best assessment across time points per RECIST v1.1 with confirmation.

[b]Based on Miettinen and Nurimen method stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment was made.

Data cutoff: Feb 15, 2018.

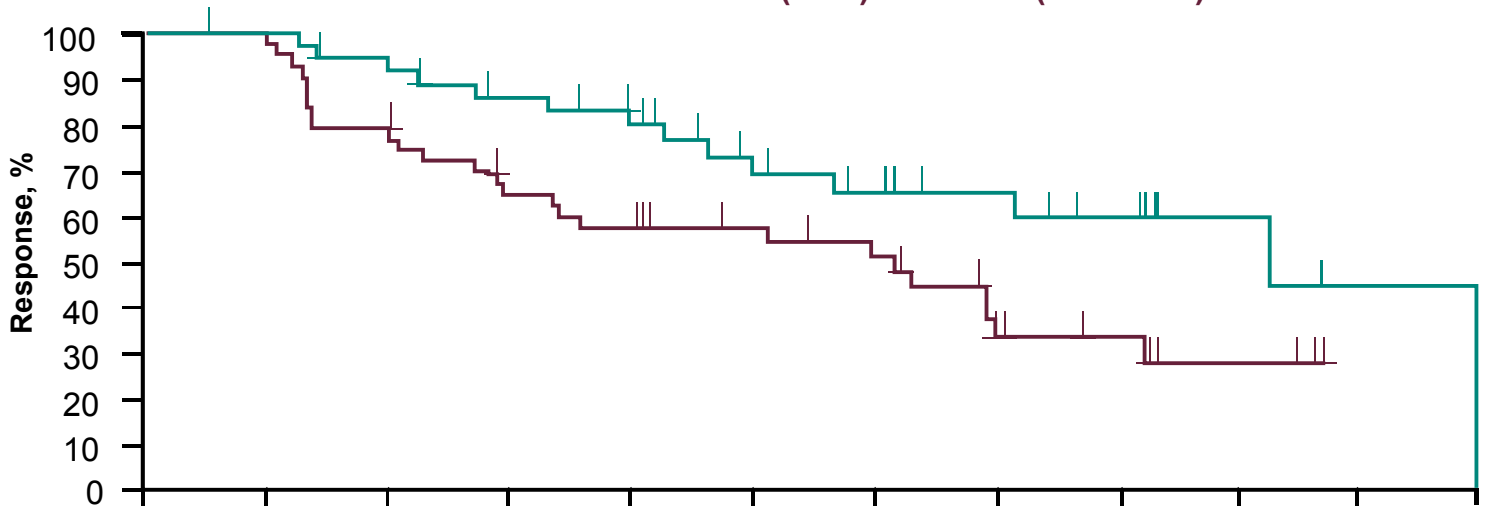
Best Percentage Change From Baseline in Target Lesion Size[a]



[a]Maximum percentage change in target lesion size based on investigator assessment in patients with post-baseline values.
Data cutoff: Feb 15, 2018.

Kaplan-Meier Analysis of Duration of Response[a]

DOR	DOR[b] ≥18 mo n (%)	Median (range),[b] mo
Pembro + D + T	4 (59.8)	18.7 (1.9+-22.1)
Placebo + D + T	3 (27.8)	12.5 (2.1-19.5+)

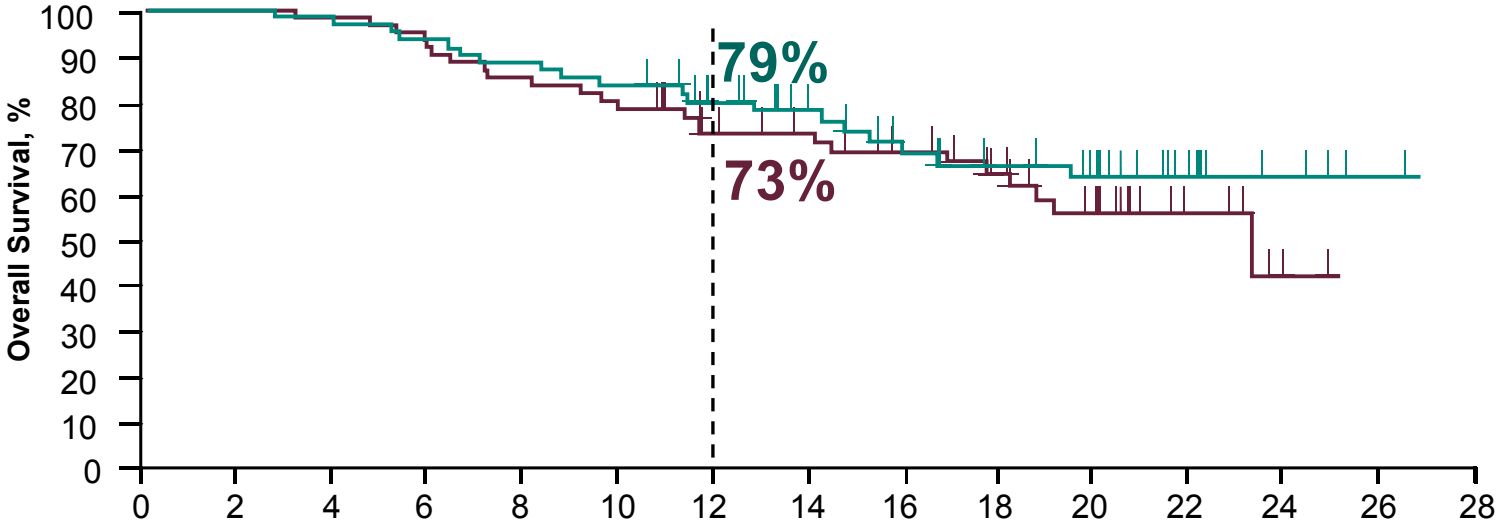


No. at risk												
Pembro + D + T	38	37	34	29	27	19	15	12	9	4	1	1
Placebo + D + T	43	43	34	27	23	19	17	10	6	3	0	0

[a]Confirmed response based on investigator assessment per RECIST v1.1.
[b]From Kaplan-Meier method for censored data.
+ indicates there was no progressive disease at last disease assessment.
Data cutoff: Feb 15, 2018.

Overall Survival

	Events, n	Median[a] (95% CI), mo	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	19	NR (19.6-NR)	0.76 (0.41-1.39)	0.18467
Placebo + D + T	24	23.4 (17.8-NR)		



No. at risk

Pembro + D + T	60	60	59	56	53	50	43	35	29	23	18	9	4	1	0
Placebo + D + T	60	60	59	55	51	47	39	36	31	25	18	7	2	0	0

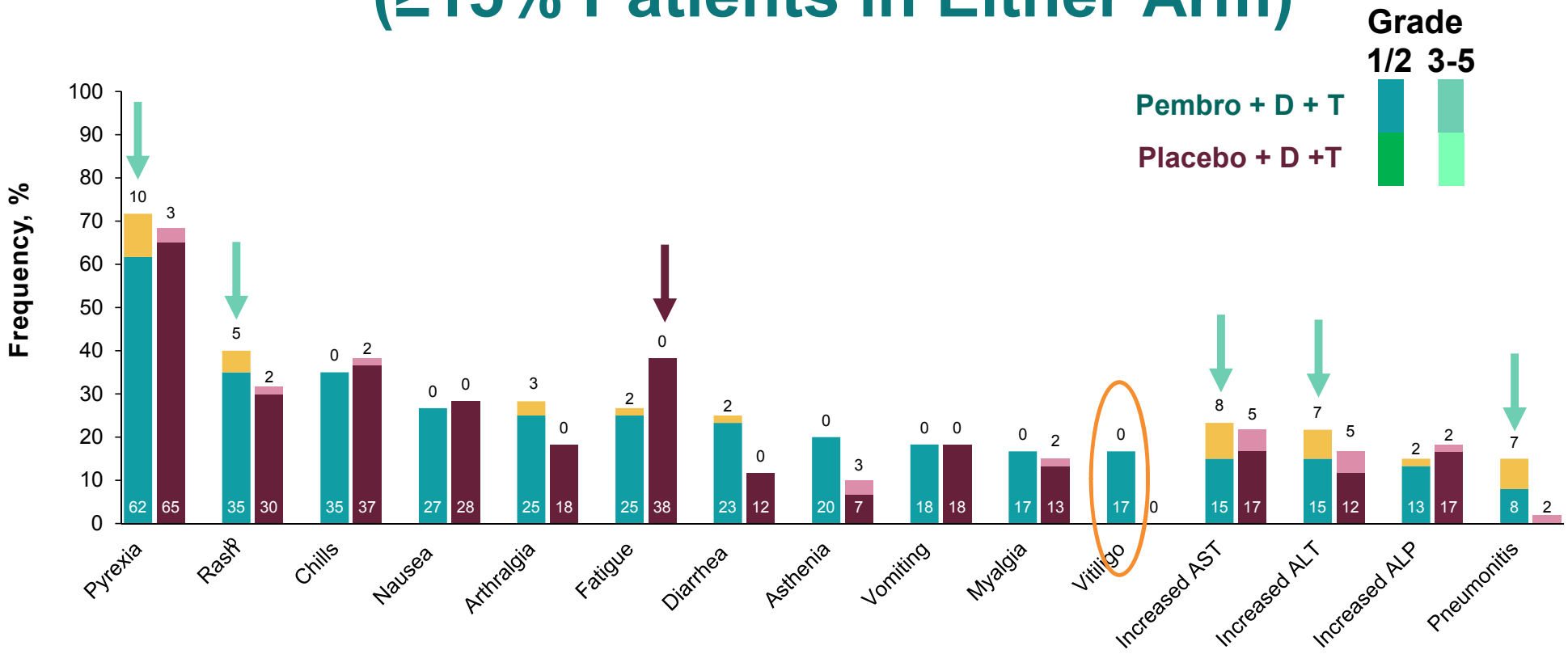
[a]Based on Kaplan-Meier estimate of overall survival.

[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided *P* value based on stratified log-rank test.

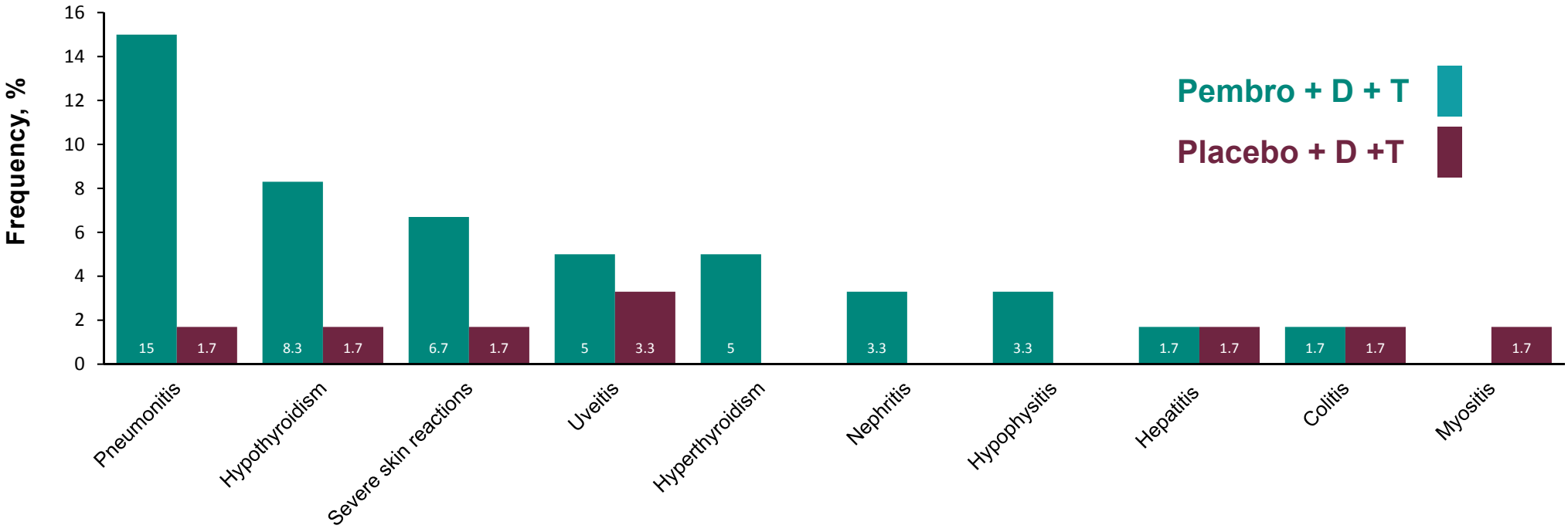
Data cutoff: Feb 15, 2018.

Treatment-Related Adverse Events[a] (≥15% Patients in Either Arm)



[a]Frequency indicated at the base of columns for grade 1/2 treatment-related adverse events, on top of the column for grade 3-5 events.
[b]Rash and maculopapular rash.
Data cutoff: Feb 15, 2018.

Immune-Mediated Adverse Events (≥1 Patients)



Data cutoff: Feb 15, 2018.

Summary and Conclusions

Pembrolizumab + D + T as first-line therapy in patients with advanced *BRAF*^{V600}-mutant melanoma showed promising efficacy and manageable tolerability

Pembrolizumab + D + T versus placebo + D + T showed

- Numerically higher PFS (not statistically significant, as per study design)
- Numerically longer duration of response
- Higher rate of grade 3-4 treatment-related AEs (most were manageable through treatment interruption or dose reduction; 1 treatment-related death in the triplet arm because of pneumonitis)
- Higher incidence of discontinuation of ≥1 study drug owing to treatment-related AEs (40%)

Role of PD-1 inhibitors as part of triplet therapy with BRAF and MEK inhibitors must be further validated in phase 3 studies

BARCELONA 2019 ESMO congress

Evaluation of Combination Treatment With Cobimetinib Plus Atezolizumab Versus Pembrolizumab in Previously Untreated Patients With Wild Type *BRAF*^{V600} Advanced Melanoma: Primary Analysis From the Phase 3 IMspire170 Trial

Ana Arance[1]; Helen Gogas[2]; Brigitte Dréno[3]; Keith Flaherty[4]; Lev Demidov[5]; Daniil Stroyakovskiy[6]; Zeynep Eroglu[7]; Pier Francesco Ferrucci[8]; Jacopo Pigozzo[9]; Piotr Rutkowski[10]; Jacek Mackiewicz[11]; Isabelle Rooney[12]; Athina Voulgari[13]; Sarah Troutman[12]; Bethany Pitcher[14]; Yibing Yan[12]; James Larkin[15]

[1]Department of Medical Oncology, Hospital Clínic Barcelona, Barcelona, Spain; [2]First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]C.H.R.U Hotel Dieu, Nantes, France; [4]Massachusetts General Hospital, Boston, Massachusetts, USA; [5]Russian Oncological Research Centers, Moscow, Russia; [6]Moscow City Oncology Hospital, Moscow, Russia; [7]Moffitt Cancer Center, Tampa, Florida, USA; [8]European Institute of Oncology – IRCCS, Milan, Italy; [9]Melanoma Oncology Unit, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; [10]Maria Sklodowska-Curie Institute – Oncology Center, Warsaw, Poland; [11]University of Medical Sciences in Poznań, Poznań, Poland; [12]Genentech, Inc., South San Francisco, California, USA; [13]Roche Products Ltd., Welwyn Garden City, United Kingdom; [14]Hoffmann-La Roche Ltd., Mississauga, Ontario, Canada; [15]Royal Marsden NHS Foundation Trust, London, United Kingdom

Introduction

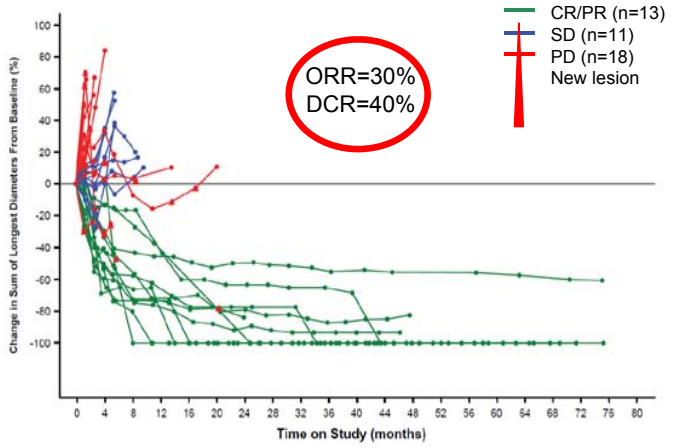
PD-1 inhibitors are approved for the treatment of patients with *BRAF* wild-type metastatic melanoma[1,2]

- With 5-year OS rates of 34–39%,[3,4] there remains a need for more effective systemic treatments

PD-L1 blockade with atezolizumab has shown efficacy in patients with metastatic melanoma[5]

Cobimetinib, a MEK inhibitor is approved in combination with vemurafenib in *BRAF*^{V600} MT metastatic melanoma[6]

Change in tumour burden over time with atezolizumab monotherapy in patients with metastatic melanoma (n=43)[5]

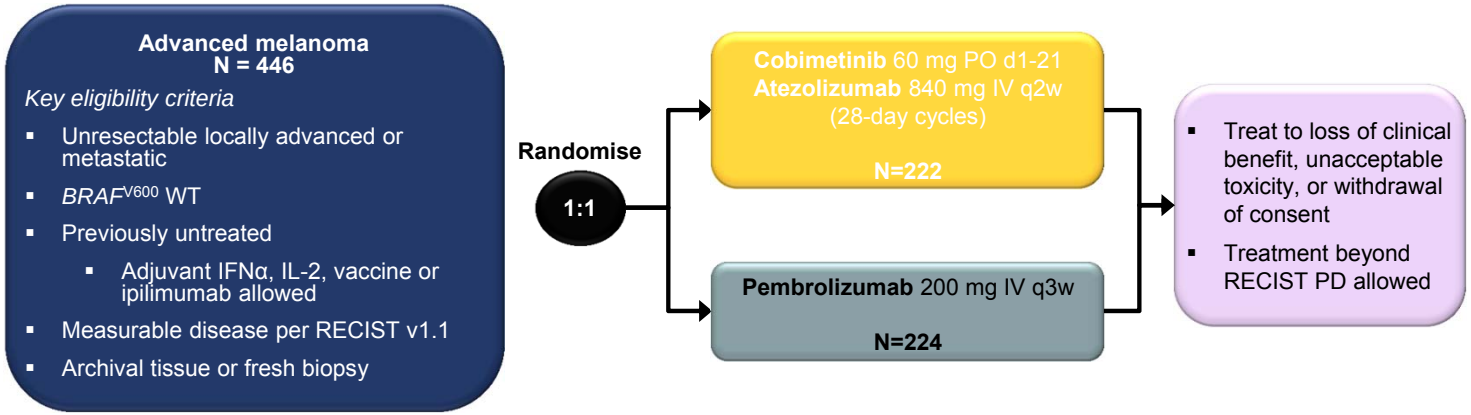


1. Robert C, et al. *N Engl J Med.* 2015;372:320-30. 2. Larkin J, et al. *N Engl J Med* 2015;373:23-34. 3. Robert C, et al. *Cancer Res.* 2019;79(suppl):CT188. 4. Topalian SL, et al. *JAMA Oncol.* 2019 Jul 25 [Epub ahead of print]. 5. Hamid O et al. *Clin Cancer Res.* 2019 Jul 29 [Epub ahead of print]. 6. Ascierto et al. *Lancet Oncol.* 2016;17:1248-60.

DCR, disease control rate; ORR, objective clinical response rate; OS, overall survival; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1.

BRAF^{V600} WT
Previously untreated

IMspire170: A Phase 3, Open-label, Multicenter, Randomised Study

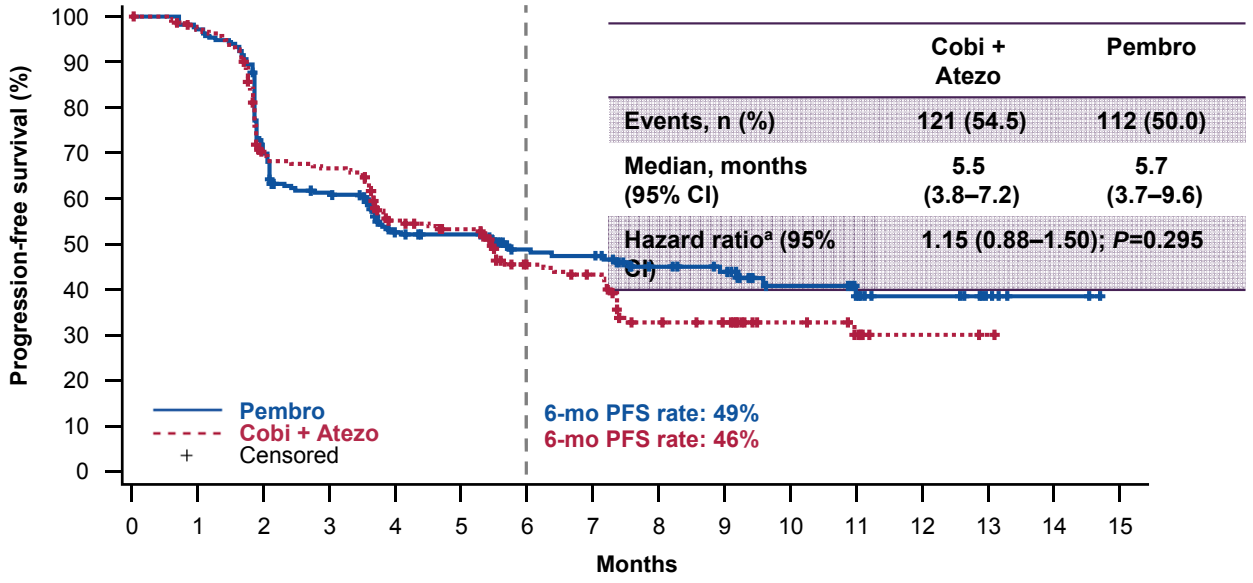


Stratification factors

- PD-L1 status (IC0 vs IC1/2/3)[a]
- LDH (≤ULN vs >ULN)
- Geographic location (North America vs Europe vs Australia/New Zealand/others)

[a]Assessed using an anti–human PD-L1 rabbit monoclonal antibody (SP142; Ventana Medical Systems).
IC, immune cell; IFNα, interferon alpha; IL-2, interleukin-2; INV, investigator; IRC, independent review committee; IV, intravenous; LDH, lactate dehydrogenase; PO, per oral; q2w, every 2 weeks; q3w, every 3 weeks; ULN, upper limit of normal.

IRC-Assessed PFS (Primary Endpoint)



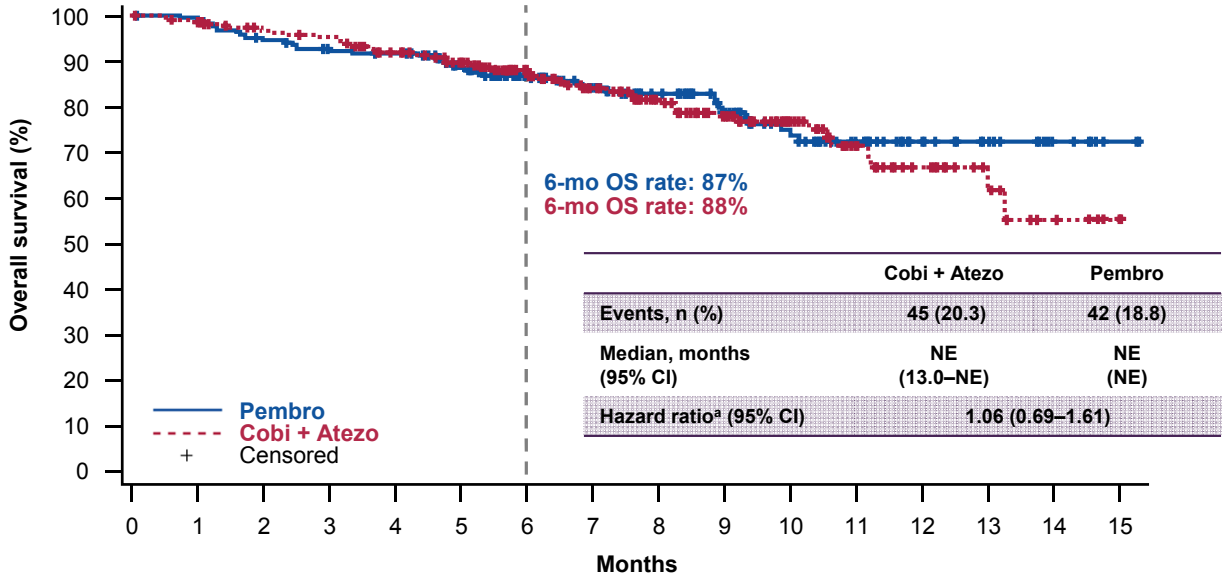
	Cobi + Atezo	Pembro
Events, n (%)	121 (54.5)	112 (50.0)
Median, months (95% CI)	5.5 (3.8–7.2)	5.7 (3.7–9.6)
Hazard ratio[a] (95% CI)	1.15 (0.88–1.50); *P*=0.295	

Number at risk

Pembro	**224**	204	150	**124**	93	88	67	65	42	38	22	20	12	6	2	NE
Cobi + Atezo	**222**	201	138	**131**	96	89	60	54	32	30	14	12	5	1	NE	NE

Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15).
[a]Stratified by PD-L1 status and baseline LDH level. CI, confidence interval; IRC, independent review committee; NE, not estimable.

First Interim Overall Survival



	Cobi + Atezo	Pembro
Events, n (%)	45 (20.3)	42 (18.8)
Median, months (95% CI)	NE (13.0–NE)	NE (NE)
Hazard ratio[a] (95% CI)	1.06 (0.69–1.61)	

Number at risk

Pembro	224	214	203	196	193	167	142	118	95	76	56	39	22	15	7	2
Cobi + Atezo	222	215	204	199	181	163	137	112	92	74	50	32	21	12	6	1

Data cutoff: April 15, 2019; median follow-up duration: 7.0 months (range, 0–15). [a]Stratified by PD-L1 status and baseline LDH level.

Conclusions

The IMspire trial was very well conducted and clarifying

The combination of cobimetinib plus atezolizumab did not demonstrate an improvement in PFS compared with pembrolizumab monotherapy, in patients with *BRAF*^{V600} wild-type advanced melanoma

Salvage Therapy after Failure from anti PD-1 Single Agent Treatment. A Study by the German ADOReg Melanoma Registry.

Michael Weichenthal, Selma Ugurel, Ulrike M. Leiter, Imke Satzger, Katharina C. Kähler, Julia Welzel, Claudia Pföhler, Ingrid Feldmann-Böddeker, Friedegund Elke Meier, Patrick Terheyden, Sebastian Haferkamp, Rudolf Herbst, Jens Ulrich, Jochen Utikal, Alexander Kreuter, Ralf Gutzmer, Dirk Schadendorf, Peter Mohr

N=200

- Metastatic Stage IV or unresectable Stage III Melanoma
- Cutaneous, mucosal or unknown primary allowed
- Failure to single agent anti-PD1 antibody treatment in any line
- No previous anti-CTLA-4 agents

In BRAF-positive patients
- Previous BRAF/MEK inhibitor treatment required

n=47 → **Ipilimumab** (3mg/kg) Q3W X4

n=77 → **Nivolumab** (1mg/kg) + **Ipilimumab** (3mg/kg) Q3W X4→ **Nivolumab** (3mg/kg Q2W)

n=18 → **BRAF-/MEK inhibitor re-challange**
Dabra/Tram, Cobi/Vem, Enco/Bini

n=58 → **Other Regimens**
Chemo: DTIC, Carboplatin/Tax, others
TVEC, TKI, others

Patient Characteristics

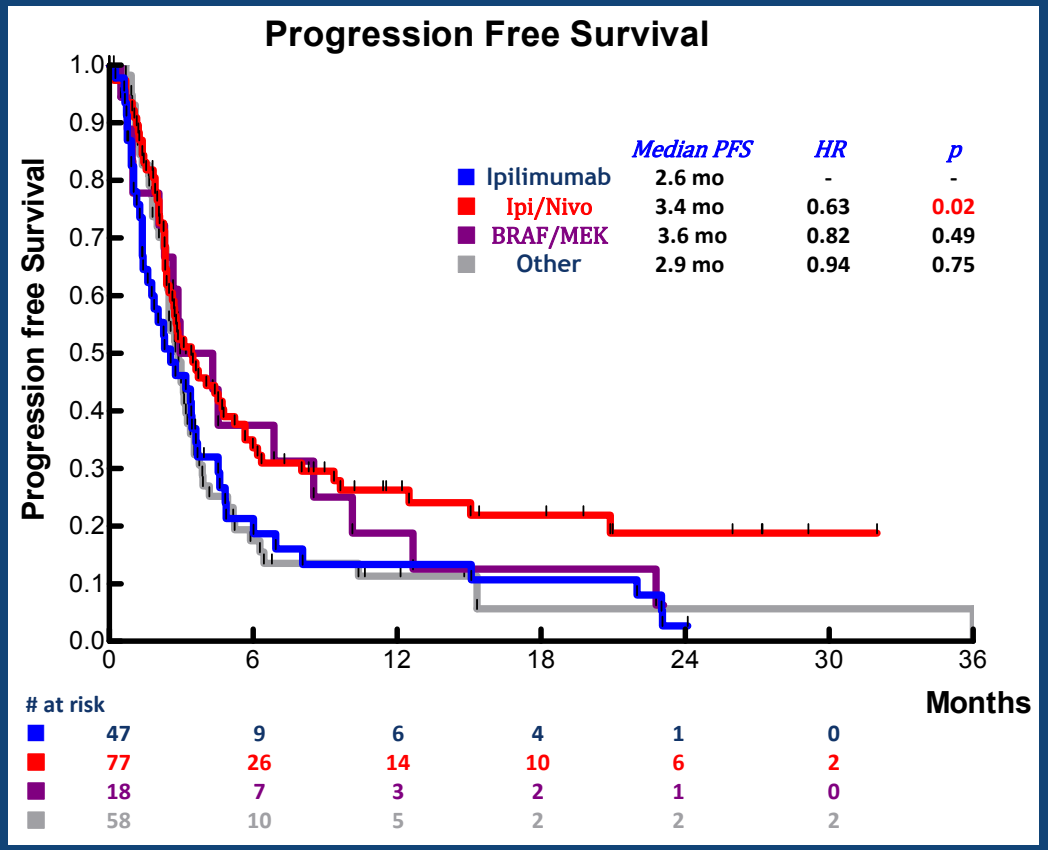
	Ipilimumab (n=47)	Ipilimumab/Nivo (n=77)	BRAF-i/Mek-i re-Challenge (n=18)	Other: Chemo, TVEC etc. (n=58)
Gender (male:female)	27 / 20	42 / 35	12 / 6	35 / 26
Median Age [years]	71.0	61.0	68.5	73.0
Mucosal Melanoma	3 (6.4 %)	5 (6.5 %)	0	3 (5.2 %)
BRAF V600 mutated	7 (14.9 %)	17 (22.1 %)	18 (100 %)	7 (12.1 %)
ECOG Performance 1 Status 2+	9 (19.1 %) 7 (14.9 %)	15 (19.4 %) 3 (3.9 %)	5 (27.8 %) 3 (16.7 %)	17 (29.3 %) 9 (15.5 %)
AJCC stage III n (%) IV	4 (8.5 %) 43 (91.5 %)	1 (1.3 %) 76 (98.7 %)	1 (5.6 %) 17 (94.4 %)	5 (8.6 %) 53 (91.4 %)
Brain metastasis	14 (29.8 %)	23 (29.9 %)	9 (50.0 %)	13 (22.4 %)
LDH > ULN, n (%)	22 (46.8 %)	20 (26.0 %)	6 (33.3 %)	34 (58.6 %)
Line of Treatment 2nd 3rd 4+	36 7 4	56 12 9	- 14 4	46 8 4

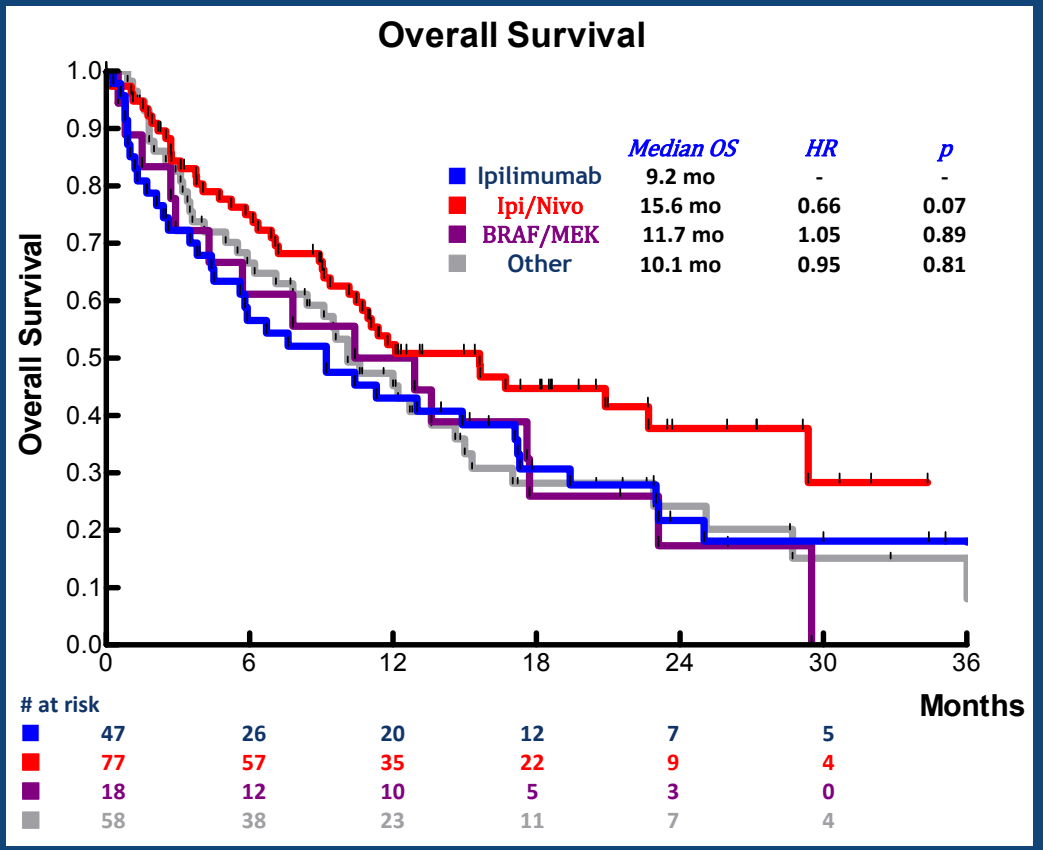
Treatment Outcome

	Ipilimumab (n=47)	Ipilimumab /Nivolumab (n=77)	BRAF-i/Mek-i re-Challenge (n=18)	Other: Chemo, TVEC etc. (n=58)
Median Follow-up	30 months	19 months	26 months	22 months
Objective Remissions	2 (4.2 %)	15 (19.5 %)*	4 (22.2 %)*	7 (12.1 %)
Disease Control Rate	9 (17.0 %)	34 (44.2 %)**	9 (50.0 %)*	14 (24.2 %)
Toxicity °III/IV or Tx Discontinuation	17 (36.2 %)	26 (33.8 %)	3 (16.7 %)	6 (10.4 %)
Median PFS	2.6 months	3.4 months	3.6 months	2.9 months
12 Month PFS Rate	13.3 %	26.2 %	18.8 %	11.3 %
Median OS	9.2 months	15.6 months	11.7 months	10.1 months
12 Months OS rate	43.0 %	52.3 %	50.0 %	45.2 %
18 Months OS rate	30.7 %	44.7 %	25.9 %	28.2 %

* $p<0.05$ ** $p<0.01$ (as compared to Ipilimumab)

Treatment Outcome





Update on Brain Metastases

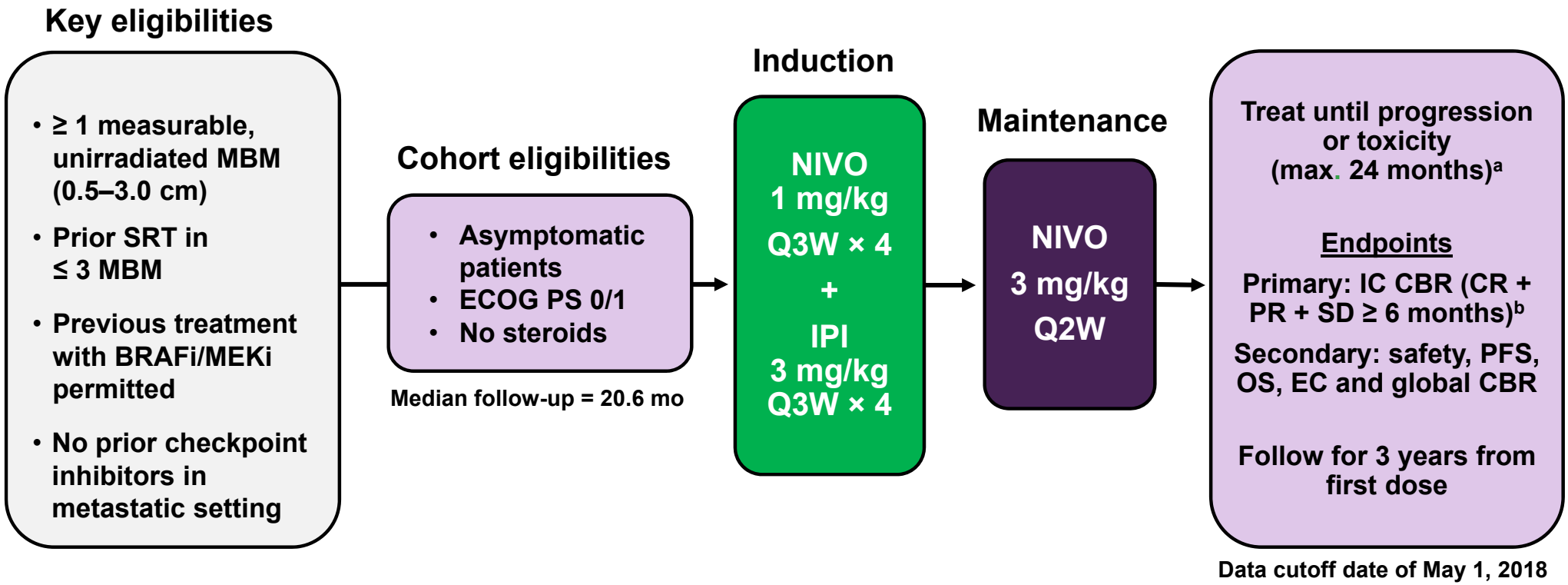
Efficacy and Safety of the Combination of Nivolumab Plus Ipilimumab in Patients With Melanoma and Asymptomatic or Symptomatic Brain Metastases (CheckMate 204)

Hussein Tawbi,[1] Peter Forsyth,[2] F. Stephen Hodi,[3] Christopher Lao,[4] Stergios Moschos,[5] Omid Hamid,[6] Michael B. Atkins,[7] Karl Lewis,[8] Reena P. Thomas,[9] John A. Glaspy,[10] Sekwon Jang,[11] Alain Algazi,[12] Nikhil I. Khushalani,[2] Michael A. Postow,[13] Anna C. Pavlick,[14] Marc Ernstoff,[15] David A. Reardon,[3] Agnes Balogh,[16] Jasmine Rizzo,[16] Kim Margolin[17]

[1]University of Texas, MD Anderson Cancer Center, Houston, TX; [2]Moffitt Cancer Center and Research Institute, Tampa, FL; [3]Dana-Farber Cancer Institute, Boston, MA; [4]University of Michigan, Ann Arbor, MI; [5]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [6]The Angeles Clinic and Research Institute, Los Angeles, CA; [7]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; [8]University of Colorado Comprehensive Cancer Center, Aurora, CO; [9]Stanford University Hospital, Palo Alto, CA; [10]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA; [11]Inova Schar Cancer Institute, Virginia Commonwealth University, Fairfax, VA; [12]University of California, San Francisco, San Francisco, CA; [13]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [14]New York University Langone Medical Center, New York, NY; [15]Roswell Park Cancer Institute, Buffalo, NY; [16]Bristol-Myers Squibb, Princeton, NJ; [17]City of Hope, Duarte, CA

Abstract Number 9501

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.

Demographic and Patient Characteristics – Asymptomatic Patients

	Patients (n = 101)[a]
Male, n/N (%)	**68/101 (67)**
Median age, years (range)	**59.0 (22–81)**
***BRAF* mutation, n/N (%)**	**66/99 (67)**
***NRAS* mutation, n/N (%)**	**7/26 (27)**
LDH > ULN, n/N (%)	**41/101 (41)**
LDH > 2 × ULN, n/N (%)	**11/101 (11)**
PD-L1 expression, n/N (%) ≥ 1% < 1%	 **44/81 (54)** **37/81 (46)**
Prior SRT, n/N (%)	**9/101 (9)**
Median of sum of intracranial target lesion diameters, mm (range)	**15 (5–91)**
Intracranial target lesions, n (%) 1–2 lesions ≥ 3 lesions	 **78/100 (78)** **22/100 (22)**

[a]Nine patients did not have extracranial disease.

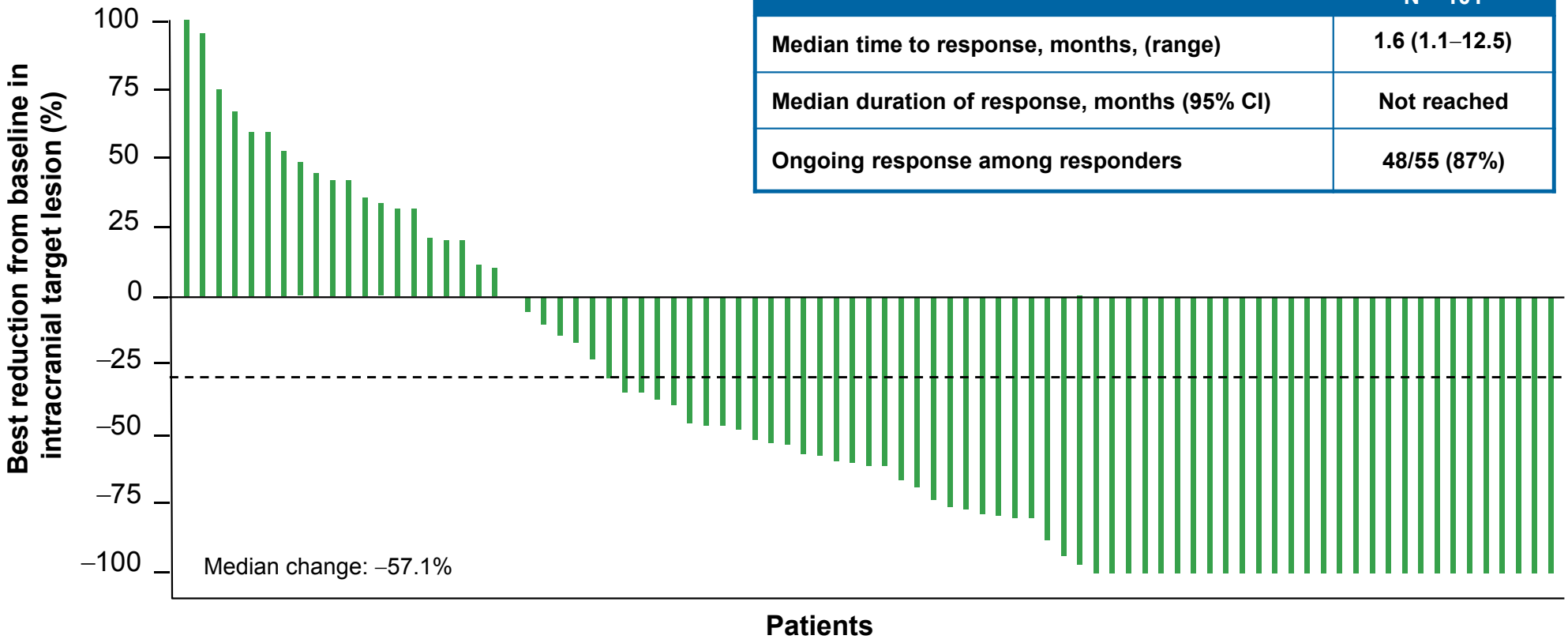
Response to Treatment – Asymptomatic Patients

	Patients (n = 101)		
	Intracranial	Extracranial	Global
Best overall response, n (%)			
Complete response	**29 (29)**	**11 (11)**	**11 (11)**
Partial response	**26 (26)**	**38 (38)**	**40 (40)**
Stable disease ≥ 6 months	**4 (4)**	**6 (6)**	**4 (4)**
Progressive disease	**27 (27)**	**16 (16)**	**28 (28)**
Not evaluable	**15 (15)**	**30 (30)[a]**	**18 (18)**
Death prior to first on-study assessment	**3 (3)**	**3 (3)**	**2 (2)**
Early discontinuation due to toxicity	**0 (0)**	**1 (1)**	**1 (1)**
Stable disease < 6 months	**8 (8)**	**15 (15)**	**10 (10)**
Other	**4 (4)**	**11 (11)**	**5 (5)**
ORR, n/N (%) (95% CI)	**55/101 (54) (44–64)**	**49/101 (49) (38–59)**	**51/101 (51) (40–61)**
CBR[b], n/N % (95% CI)	**59/101 (58) (48–68)**	**55/101 (54) (44–64)**	**55/101 (54) (44–64)**

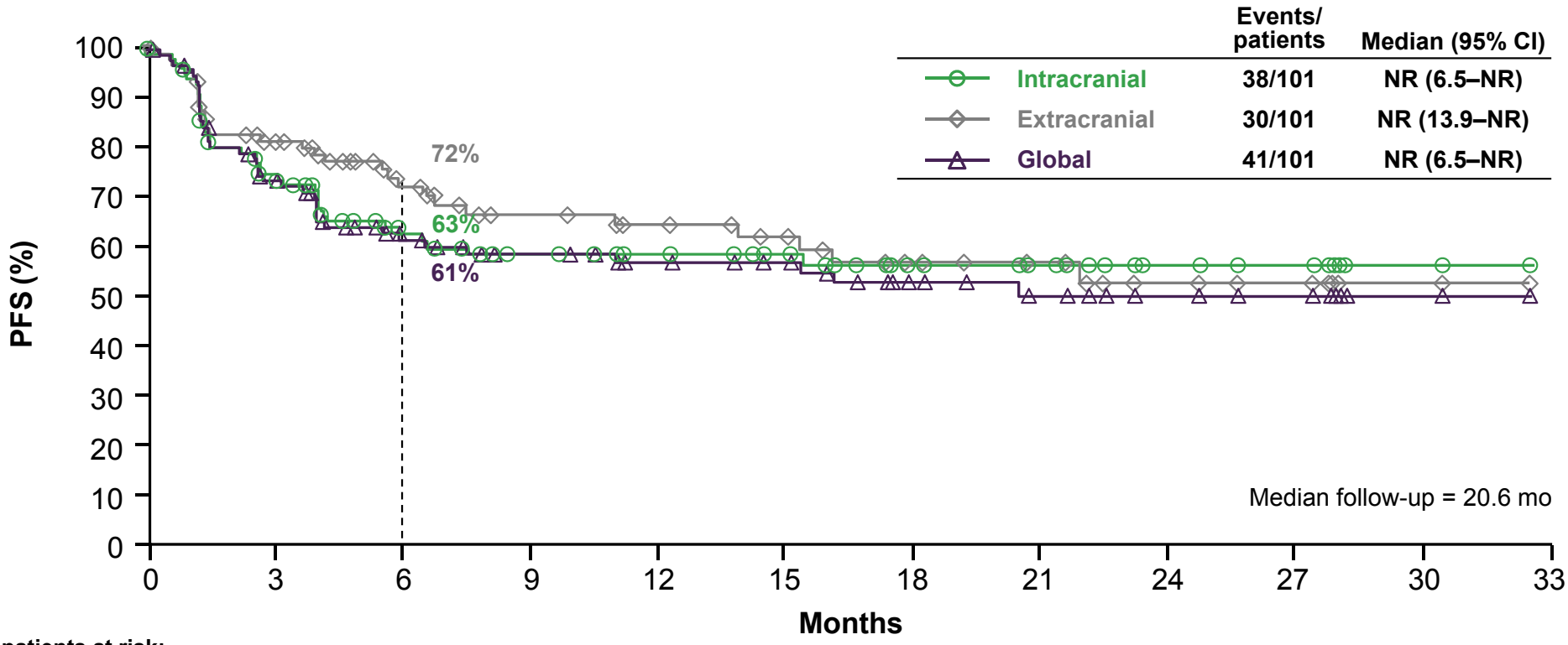
[a]Seven of these patients did not have extracranial disease at baseline; [b]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

Intracranial Tumor Burden Change and Characteristics of Intracranial Response – Asymptomatic Patients

	N = 101
Median time to response, months, (range)	1.6 (1.1–12.5)
Median duration of response, months (95% CI)	Not reached
Ongoing response among responders	48/55 (87%)



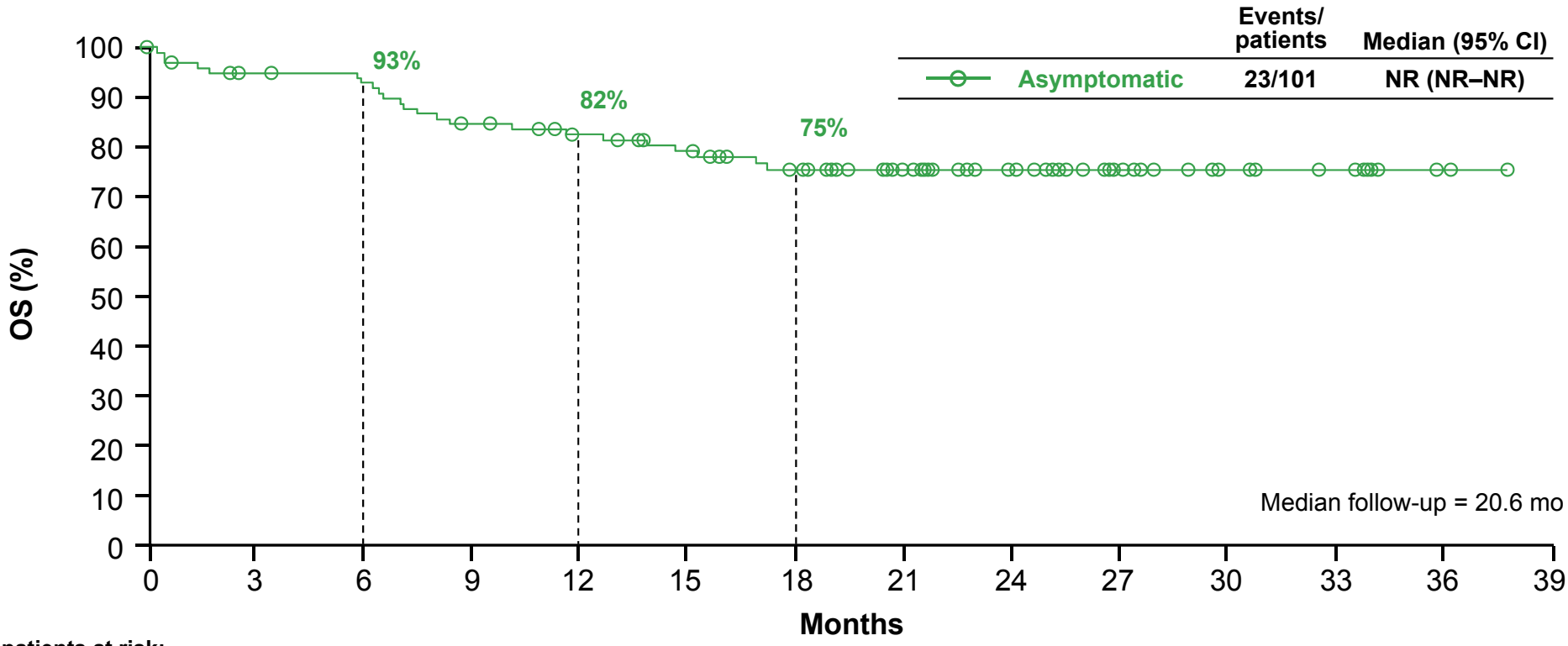
Progression-Free Survival – Asymptomatic Patients



Number of patients at risk:

Intracranial:	101	65	46	38	34	30	21	18	10	8	2	0
Extracranial:	101	62	42	33	29	25	19	16	9	7	2	0
Global:	101	64	45	38	33	30	21	17	10	8	2	0

Overall Survival – Asymptomatic Patients



Number of patients at risk:

Asymptomatic:	101	92	89	80	74	67	58	47	35	22	15	8	2	0

Summary − Asymptomatic Patients

- ORR was 54%, with an estimated 6-month PFS rate of 63%
- At a median follow-up of 20.6 months, **median OS** has not yet been reached
- These results are paralleled and confirmed in an independent Australian study[1]
- Patients in this study cohort were a select population without *any* neurologic symptoms or steroid therapy
- Questions concerning symptomatic patients led to an amendment to allow enrollment of up to 20 patients with symptomatic disease to explore NIVO+IPI in these patients

1. Long GV, et al. *Lancet Oncol.* 2018;19:672−681.

Background – Symptomatic Cohort

- Patients with symptomatic MBM are more challenging to treat
  - Patients tend to deteriorate quickly
  - Steroid use may reduce the effectiveness of immunotherapy

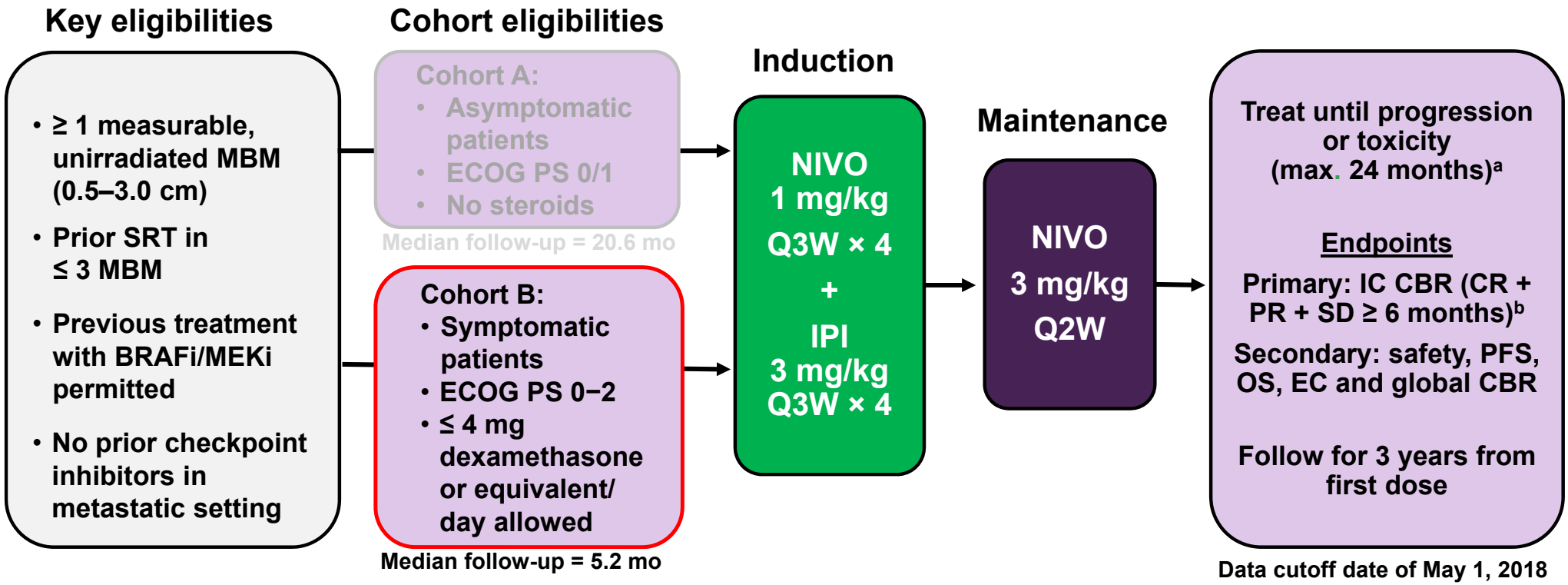
Treatment	Patients	ORR	DOR
IPI[1]	21	5%	Not reported
NIVO[2]	16	6%	Not reached
Dabrafenib+ Trametinib[3]	17[a]	59%	4.5 mo

[a]*BRAF* mutant patients.

- Here we provide the first report of safety and efficacy of NIVO+IPI in patients with MBM who are symptomatic and/or on steroids

1. Margolin K, et al. *Lancet Oncol*. 2012;13:459−465; 2. Long GV, et al. *Lancet Oncol.* 2018;19:672−681; 3. Davies MA, et al. *Lancet Oncol.* 2017;18:863−873.

CheckMate 204 Study Design with Cohort B



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.

Demographic and Patient Characteristics – Symptomatic Patients

	Patients (n = 18)[a]
Male, n/N (%)	**13/18 (72)**
Median age, years (range)	**59.5 (29–80)**
***BRAF* mutation, n/N (%)**	**8/16 (50)**
***NRAS* mutation, n/N (%)**	**1/2 (50)**
LDH > ULN, n/N (%)	**8/17 (47)**
LDH > 2 × ULN, n/N (%)	**2/17 (12)**
PD-L1 expression, n/N (%) ≥ 1% < 1%	 **6/10 (60)** **4/10 (40)**
Prior SRT, n/N (%)	**0**
Median of sum of intracranial target lesion diameters, mm (range)	**26 (7–86)**
Intracranial target lesions, n/N (%) 1–2 lesions ≥ 3 lesions	 **11/18 (61)** **7/18 (39)**
Steroid use at baseline, n/N (%)	**11/18 (61)**

[a]One patient did not have extracranial disease.

Response to Treatment – Symptomatic Patients

	Patients (n = 18)		
	Intracranial	Extracranial	Global
Best overall response, n (%)			
Complete response	**2 (11)**	**0**	**0**
Partial response	**2 (11)**	**4 (22)**	**4 (22)**
Stable disease ≥ 6 months	**0**	**0**	**0**
Progressive disease	**10 (56)**	**6 (33)**	**8 (44)**
Not evaluable	**4 (22)**	**8 (44)[a]**	**6 (33)**
Death prior to first on-study assessment	**2**	**1**	**1**
Early discontinuation due to toxicity	**0**	**0**	**0**
Stable disease < 6 months	**2**	**4**	**2**
Other	**0**	**3**	**3**
ORR, n/N (%) (95% CI)	**4/18 (22) (6–48)**	**4/18 (22) (6–48)**	**4/18 (22) (6–48)**
CBR,[b] n/N (%) (95% CI)	**4/18 (22) (6–48)**	**4/18 (22) (6–48)**	**4/18 (22) (6–48)**

[a] One of these patients did not have extracranial disease at baseline; [b]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

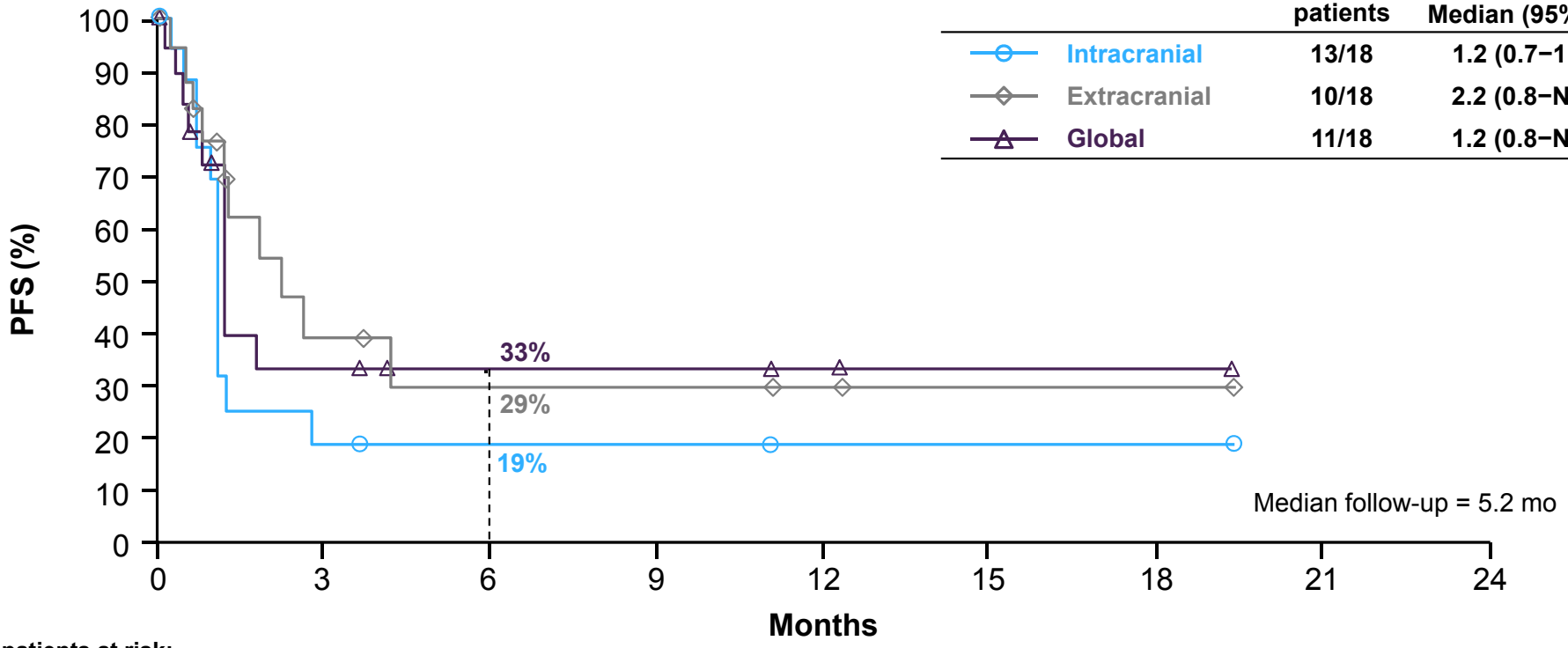
Symptomatic Cohort Responders

Intracranial response	*BRAF* status	NIVO+IPI induction doses	Maintenance doses	Steroid use at baseline
CR	Mutant	4	37	Yes
CR	Wild type	1	23	No
PR	Mutant	4	23	No
PR	Not reported	3	0[a]	No

- Median time to intracranial response of 4.1 (1.0−6.9) months; median duration of response not reached
- 3 of 4 (75%) with ongoing responses

[a]Patient discontinued treatment due to toxicity.

Progression-Free Survival – Symptomatic Patients

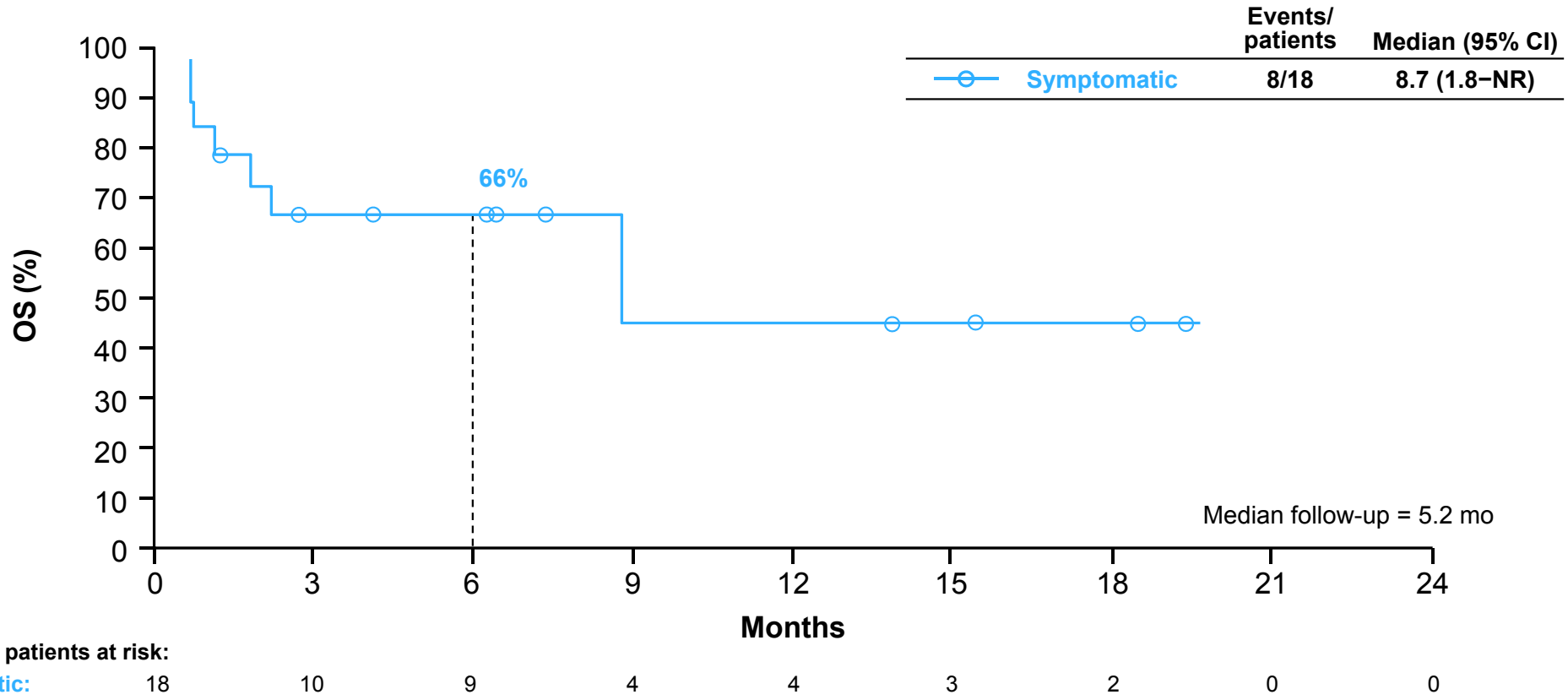


	Events/ patients	Median (95% CI)
Intracranial	13/18	1.2 (0.7–1.3)
Extracranial	10/18	2.2 (0.8–NR)
Global	11/18	1.2 (0.8–NR)

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

Overall Survival − Symptomatic Patients



Summary – Symptomatic Patients

- NIVO+IPI showed intracranial antitumor activity in symptomatic patients
  - ORR was 22% (2 CRs and 2 PRs)
  - Median OS was 8.7 months, with a 6-month survival rate of 66%
- Median number of NIVO+IPI doses received was 1 (range 1−4; 10 of 18 patients with one dose)
  - 4 patients entered the maintenance phase

Safety Summary − Both Cohorts

n (%)	Asymptomatic[a] n = 101		Symptomatic n = 18	
	Any grade	Grade 3−4	Any grade	Grade 3−4
Treatment-related AEs	97 (96)	55 (54)	16 (89)	10 (56)
Treatment-related nervous system AEs	35 (35)	7 (7)	3 (17)	3 (17)
Treatment-related AEs leading to discontinuation	29 (29)	19 (19)	2 (11)	0
Treatment-related nervous system AEs leading to discontinuation	2 (2)	2 (2)	0	0

[a]One death reported: treatment-related grade 5 myocarditis (previously reported).[1]

1. Johnson DB, et al. *N Engl J Med*. 2016;375:1749−1755.

Treatment-Related Neurologic AEs – Both Cohorts

Events reported in ≥ 2% of patients, n (%)	Asymptomatic[a] n = 101		Symptomatic n = 18	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Patients with any AEs	**35 (35)**	**7 (7)**	**3 (17)**	**3 (17)**
Headache	**20 (20)**	**3 (3)**	**1 (6)**	**1 (6)**
Paresthesia	**4 (4)**	**0**	**0**	**0**
Dysgeusia	**3 (3)**	**0**	**0**	**0**
Peripheral sensory neuropathy	**3 (3)**	**0**	**0**	**0**
Aphasia	**2 (2)**	**0**	**0**	**0**
Brain edema	**2 (2)**	**2 (2)**	**0**	**0**
Intracranial hemorrhage	**2 (2)**	**1 (1)**	**0**	**0**
Seizure	**2 (2)**	**0**	**0**	**0**
Amnesia	**0**	**0**	**1 (6)**	**1 (6)**
Dysarthria	**0**	**0**	**1 (6)**	**1 (6)**
Lethargy	**0**	**0**	**1 (6)**	**0**
Partial seizures	**0**	**0**	**1 (6)**	**1 (6)**
Syncope	**1 (1)**	**1 (1)**	**1 (6)**	**1 (6)**

[a]One death reported: treatment-related grade 5 myocarditis (previously reported).[1]

1. Johnson DB, et al. *N Engl J Med*. 2016;375:1749–1755.

Conclusions

- The safety profile of NIVO+IPI for asymptomatic and symptomatic patients with MBM was similar to that of patients without brain metastases[1,2]
- The durable intracranial responses observed in patients with asymptomatic brain metastases supports the use of NIVO+IPI as first-line therapy
- Symptomatic patients remain difficult to treat, but some can benefit from NIVO+IPI
- Further studies in patients with symptomatic brain metastases need to
  - Facilitate and accelerate the screening phase to enable rapid treatment
  - Evaluate the incorporation or sequencing of radiation therapy
  - Incorporate targeted therapies and/or steroid-sparing agents

1. Hodi FS, et al. *Lancet Oncol*. 2016;17:1558−1568; 2. Hodi FS, et al. *Lancet Oncol.* 2018;19:1480−1492.

BARCELONA 2019 ESMO congress

Melanoma Institute Australia

Long-term Outcomes from the Randomized Ph 2 Study of Nivolumab or Nivolumab + Ipilimumab in Patients With Melanoma Brain Metastases: Anti-PD1 Brain Collaboration (The ABC Trial)

Georgina V. Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Michael P. Brown, Maria Gonzalez, Alexander Guminski, Richard A. Scolyer, Louise Emmett, Alexander M. Menzies, Grant A. McArthur

esmo.org

THE UNIVERSITY OF SYDNEY

Study Design

Total 76 Patients Recruited

- **Melanoma Brain Metastases ≥ 5mm & < 40mm**
- **No previous**
  - **Anti-CTLA-4**
  - **Anti-PD-1 or -PD-L1 agents**
- **Previous BRAFi+MEKi allowed**
- **ECOG PS 0-2**
- **No serious autoimmune disease**
- **No corticosteroids**

(Cohort C > 10mg prednisone allowed)

R 1:1
up to n=51

A
No prior local brain Rx & asymptomatic
n=35
Nivolumab + Ipilimumab

B
No prior local brain Rx & asymptomatic
n=25
Nivolumab

C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=16
Nivolumab

Primary Endpoint: **Intracranial Response Rate ≥ wk 12**

Secondary Endpoints: Extracranial Response Rate

Overall Response Rate

PFS (Intracranial, Extracranial, Overall)

Overall Survival

Presented by Georgina V Long @ProfGLongMI

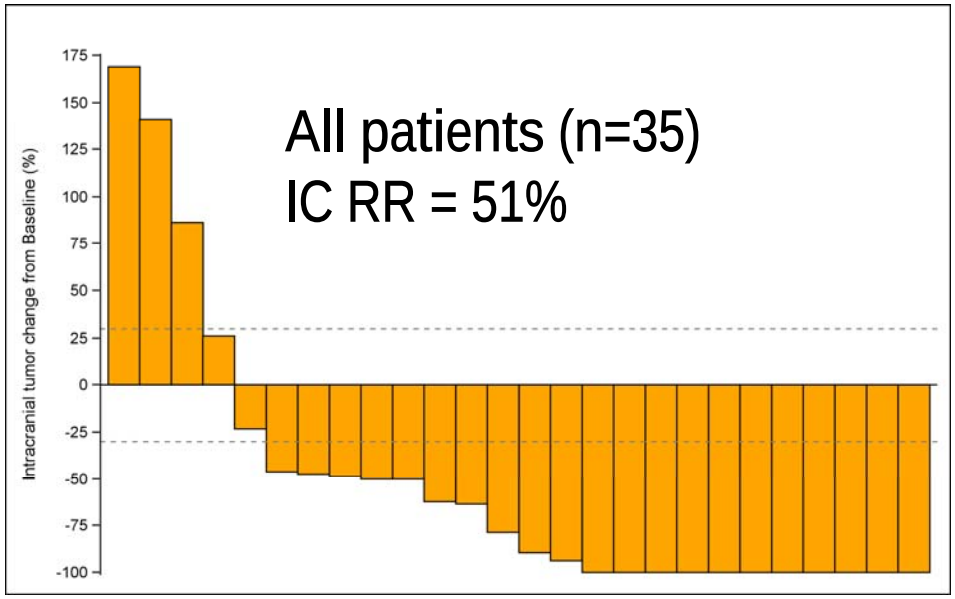
Patient Characteristics

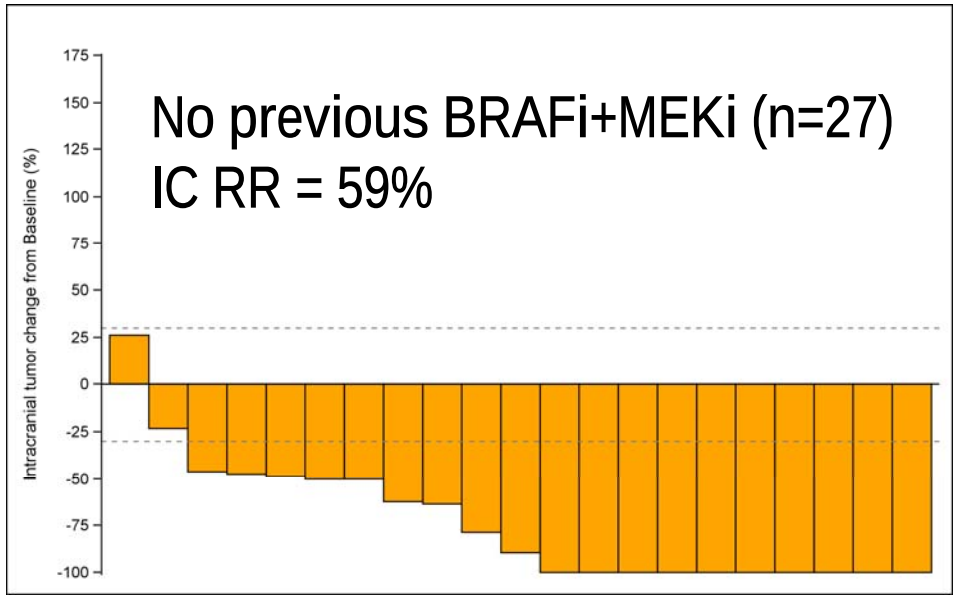
	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo † N=16
Age, median (range)	59 (29-76)	63 (31-86)	51 (28-73)
Sex, male n (%)	29 (83%)	19 (76%)	11 (69%)
ECOG performance status, n (%)			
0-1	34 (97%)	25 (100%)	15 (94%)
2	1 (3%)	0 (0%)	1 (6%)
LDH > ULN, n (%)	18 (51%)	14 (58%)	3 (19%)
V600 BRAF mutation-positive, n (%)	19 (54%)	14 (56%)	13 (81%)
Target brain metastases, n (%)			
1	11 (31%)	6 (24%)	1 (6%)
2-4	10 (29%)	14 (56%)	7 (44%)
>4	14 (40%)	5 (20%)	8 (50%)
Extracranial metastases, n(%)	30 (86%)	21 (84%)	12 (75%)
Prior BRAFi+MEKi	8 (23%)	6 (24%)	12 (75%)

† Previous local treatment (n=16), neurological symptoms (n=10), leptomeningeal disease (n=4)

Presented by Georgina V Long @ProfGLongM

Cohort A: Nivolumab + Ipilimumab
Intracranial Response



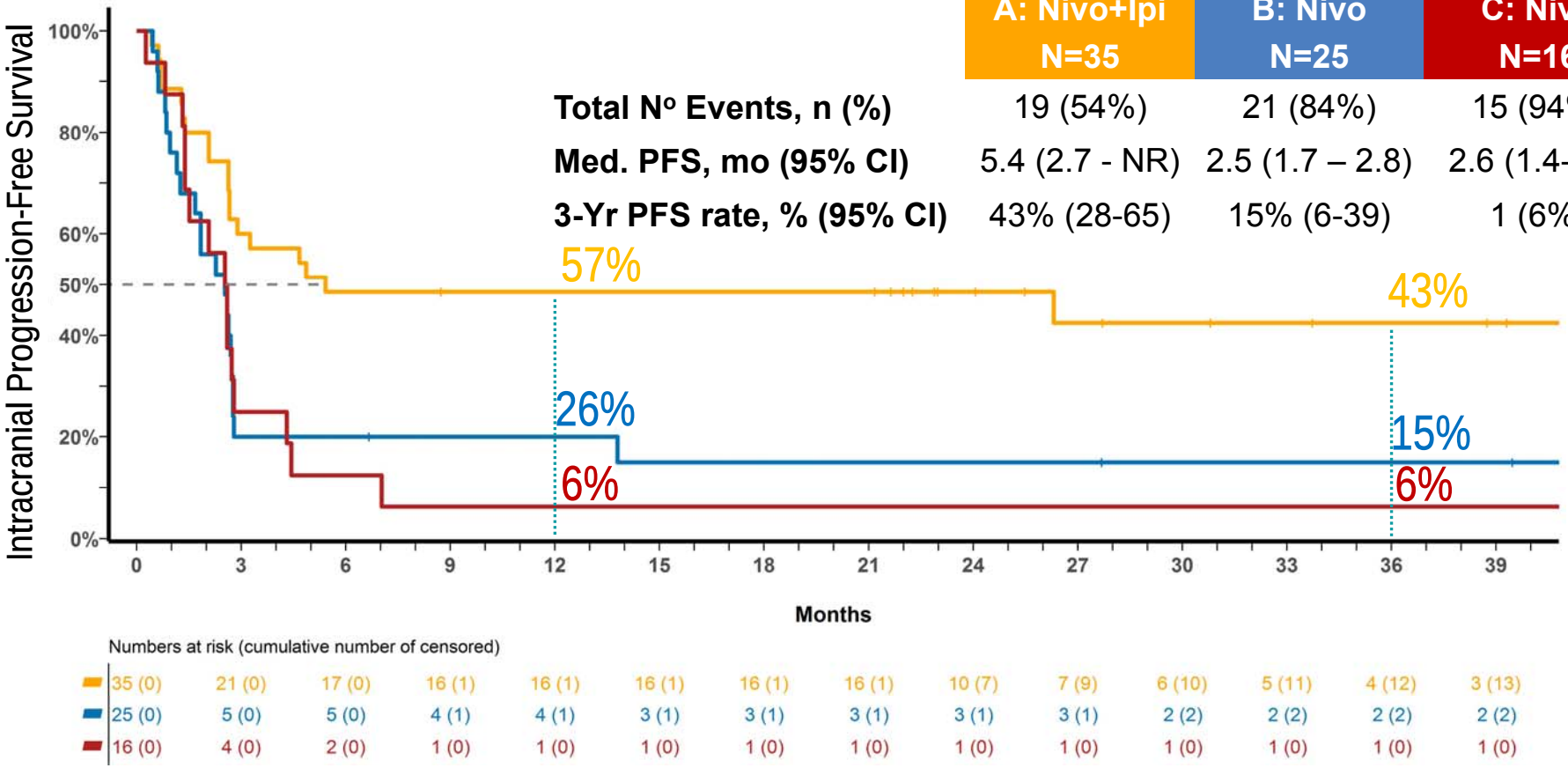


Previous BRAFi+MEKi
ORR = 25% (2/8)

Presented by Georgina V Long @ProfGLongMI

Intracranial Progression-Free Survival

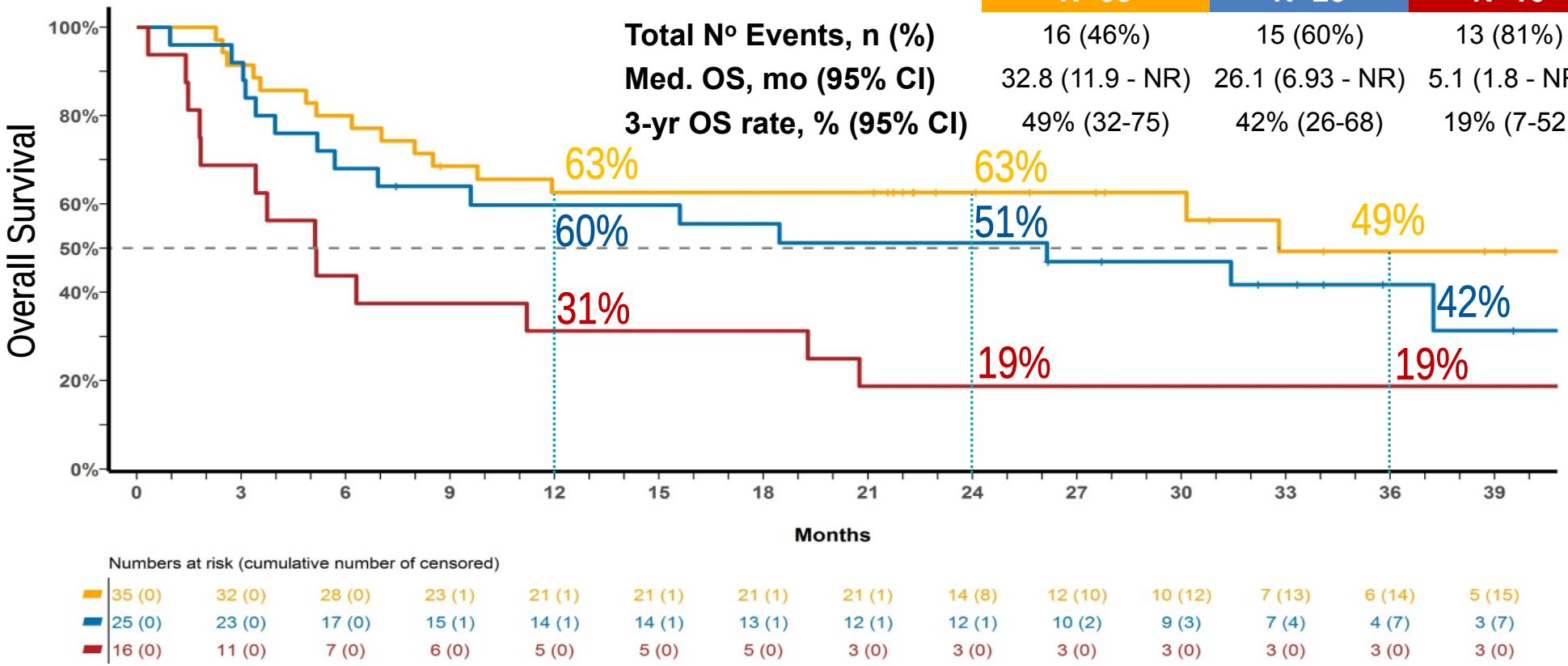
	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	19 (54%)	21 (84%)	15 (94%)
Med. PFS, mo (95% CI)	5.4 (2.7 - NR)	2.5 (1.7 – 2.8)	2.6 (1.4-4.4)
3-Yr PFS rate, % (95% CI)	43% (28-65)	15% (6-39)	1 (6%)



Presented by Georgina V Long @ProfGLongMI

Overall Survival

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo N=16
Total Nº Events, n (%)	16 (46%)	15 (60%)	13 (81%)
Med. OS, mo (95% CI)	32.8 (11.9 - NR)	26.1 (6.93 - NR)	5.1 (1.8 - NR)
3-yr OS rate, % (95% CI)	49% (32-75)	42% (26-68)	19% (7-52)



Presented by Georgina V Long @ProfGLongMIA

Subsequent Therapy After Intracranial PD

	A: Nivo+Ipi N=20	B: Nivo N=16	C: Nivo N=8
Any treatment, n (%)	**(57%)**	**(64%)**	**(50%)**
Local therapy			
Radiotherapy	7 (35%)	12 (75%)	2 (25%)
Surgery	3 (15%)	2 (12%)	2 (25%)
Systemic			
BRAF/MEKi	9 (45%)	9 (56%)	5 (62%)
Ipilimumab	4 (20%)	7 (44%)	2 (25%)
Anti-PD-1	5 (25%)	4 (25%)	0 (0%)
Ipilimumab + Anti-PD-1	5 (25%)	9 (56%)	1 (12%)
Chemotherapy	2 (10%)	0 (0%)	0 (0%)

Presented by Georgina V Long @ProfGLongMI

Treatment-Related Adverse Events

	A: Ipi+Nivo N=35	B: Nivo N=25	C: Nivo † N=16
Treatment-related AEs, n (%)	34 (97%)	17 (68%)	8 (50%)
Grade 3/4 treatment-related AEs, n (%)	19 (54%)	5 (20%)	2 (13%)
Treatment-related SAE, n (%)	16 (46%)	1 (4%)	2 (13%)
Discontinuation due to AE*	5 (14%)	1 (4%)	0 (0%)

- No new or unexpected AEs
- 4/76 (5%) pts had neurological SAE: 1 radionecrosis^, 1 seizure, 2 headache
- No deaths due to treatment-related AE

SAE; Serious Adverse Event
*Pts with grade 3/4 treatment related AE in Cohort A were allowed to continue nivolumab monotherapy if recovered and deemed due to ipilim
^ Pt in cohort C, prior SRS

Conclusions

Nivolumab combined with ipilimumab or nivolumab alone have activity in untreated asymptomatic melanoma brain metastases. Without prior local therapy or BRAF/MEKi;

- **Nivo + Ipi Intracranial: Response Rate = 59%; 3-year PFS 48%**
- **Nivo alone Intracranial: Response Rate = 21%; 3-year PFS 14%**

Intracranial and extracranial responses were mostly concordant

Activity of nivo+/- ipi is low after BRAF/MEKi, after multiple modality therapy, or in pts with leptomeningeal/symptomatic intracranial melanoma

There were no unexpected toxicities and quality of life was maintained

Presented by Georgina V Long @ProfGLongMI