

The logo for the Associazione Italiana di Oncologia Medica (AIM) features the letters 'Aim' in a stylized font. The 'A' is green, the 'i' is red, and the 'm' is black. A green arc is positioned above the 'i' and 'm'.

Associazione Italiana di Oncologia Medica
SEZIONE REGIONE LAZIO

The Best of the Year 2018

MELANOMA: THE BEST OF THE YEAR 2018

Dott.ssa Silvia Quadrini
UOC Oncologia ASL Frosinone

ROMA - 19 dicembre 2018

NH Collection Vittorio Veneto

The Best of the Year 2018: MELANOMA



RO
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The Best of the Year 2018: MELANOMA



- CHIRURGIA
- TERAPIA ADIUVANTE
- TERAPIA PER MALATTIA AVANZATA

Management of Sentinel Node Positive Melanoma



PRESENTED AT: **ASCO ANNUAL MEETING '17** | **#ASCO17** Presented by: Vernon K. Sondak, MD

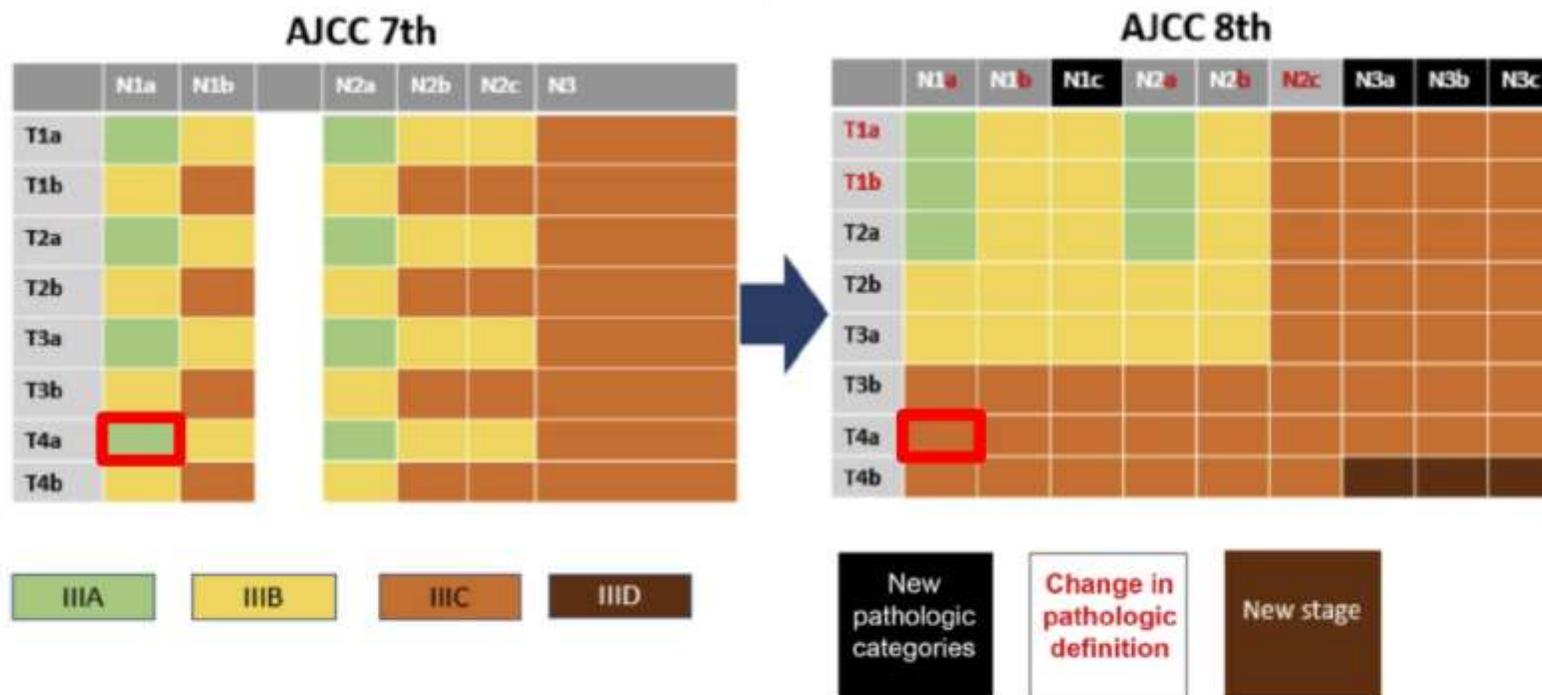
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Melanoma Recent Events

- AJCC 8th edition staging implemented 1/1/2018
 - Database of >46,000 stage I-III melanoma pts dx'd since 1998
- MSLT2
 - No difference in MSS for immediate LND v nodal observation for SLN positive pts

AJCC Staging

Stage III

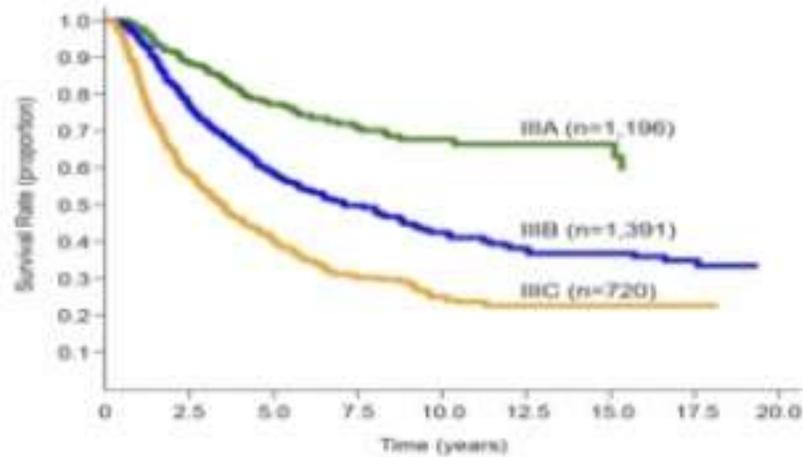


Grob et al, Eur J Ca, 2018

Can we prevent stage III recurrences and stage IV?

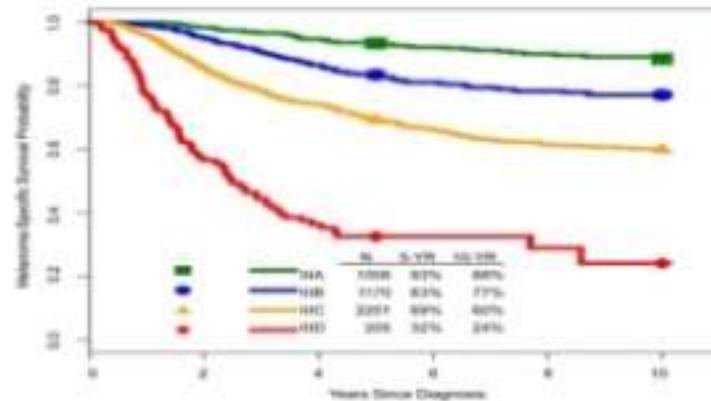
Overall Survival for Patients With Stage III Disease AJCC 7th and 8th Editions

Staging guidelines IIIA–C, version 7¹



Balch CM et al. *J Clin Oncol* 2009

Staging guidelines IIIA–D, version 8²



Gerstenwald JE et al. *CA Cancer J Clin* 2017

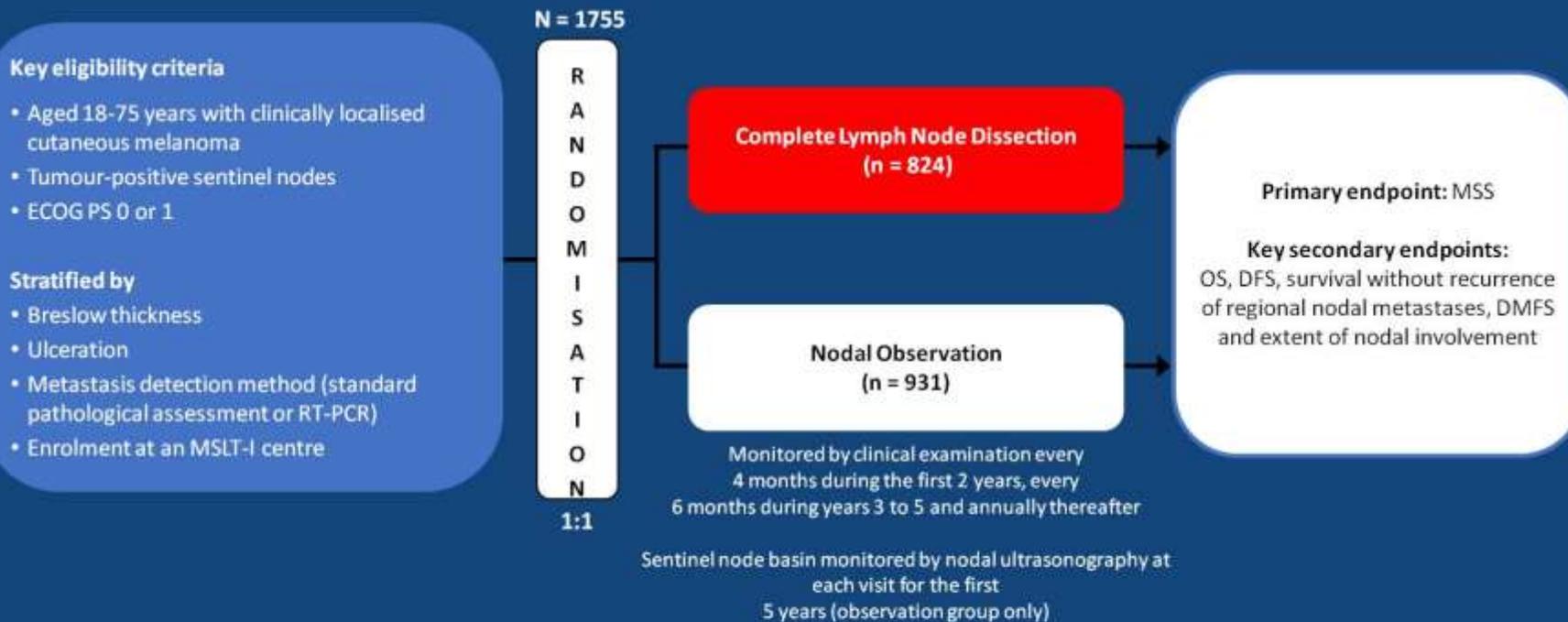
Stage	10-year OS, %	
	7th ed ¹	8th ed ²
IIIA	~68 ¹	88
IIIB	~42 ¹	77
IIIC	~25 ¹	60
IIID	–	24

³Survival rate estimated from OS curves.

Mario Mandalà- AIOM National Congress Rome 2018

MSLT-II: Study Design

Phase 3 Trial Evaluating CLND vs Observation With Nodal Ultrasonography in Node-Positive Intermediate-Thickness Melanoma



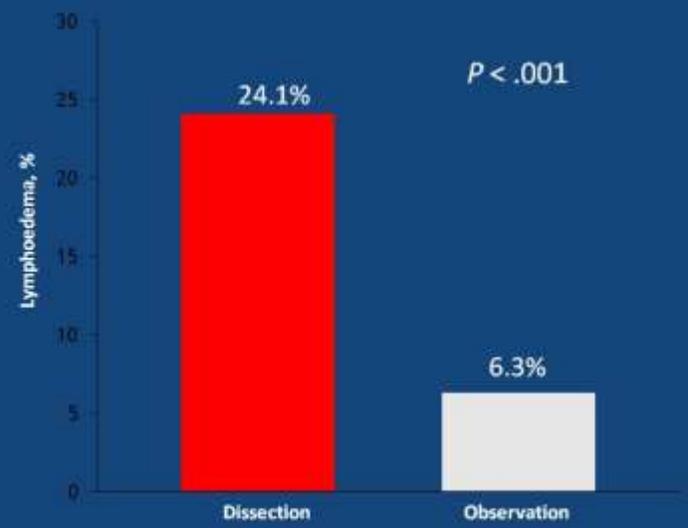
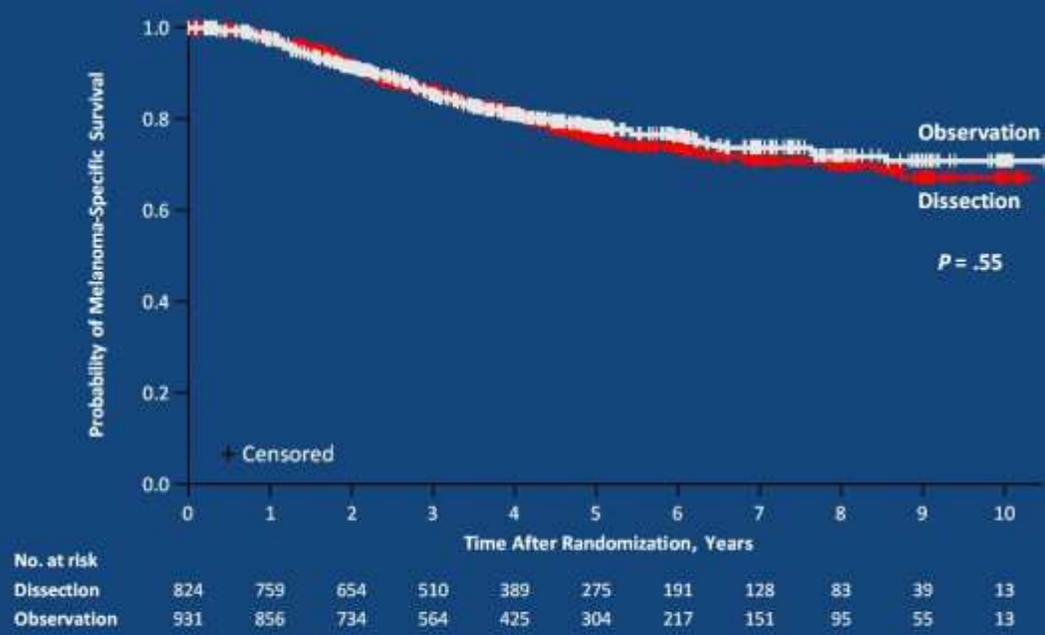
PRESENTED AT: **2018 ASCO ANNUAL MEETING**

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PRESENTED BY: A.C.J. van Akkooi

MSLT-II: Key Results

CLND Was Not Associated With Improved Melanoma-Specific Survival vs Observation in Patients With Sentinel Node Metastases



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FINAL ANALYSIS OF DECOG-SLT TRIAL: NO SURVIVAL BENEFIT FOR COMPLETE LYMPH NODE DISSECTION IN MELANOMA PATIENTS WITH POSITIVE SENTINEL NODE

Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, Sunderkötter C, Kaatz M, Schatton K, Lehmann P, Vogt T, Ulrich J, Herbst R, Gehring W, Simon JC, Keim U, Martus P, Garbe C

German Dermatologic Oncology Group (DeCOG)

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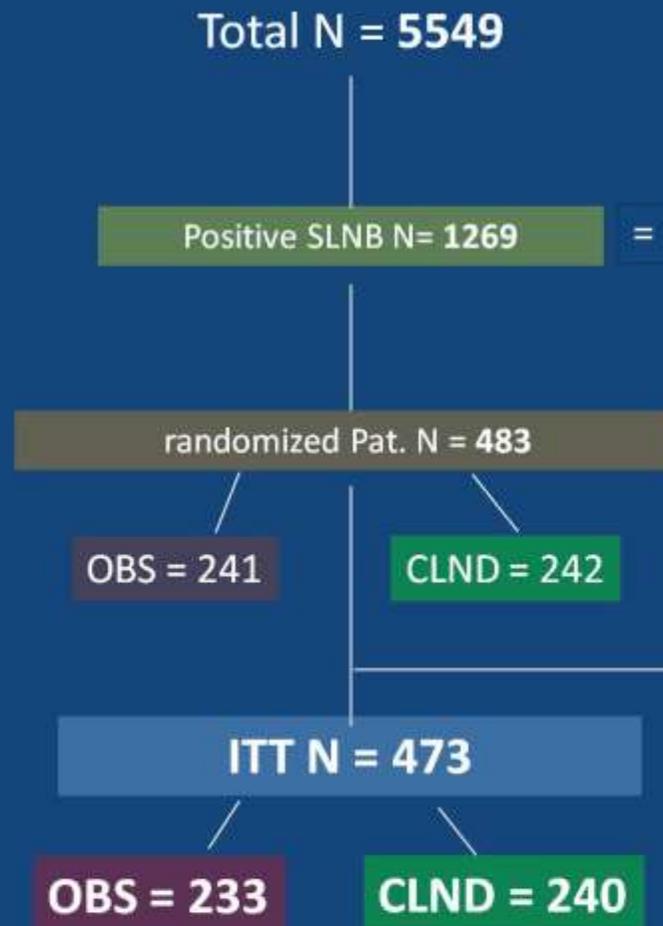
PRESENTED BY: Ulrike Leiter

7

Flow chart

Enrolment was performed from January 2006 to December 2014

Update:
Median follow up of 72 months



Included	483
Not included	786
Inclusion criteria failed	313
Patient refused rand.	225
n.a.	247
Total	786

Dropouts	N= 10
Macro metastases	5
Second. malignoma	1
Age	1
Localization	3

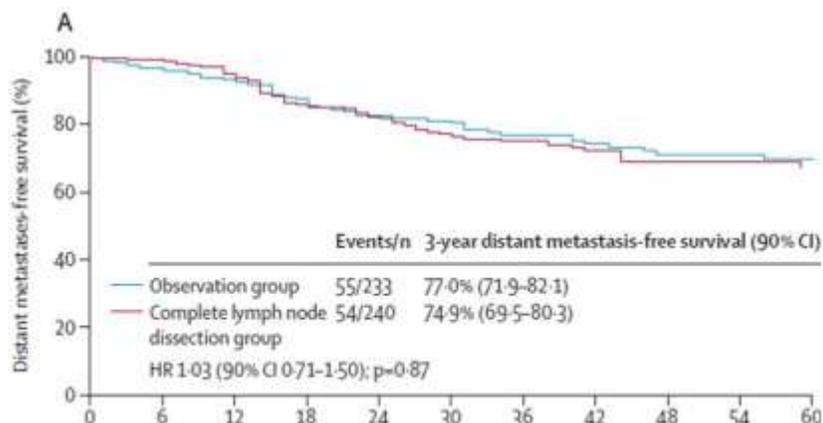
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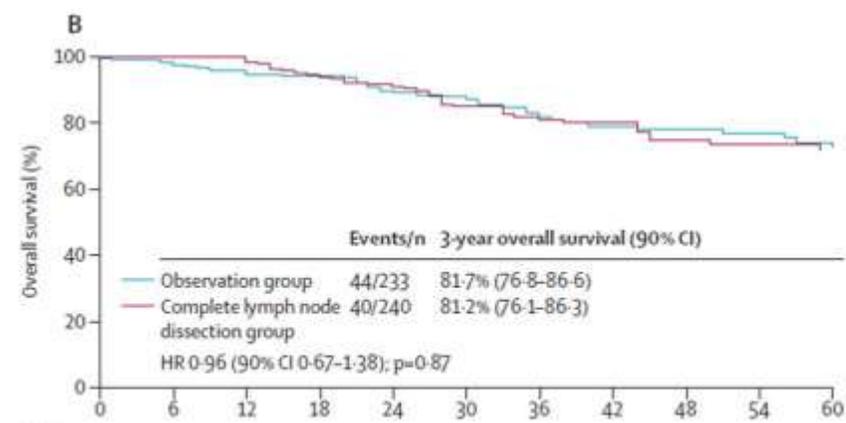
DECOG 3-years Survival Data

Distant metastases free survival



	0	6	12	18	24	30	36	42	48	54	60
Number at risk											
Observation group	233	203	186	165	144	125	99	75	61	54	45
Complete lymph node dissection group	240	195	181	150	136	110	94	75	56	48	36

Overall survival



	0	6	12	18	24	30	36	42	48	54	60
Number at risk											
Observation group	233	206	191	178	157	136	109	81	69	60	49
Complete lymph node dissection group	240	197	190	162	150	119	102	82	60	50	38

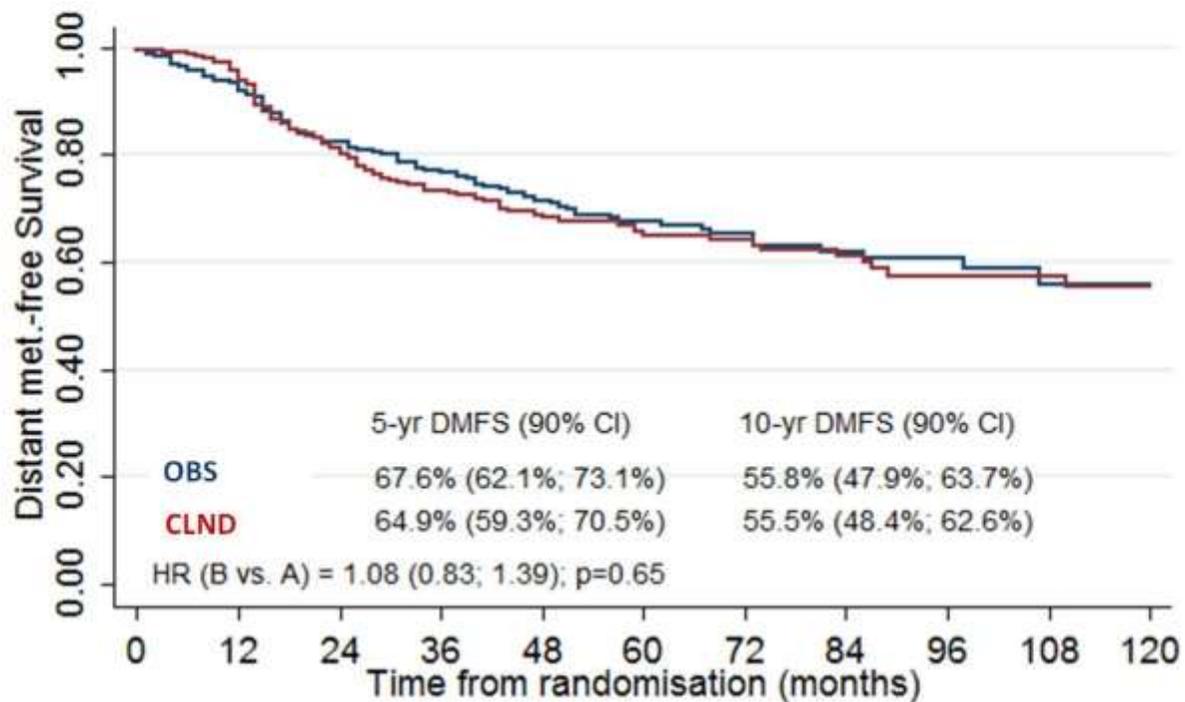
Leiter et al., The Lancet Oncology 2016;17:757-767

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DECOG final analysis - Distant metastasis-free Survival



Number at risk

OBS	233	211	181	157	135	107	80	55	37	17	7
CLND	240	214	180	153	124	94	73	52	37	30	19

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Data cut-off date: Feb. 1st 2018

Conclusions

DECOG SLT underpowered
MSLTII changed practice

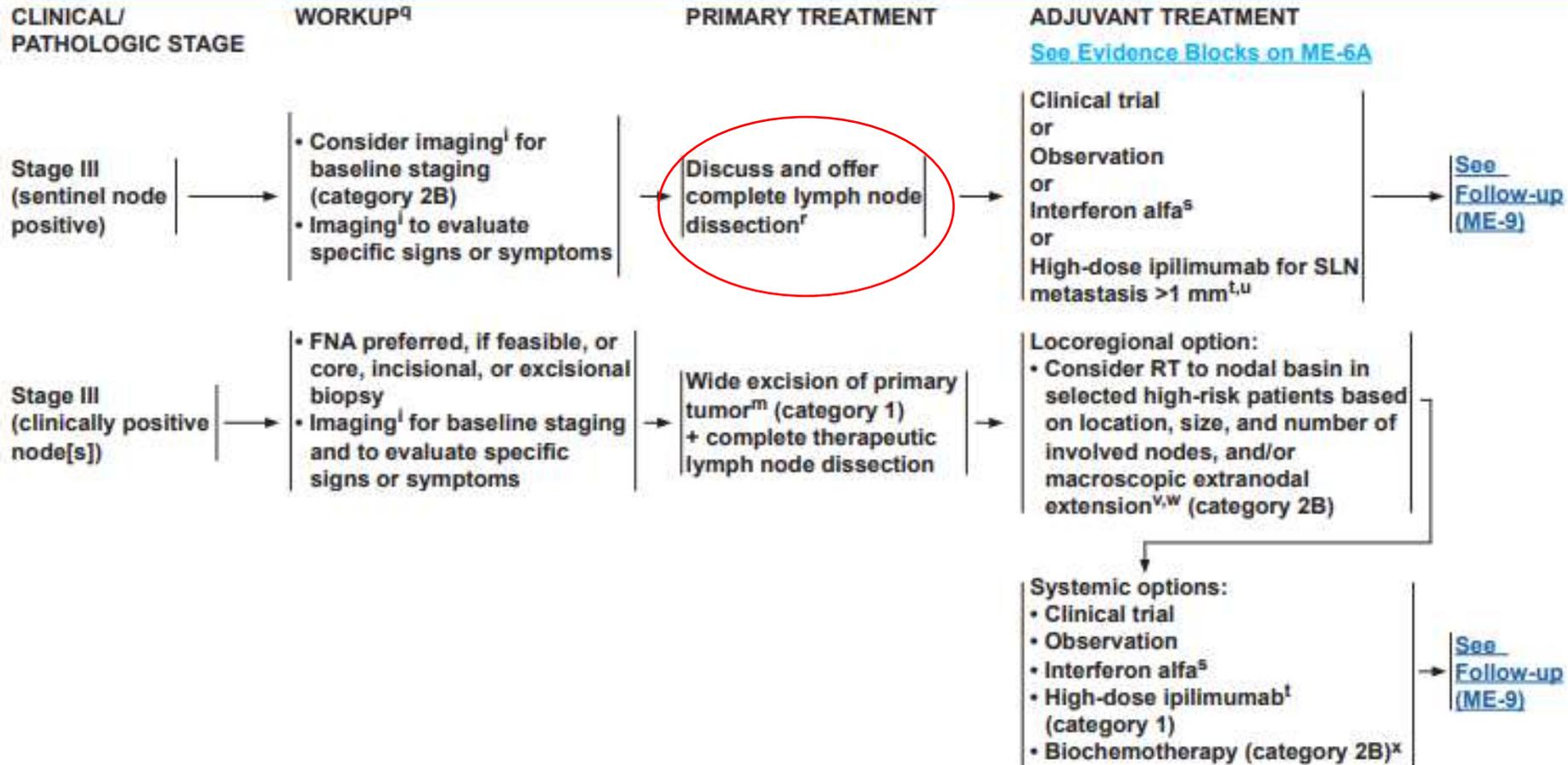
CLND may still be appropriate in some cases:

- Unable to complete surveillance
- Lack of access to nodal ultrasounds
- Pt preference
- Larger tumor burden in SLN

Requires Nodal US with clinical examination
Every 4 mo- year 0-2 with nodal US
Every 6 mo -year 3-5 with nodal US
Annually - year 6 and beyond

Patient Education: Awareness of increased risk of nodal recurrences

 CLND is still recommended for patients with clinically evident nodal metastases



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National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2019 Cutaneous Melanoma

CLINICAL/ PATHOLOGIC STAGE	WORKUP ⁵	PRIMARY TREATMENT
Stage IIIA (sentinel node positive)	<ul style="list-style-type: none">• Consider imaging^l for baseline staging• Imaging^l to evaluate specific signs or symptoms	Nodal basin ultrasound (US) surveillance ^t or Complete lymph node dissection (CLND) ^u
Stage IIIB/C/D (sentinel node positive)	Imaging ^l for baseline staging and to evaluate specific signs or symptoms	
Stage III (clinically positive node[s])	See ME-5	

Trattamento della malattia iniziale

Q14: Nei pazienti con linfonodo sentinella istologicamente positivo è indicata la dissezione linfonodale di completamento?

- **GRADE**

RACCOMANDAZIONE:

Nei pazienti con linfonodo sentinella istologicamente positivo la dissezione linfonodale di completamento può essere presa in considerazione come opzione di prima intenzione

Forza della raccomandazione: POSITIVA DEBOLE

Qualità globale delle evidenze: BASSA

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Adjuvant trials 2010-2016

Trial	No. pts	Experimental arm vs. obs	HR for disease recurrence	HR for OS
AVAST-M	1,343	Bevacizumab vs. observation	0.83 (p=0.03)	0.97 (p=0.76)
DERMA	1,388	MAGE A3 ASCI vs. placebo	<i>All patients</i> 1.013 (p=0.86) <i>Gene signature +ve</i> 1.11 (p=0.4821)	<i>All patients</i> 1.065 (p=0.52)
ECOG 4697	815	GMCSF vs. placebo (HLA-A2 positive peptide vs. placebo)	p = 0.131, (HR 0.88, 95% CI 0.74-1.04)	p = 0.528 (HR 0.95, 95% CI 0.77-1.15)
Interferon meta-analysis	7699 15 trials 11 IPD	IFN vs. no treatment	HR=0.86, CI 0.81-0.91; P<0.00001	HR=0.90, CI 0.85-0.97; P=0.003 5 year survival benefit 3%

Adjuvant therapy 2017-18

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab
in Resected Stage III or IV Melanoma

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib
in Stage III BRAF-Mutated Melanoma

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

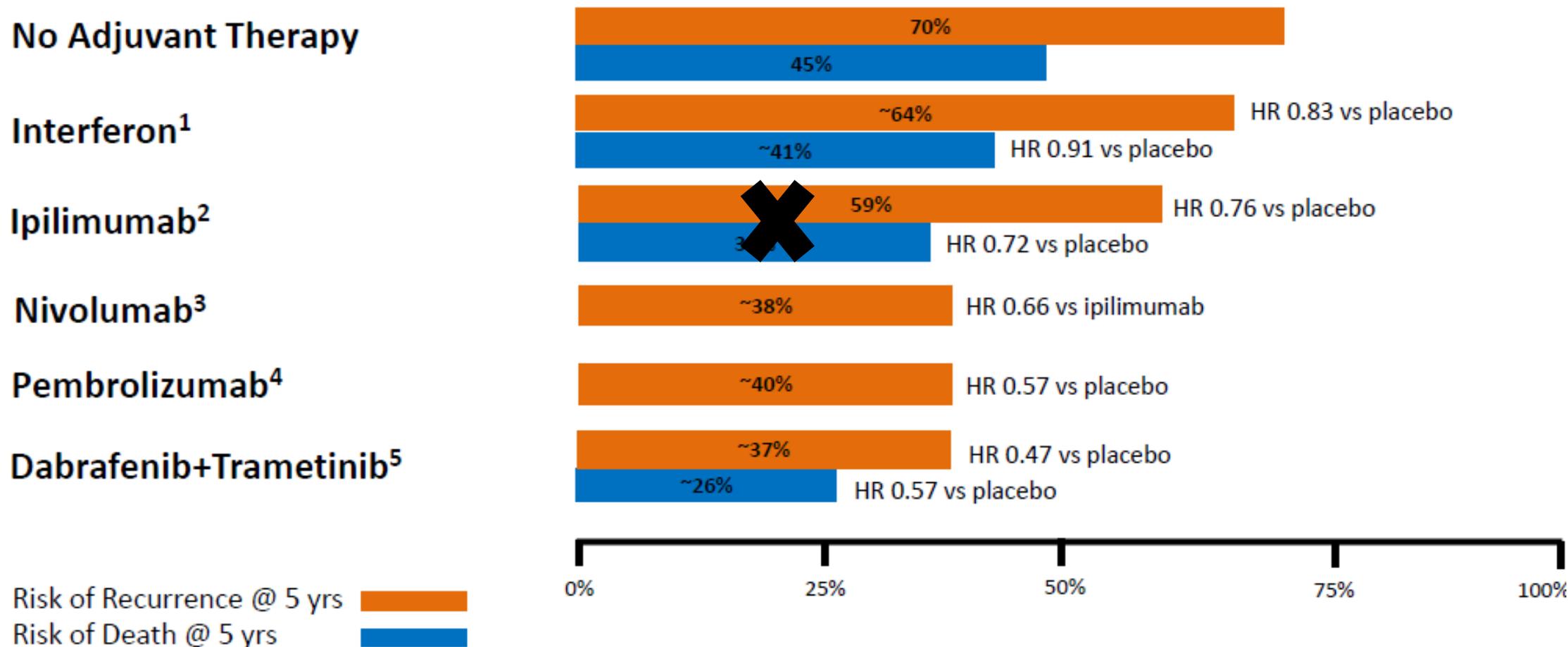
Adjuvant Pembrolizumab versus Placebo
in Resected Stage III Melanoma

The Lancet Oncology 2018

Adjuvant vemurafenib versus placebo in BRAF^{V600E} mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, phase 3 trial

Mario Mandalà- AIOM National Congress Rome 2018

Resected Stage III Melanoma & Adjuvant Systemic Therapy



Risk of no adjuvant therapy at 5 years from Eggermont et al. NEJM 2016. The % shown for drug therapies determined from the risk reduction (HR).

¹Eggermont et al NEJM 2016. ²Eggermont et al NEJM 2016. ³Eggermont et al NEJM 2018. ⁴Lone GV et al. NEJM 2017. ⁵Eggermont et al NEJM 2018.

Georgina V Long, MIA

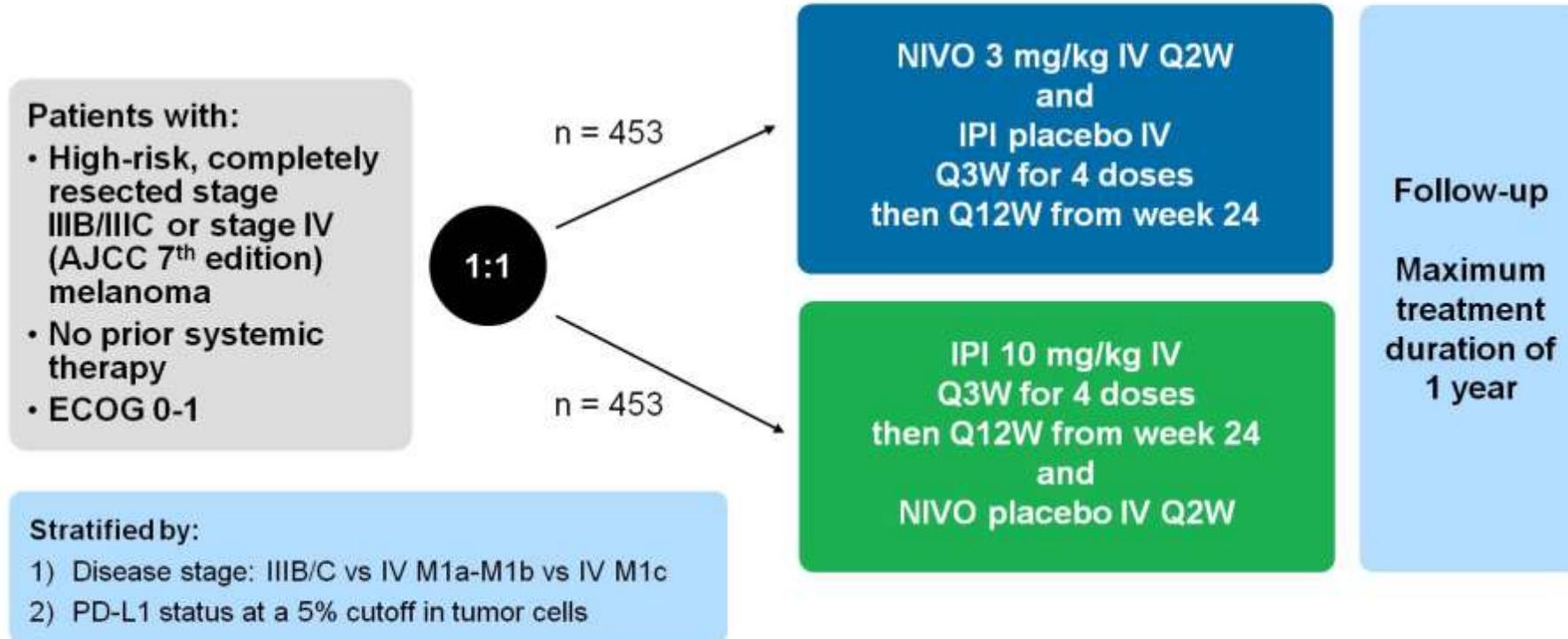
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 - IMMUNOTERAPIA
 - TERAPIA TARGET
 - TRIALS IN CORSO

Weber et al: #9502

CheckMate 238: Study Design



Enrollment period: March 30, 2015 to November 30, 2015

Baseline Patient Characteristics and Treatment Summary

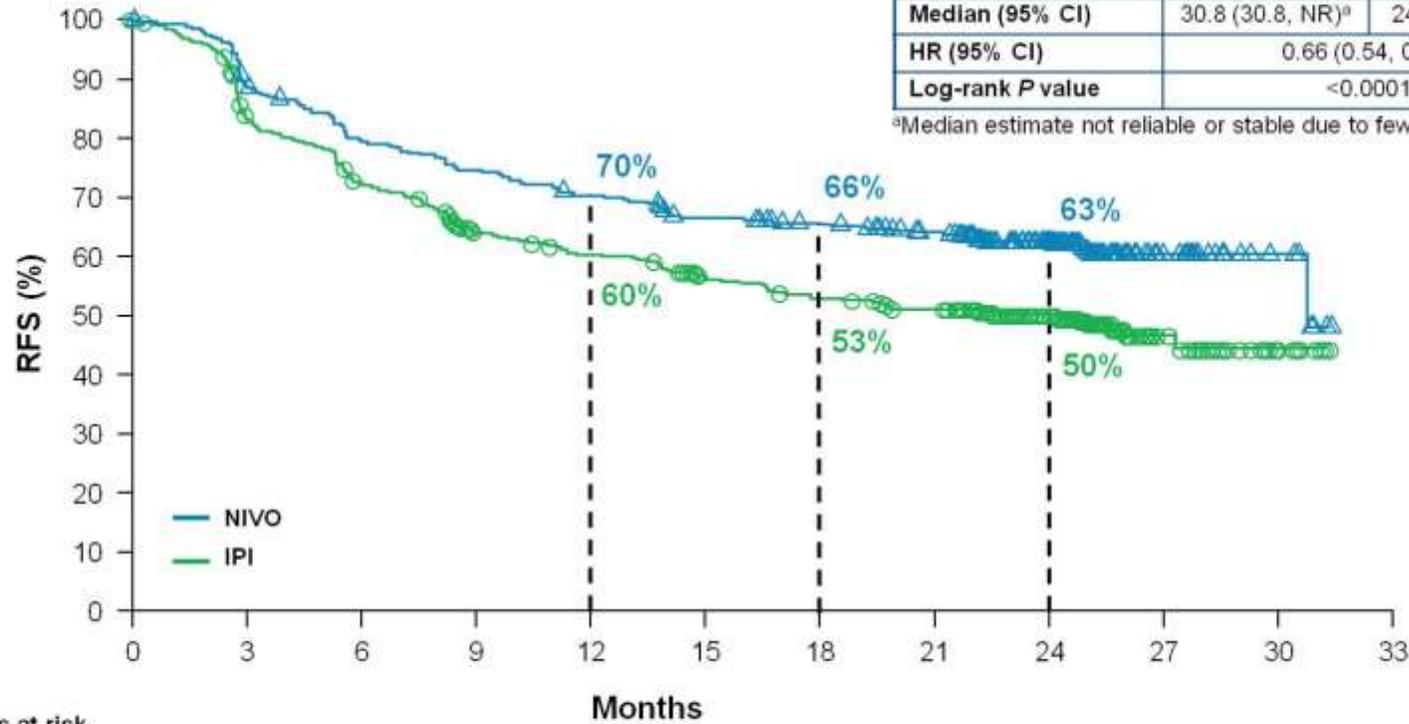
	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression $\geq 5\%$, %	34	34
<i>BRAF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

- Median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group
- 61% of patients in the NIVO group and 27% in the IPI group completed 1 year of treatment

Primary Endpoint: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR) ^a	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank P value	<0.0001	

^aMedian estimate not reliable or stable due to few patients at risk.



Number of patients at risk

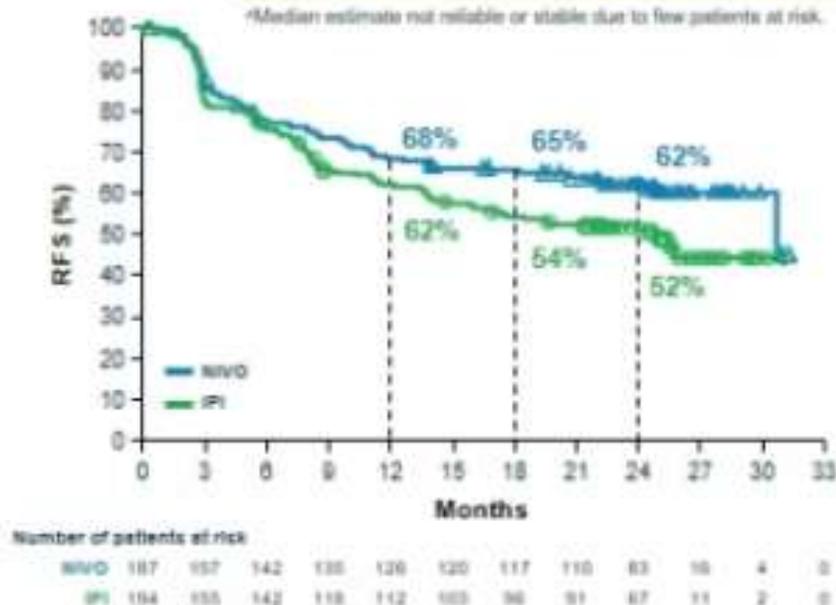
	0	3	6	9	12	15	18	21	24	27	30	33
NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

CheckMate 238: subgroup analysis of RFS: *BRAF* mutation status

BRAF Mutant

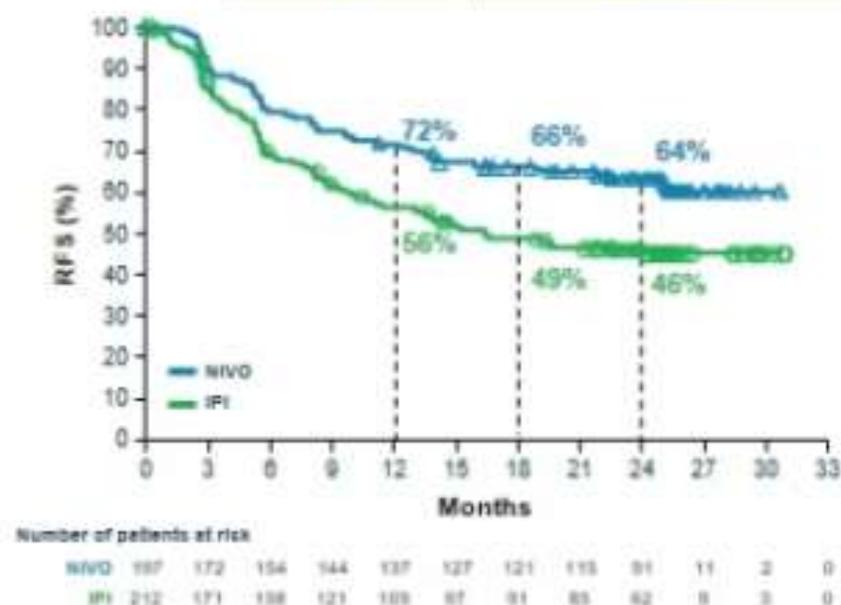
	NIVO	IP1
Events/patients, n/n	73/187	53/194
Median (95% CI)	30.8 (20.8, NR)*	24.8 (14.8, NR)
HR (95% CI)	0.73 (0.54, 0.98)	

*Median estimate not reliable or stable due to few patients at risk.



BRAF Wild type

	NIVO	IP1
Events/patients, n/n	75/197	117/212
Median (95% CI)	NR	16.8 (11.4, NR)
HR (95% CI)	0.61 (0.45, 0.82)	



Bringing I-O to earlier disease stage

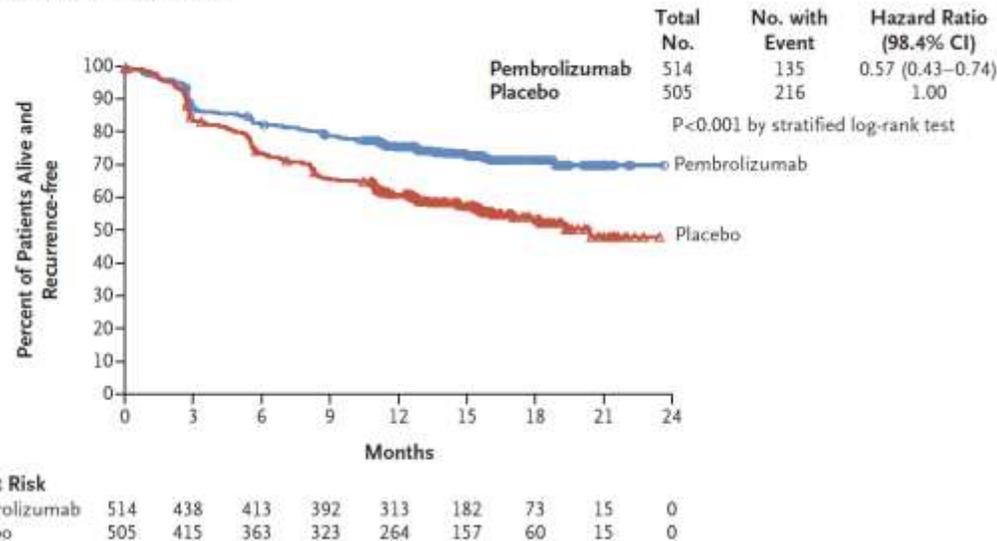
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

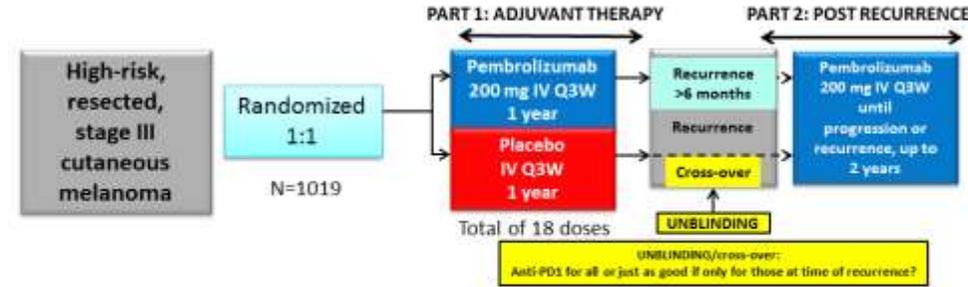
Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., P.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suci, Ph.D., and Caroline Robert, M.D., Ph.D.

A Overall Intention-to-Treat Population



EORTC 1325/KEYNOTE-54: Study Design

L. Eggermont AACR 2018



Stratification factors:

- ✓ Stage: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ Region: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- RFS (per investigator) in overall population, and RFS in patients with PD-L1-positive tumors

Secondary Endpoints:

- DMFS and OS in all patients, and in patients with PD-L1-positive tumors; Safety, Health-related quality of life



The future of cancer therapy

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- TERAPIA ADIUVANTE
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 - TERAPIA TARGET
 - TRIALS IN CORSO

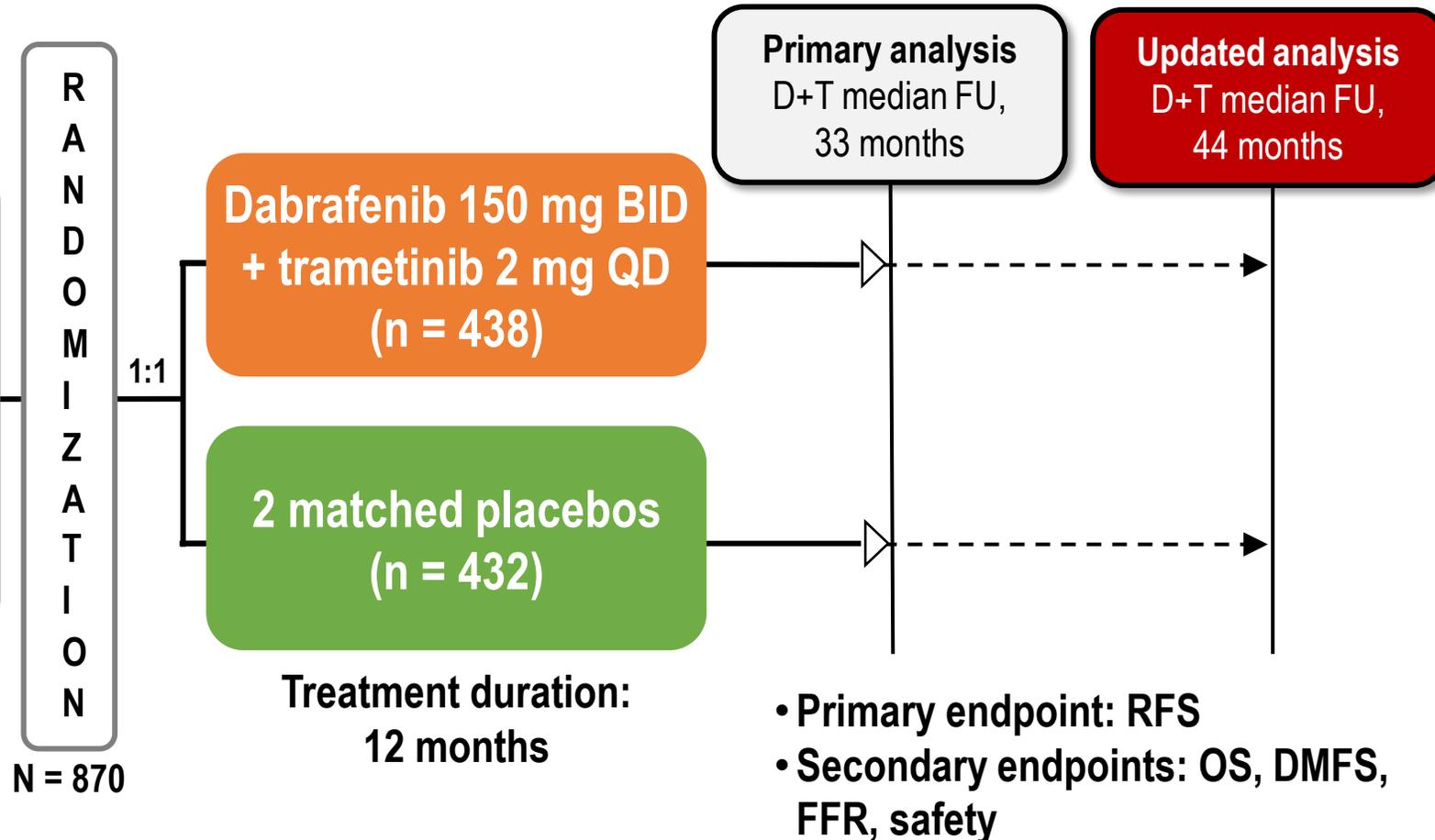
COMBI-AD: STUDY DESIGN—EXTENDED FOLLOW-UP ANALYSIS

Key eligibility criteria

- Completely resected stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy
- Tissue collection was mandatory at baseline and optional upon recurrence

Stratification

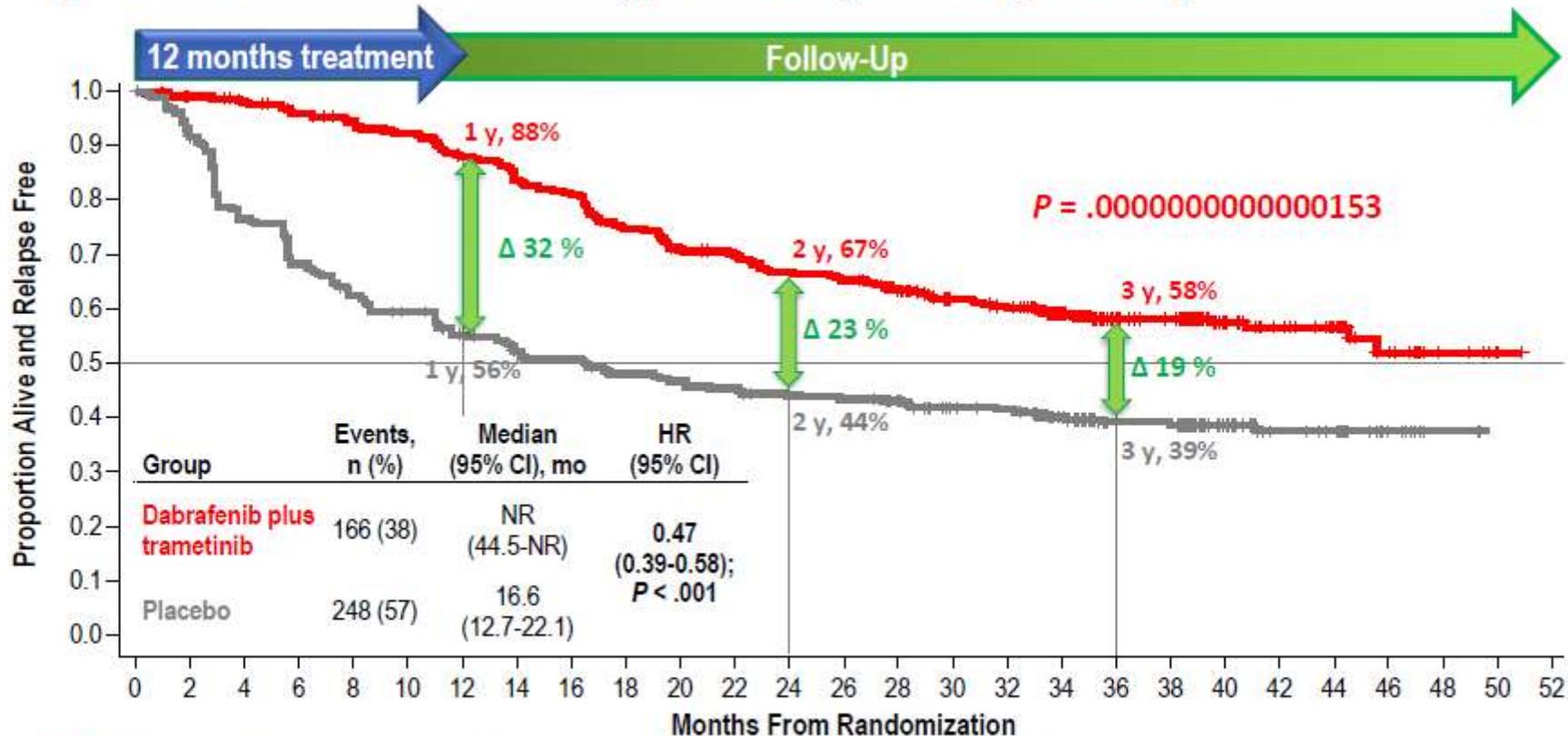
- *BRAF* mutation status (V600E, V600K)
- Disease stage (IIIA, IIIB, IIIC)



BID, twice daily; DMFS, distant metastasis-free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

Relapse-free survival (primary endpoint)



No. at Risk

Months From Randomization	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

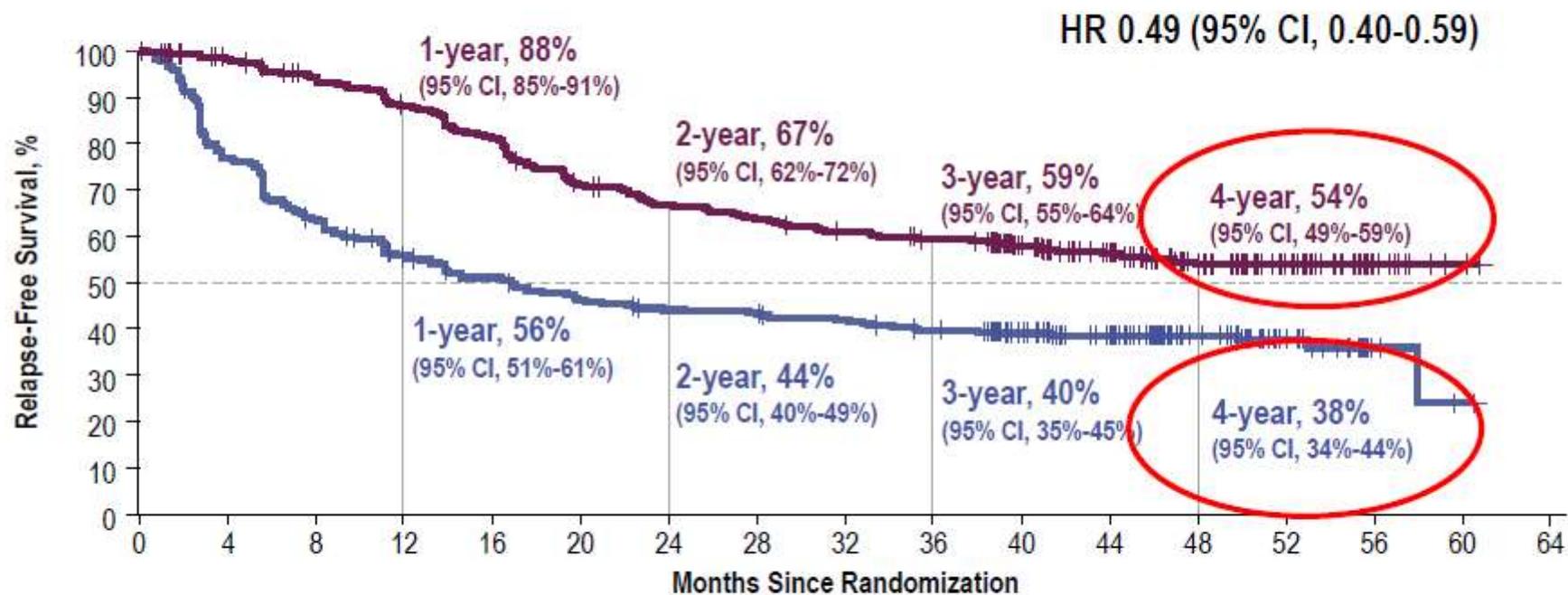
NR, not reached



Data cutoff: 30 June 2017.

Slide modified from A. Hauschild, ESMO 2017 Congress, Abstract LBA6_PR; Long GV et al NEJM 2017

RELAPSE-FREE SURVIVAL

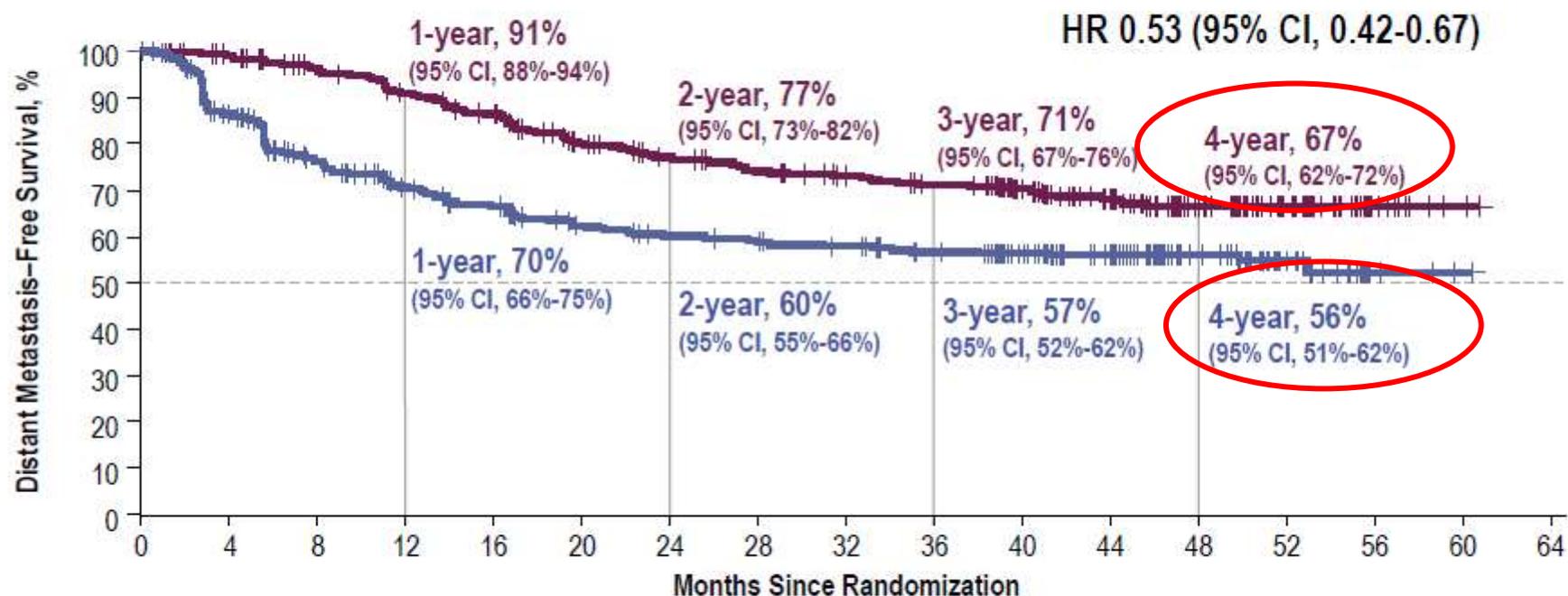


No. at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0



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DISTANT METASTASIS-FREE SURVIVAL



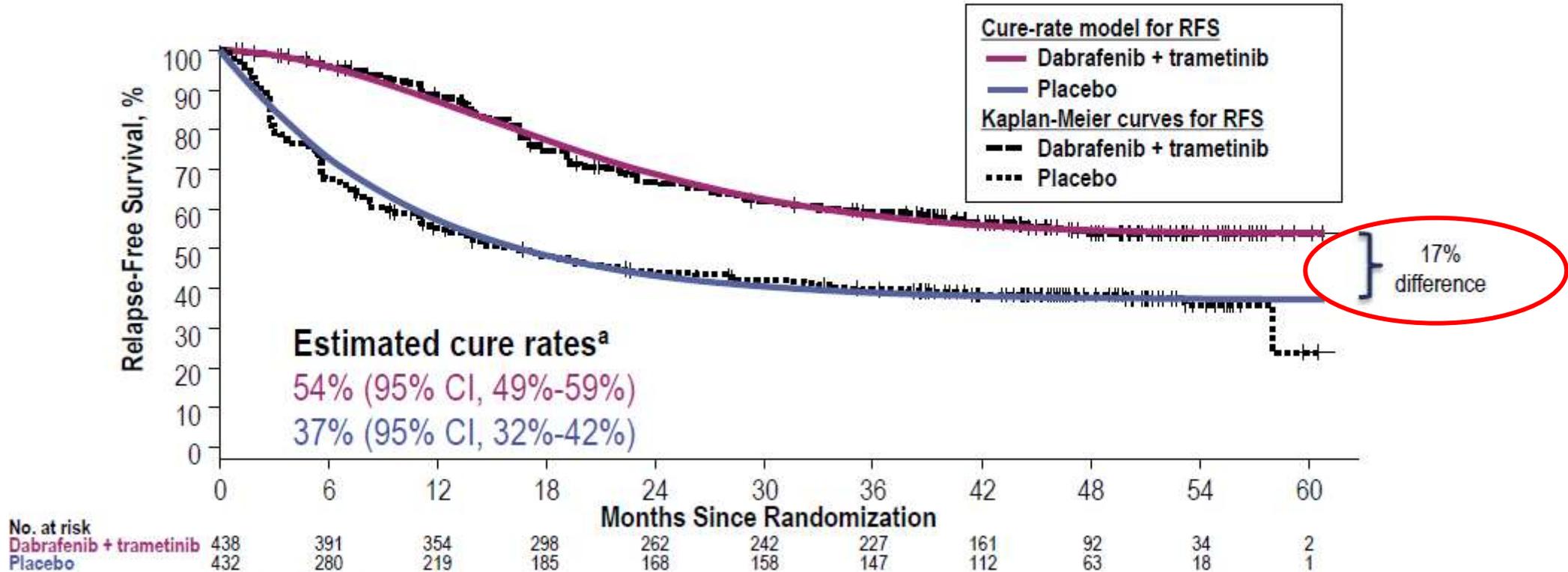
No. at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
Dabrafenib + trametinib	438	407	381	352	327	285	265	252	238	229	185	150	92	47	13	2	0
Placebo	432	330	265	221	201	179	169	165	159	149	130	108	64	28	4	1	0



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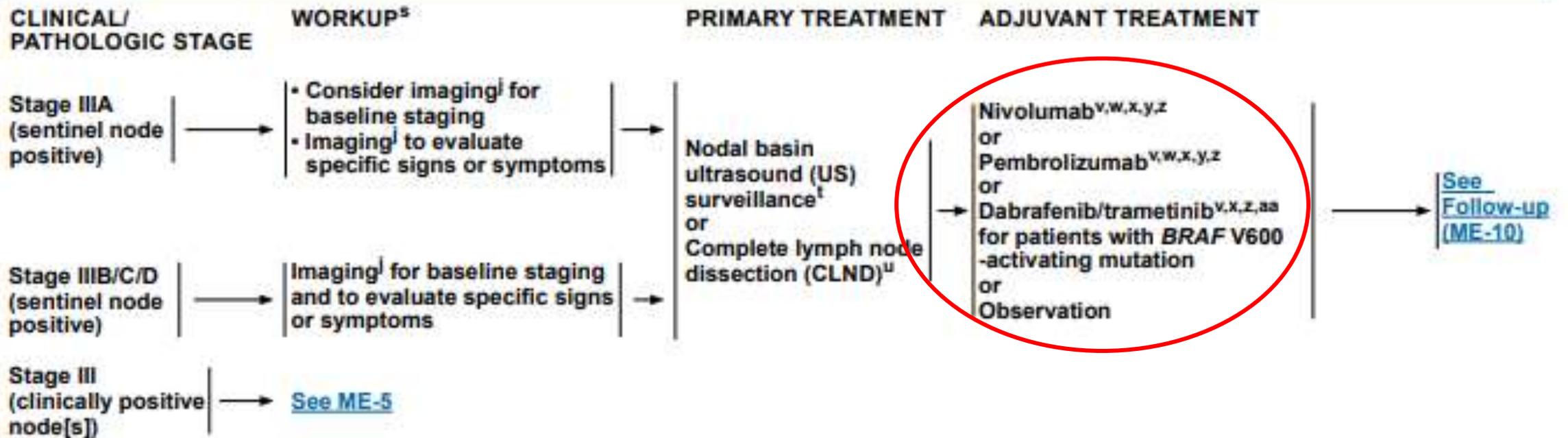
CURE-RATE MODEL RESULTS

A higher proportion of patients are estimated to be relapse-free long term with D + T vs placebo



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Linee Guida NCCN



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Bringing I-O to earlier disease stage

Ongoing clinical trials

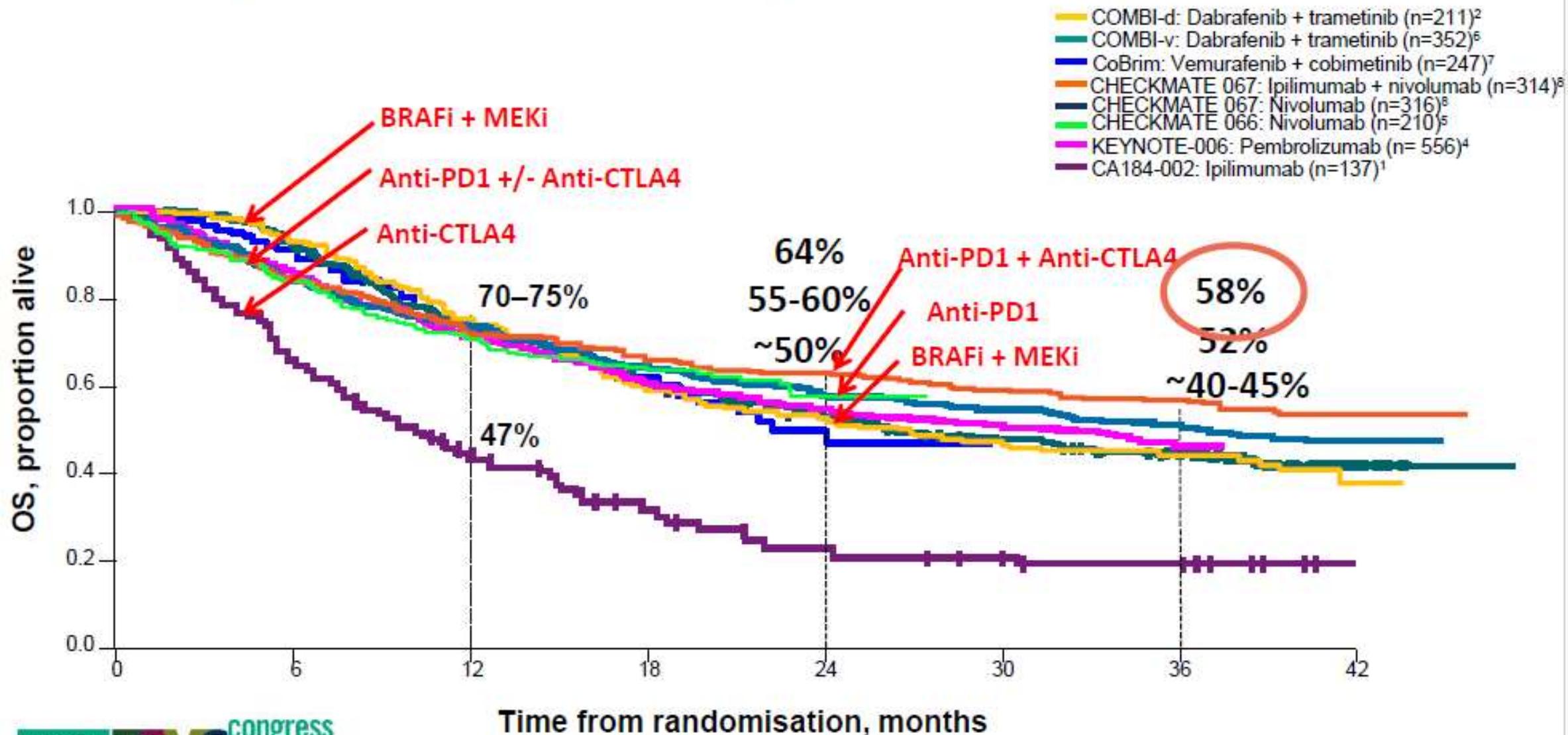
- **BMS CA209915:** A phase III, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab or ipilimumab plus nivolumab after complete resection of Stage IIIb/c or Stage IV melanoma subjects who are at high risk for recurrence
- **KEYNOTE 716:** Adjuvant therapy with pembrolizumab versus placebo in resected high risk Stage II Melanoma: a randomized, double-blind phase 3 study

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Overall Survival in Advanced Melanoma



The Best of the Year 2018: MELANOMA



- TERAPIA PER MALATTIA AVANZATA
 - IMMUNOTERAPIA
 - TERAPIA TARGET
 - TRIALS IN CORSO

Overall Survival at 4 years of Follow-up in a Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma (CheckMate 067)

F. Stephen Hodi,¹ Vanna Chiarion-Sileni,² Rene Gonzalez,³ Jean-Jacques Grob,⁴ Piotr Rutkowski,⁵ C. Lance Cowey,⁶ Christopher D. Lao,⁷ Dirk Schadendorf,⁸ John Wagstaff,⁹ Reinhard Dummer,¹⁰ Pier Francesco Ferrucci,¹¹ Michael Smylie,¹² Andrew G. Hill,¹³ David Hogg,¹⁴ Ivan Marquez-Rodas,¹⁵ Joel Jiang,¹⁶ Jasmine Rizzo,¹⁶ James Larkin,^{17*} Jedd D. Wolchok^{18*}

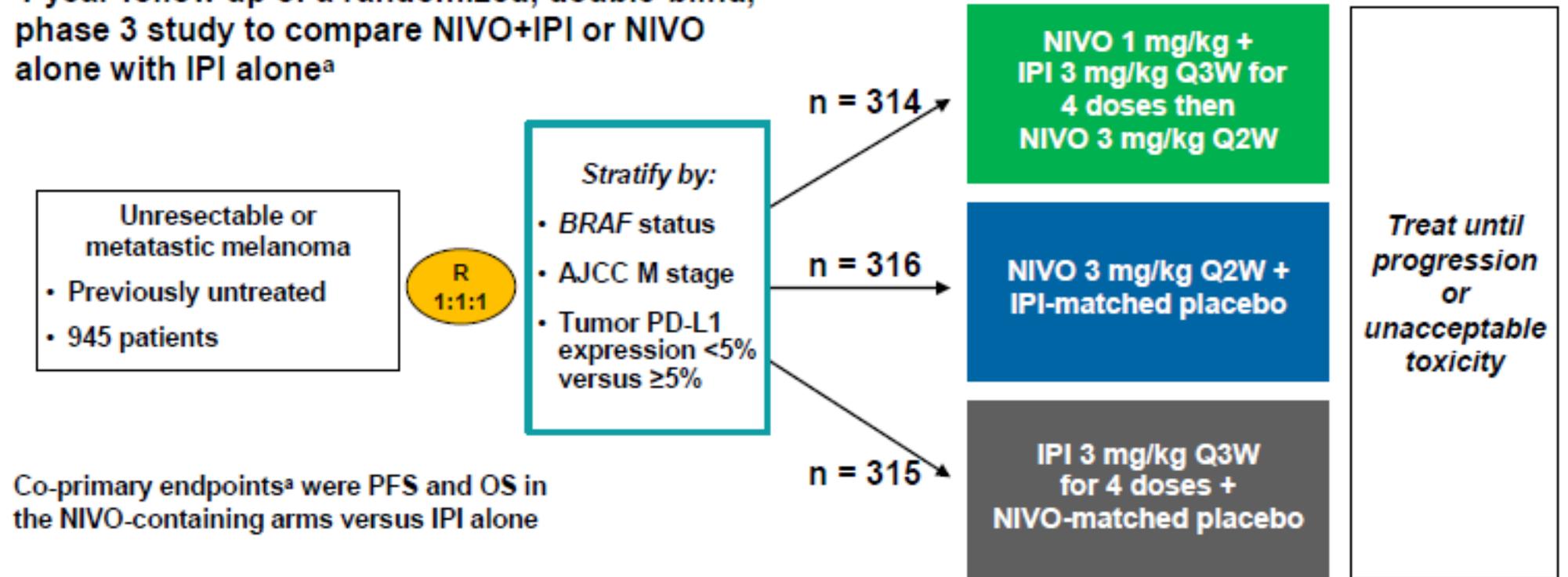
¹Dana-Farber Cancer Institute, Boston, MA, USA; ²Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; ³University of Colorado Cancer Center, Denver, CO, USA; ⁴Aix-Marseille University, APHM Hospital CHU Timone, Marseille, France; ⁵Maria Skłodowska-Curie Institute - Oncology Center, Warsaw, Poland; ⁶Texas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

*Contributed equally to this study.

Abstract Number LBA44

CheckMate 067: Study Design

4-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: May 10, 2018; minimum follow-up of 48 months for all patients

^aThe study was not powered for a comparison between NIVO+IPI and NIVO

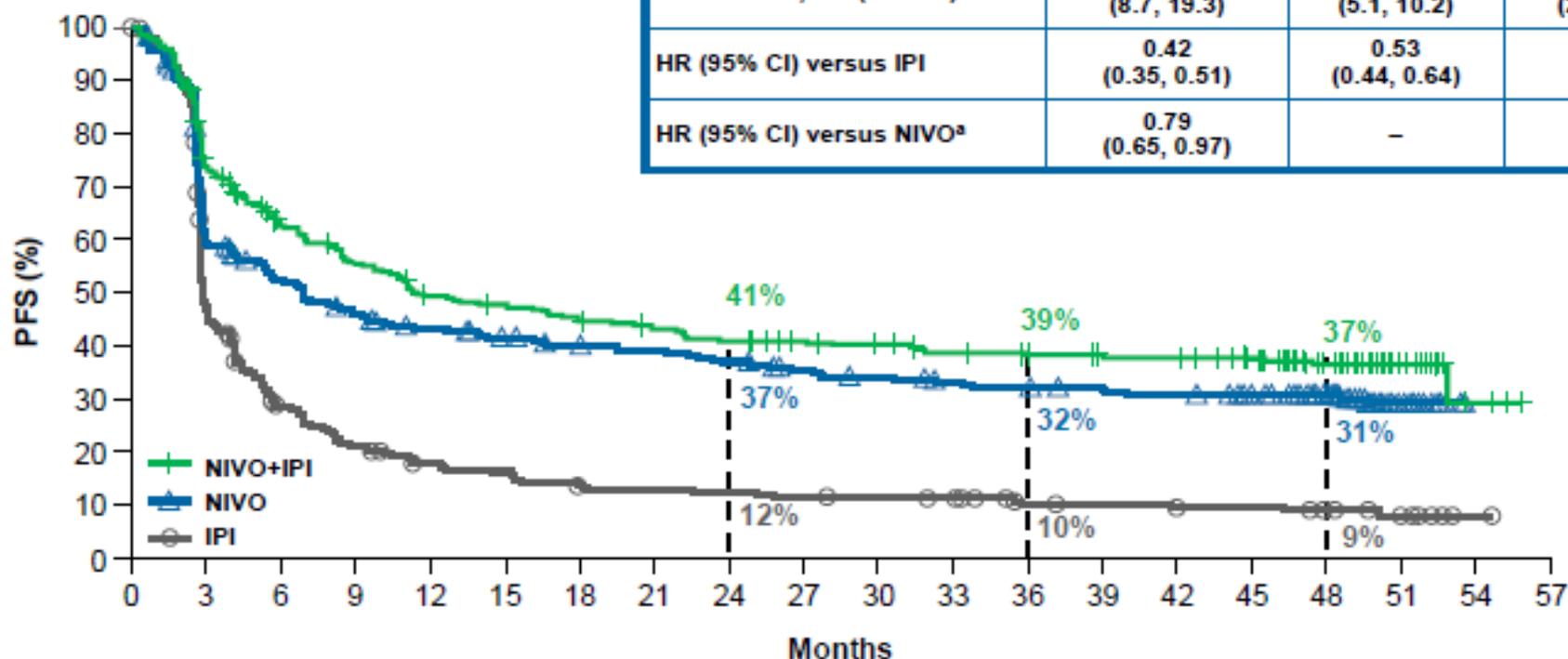
Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	58.3 (52.6, 63.8)	44.6 (39.1, 50.3)	19.0 (14.9, 23.8)
Best overall response, %			
Complete response	21.3	17.7	5.1
Partial response	36.9	26.9	14.0
Stable disease	12.1	9.5	21.6
Progressive disease	23.6	38.3	50.5
Unknown	6.1	7.6	8.9
Median duration of response, months (95% CI)	50.1 (44.0, NR)	NR (45.7, NR)	14.4 (8.3, NR)

NR = not reached

Progression-Free Survival

	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) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	-
HR (95% CI) versus NIVO ^a	0.79 (0.65, 0.97)	-	-

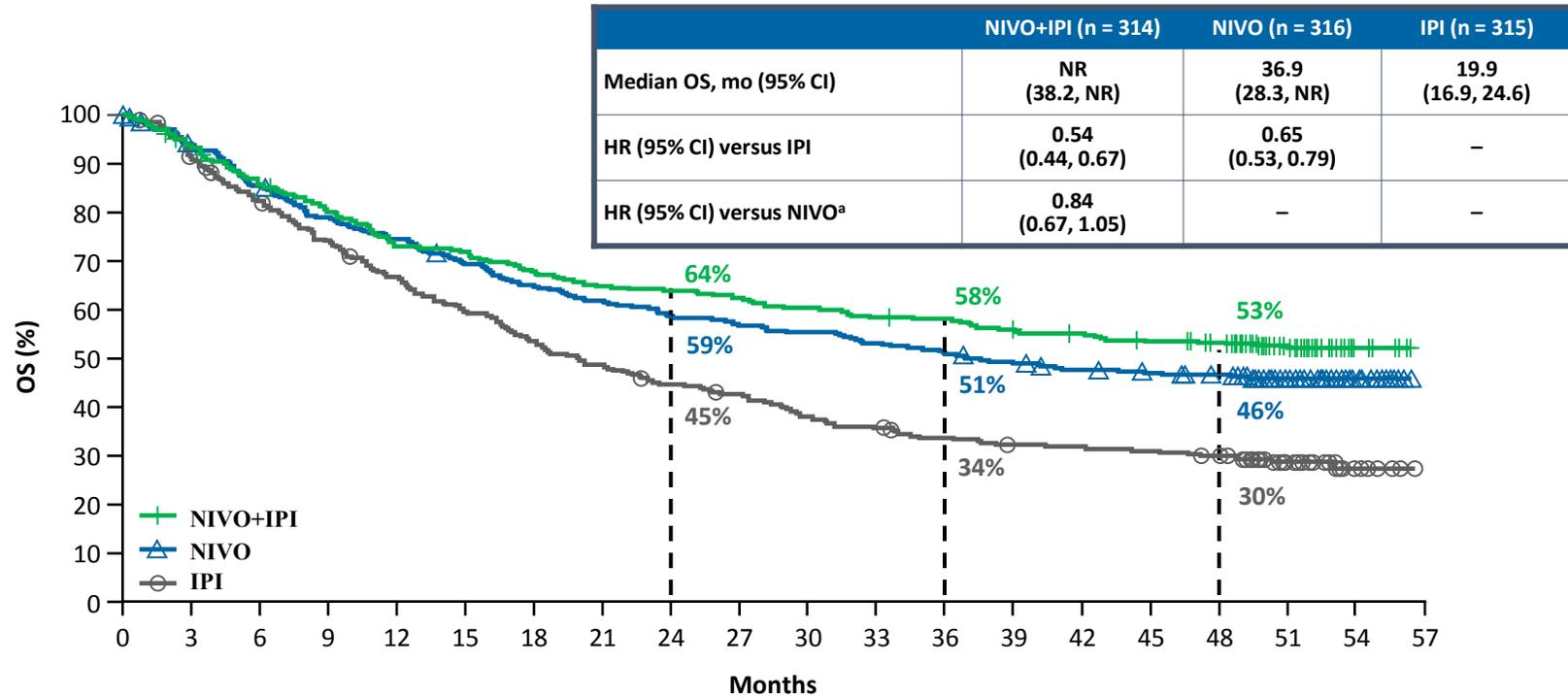


Patients at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
NIVO+IPI	314	218	175	155	138	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	108	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

^aDescriptive analysis

Overall Survival



Patients at risk:

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
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

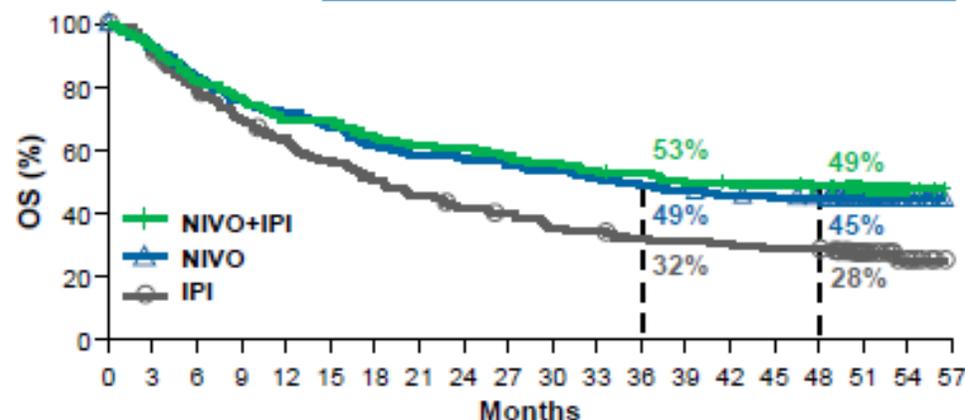
^aDescriptive analysis

Hodi FS et al. Lancet Oncol 2018

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

BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	39.1 (27.5, NR)	34.4 (24.1, NR)	18.5 (14.1, 22.7)
HR (95% CI) versus IPI	0.60 (0.47, 0.77)	0.65 (0.51, 0.83)	-
HR (95% CI) versus NIVO*	0.92 (0.71, 1.20)	-	-



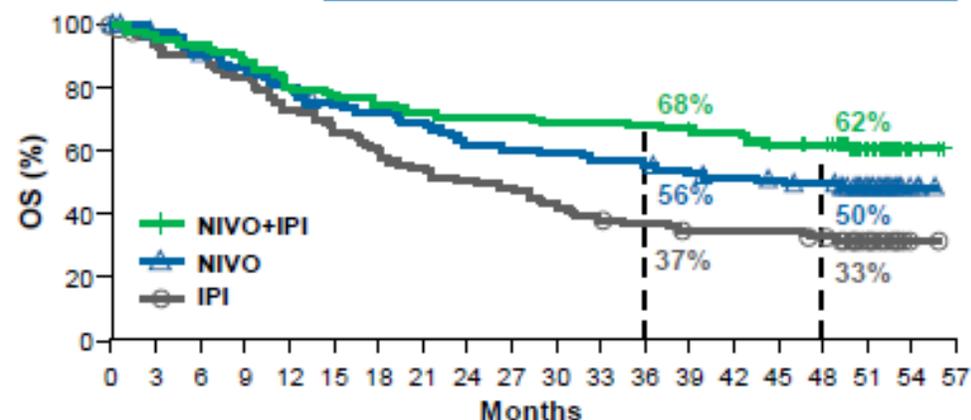
Patients at risk:

NIVO+IPI	211	193	169	156	143	141	132	126	125	119	115	109	108	102	99	98	94	54	6	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	96	93	56	12	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	33	9	0

*Descriptive analysis

BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	45.5 (26.4, NR)	24.6 (17.9, 31.0)
HR (95% CI) versus IPI	0.45 (0.30, 0.67)	0.64 (0.44, 0.93)	-
HR (95% CI) versus NIVO*	0.70 (0.46, 1.07)	-	-

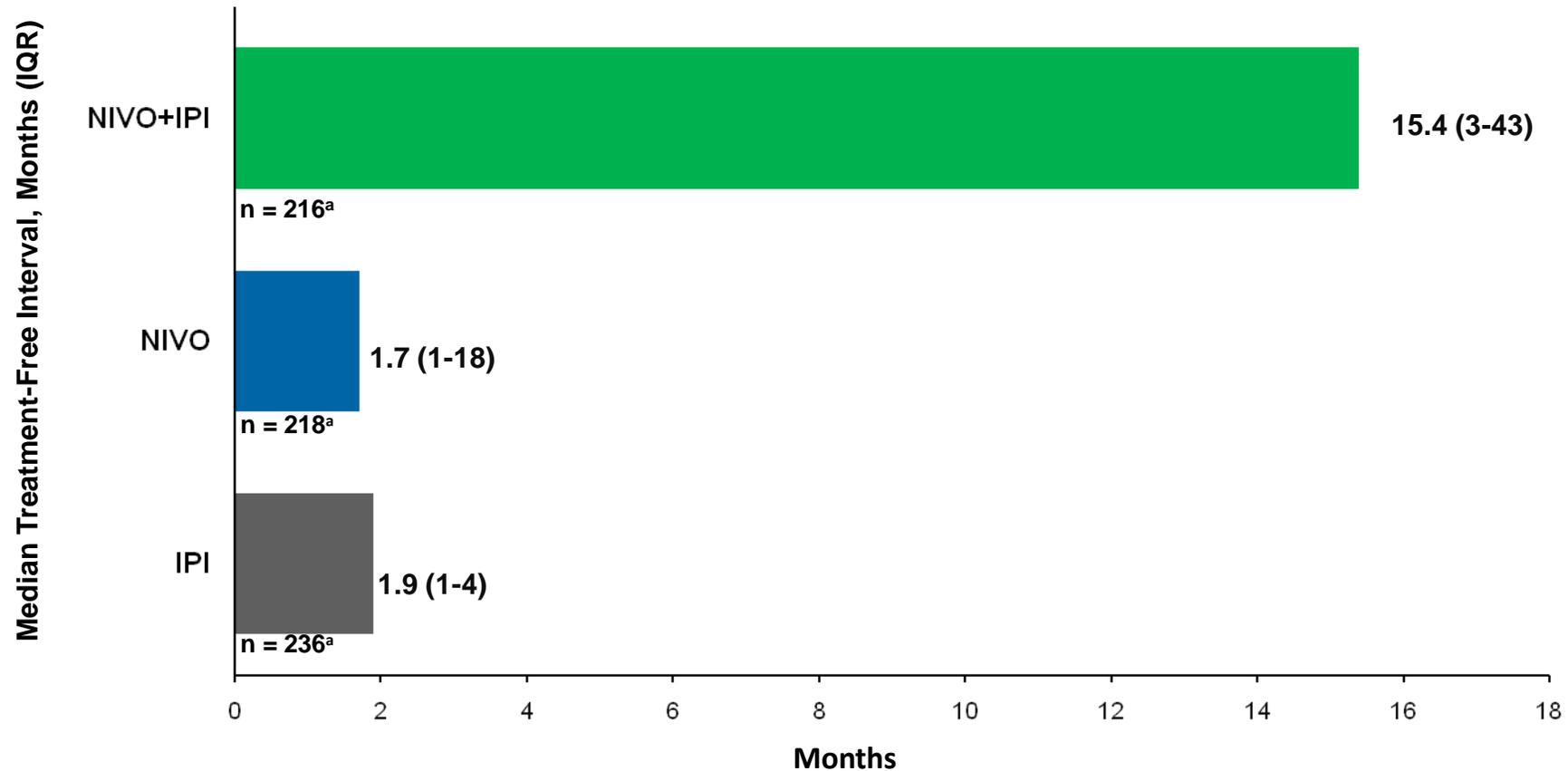


Patients at risk:

NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	62	60	42	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	46	44	42	29	6	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	35	32	32	32	29	17	2	0

Treatment-Free Interval at 4 Years in Patients Who Discontinued Study Therapy

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

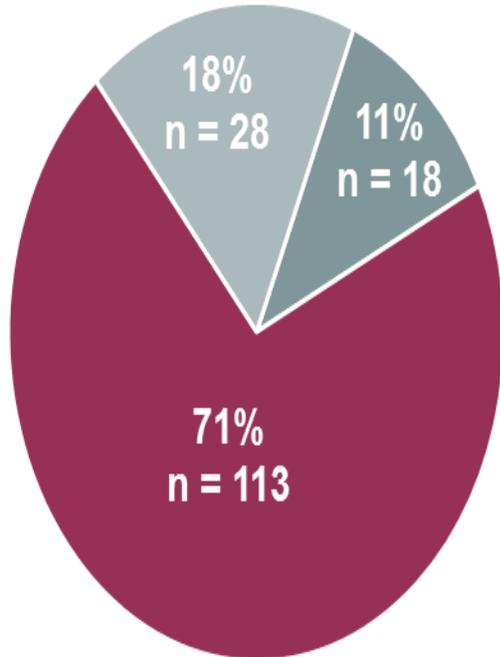


^aFor the combination, 216 patients were included in the treatment-free interval analysis and 97 were excluded (ie, still on study treatment, died and never received subsequent systemic therapy, or lost to follow-up), for nivolumab 218 patients were included and 95 were excluded, and for ipilimumab 236 patients were included and 75 were excluded

Patients Alive at 4 Years

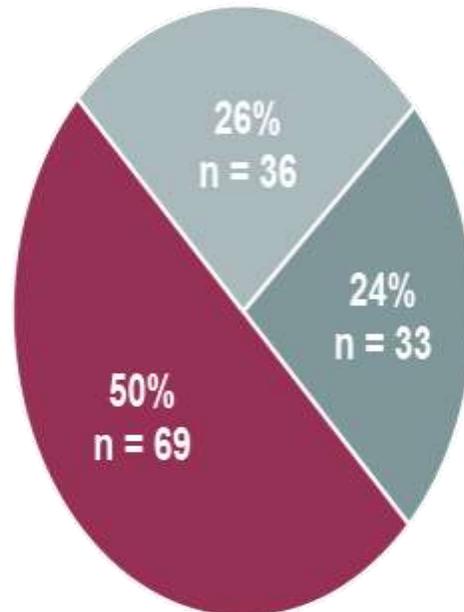


NIVO+IPI (n = 159)



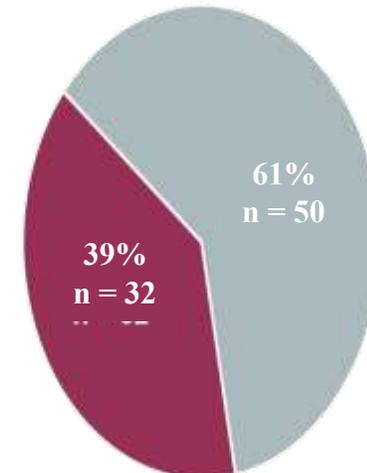
Median follow-up 51.6 mo (IQR 50.4-52.8)

NIVO (n = 138)



Median follow-up 51.7 mo (IQR 50.4-52.9)

IPI (n = 82)



Median follow-up 51.4 mo (IQR 50.4-52.7)

- **At the time of the 4-year follow-up, 71% of patients in the NIVO+IPI group were treatment free, which is increased from that observed at the 3-year follow-up (67%; 114/170)**

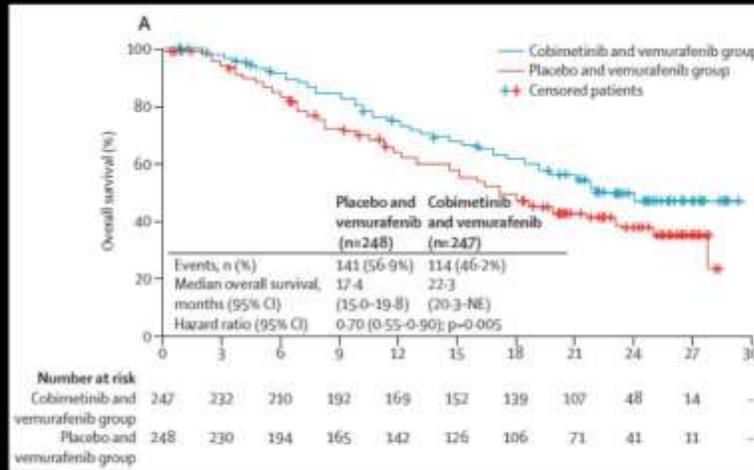
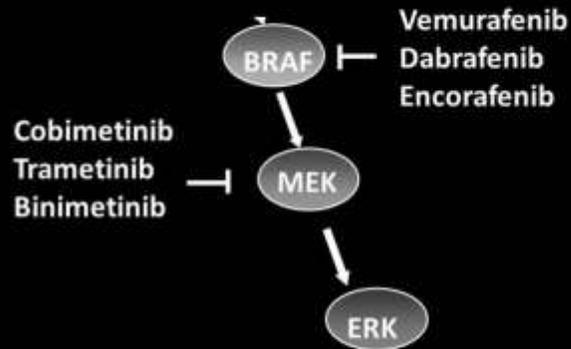
Summary

- A durable, sustained clinical benefit can be achieved with first-line NIVO+IPI or NIVO alone in patients with advanced melanoma
 - Benefit was observed across clinically relevant subgroups, including *BRAF* mutation status
 - NIVO+IPI and NIVO showed improved efficacy over IPI regardless of tumor PD-L1 expression as stratified on study
- Continued separation of the survival curves indicated sustained improvement for NIVO+IPI vs NIVO
 - Median OS has been reached for IPI and NIVO but not NIVO+IPI
 - NIVO+IPI patients who discontinued treatment early due to an AE had survival benefit similar to the overall population
- First-line NIVO+IPI may reduce the need for subsequent therapy or delay its use
- The safety profile was similar to the prior analysis, with no new safety signals and no additional treatment-related deaths

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 - TERAPIA TARGET
 - TRIALS IN CORSO

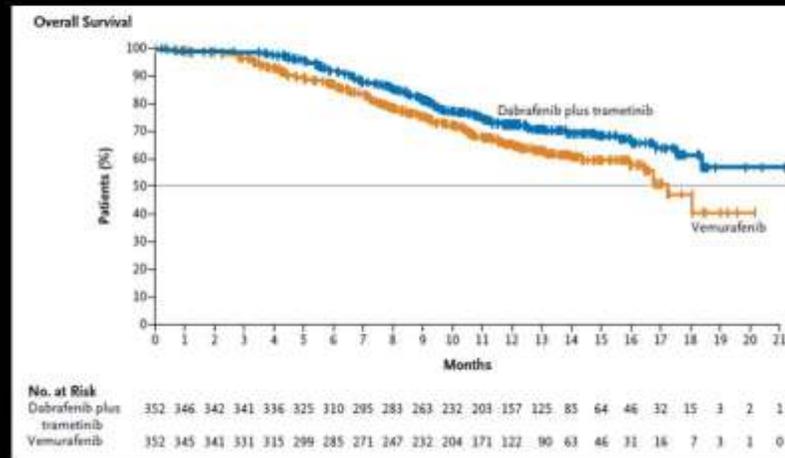


5 year OS D+T = 28%

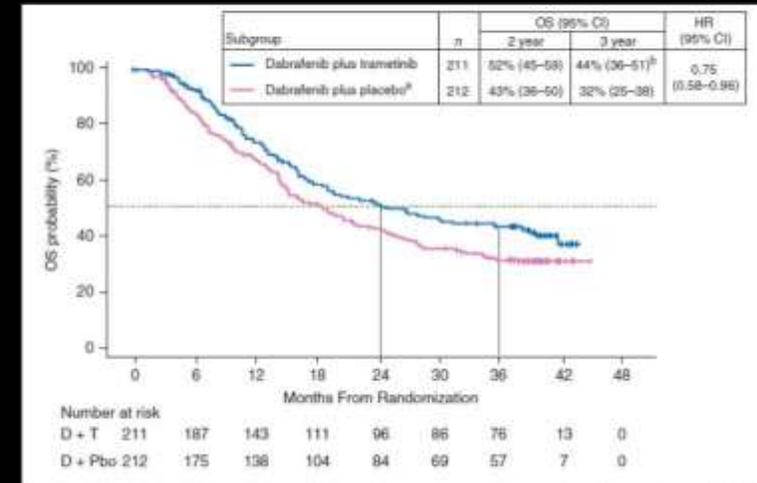
5 yr OS =51% with nl LDH and < 3 sites of mets

Long et al, 2018, JCO

Ascierto et al, Lancet Oncol, 2016



Robert et al, NEJM, 2015



Long et al, Ann Oncol, 2017

Summary of Target Therapy studies

Characteristic	ORR	Median PFS	Median OS	OS (%)			≥3 met. sites	LDH>ULN	I-O post	Discontinuation
				1Y	2Y	3Y				
COBRIM¹	70%	12.3	22.3	75%	48%	--	-	46%	18%	16.6%
COMBI-d²	68%	11.0	25.1	74%	52%	44%	48%	36%	20%	14%
COMBI-v³	67%	12.1	26.1	72%	53%	45%	50%	34%	9%	16%
COLUMBUS⁴	76%	14.9	33.6	75.5%	57.6%		45%	29%	20%	15%
	64% BIRC*									6% drug related

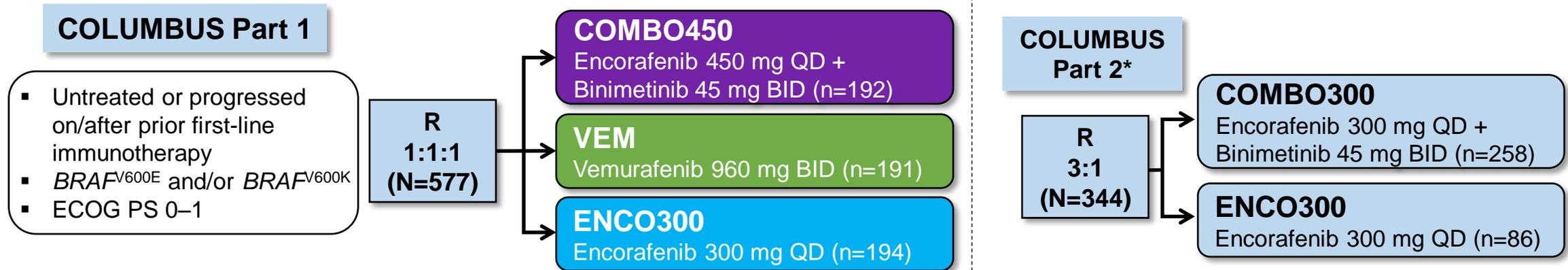
COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCC300=encorafenib 300 mg QD; LDH=lactate dehydrogenase; BIRC = Blinded Independent Review Committee; ULN=upper limit of normal; VEM=vemurafenib 960 mg BID.

- 1.Larkin J et al. N Engl J Med 2014;371:1867
- 2.Long GV et al Lancet 2015;386:444
- 3.Robert C et al N Engl J Med 2015;372:30-39
- 4.Dummer R. et al Lancet Oncol 2018;published online September 2018

Overall Survival in COLUMBUS: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) vs Vemurafenib (VEM) or ENCO in *BRAF*-Mutant Melanoma

Reinhard Dummer, Paolo A. Ascierto, Helen J. Gogas, Ana Arance, Mario Mandala, Gabriella Liskay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Vanna Chiarion-Sileni, Caroline Dutriaux, Jan Willem B. de Groot, Naoya Yamazaki, Carmen Loquai, Laure A. Moutouh-de Parseval, Michael D. Pickard, Victor Sandor, Caroline Robert, Keith T. Flaherty

Study Design and Objectives



Efficacy update with additional follow-up of 18 months:

OS:

- Secondary endpoint†
- Planned after 232 events in the COMBO450 and VEM groups combined
- Median duration of follow-up‡: 36.8 months

PFS:

- Primary endpoint
- Median duration of follow-up‡: 32.1 months

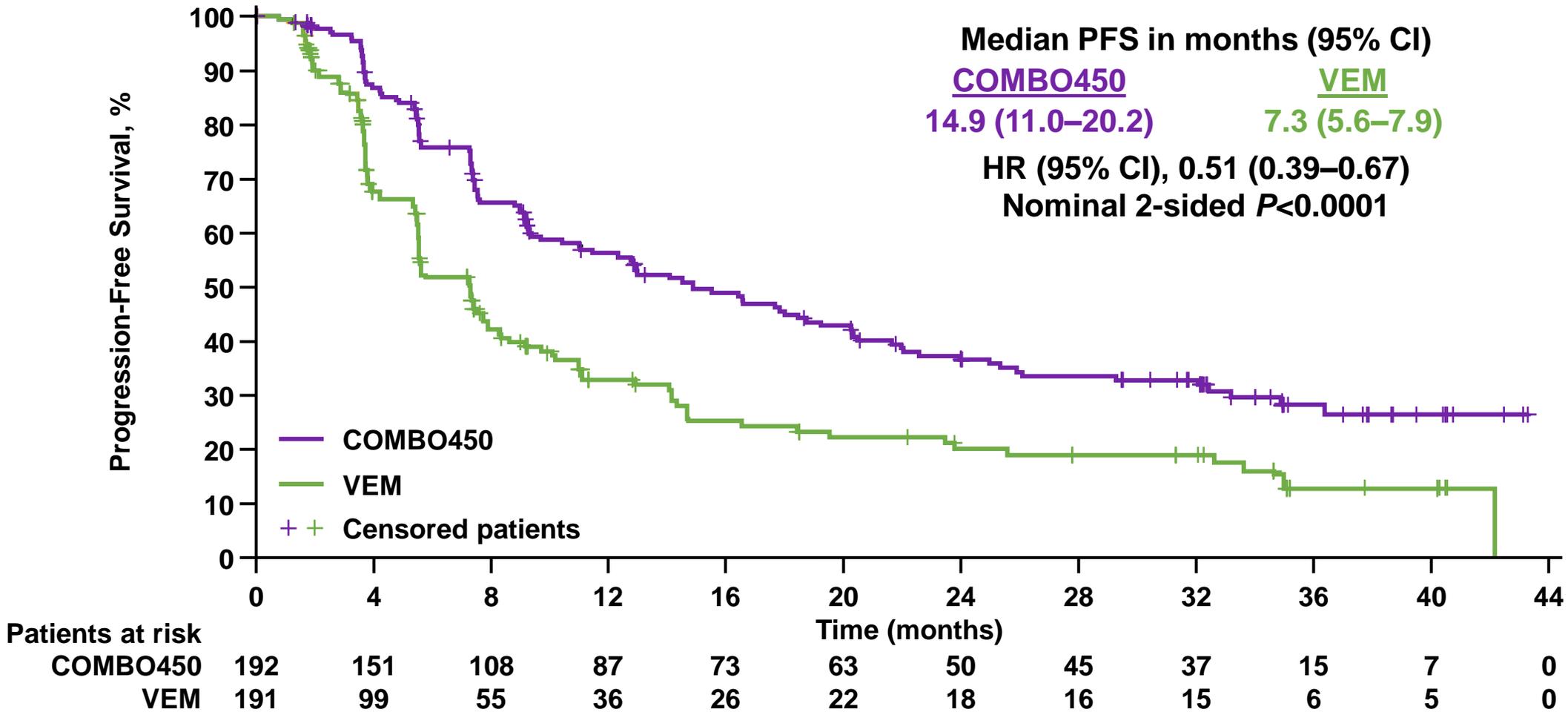
COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; R=randomization; VEM=vemurafenib 960 mg BID.

*Amendment requested by FDA.

†Included in hierarchical testing approach.

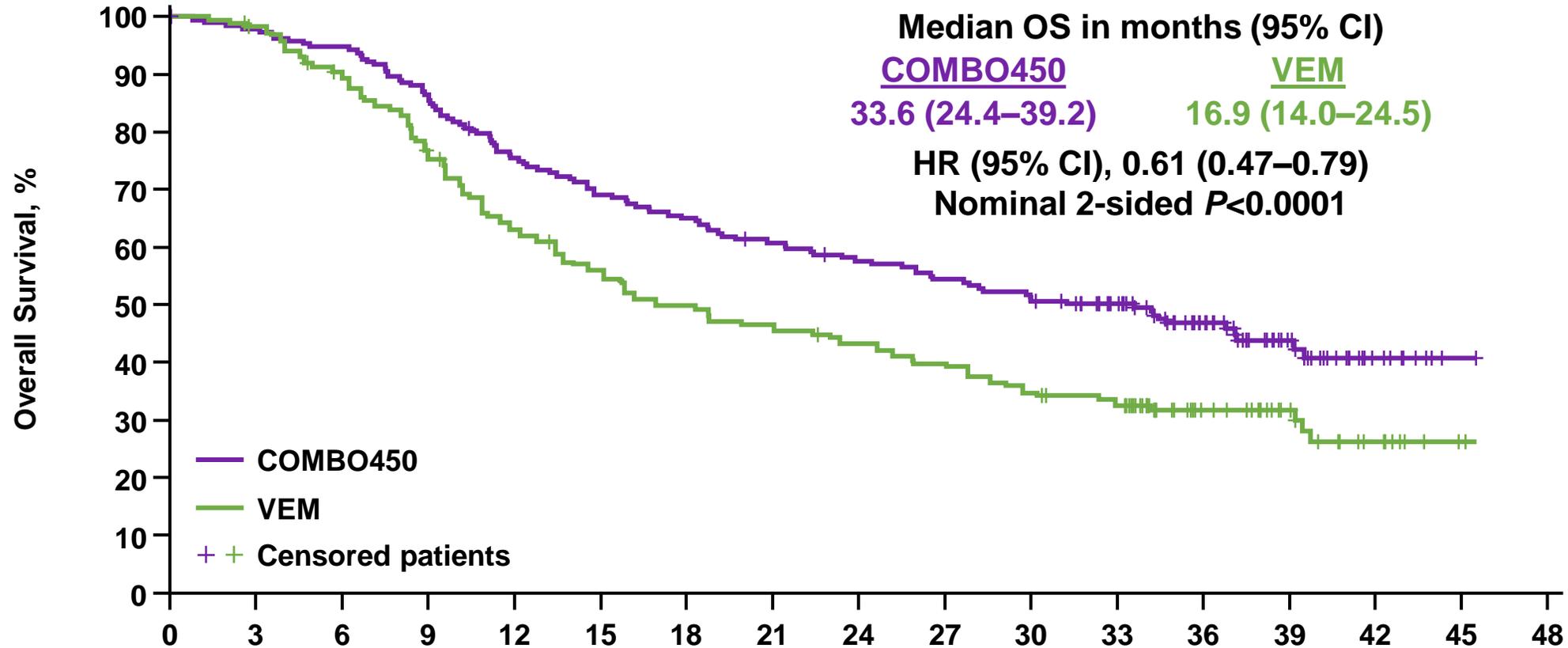
‡Median follow-up of patients assessed using reverse Kaplan-Meier approach (i.e. median potential follow-up).

Updated Progression-Free Survival: COMBO450 vs VEM



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; HR=hazard ratio; PFS=progression-free survival; VEM=vemurafenib 960 mg BID.

Overall Survival: COMBO450 vs VEM



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
COMBO450	192	188	182	166	144	132	124	115	108	102	95	82	57	30	9	1	0
VEM	191	184	166	140	115	100	89	83	77	71	62	56	30	19	8	1	0

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; HR=hazard ratio; OS=overall survival; VEM=vemurafenib 960 mg BID.

Conclusions

- COMBO450 showed improved OS vs VEM: 33.6 mo vs 16.9 mo (HR 0.61; nominal 2-sided $P < 0.0001$)
- Updated PFS results remained the same as previously reported: median PFS 14.9 mo¹
- Performance of VEM in COLUMBUS was consistent with historical data for ORR, PFS, and OS^{2,3}
- Use of subsequent systemic therapies in COLUMBUS was similar to phase 3 studies of established BRAFi/MEKi therapies^{2,4}
- COMBO450 showed a favorable tolerability profile and no new safety concerns

Encorafenib plus binimetinib combination therapy provides a new efficacy benchmark for targeted therapy and it is a promising treatment option for patients with *BRAF*^{V600}-mutant melanoma

BRAFi=BRAF Inhibitor; COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; HR=hazard ratio; MEKi=MEK Inhibitor; OS=overall survival; PFS=progression-free survival; VEM=vemurafenib 960 mg BID.

1. Dummer R, et al. *Lancet Oncol.* 2018;19:603-615.

2. Ascierto PA, et al. *Lancet Oncol.* 2016;17:1248-1260.

3. Robert C, et al. *Eur J Cancer.* 2015;51:S663-S664.

4. Long GV, et al. *Ann Oncol.* 2017;28:1631-1639.

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ANNUAL MEETING

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PRESENTED BY: Reinhard Dummer

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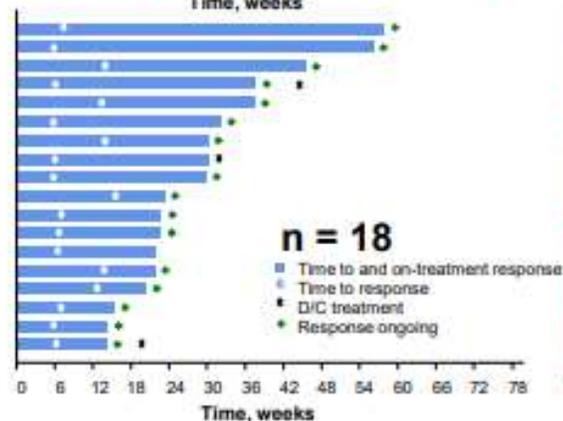
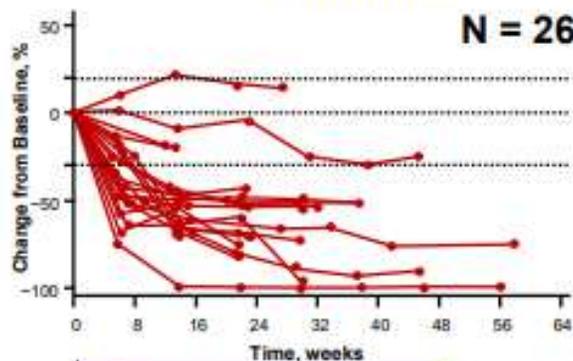
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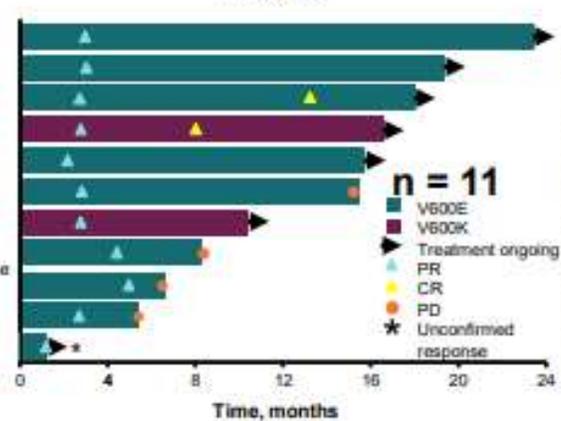
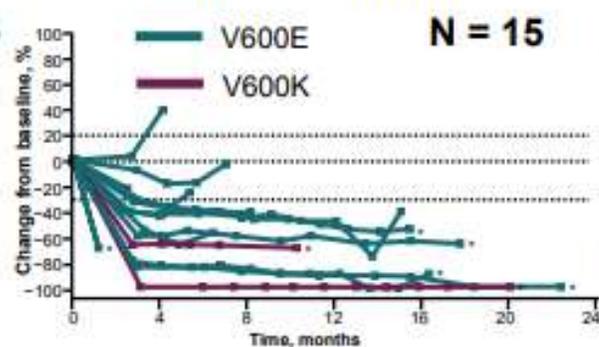
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 - TERAPIA TARGET
 - TRIALS IN CORSO

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

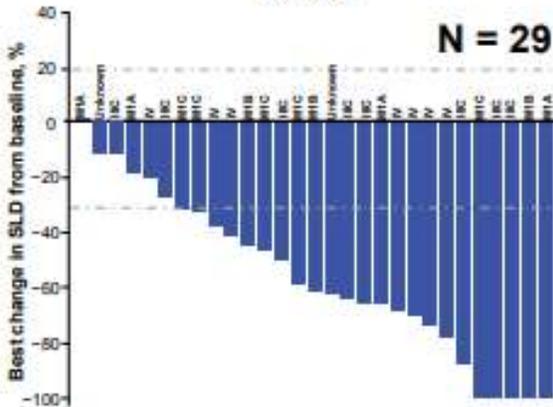
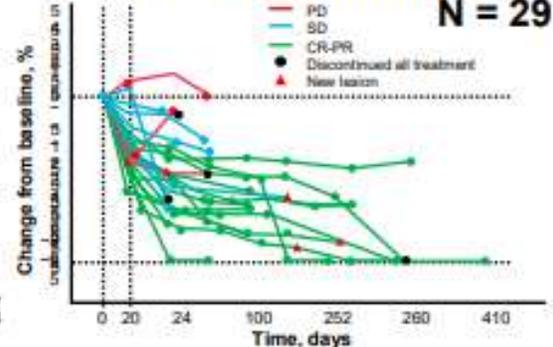
Dabrafenib + Trametinib + Durvalumab¹



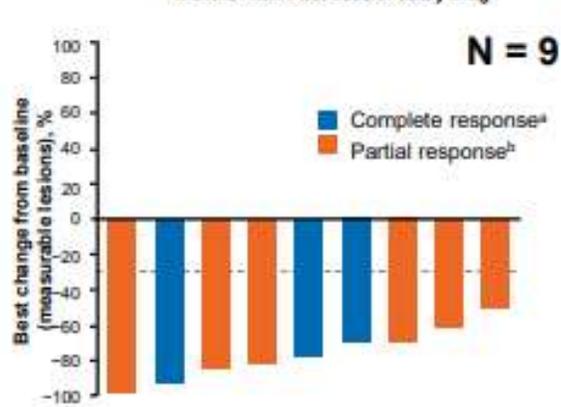
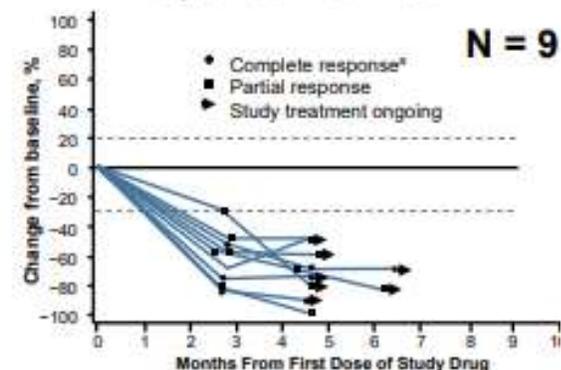
Dabrafenib + Trametinib + Pembrolizumab^{2,3}



Vemurafenib + Cobimetinib + Atezolizumab⁴



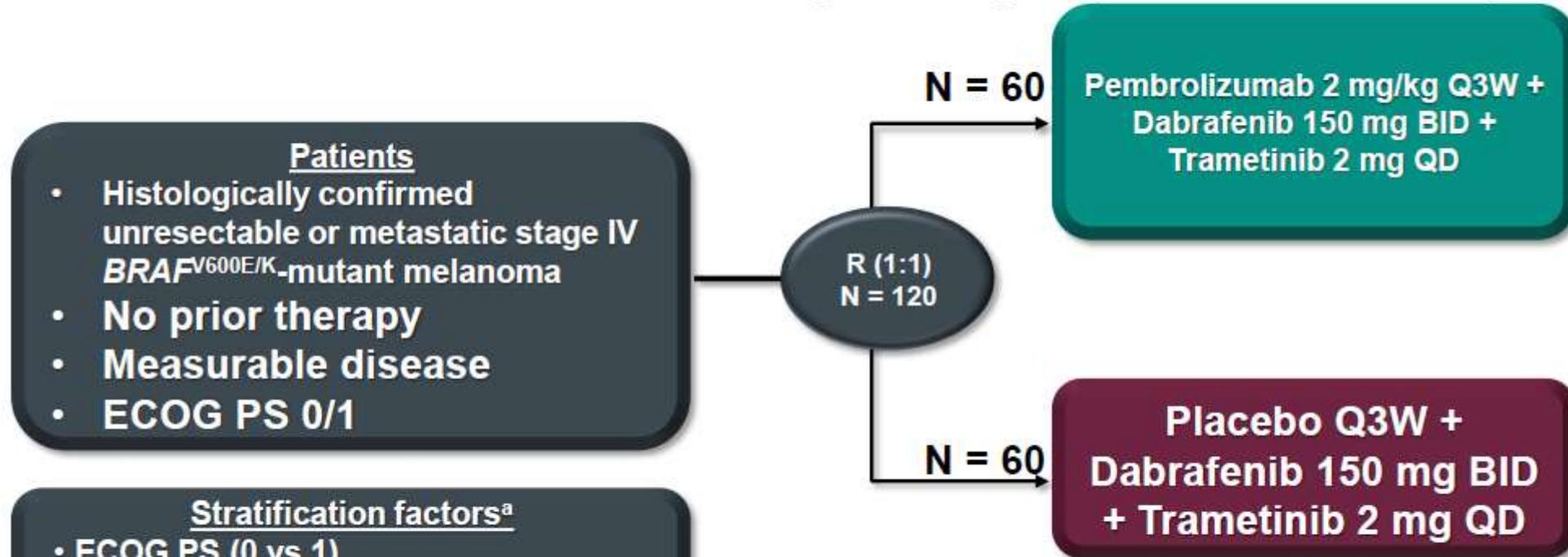
Dabrafenib + Trametinib + Spartalizumab⁵



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].

KEYNOTE-022 Part 3 Study Design (NCT02130466)



Patients

- Histologically confirmed unresectable or metastatic stage IV *BRAF*^{V600E/K}-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors^a

- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

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

^aOwing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.



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- CHIRURGIA



- TERAPIA ADIUVANTE



- TERAPIA PER MALATTIA AVANZATA

