Revolution in der adjuvanten Therapie des Melanoms? Was bleibt? Was wird sich verändern?

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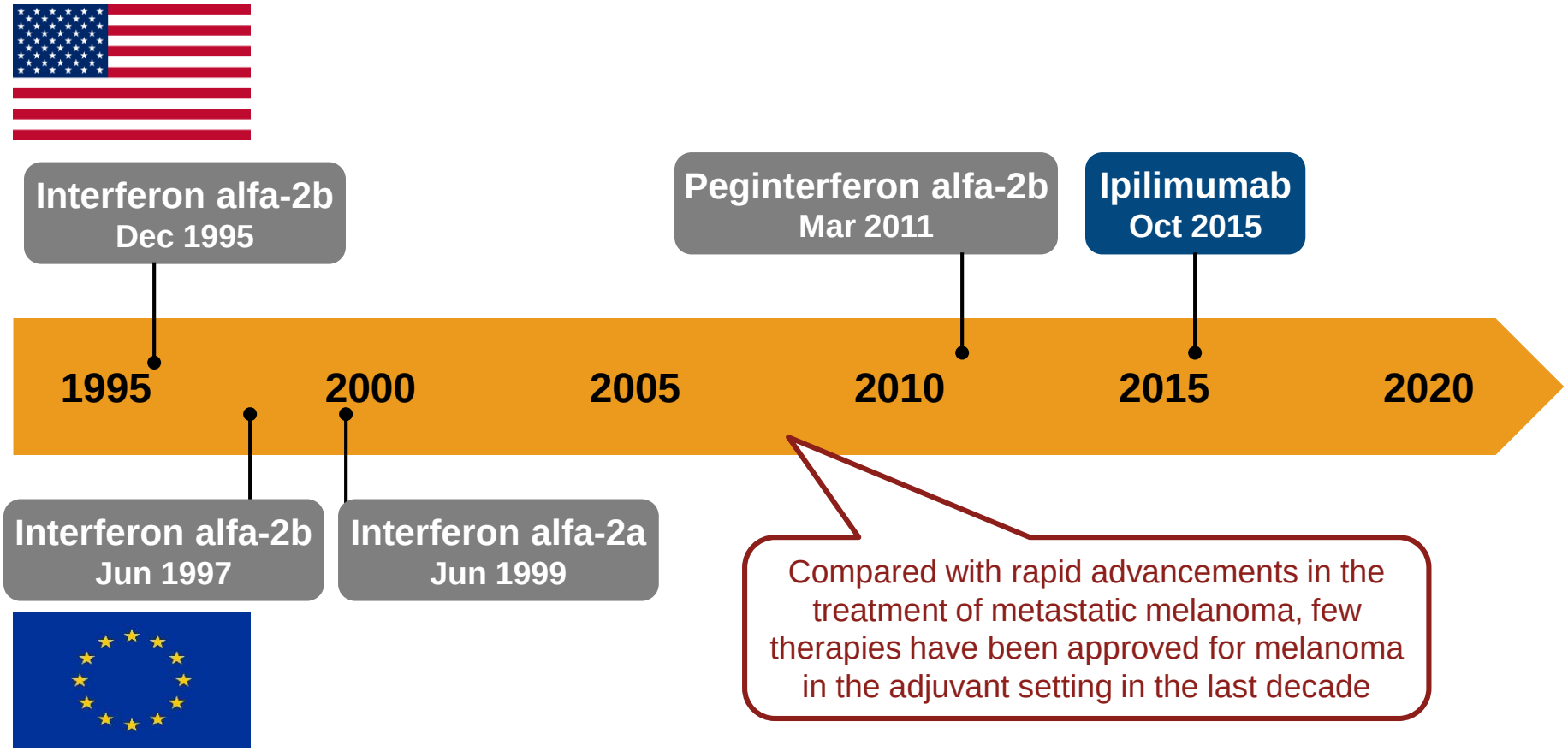
Oktober 2017

Approved treatments for melanoma in the adjuvant setting[1-4]



1. Available at: https://www.cancer.gov/about-cancer/treatment/drugs/melanoma. Accessed 11 September 2017;
2. Available at: http://www.emaeuropa.edu. Accessed 11 September 2017.
3. https://www.thepharmaletter.com/article/new-indication-for-roferon-a-approved-in-eu. Accessed 3 Oct 2017
4. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000281/WC500034675.pdf Accessed 3 Oct 2017.

Adjuvant trials leading to regulatory approval in the U.S.

Study	Stage	N	Treatment Regimen	Follow-up Median, yr	RFS (HR)	OS (HR)
E1684	T4, N+	287	**HD-IFN** vs observation	6.9	**0.61**	**0.67**
E1690	T4, N+	642	**HD-IFN** or LD-IFN vs observation	6.6	**0.81**	**-**
E1694	T4, N+	880	**HD-IFN** vs GMK vaccine	2.1	**0.75**	**0.76**
EORTC 18991	N1,2	1256	**Pegylated IFN** vs observation	7.6	**0.87**	**-**
EORTC 18071	N1,2,3	951	**Ipilimumab 10 mg/kg** vs placebo	5.3	**0.76**	**0.72**

HD-IFN: IFN-α2b 20 MU/m^2/day IV for 1 month then 10 MU/m^2 SC TIW for 11 months.
Pegylated IFN-α: pIFN-α2b 6 μg/kg/week SC for 8 weeks then 3 μg/kg/week for 5 years.
EORTC 18071: Ipilimumab 10 mg/kg IV every 21 days × 4 then every 12 weeks for 3 years.
Tarhini AA, et al. *J Clin Oncol.* 2017;35:(suppl; abstr 9500).

Use of Adjuvant Interferon Therapy in the USA (2002-10)

Treatment	Stage IIB (n=125) %	Stage IIC (n=68) %	Stage III (n=196) %	Stage IV- NED (n=28) %
No treatment	52.8	35.3	21.0	21.4
Other treatment	7.2	2.9	4.1	64.2
IFN treatment	40.0	61.8	75.0	14.3

Micheal Atkins ASCO 2016

Use of Adjuvant Interferon Therapy in the USA (2002-10)

Treatment	Stage IIB (n=125) %	Stage IIC (n=68) %	Stage III (n=196) %	Stage IV- NED (n=28) %
No treatment	52.8	35.3	21.0	21.4
treatment	40.0	61.8	75.0	14.3

New unpublished data suggest:

Only 30% of patients in stage III get adjuvant therapy

Micheal Atkins ASCO 2016; personal communication Peter Mohr, MD

Treatment patterns Stage IIIB/IIIC melanoma in France, Germany and the United Kingdom (MELABIS) (2009-11)

Treatment	France (n=199) %	Germany (n=146) %	United Kingdom (n=195) %	Overall (n=588) %
No treatment	93.0	66.5	97.4	86.7
Other Treatment	4.5	0.6	2.6	2.7
High-dose IFN	1.5	11.0	0	3.8
Intermediate IFN	0.5	4.9	0	1.6
Low-dose IFN	0	15.2	0	4.5
Pegylated-IFN	0	1.8	0	1.6

Harries M, Mohr P, Grange F, et al. Int J Clin Pract. 2017 May 71(5)

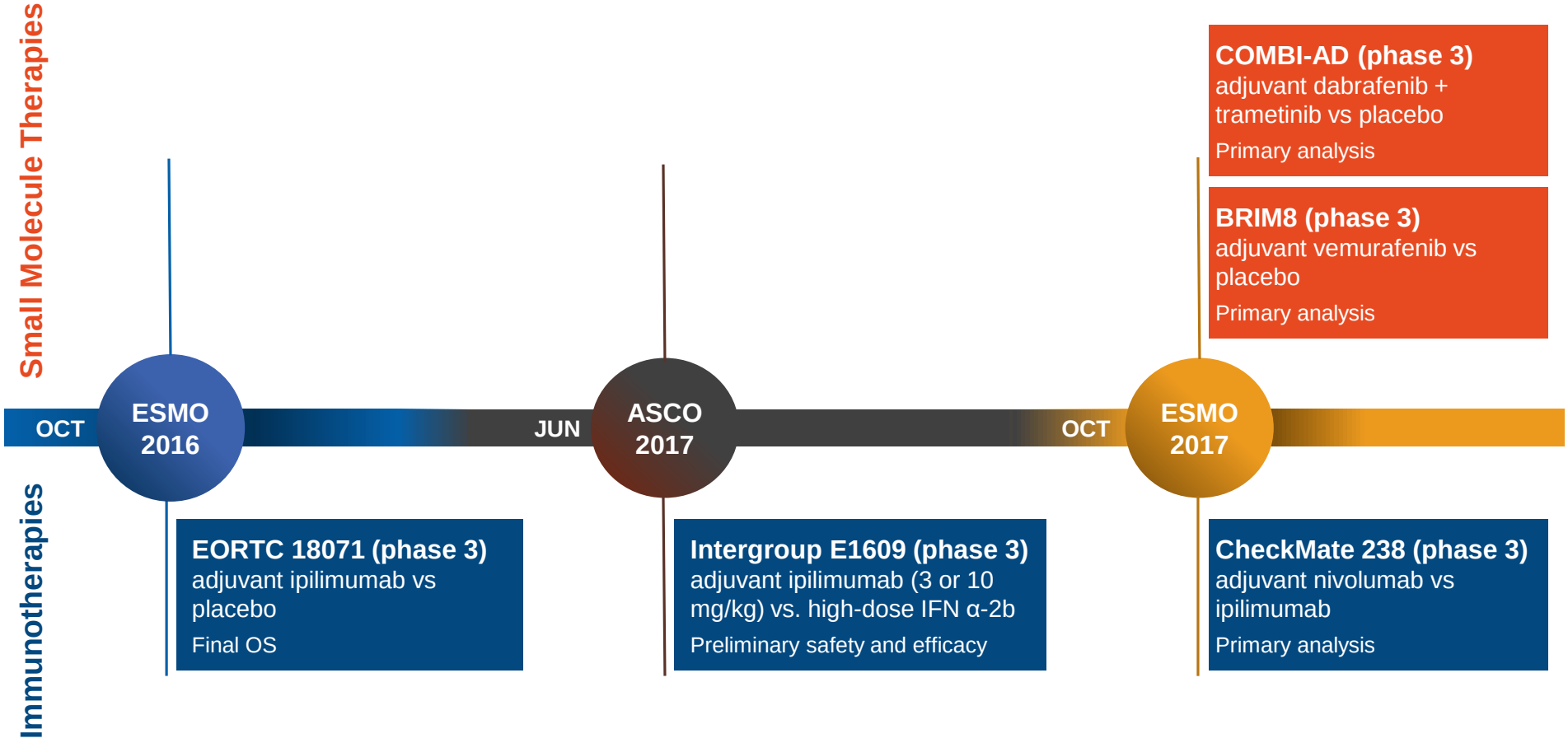
Benefits of Adjuvant Interferon in Meta Analysis

Overall Risk

Dose	Event Free Survival	Overall Survival
High (N=1196)	0.83 (0.72-0.96)	0.93 (0.80-1.08)
Peg-IFN (N=1256)	0.83 (0.76-1.00)	0.96 (0.82-1.11)
Intermediate (N=2243)	0.84 (0.74-0.95)	0.91 (0.79-1.04)
Low (N=2732)	0.85 (0.77-0.94)	0.86 (0.77-0.96)
Very low (N=484)	0.99 (0.80-1.23)	0.96 (0.76-1.21)
Overall (95%CI)	**0.86 (0.81-0.91)**	**0.90 (0.85-0.97)**

Natalie et al. European Journal of Cancer 82 (2017) 171e183

Key melanoma data highlighting recent developments in the adjuvant setting



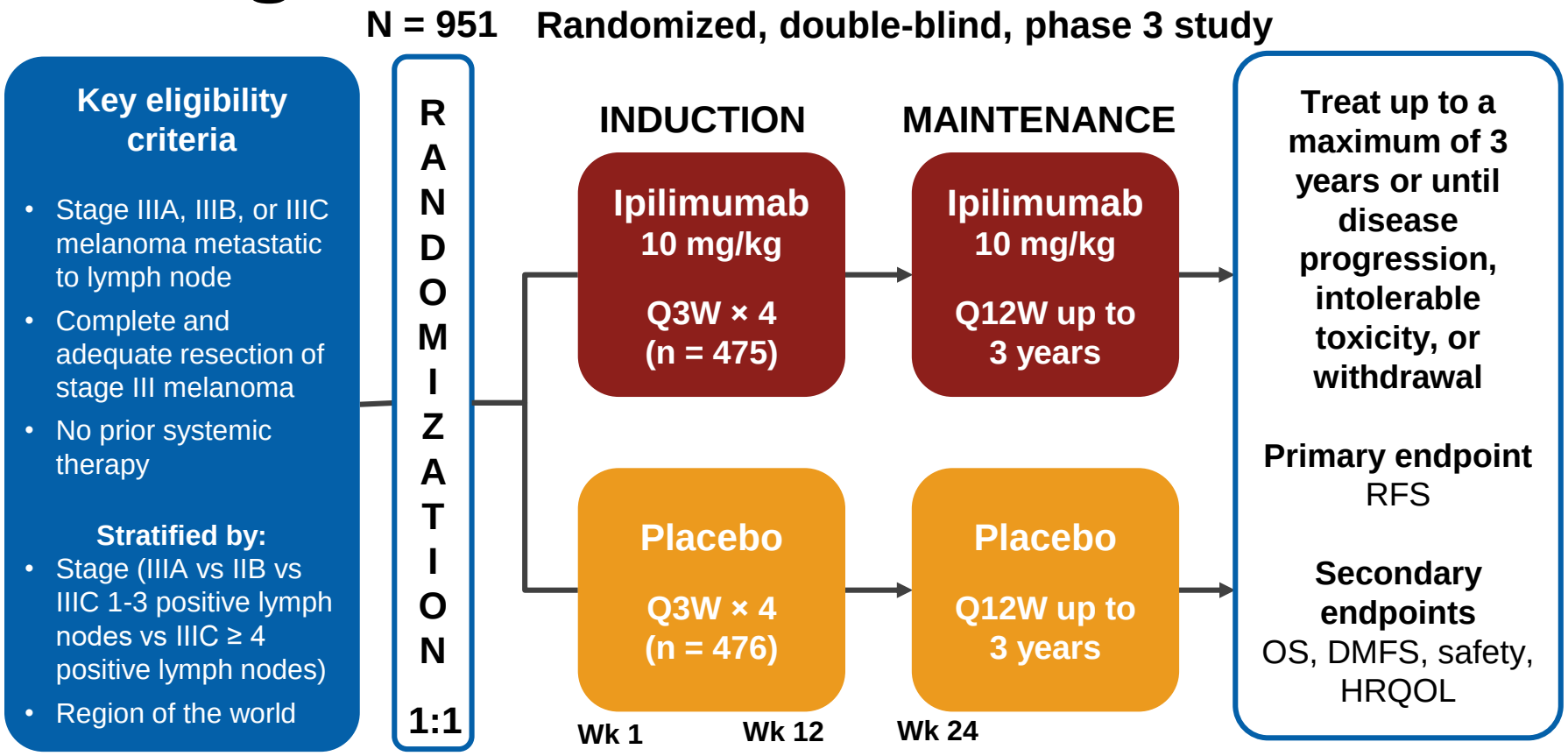
Clinicaltrials.gov EORTC 18071: NCT00636168; Intergroup E1609: NCT01274338; COMBI-AD: NCT01682083; BRIM8: NCT01667419; CheckMate 238: NCT02388906

Agenda

1. EORTC 18071: Adjuvant ipilimumab vs placebo
2. COMBI-AD: Adjuvant dabrafenib + trametinib vs placebo
3. BRIM8: Adjuvant vemurafenib vs placebo
4. CheckMate 238: Adjuvant nivolumab vs ipilimumab

EORTC 18071:
Adjuvant ipilimumab vs placebo

EORTC 18071: phase 3 study design[1,2]

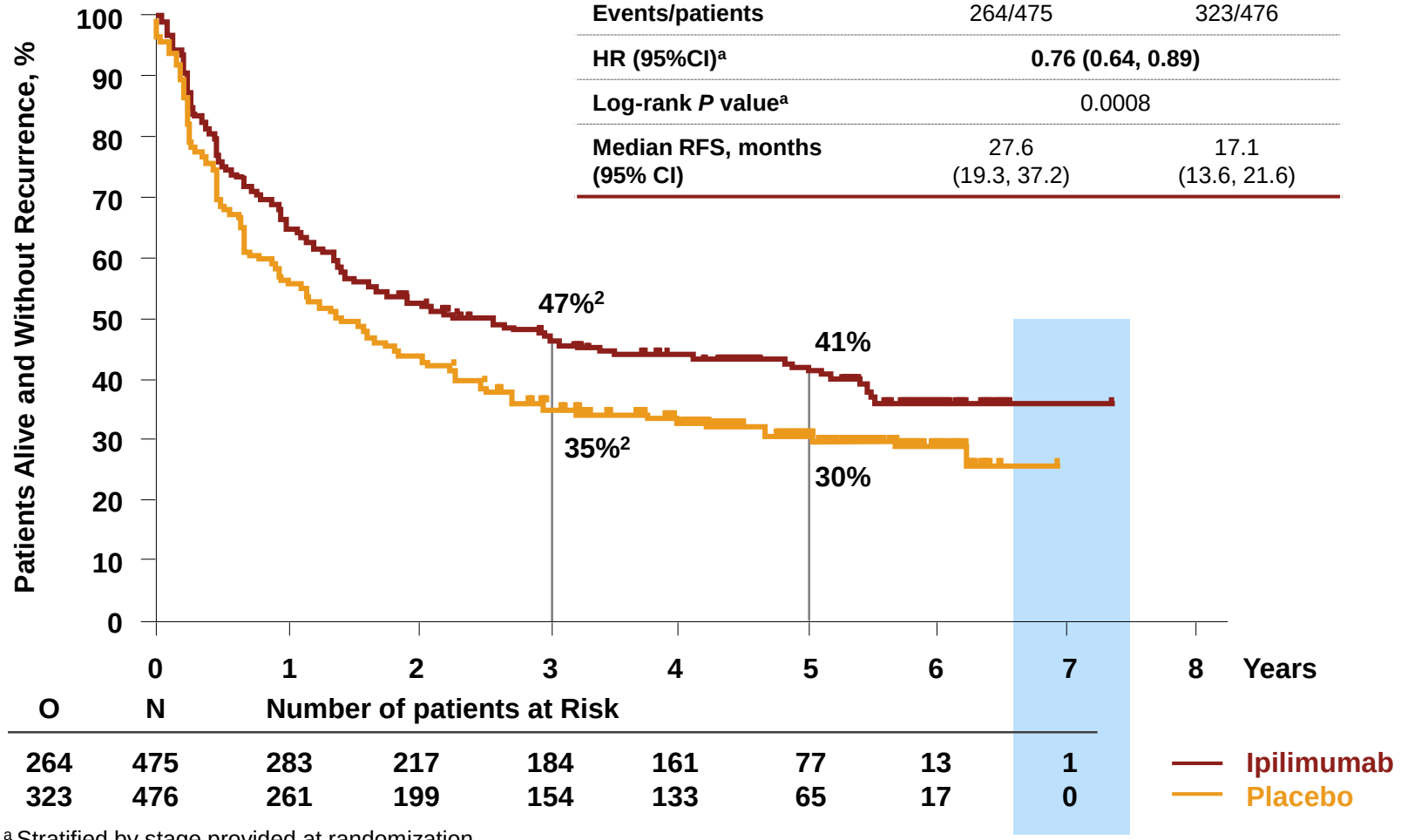


DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.

1. Eggermont AM, et al. *J Clin Oncol* 2014;32:5s(suppl; abstr LBA9008); 2. Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

EORTC 18071: RFS[1,2]

	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95%CI)[a]	**0.76 (0.64, 0.89)**	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

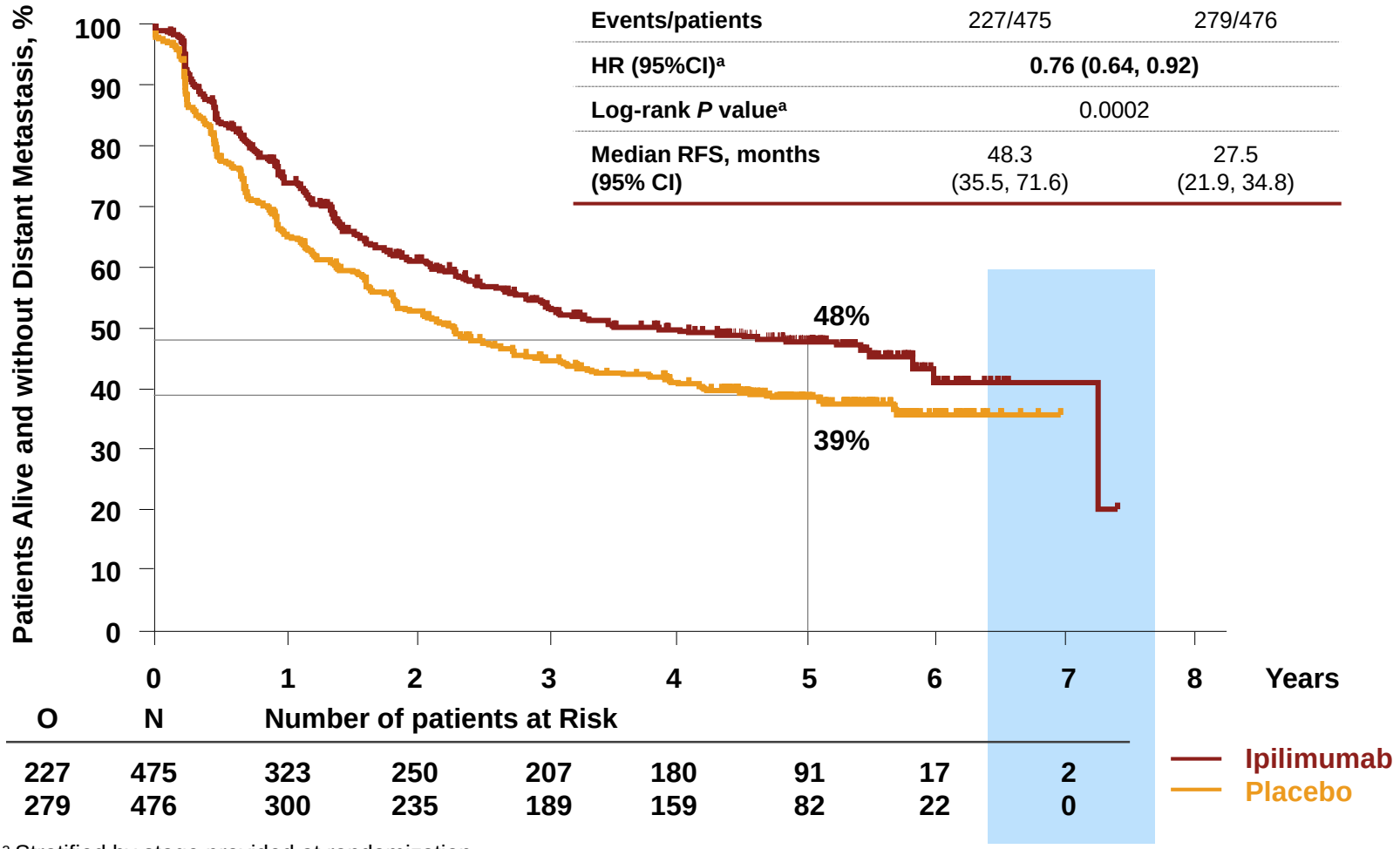


[a] Stratified by stage provided at randomization.
CI, confidence interval.

1. Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR]; 2. Eggermont AM, et al. *Lancet Oncol*. 2015;16:522-530.

EORTC 18071: DMFS

	Ipilimumab	Placebo
Events/patients	227/475	279/476
HR (95%CI)[a]	**0.76 (0.64, 0.92)**	
Log-rank *P* value[a]	0.0002	
Median RFS, months (95% CI)	48.3 (35.5, 71.6)	27.5 (21.9, 34.8)

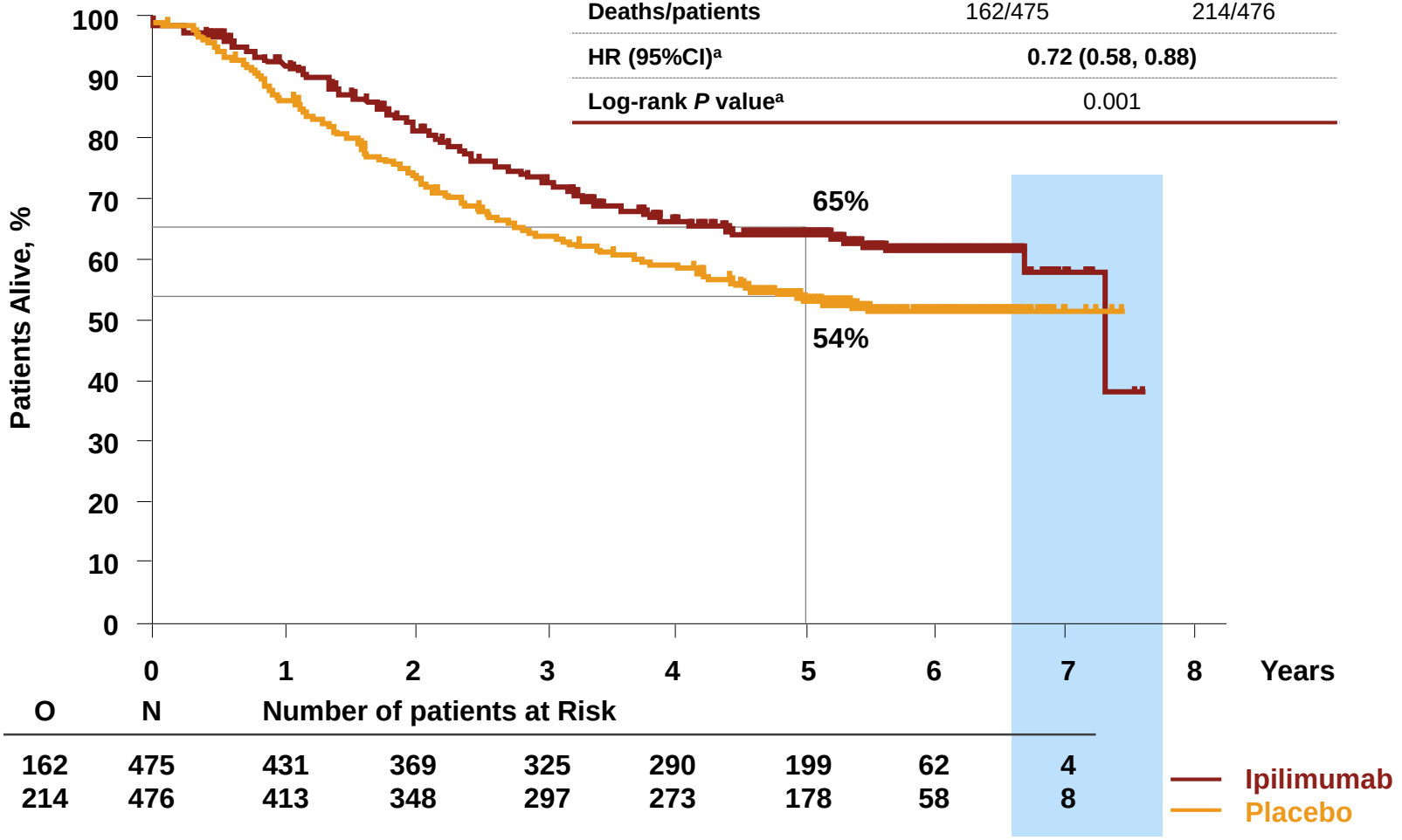


[a] Stratified by stage provided at randomization.

Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

EORTC 18071: OS

	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95%CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	



[a] Stratified by stage provided at randomization.

Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

EORTC 18071: Post-relapse therapies

	Patients With an RFS Event	
Post-relapse Therapy, %[a]	**Ipilimumab (n = 264)**	**Placebo (n = 323)**
Any antitumoral therapy	73.5	77.4
Chemotherapy	15.2	16.1
Radiotherapy	7.2	5.9
Surgery	15.5	9.6
Chemoradiotherapy	0.4	1.2
Other	12.5	11.1
Ipilimumab	9.1	23.5
Anti–PD-1 agent	9.1	9.3
BRAF inhibitor	23.9	27.2

[a] Patients could receive more than 1 subsequent antitumoral therapy.
Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

EORTC 18071: safety summary

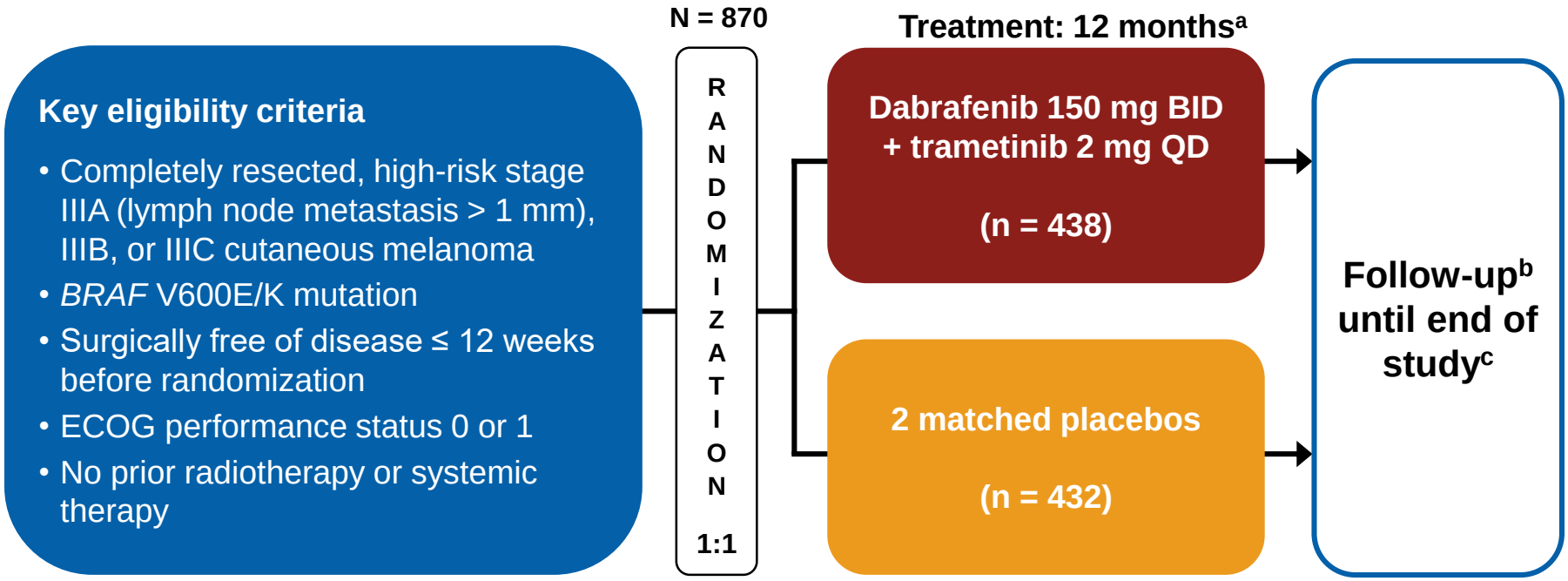
	Ipilimumab (n = 471)		Placebo (n = 474)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.7	54.1	91.1	26.2
Treatment-related AE, %	94.1	45.4	59.9	4.0
Treatment-related AE leading to discontinuation, %	48.0	32.9	1.5	0.6
Any immune-related AE, %	90.4	41.6	39.7	2.7

- No new deaths due to drug-related AEs compared with the primary analysis
  - 5 patients (1.1%) in the ipilimumab group
    - 3 patients with colitis (2 with gastrointestinal perforations)
    - 1 patient with myocarditis
    - 1 patient had multiorgan failure with Guillain-Barré syndrome
  - No deaths related to study drug in the placebo group

Eggermont A, et al. ESMO. 2016;[abstr LBA2_PR].

COMBI-AD:
Adjuvant dabrafenib + trametinib vs placebo

COMBI-AD: phase 3 study design



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

- **Primary endpoint:** RFS[d]
- **Secondary endpoints:** OS, DMFS, FFR, safety

BID, twice daily; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.

[a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b] Patients were followed for disease recurrence until the first recurrence and thereafter for survival; [c] The study will be considered complete and final OS analysis will occur when ≈ 70% of randomized patients have died or are lost to follow-up; [d] New primary melanoma. considered as an event.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: study analyses and endpoints

- Efficacy analyses included all patients (intent-to-treat population), and safety analyses included all patients who received ≥ 1 dose of randomized treatment (safety population)
- OS was to be tested only if the primary endpoint (RFS) significantly favored the combination arm
  - OS statistical significance boundary (O'Brien-Fleming) for first interim analysis, *P* = .000019
- All recurrence analyses were based on investigator assessment and defined as follows:
  - RFS: time from randomization to disease recurrence or death from any cause
    - Study was designed to provide > 90% power (assuming ≈ 410 RFS events observed) to detect an HR of 0.71 with an overall 2-sided type I error rate of 5%
  - DMFS: time from randomization to date of first distant metastasis or death, whichever occurred first
  - FFR: time from randomization to recurrence, with censoring of patients dying from causes other than melanoma or treatment-related toxicity

HR, hazard ratio.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: baseline characteristics and demographics

Category[a]	Dabrafenib Plus Trametinib (n = 438)	Placebo (n = 432)	Total (N = 870)
Median age (range), years	50 (18-89)	51 (20-85)	50 (18-89)
Male, n (%)	195 (45)	193 (45)	388 (45)
***BRAF* mutation status, n (%)**			
V600E	397 (91)	395 (91)	792 (91)
V600K[b]	41 (9)	37 (9)	78 (9)
ECOG performance status of 0, n (%)	402 (92)	390 (90)	792 (91)
Disease stage, n (%)			
IIIA	83 (19)	71 (16)	154 (18)
IIIB	169 (39)	187 (43)	356 (41)
IIIC	181 (41)	166 (38)	347 (40)
III (unspecified)	5 (1)	8 (2)	13 (1)

[a] Reported for patients with available data.
[b] One patient had both *BRAF* V600E and *BRAF* V600K mutations and was included in the V600K subset.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

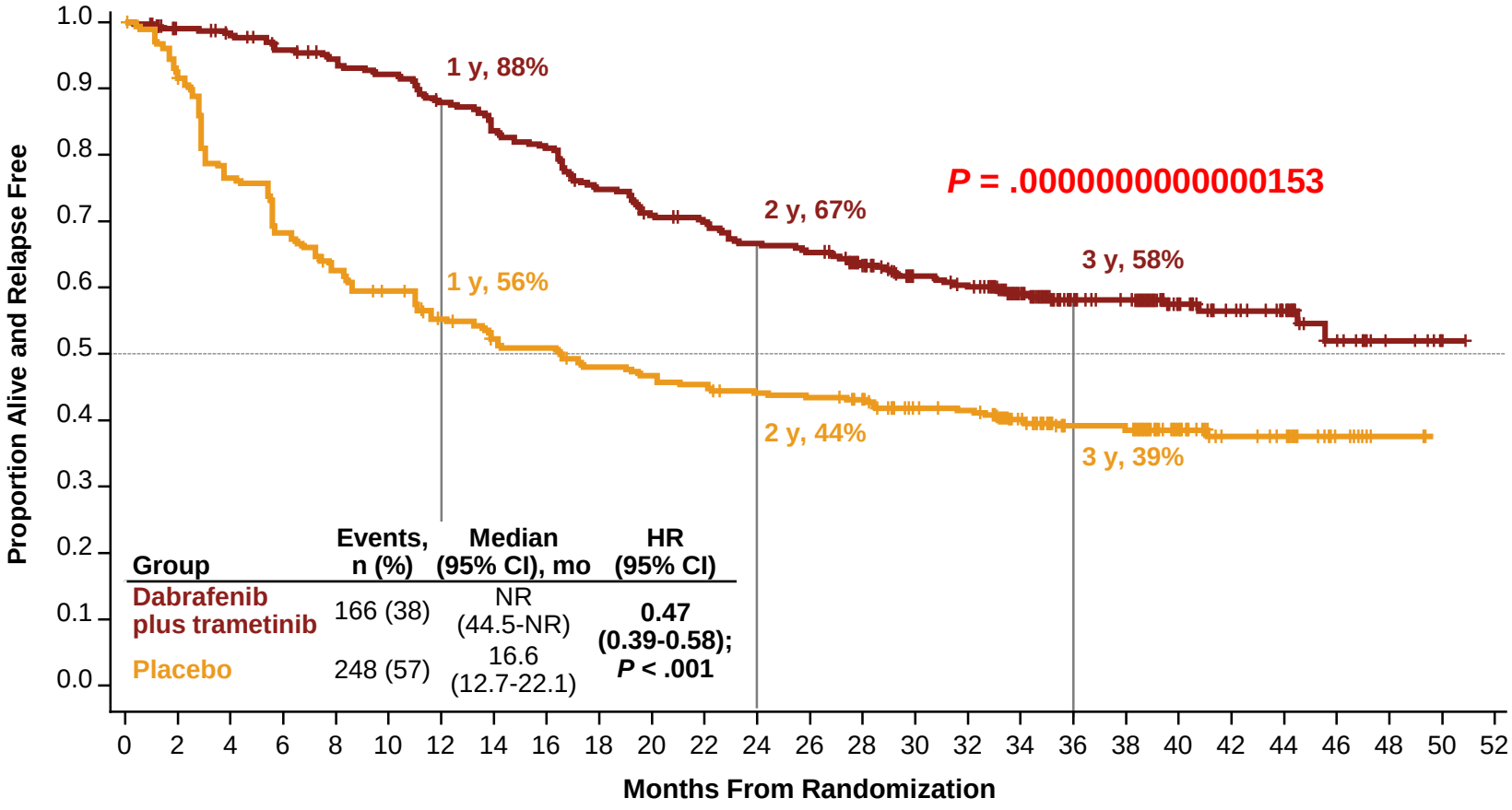
COMBI-AD: baseline characteristics and demographics (cont)

Category[a]	Dabrafenib Plus Trametinib (n = 438)	Placebo (n = 432)	Total (N = 870)
Number of positive lymph nodes, n (%)			
1	177 (40)	183 (42)	360 (41)
2 or 3	158 (36)	150 (35)	308 (35)
≥ 4	73 (17)	72 (17)	145 (17)
Type of lymph node involvement, n (%)			
Microscopic	152 (35)	157 (36)	309 (36)
Macroscopic	158 (36)	161 (37)	319 (37)
Not reported	128 (29)	114 (26)	242 (28)
Primary tumour ulceration, n (%)			
Yes	179 (41)	177 (41)	356 (41)
No	253 (58)	249 (58)	502 (58)
In-transit disease, n (%)			
Yes	51 (12)	36 (8)	87 (10)
No	387 (88)	395 (91)	782 (90)

[a] Reported for patients with available data.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

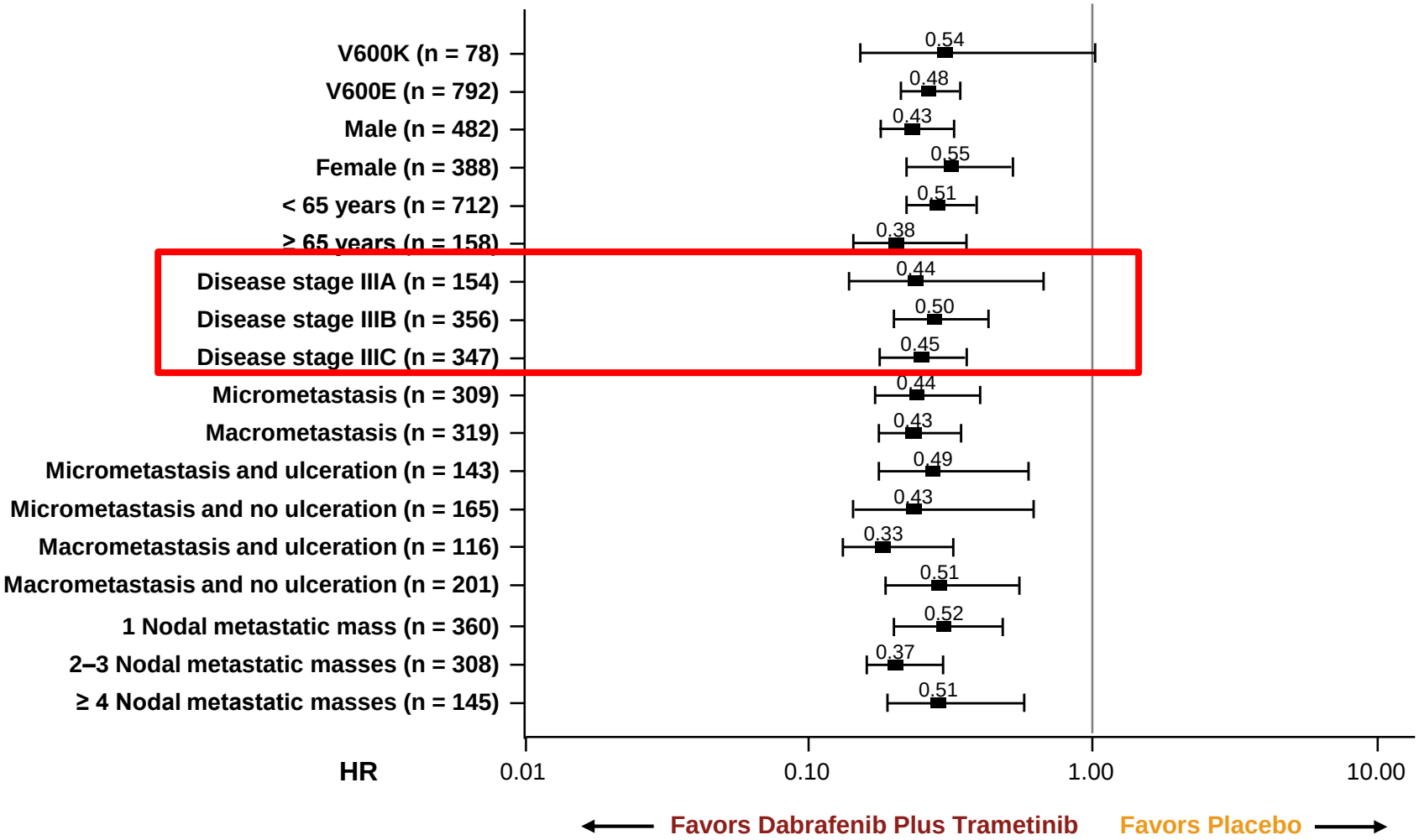
COMBI-AD: RFS



No. at Risk																											
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

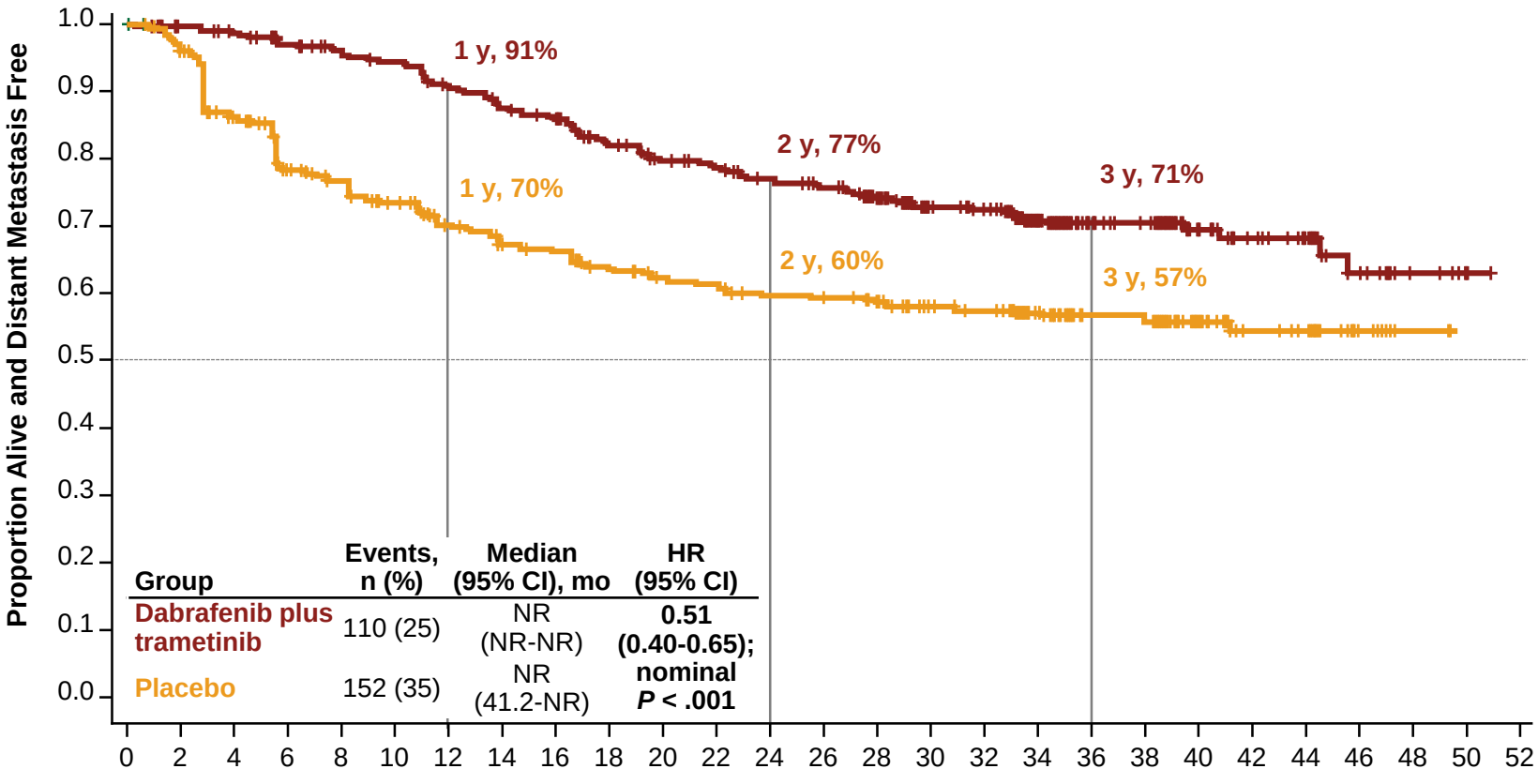
Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: RFS by subgroup



Hauschild A, ESMO. 2017;[abstr LBA6_PR].

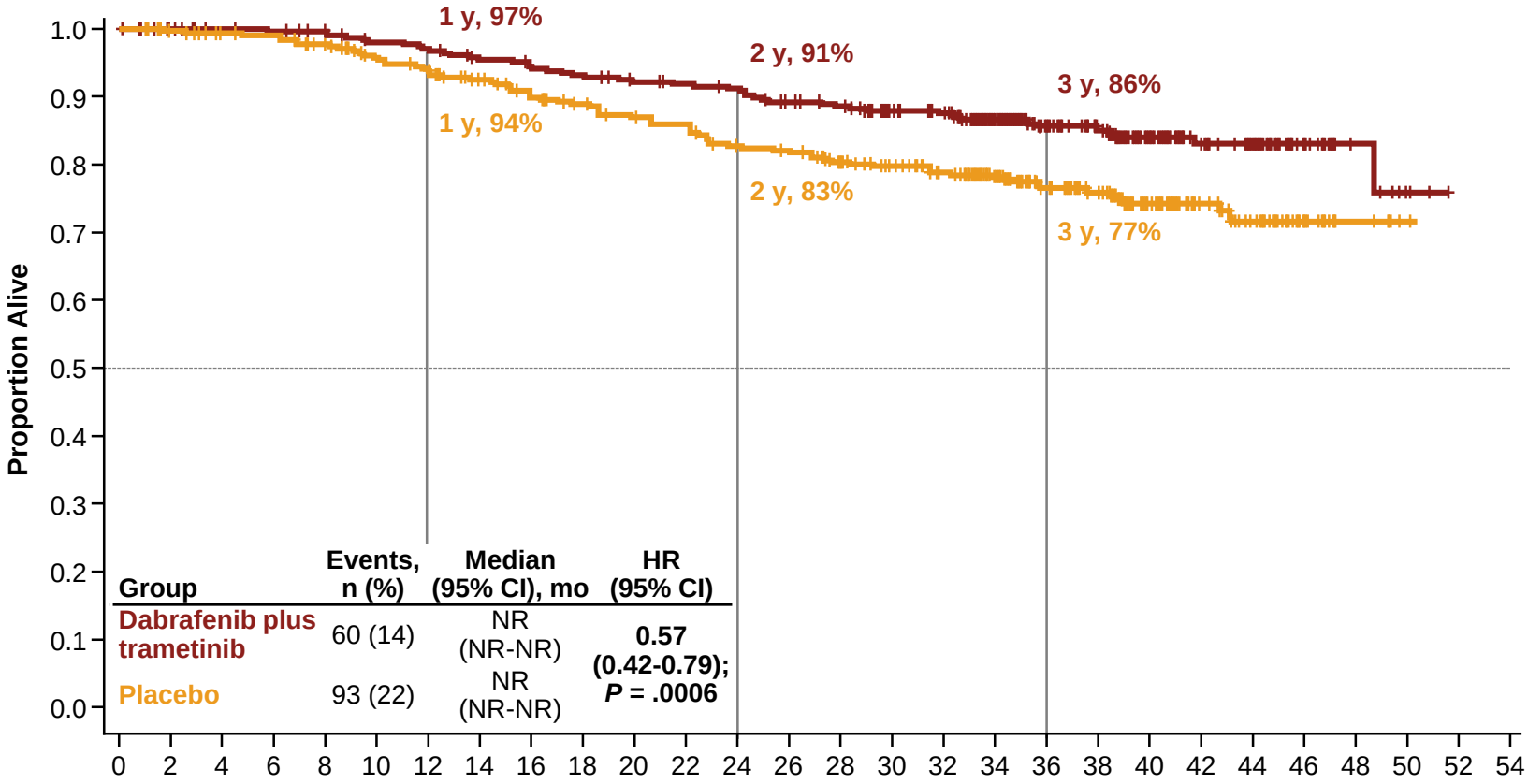
COMBI-AD: DMFS



No. at Risk																											
Dabrafenib plus trametinib	438	413	407	390	381	373	353	336	327	302	285	278	265	258	235	203	195	146	116	110	66	52	42	19	7	2	0
Placebo	432	392	330	282	265	247	221	206	201	187	179	176	169	168	159	144	140	107	88	87	51	33	30	9	3	0	0

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: OS (first interim analysis)



No. at Risk																										
Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: post-recurrence therapy among patients with relapse

Post-recurrence Therapy (relapsed patients)	Dabrafenib Plus Trametinib (n = 163)	Placebo (n = 247)
Any post-recurrence anticancer therapy, n (%)	148 (91)	217 (88)
Surgery	78 (48)	131 (53)
Radiotherapy	60 (37)	72 (29)
Any systemic post-recurrence anticancer therapy, n (%)	120 (74)	183 (74)
Small molecule–targeted therapy	**63 (39)**	**137 (55)**
Any BRAF inhibitor[a]	63 (39)	137 (55)
Any MEK inhibitor[b]	47 (29)	77 (31)
Immunotherapy	**89 (55)**	**103 (42)**
Anti–PD-1/PD-L1	71 (44)	68 (28)
Anti–CTLA-4	53 (33)	68 (28)
Interferon	6 (4)	11 (4)
T-VEC	0	1 (< 1)
Biologic therapy	1 (1)	1 (< 1)
Chemotherapy	20 (12)	23 (9)
Investigational treatment	6 (4)	19 (8)
Other therapy	2 (1)	0
Median time from disease recurrence to start of systemic post-recurrence therapy, excluding radiotherapy and surgery (range), weeks	7.1 (0-136)	7.3 (0-78)

CTLA-4, cytotoxic T-lymphocyte–associated 4; PD-1, programmed cell death 1; PD-L1 programmed cell death ligand 1; T-VEC, talimogene laherparepvec.

[a] Included dabrafenib, vemurafenib, and encorafenib; [b] Included trametinib, cobimetinib, and binimetinib. Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: safety summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Any grade 3/4 AE	**180 (41)**	**61 (14)**
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal AEs related to study drug	0	0
AEs leading to dose interruption	**289 (66)**	**65 (15)**
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation	**114 (26)**	**12 (3)**

AE, adverse event; SAE, serious adverse event.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

COMBI-AD: common AEs

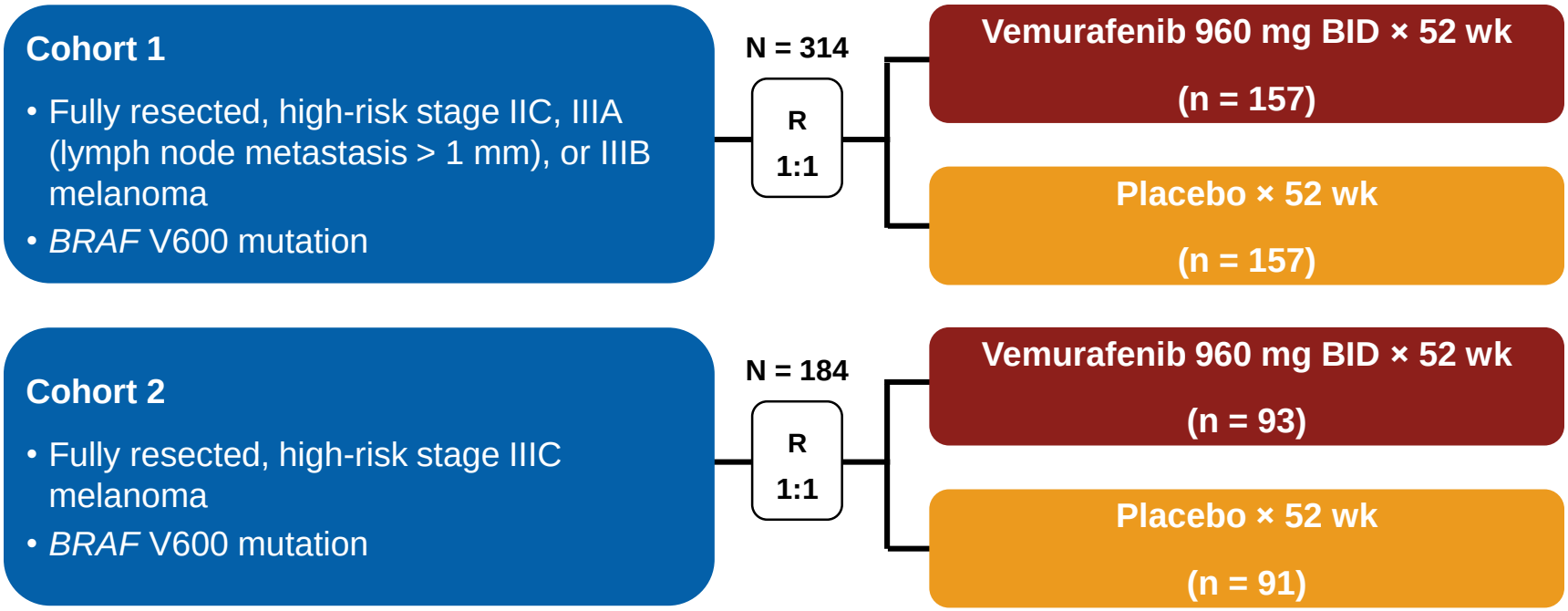
AEs, n (%)	Dabrafenib Plus Trametinib (n = 435)		Placebo (n = 432)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any AE (> 20% with dabrafenib plus trametinib)[a]	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	**273 (63)**	23 (5)	**47 (11)**	2 (< 1)
Fatigue	**204 (47)**	19 (4)	122 (28)	1 (< 1)
Nausea	**172 (40)**	4 (< 1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	**161 (37)**	6 (1)	19 (4)	0
Diarrhea	**144 (33)**	4 (< 1)	**65 (15)**	1 (< 1)
Vomiting	**122 (28)**	4 (< 1)	43 (10)	0
Arthralgia	**120 (28)**	4 (< 1)	**61 (14)**	0
Rash	**106 (24)**	0	47 (11)	1 (< 1)

[a] Eleven patients (3%) in the treatment arm and 10 patients (2%) in the placebo arm had new primary melanomas; 8 (2%) and 7 (2%), respectively, had cutaneous squamous cell carcinoma/keratoacanthoma; 19 (4%) and 14 (3%), respectively, had basal cell carcinoma; and 10 (2%) and 4 (1%), respectively, had noncutaneous malignancies.

Hauschild A, ESMO. 2017;[abstr LBA6_PR].

BRIM8:
Adjuvant vemurafenib vs placebo

BRIM8: phase 3 study design



Stratification
- Cohort 1: Disease stage and geographic region
- Cohort 2: Geographic region

- **Primary endpoint:** DFS
- **Secondary endpoints:** DMFS, OS, safety, HRQoL

Current analysis: median follow-up of 31 months (≈ 2.6 y) for cohort 1 and 34 months (≈ 2.8 y) for cohort 2

DFS, disease-free survival.
Lewis K, et al. ESMO. 2017;[abstr LBA7_PR].

BRIM8: Statistical assumptions

	Median DFS assumptions	Target HR	DFS events needed
Cohort 1 = 314 (Stage IIC, IIIA[a], IIIB)	Placebo = 24.0 months Vemurafenib = 40.0 months	HR = 0.60	120 events
Cohort 2 = 184 (Stage IIIC)	Placebo = 7.7 months Vemurafenib = 13.3 months	HR = 0.58	105 events

- **Hierarchical testing of DFS in C2 before C1 was prespecified to maintain an overall Type I error rate <0.05 (two-sided)**
- **Only a *p*-value for C2 of ≤0.05, would provide the opportunity for the analysis of C1 to be considered statistically significant.**

DFS, disease-free survival; HR, hazard ratio.

[a] Patients with stage IIIA melanoma were eligible if they had one or more nodal metastasis >1 mm in diameter.

Lewis K et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LB7_PR.

BRIM8: baseline characteristics

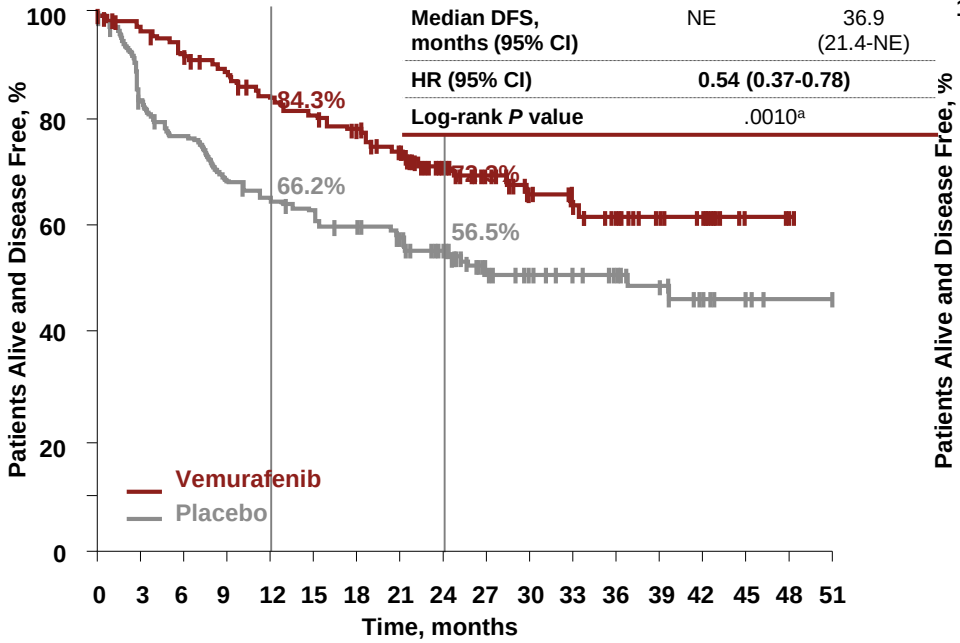
	Cohort 2 (N = 184)		Cohort 1 (N = 314)	
	Vemurafenib (n = 93)	**Placebo (n = 91)**	**Vemurafenib (n = 157)**	**Placebo (n = 157)**
Age, median years (range)	55.0 (21-80)	50.0 (19-77)	51.0 (18-77)	49.0 (26-79)
Male, n (%)	52 (56)	59 (65)	84 (54)	88 (56)
Pathologic stage, n (%)				
IIC	-	-	15 (10)	12 (8)
IIIA	-	-	36 (23)	39 (25)
IIIB	-	-	106 (68)	106 (68)
IIIC	**93 (100)**	**91 (100)**	-	-
Presence of tumor ulceration status, n/N (%)	57/85 (67)	49/78 (63)	63/144 (14)	49/143 (34)
Presence of first metachronous nodal recurrence, n/N (%)	29/93 (31)	32/90 (36)	26/157 (17)	36/157 (23)
Lymph node type at baseline, n/N (%)				
Micrometastasis	0	0	84/142 (59)	76/145 (52)
Macrometastasis	30/93 (32)	27/91 (30)	58/142 (41)	69/145 (48)
N3	63/93 (68)	64/91 (70)	0	0
ECOG PS, n/N (%)				
0	81/92 (88)	78/91 (86)	143/155 (92)	136/157 (87)
1	11/92 (12)	13/91 (14)	12/155 (8)	21/157 (13)

Lewis K et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LB7_PR.

BRIM8: DFS (primary endpoint)

Cohort 1 (stage IIC-IIIB)

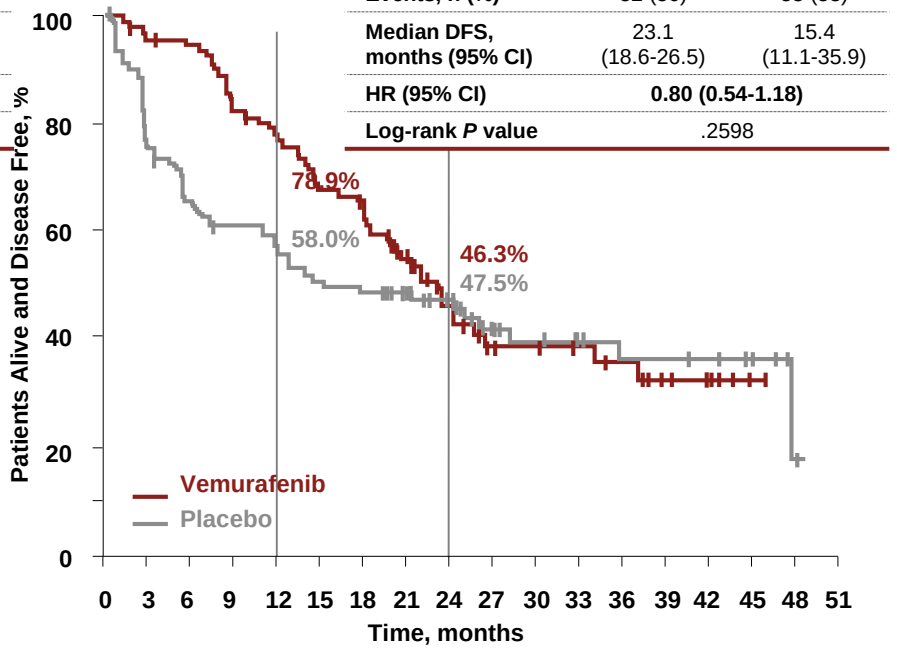
	Vemurafenib (n = 157)	Placebo (n = 157)
Events, n (%)	45 (29)	72 (46)
Median DFS, months (95% CI)	NE	36.9 (21.4-NE)
HR (95% CI)	**0.54 (0.37-0.78)**	
Log-rank *P* value	.0010[a]	



No. at risk																	
Vemurafenib	157	146	137	129	120	115	107	94	72	49	38	31	26	18	15	4	2	-
Placebo	157	129	118	106	100	94	90	79	65	43	35	31	28	22	12	3	1	-

Cohort 2 (stage IIIC)

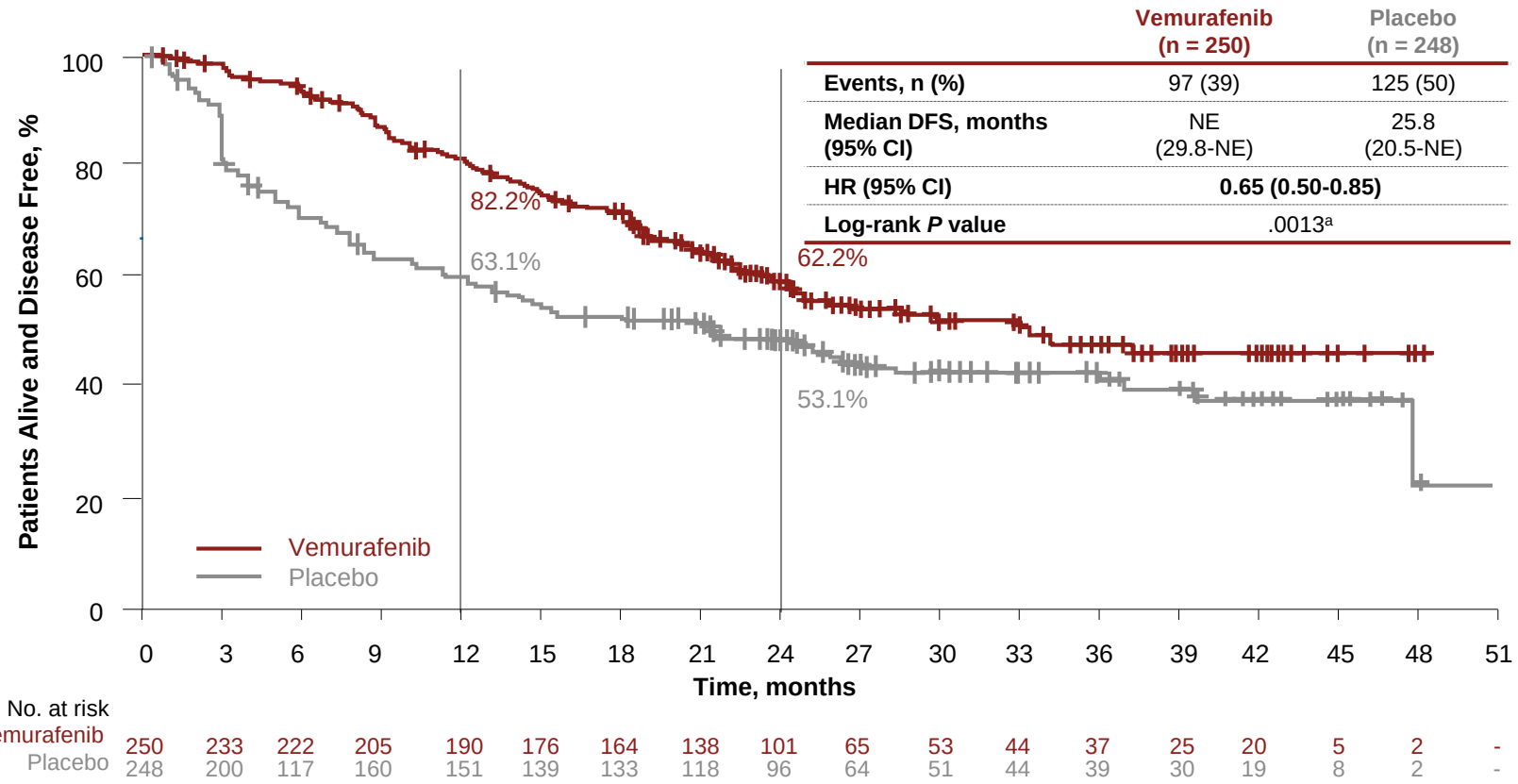
	Vemurafenib (n = 93)	Placebo (n = 91)
Events, n (%)	52 (56)	53 (58)
Median DFS, months (95% CI)	23.1 (18.6-26.5)	15.4 (11.1-35.9)
HR (95% CI)	**0.80 (0.54-1.18)**	
Log-rank *P* value	.2598	



No. at risk																	
Vemurafenib	93	87	85	76	70	61	57	44	29	16	15	13	11	7	5	1	-	-
Placebo	91	71	59	54	51	45	43	39	31	21	16	13	11	8	7	5	1	-

[a] Cannot be considered significant because primary endpoint was not met in cohort 2.
Lewis K, et al. ESMO. 2017 [abstract LBA7_PR].

BRIM8: prespecified exploratory DFS analysis in the pooled ITT population

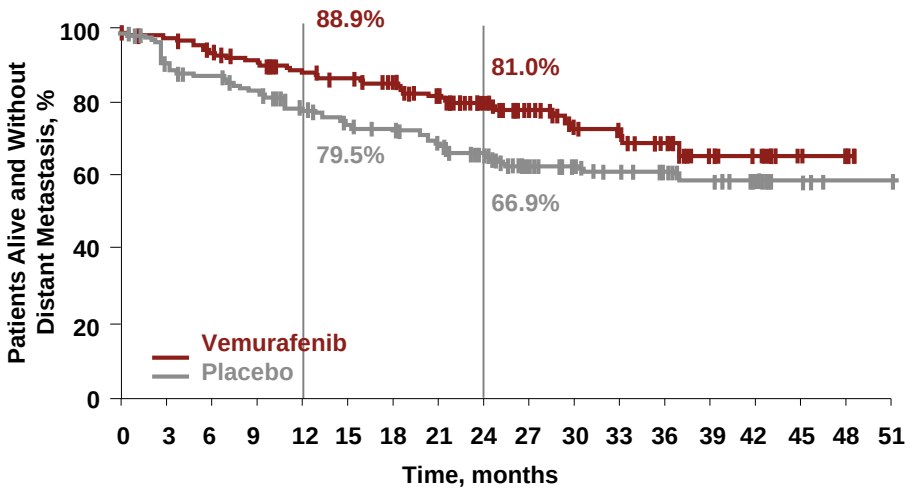


	Vemurafenib (n = 250)	Placebo (n = 248)
Events, n (%)	97 (39)	125 (50)
Median DFS, months (95% CI)	NE (29.8-NE)	25.8 (20.5-NE)
HR (95% CI)	**0.65 (0.50-0.85)**	
Log-rank *P* value	.0013[a]	

ITT, intention-to-treat.
[a] Not significant because the primary endpoint was not met in cohort 2.
Lewis K, et al. ESMO. 2017 [abstract LBA7_PR].

BRIM8: DMFS

Cohort 1 (stage IIC-IIIB)

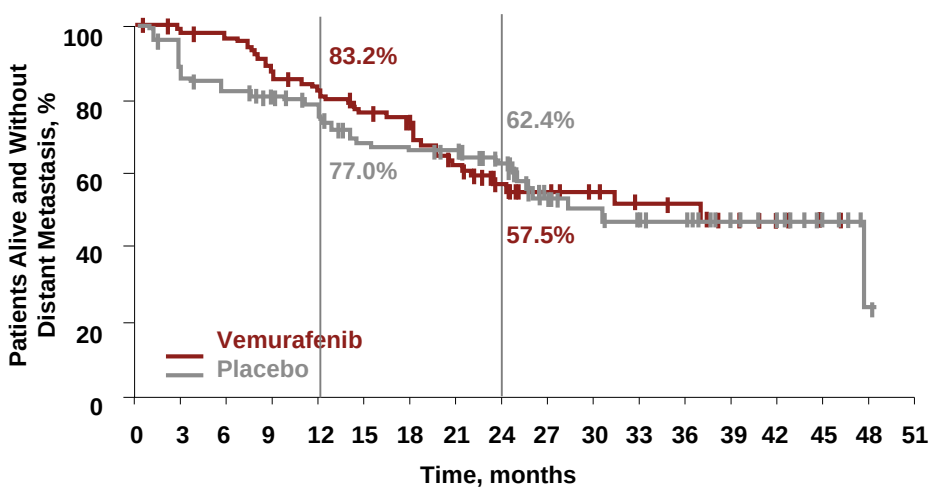


No. at risk

Vemurafenib	157	147	139	132	122	118	110	88	76	52	40	33	27	18	15	4	2
Placebo	157	140	133	126	113	101	88	83	67	44	36	31	28	22	12	3	1

Cohort 1 (IIC – IIIB)	Vemurafenib (n = 157)	Placebo (n = 157)
Events, n (%)	34 (22)	52 (33)
Median DMFS, months (95% CI)	NE	NE (36.9-NE)
HR (95% CI)	0.58 (0.37-0.90)	
Log-rank *P* value	.0133[a]	

Cohort 2 (stage IIIC)



No. at risk

Vemurafenib	93	89	88	78	73	65	59	45	30	19	16	13	11	7	5	1
Placebo	91	79	70	64	58	48	48	42	33	22	17	13	12	8	7	5	1

Cohort 2 (IIIC)	Vemurafenib (n = 93)	Placebo (n = 91)
Events, n (%)	38 (41)	37 (41)
Median DMFS, months (95% CI)	37.2 (22.1-NE)	30.7 (24.5-NE)
HR (95% CI)	0.91 (0.57-1.44)	
Log-rank *P* value	.6815[a]	

[a] Cannot be considered significant because the primary endpoint was not met in cohort 2.

Lewis K, et al. ESMO. 2017 [abstract LBA7_PR].

BRIM8: safety summary

	Vemurafenib (n = 247)	Placebo (n = 247)
Dose intensity, median %	82	99
Treatment duration, median days	364	364
Any grade AEs, n (%)	246 (100)	219 (89)
Grade 3-4 AEs, n (%)	**141 (57)**	37 (15)
Grade 5 AEs, n (%)	**1 (<1)[a]**	0
Treatment discontinuation for AEs, n (%)	**49 (20)[b]**	5 (2.0)[b]

[a] Refers to a case of a patient who died 2 months after hospitalization for hypertension; brain imaging revealed hemorrhage in a cerebral lesion consistent with metastasis. The patient had surgery for the cerebral hemorrhage and was subsequently discharged. The death was not considered to be related to the study drug.

[b] Treatment discontinuation for AEs by cohort: cohort 1 – 13 (14%) for vemurafenib vs 0 for placebo; cohort 2 – 34 (22%) for vemurafenib vs 5 (3%) for placebo.

Lewis K et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LB7_PR.

BRIM8: common any-cause AEs (≥ 15% any grade, any arm)

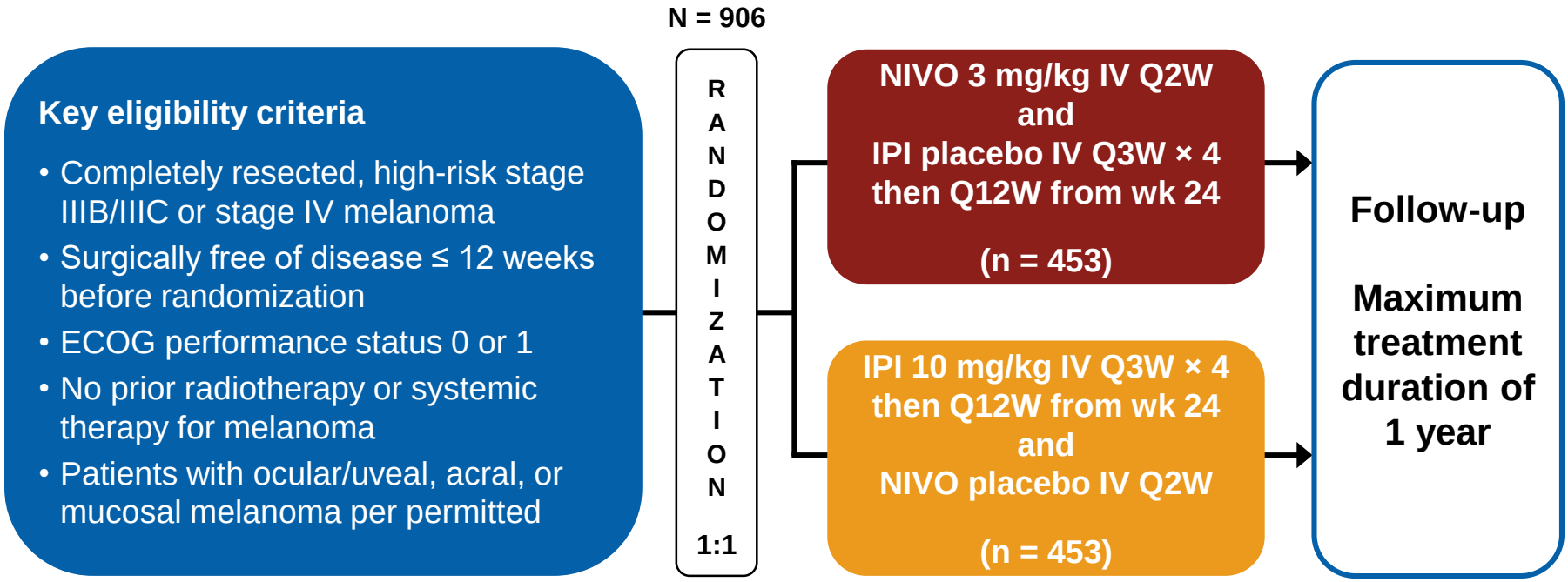
	Vemurafenib (n = 247)		Placebo (n = 247)	
	Any grade, %	Grade 3/4, %	Any grade, %	Grade 3/4, %
Any	100	57	89	15
Arthralgia	**61**	7[a]	22	0
Alopecia	**38**	< 1[a]	6	0
Rash	**37**	6	12	1
Hyperkeratosis	**35**	1[a]	2	0
Nausea	35	< 1[a]	18	0
Photosensitivity reaction	**34**	2[a]	4	0
Fatigue	**32**	3[a]	28	< 1[a]
Pruritus	29	< 1[a]	12	0
Diarrhoea	26	2[a]	17	< 1[a]
Headache	**20**	0	17	0
Dry skin	19	0	7	0
Pain in extremity	19	< 1[a]	8	0
Pyrexia	**18**	0	7	0

[a] All events were grade 3..

Lewis K et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LB7_PR.

CheckMate 238
Adjuvant nivolumab vs ipilimumab

CheckMate 238: phase 3 study design



Stratification
- Disease stage (IIIB/C vs IV M1a-M1b vs IV M1c)
- PD-L1 status at a 5% cutoff in tumor cells

- **Primary endpoint:** RFS
- **Secondary endpoints:** OS, safety, RFS by PD-L1 tumor expression, HRQoL

Current analysis: interim analysis; median follow-up, 1.5 years (360 events)

HRQoL, health-related quality of life; IPI, ipilimumab; NIVO, nivolumab.

Weber J, et al. ESMO. 2017;[abstr LBA8_PR].

CheckMate 238: baseline patient characteristics

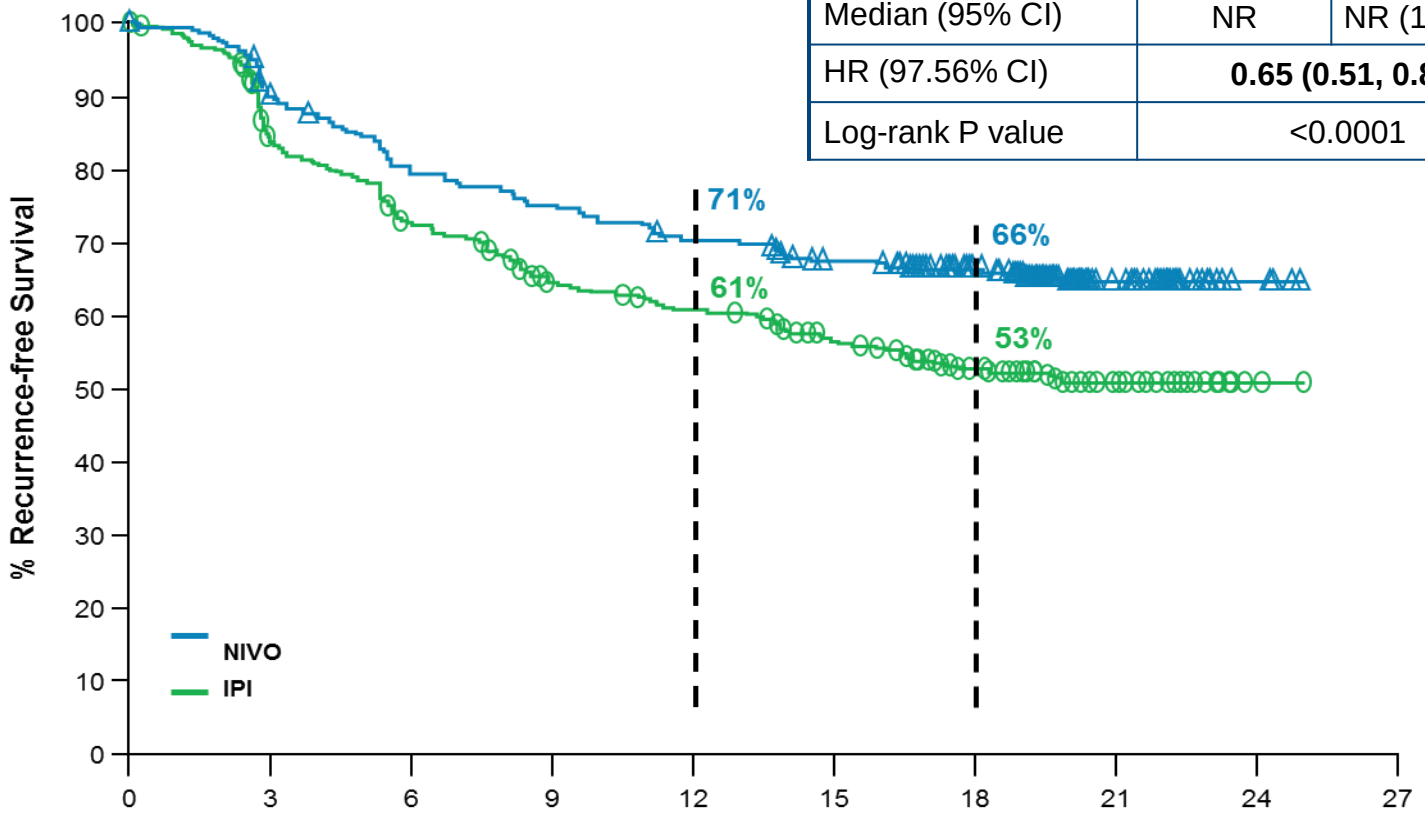
	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage, IIIB + IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB + IIIC)	60	58
Ulceration (% of stage IIIB + IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastasis (% stage IV)	17	17
PD-L1 expression ≥ 5%, %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91

- Most patients had cutaneous melanoma (85%); 4% had acral and 3% had mucosal melanoma
- All 905 patients were off treatment at the data cutoff; number of median doses were 24 (range, 1-26) for NIVO and 4 (range, 1-7) for IPI
- **397 patients completed 1 year of treatment (NIVO, 61%; IPI, 27%)**

LDH, lactate dehydrogenase; ULN, upper limit of normal.
Weber J, et al. ESMO. 2017 [abstract LBA8_PR].

CheckMate 238: RFS primary endpoint

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	**0.65 (0.51, 0.83)**	
Log-rank P value	<0.0001	



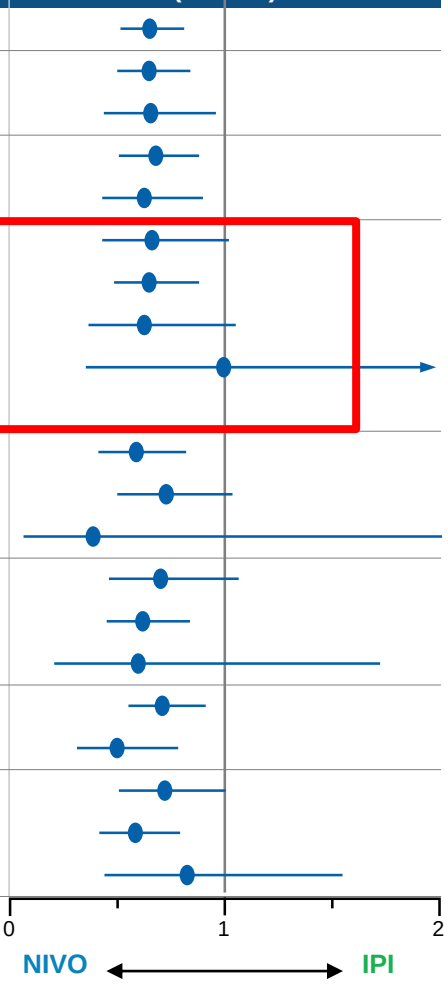
Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

Weber J et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LBA8_PR.

CheckMate 238: RFS by pre-specified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	154/453	206/453	0.66 (0.53, 0.81)
Age	<65 years	106/333	147/339	0.65 (0.51, 0.84)
	≥65 years	48/120	59/114	0.66 (0.45, 0.97)
Sex	Male	99/258	133/269	0.68 (0.53, 0.88)
	Female	55/195	73/184	0.63 (0.44, 0.89)
Stage (CRF)	Stage IIIb	41/163	54/148	0.67 (0.44, 1.00)
	Stage IIIc	79/204	109/218	0.65 (0.49, 0.87)
	Stage IV M1a-M1b	25/62	35/66	0.63 (0.38, 1.05)
	Stage IV M1c	8/20	8/21	1.00 (0.37, 2.66)
	Not reported	1/2	0/0	
Stage III: Ulceration	Absent	58/201	94/216	0.59 (0.42, 0.82)
	Present	60/153	64/135	0.73 (0.51, 1.04)
	Not reported	2/15	5/15	0.39 (0.07, 2.00)
Stage III: Lymph node involvement	Microscopic	41/125	55/134	0.71 (0.47, 1.07)
	Macroscopic	72/219	101/214	0.62 (0.46, 0.84)
	Not reported	7/25	7/18	0.60 (0.21, 1.72)
PD-L1 status	<5%/indeterminate	123/300	149/299	0.71 (0.56, 0.90)
	≥5%	31/152	57/154	0.50 (0.32, 0.78)
***BRAF* mutation status**	Mutant	63/187	84/194	0.72 (0.52, 1.00)
	Wild-type	67/197	105/214	0.58 (0.43, 0.79)
	Not reported	24/69	17/45	0.83 (0.45, 1.54)

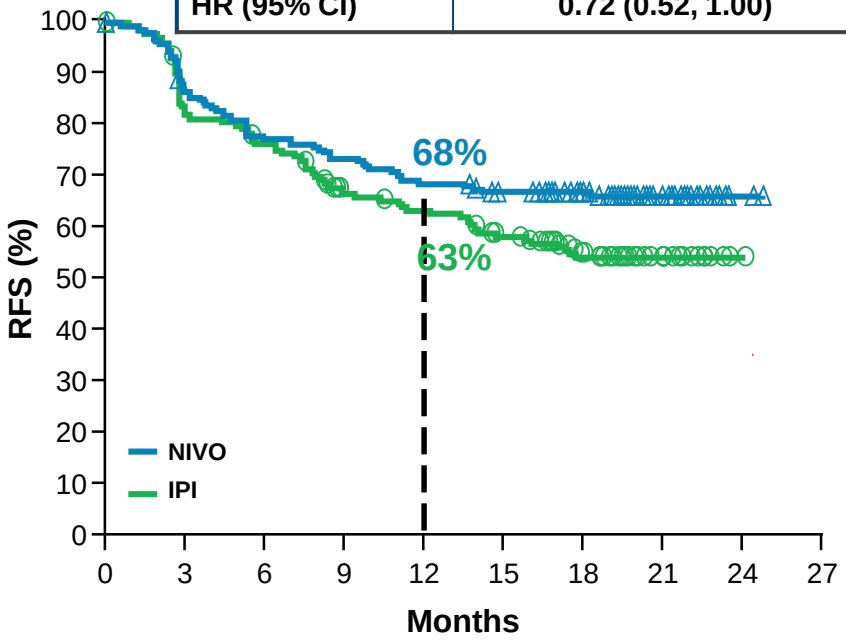


Weber J et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LBA8_PR.

CheckMate 238: RFS by *BRAF* mutation status

BRAF Mutant

	NIVO	IPI
Events/patients	63/187	84/194
Median (95% CI)	NR	NR (16.1, NR)
HR (95% CI)	**0.72 (0.52, 1.00)**	

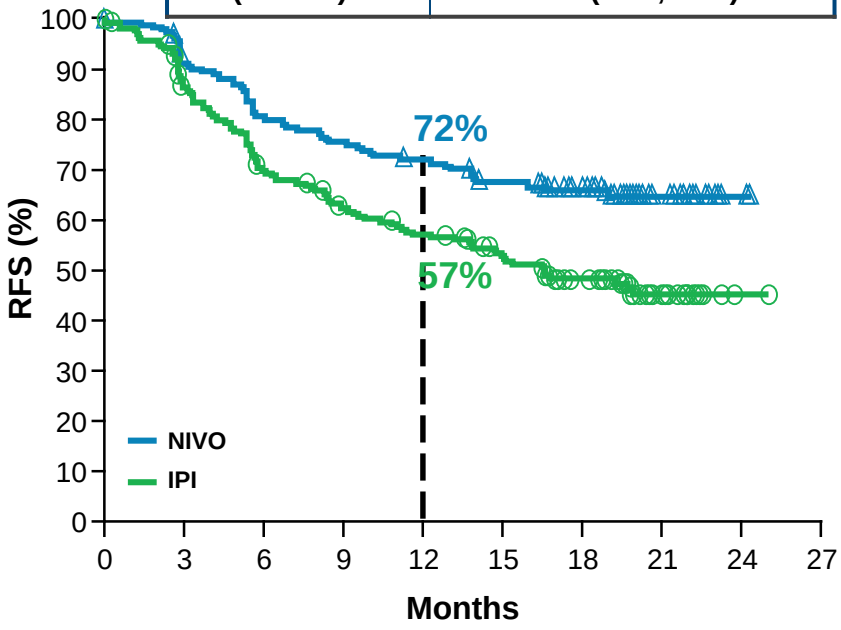


Number of patients at risk

NIVO	187	159	142	135	126	118	102	32	2	0
IPI	194	155	142	118	112	100	78	26	1	0

BRAF Wild type

	NIVO	IPI
Events/patients	67/197	105/214
Median (95% CI)	NR	16.6 (12.3, NR)
HR (95% CI)	**0.58 (0.43, 0.79)**	



Number of patients at risk

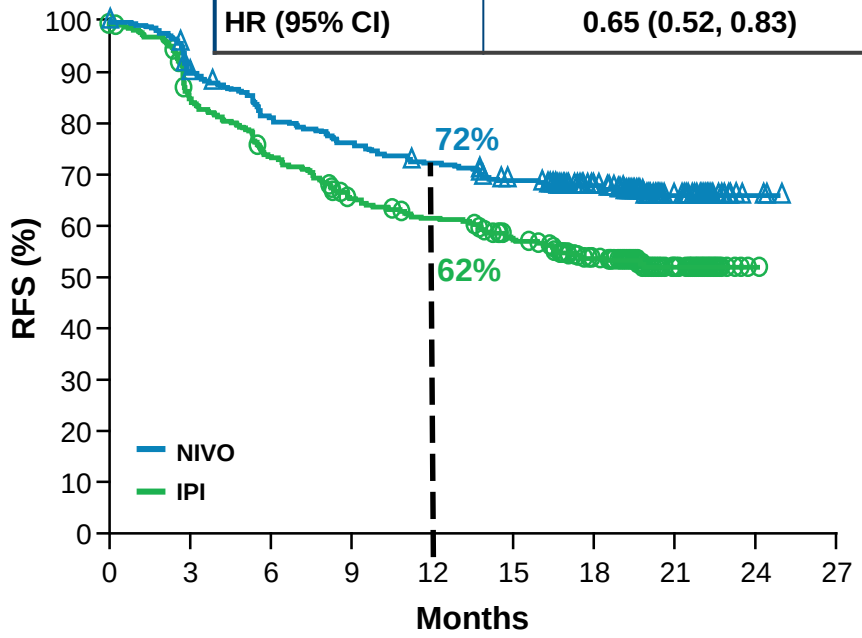
NIVO	197	175	154	145	137	127	108	26	2	0
IPI	214	174	140	122	111	96	80	22	1	0

Weber J et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LBA8_PR.

CheckMate 238: RFS by disease stage

Stage III

	NIVO	IPI
Events/patients	120/367	163/366
Median (95% CI)	NR	NR (16.6, NR)
HR (95% CI)	**0.65 (0.52, 0.83)**	

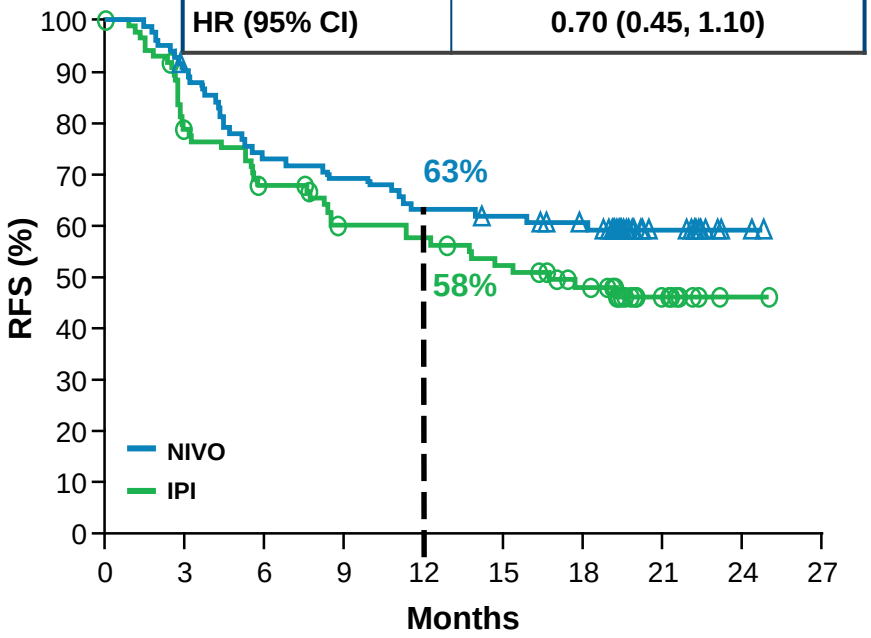


Number of patients at risk

NIVO	367	322	290	272	257	239	203	58	3	0
IPI	366	299	259	223	208	186	152	45	1	0

Stage IV

	NIVO	IPI
Events/patients	33/82	43/87
Median (95% CI)	NR (15.9, NR)	16.8 (8.5, NR)
HR (95% CI)	**0.70 (0.45, 1.10)**	

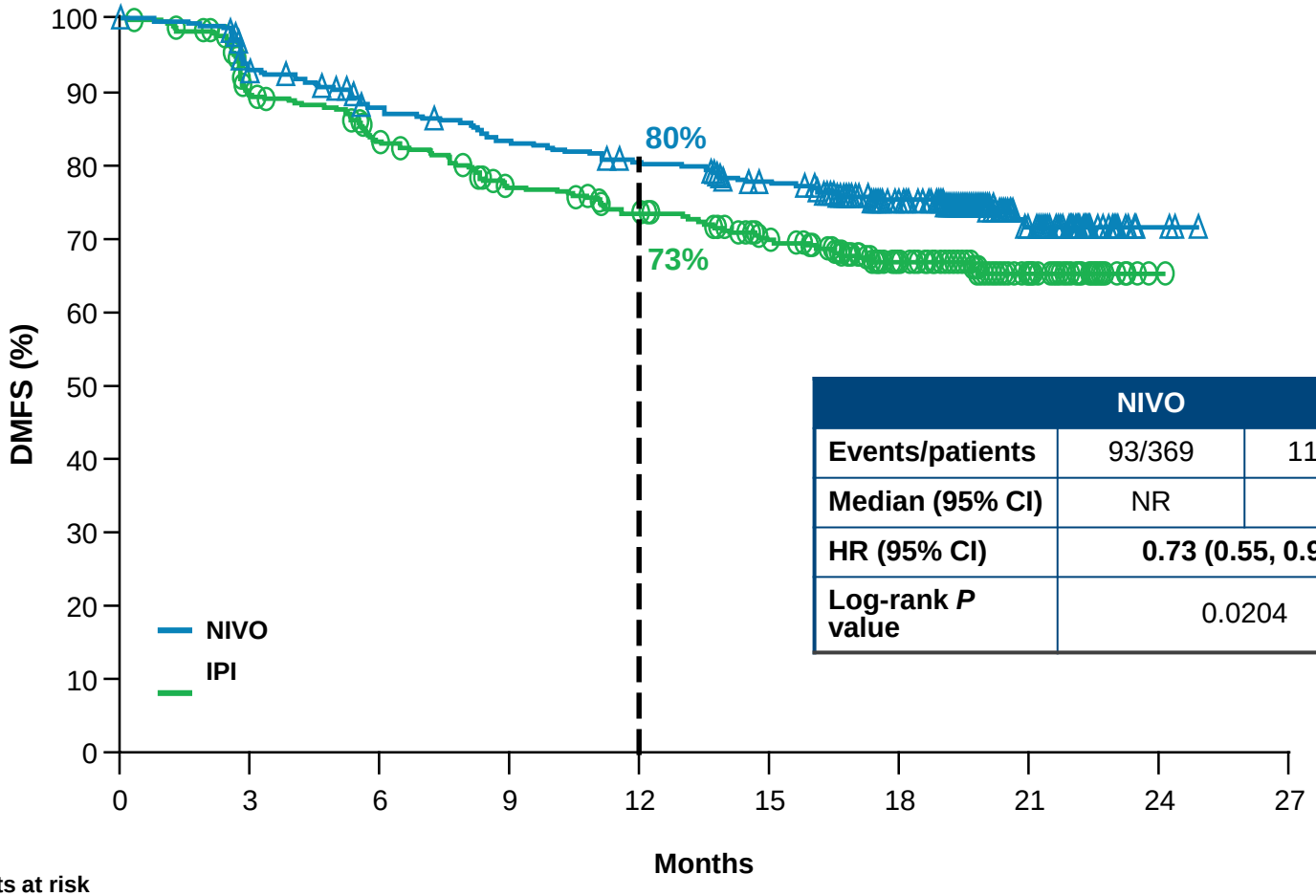


Number of patients at risk

NIVO	82	73	59	56	51	49	43	12	2	0
IPI	87	65	55	46	44	39	32	11	1	0

Weber J et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LBA8_PR.

CheckMate 238: DMFS for stage III patients



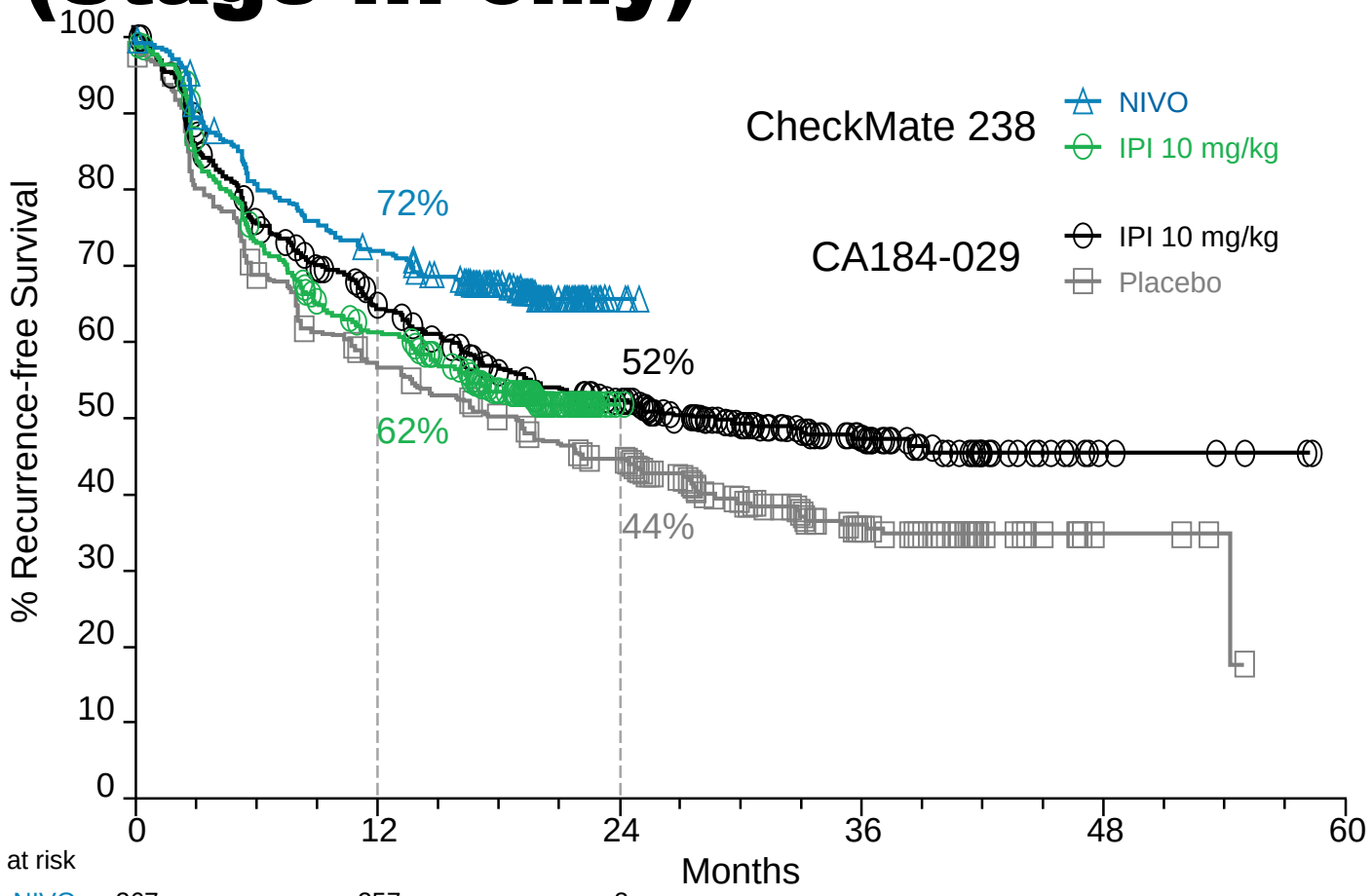
	NIVO	IPI
Events/patients	93/369	115/366
Median (95% CI)	NR	NR
HR (95% CI)	**0.73 (0.55, 0.95)**	
Log-rank *P* value	0.0204	

Number of patients at risk

NIVO	369	335	309	292	280	264	214	62	3	0
IPI	366	312	284	254	239	217	176	51	1	0

Weber J et al. Presented at: ESMO 2017. Madrid, Spain. Abstract LBA8_PR.

RFS: CA184-029 and CheckMate 238 (Stage III only)



Number of patients at risk

NIVO	367	257	3	–	–	–
IPI 10 mg/kg	366	208	1	–	–	–
IPI 10 mg/kg	475	276	205	67	5	0
Placebo	476	260	193	62	4	0

R. Dummer Discussant LBA8_PR ESMO. 2017

CheckMate 238: post-protocol treatment

Treatment, n (%)[a]	NIVO (n = 453)	IPI (n = 453)
Any	129 (28.5)	171 (37.7)
Systemic therapy	**90 (19.9)**	**136 (30.0)**
Chemotherapy	25 (5.5)	24 (5.3)
Immunotherapy	**50 (11.0)**	**104 (23.0)**
Anti–PD-1 agent	1 (0.2)	2 (0.4)
Nivolumab[b]	**17 (3.8)**	**43 (9.5)**
Pembrolizumab	**10 (2.2)**	**63 (13.9)**
Other CTLA-4 inhibitor	1 (0.2)	1 (0.2)
Ipilimumab	35 (7.7)	15 (3.3)
Ipilimumab/nivolumab combination	3 (0.7)	1 (0.2)
BRAF inhibitor	41 (9.1)	40 (8.8)
MEK inhibitor	31 (6.8)	40 (8.8)
BRAF/MEK combination	3 (0.7)	1 (0.2)
Surgery[c]	69 (15.2)	64 (14.1)
Radiotherapy	24 (5.3)	26 (5.7)

[a] Patients may have received ≥ 1 type of post-protocol therapy, and ≥ 1 agent within each type. All percentages are based on the total number of patients in each group; [b] May include patients treated in combination with IPI; [c] Indicates tumor resection for diagnostic purposes and biopsies.

Weber J, et al. ESMO. 2017;[abstr LBA8_PR].

CheckMate 238: safety summary

	NIVO (n = 452)		IPI (n = 453)	
AE, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	**385 (85)**	**65 (14)**	**434 (96)**	**208 (46)**
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	**35 (8)**	**16 (4)**	**189 (42)**	**136 (30)**

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both > 100 days after the last dose

Weber J, et al. ESMO. 2017;[abstr LBA8_PR].

CheckMate 238: treatment-related select AEs

	NIVO (n = 452)		IPI (n = 453)	
AE, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Skin	201 (44.5)	5 (1.1)	271 (59.8)	27 (6.0)
Gastrointestinal	114 (25.2)	**9 (2.0)**	219 (48.3)	**76 (16.8)**
Hepatic	41 (9.1)	**8 (1.8)**	96 (21.2)	**49 (10.8)**
Pulmonary	6 (1.3)	0	11 (2.4)	4 (0.9)
Renal	6 (1.3)	0	7 (1.5)	0
Hypersensitivity/infusion reaction	11 (2.4)	1 (0.2)	9 (2.0)	0
Endocrine				
Adrenal disorder	6 (1.3)	2 (0.4)	13 (2.9)	4 (0.9)
Diabetes	2 (0.4)	1 (0.2)	1 (0.2)	0
Pituitary disorder	8 (1.8)	2 (0.4)	56 (12.4)	13 (2.9)
Thyroid disorder	**92 (20.4)**	3 (0.7)	57 (12.6)	4 (0.9)

- Median time to onset to treatment-related select AEs was generally shorter for patients receiving IPI (range 2.6-10 wk) than for those receiving NIVO (range, 3.3-14.2 wk)

Weber J, et al. ESMO. 2017;[abstr LBA8_PR].

Immunotherapy Targeted therapy

Ongoing Adjuvant Trials[a]

Study	KEYNOTE 054 (Ph 3)	ECOG 1609 (Ph 3)	CheckMate 238 (Ph 3)	EORTC 18081 (Ph 3)	SWOG S1404 (Ph 3)	CheckMate 915 (Ph 3)	IMMUNED (Ph 2)	BRIM8 (Ph 3)	COMBI-AD (Ph 3)
Design	PEMBRO vs PBO	HD IPI or LD IPI vs HD IFN-α	NIVO vs IPI	PEG-IFN 2 years vs obs	PEMBRO vs IPI or HD IFN-α	NIVO+IPI vs NIVO	NIVO+IPI or NIVO vs PBO	Vem vs PBO	Dab + Tram vs PBO
Patient pop	Compl. resected, stage IIIA (if N1a, at least 1 mets > 1mm); stage IIIB or IIIC; no in-transit mets	Compl. resected stage IIIB/C or stage IV (M1a/M1b)	Compl. resected, high-risk stage IIIB/C or IV	Compl. resected, ulcerated primary melanoma > 1mm	Compl. resected, high-risk stage IIIA (N2a), IIIB, IIIC, or IV	Compl. resected, high-risk stage IIIB/C/D or IV NED[b]	Compl. resected, stage IV NED	Surgically resected, stage IIC-IIIC, BRAF mutant melanoma at high risk for recurrence	Compl. resected, BRAF+, high-risk stage IIIA (LN mets > 1 mm), IIIB, or C. Stage I/II with initial resect. LN recurrence
Accrual goal	900	1500	800	1200	1378	900	312	503	852
Primary endpoint	RFS/RFS in PD-L1+	OS/RFS	RFS	RFS	OS/RFS/ PD-L1+	RFS	PFS	DFS	RFS
Status (primary compl)	Ongoing (Aug 2017)	Ongoing (May 2018)	Ongoing (Nov 2018)	Closed	Recruiting (Jun 2020)	Recruiting (Dec 2020)	Recruiting (Jun 2021)	Ongoing (Jun 2017)	Ongoing (Dec 2017)

[a]Select trials in cutaneous melanoma are shown. [b]Note staging based on AJCC Staging 8th Edition. www.clinicaltrials.gov. Accessed September 2017.; PEMBRO: pembrolizumab; IPI: ipilimumab; IFN: interferon; NIVO: nivolumab, Vem: vemurafenib; Dab + Tram: Dabrafenib + Trametinib

Clinicaltrials.gov Keynote054: NCT02362594; EORTC 18071: NCT00636168; Intergroup E1609: NCT01274338; EORTC 18081: NCT01502696; SWOG S1404 : NCT02506153; CheckMate 915: NCT03068455; IMMUNED: NCT02523313; COMBI-AD: NCT01682083; BRIM8: NCT01667419; CheckMate 238: NCT02388906

Zusammenfassung Adjuvante Therapie (Peter Mohr, MD)

- Verlängertes OS ist das wichtigste Ziel der adjuvanten Therapie, aber schwer zu erreichen!
- Safety/benefit ratio wird von FDA/EMA berücksichtigt
- Interferon: Meta-Analyse zeigen ein verbessertes rezidiv-freies Überleben 10% und ges. Überleben 3-5 %
- Keine adjuvanten Studien im Stadium IIa,b des Melanoms: Interferon „for ever“?
- Ipilimumab zeigt Vorteile im RFS und OS; Toxizität, keine Zulassung in Europa!

Adjuvante Therapie Zukunft
(Peter Mohr, MD)

- **Vemurafenib verbessert das RFS Im Stadium IIC-IIIB aber nicht IIIC; Zulassung?**
- **Dabrafenib und Trametinib werden neuer Standard im Stadium III bei BRAF mutierten Patienten!**
- **Nivolumab wird neuer Standard in der adjuvanten Therapie im Stadium III und IV**
- **Wann wird bei BRAF pos. Patienten ein BRAF + MEK Inhibitor und wann anti-PD-1 verwendet werden?**
- **Werden die Therapien bei progredienten Patienten erneut im Stadium IV wirken?**
- **Weitere Studienergebnisse werden 2018 kommen**


Danke!