ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

Aiom
Associazione Italiana di Oncologia Medica

CONVEGNO NAZIONALE AIOM GIOVANI.
"2019: NEWS IN ONCOLOGY"
Perugia, 05-06 luglio 2019

Melanoma update: il ruolo delle terapie adiuvanti

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INT Pascale (NA)

Goals of Adjuvant Treatment

Improve RFS and DMFS

- Patients value time without disease
- Delay relapse at distant sites

Improve OS

- Increasingly difficult to show
- Potential for cure

Acceptable risk-benefit ratio

DMFS, distant metastasis-free survival; OS, overall survival; RFS, recurrence-free survival

1. Lorigan P (discussant). Presented at ASCO 2016. 2. van Zeijl MC, et al. *Eur J Surg Oncol* 2017;43:534–543. 3. Mohr P (discussant). Presented at ASCO 2017.
4. Grossmann KF, Margolin K. *Ther Adv Med Oncol* 2015;7:181–191.

Which Factors Help Define Risk of Recurrence?[1]

Primary tumor depth/ Breslow thickness

Regional metastatic burden
(number of metastatic nodes and whether micro- or macro-metastatic)

Ulceration

Location and extent of distant metastatic disease

Incorporated into AJCC staging for The 8th edition

Mitotic rate
(included in the 7th, but not 8th, edition of AJCC staging manual)[a2,3]

[a]Removed because a multivariate analysis of factors predicting melanoma specific survival (MSS) among 7568 patients with T1 N0 melanoma demonstrated that mitotic rate was not a statistically significant predictor of MSS as either tumor thickness or ulceration.[3]

AJCC, American Joint Committee on Cancer

1. Davar D, Kirkwood JM. *Cancer Treat Res* 2016;167:181–208. 2. Amin MB et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017. 3. Gershenwald JE, et al. *CA Cancer J Clin* 2017;67:472–492.

Recurrence Risk Factors by AJCC Stage (8th Edition)[1,2]

Risk factors for recurrence

AJCC pathologic stage	Staging	Thickness (T1-T4)	Ulceration (a/b)	No. of tumor-involved regional LNs, presence of in-transit, satellite, and/or microsatellite mets (no/yes)	Distant metastasis (M)	Consider adjuvant therapy?
IIA	T2b; N0; M0	>1.0–2.0 mm (T2)	Yes (b)	None (N0)	None (M0)	
	T3a; N0; M0	>2.0–4.0 mm (T3)	No (a)	None (N0)	None (M0)	
IIB	T3b; N0; M0	>2.0–4.0 mm (T3)	Yes (b)	None (N0)	None (M0)	✔
	T4a; N0; M0	>4.0 mm (T4)	No (a)	None (N0)	None (M0)	✔
IIC	T4b; N0; M0	>4.0 mm (T4)	Yes (b)	None (N0)	None (M0)	✔
IIIA	T1a/b[a]-T2a; N1a or N2b; M0	<1 mm (T1); >1.0–2.0 mm (T2)	No or yes (a/b)	N1a - 1 clinically occult, no; N2b - 2–3 at least 1 clinically detected, no	None (M0)	✔
IIIB	T0; N1b, N1c; M0	No evidence of primary tumor (T0)	—	N1b - 1 clinically detected, No; N1c - no regional lymph node disease, yes	None (M0)	✔
	T1a/b[a]-T2a; N1b/c or N2b; M0	<1 mm (T1); >1.0–2.0 mm (T2)	No or yes (a/b)	N1b - 1 clinically detected, no; N1c - no regional lymph node disease, yes; N2b - 2–3 at least 1 clinically detected, no	None (M0)	✔
	T2b/T3a; N1a-N2b; M0	>1.0–2.0 mm (T2); >2.0–4.0 mm (T3)	No or yes (a/b)	N1a - 1 clinically occult, no; N2b - 2–3 at least 1 clinically detected, no	None (M0)	✔
IIIC	T0; N2b, N2c, N3b, or N3c; M0	No evidence of primary tumor (T0)	—	N2b - 2–3 at least 1 clinically detected, no; N2c - 1 clinically occult or clinically detected, yes; N3b – ≥4 at least 1 clinically detected, or any number of matted nodes, no; N3c - ≥2 clinically occult or clinically detected, and/or any number of matted nodes, yes	None (M0)	✔
	T1a[a]-T3a; N2c or N3a/b/c; M0	<0.8 mm (T1); >1.0–2.0 mm (T2); >2.0–4.0 mm (T3)	No (a)	N2c - 1 clinically occult or clinically detected, yes; N3a - ≥4 clinically occult, no; N3b - ≥4 at least 1 clinically detected or any number of matted nodes, no; N3c - ≥2 clinically occult or clinically detected, and/or any number of matted nodes, yes	None (M0)	✔
	T3b/T4a; any N ≥ N1; M0	>2.0–4.0 mm (T3); >4.0 mm (T4)	No or yes (a/b)	Any N (≥ N1 - 1 tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes)	None (M0)	✔
	T4b; N1a-N2c; M0	>4.0 mm (T4)	Yes (b)	N1a - 1 clinically occult, no; N2c - 1 clinically occult or clinically detected, yes	None (M0)	✔
IIID	T4b; N3a/b/c; M0	>4.0 mm (T4)	Yes (b)	N3a - ≥4 clinically occult, no; N3b - ≥4 at least 1 clinically detected or any number of matted nodes, no; N3c - ≥2 clinically occult or clinically detected, and/or any number of matted nodes, yes	None (M0)	✔
IV	Any T or Tis; any N; M1	Any (T1-T4) or melanoma in situ (Tis)	Any	Any N	Yes (M1)	✔ (if limited/ resectable disease)

[a]T1a < 0.8 mm without ulceration; T1b < 0.8 mm with ulceration or 0.8–1.00 mm with or without ulceration. 1. Amin MB et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York: Springer; 2017. 2. Davar D, Kirkwood JM. *Cancer Treat Res* 2016;167:181–208.

Revised AJCC Staging Guidelines

Letter to the Editor

Eighth American Joint Committee on Cancer (AJCC) melanoma classification: Let us reconsider stage III

Jean Jacques Grob [a,*], Dirk Schadendorf [b], Paul Lorigan [c], Paolo Ascierto [d], James Larkin [e], Paul Nathan [f], Caroline Robert [g], Axel Hauschild [h], Jeffrey Weber [i], Adil Daud [j], Omid Hamid [k], Reinhard Dummer [l], Johan Hansson [m], Christoph Hoeller [n], Jacob Schachter [o], Alexander C.J. Van Akkooi [p], Claus Garbe [q]

Stage III

AJCC Version 7

	N1a	N1b		N2a	N2b	N2c	N3
T1a							
T1b							
T2a							
T2b							
T3a							
T3b							
T4a							
T4b							

IIIA IIIB IIIC IIID

AJCC Version 8

	N1a	N1b	N1c	N2a	N2b	N2c	N3a	N3b	N3c
T1a									
T1b									
T2a									
T2b									
T3a									
T3b									
T4a									
T4b									

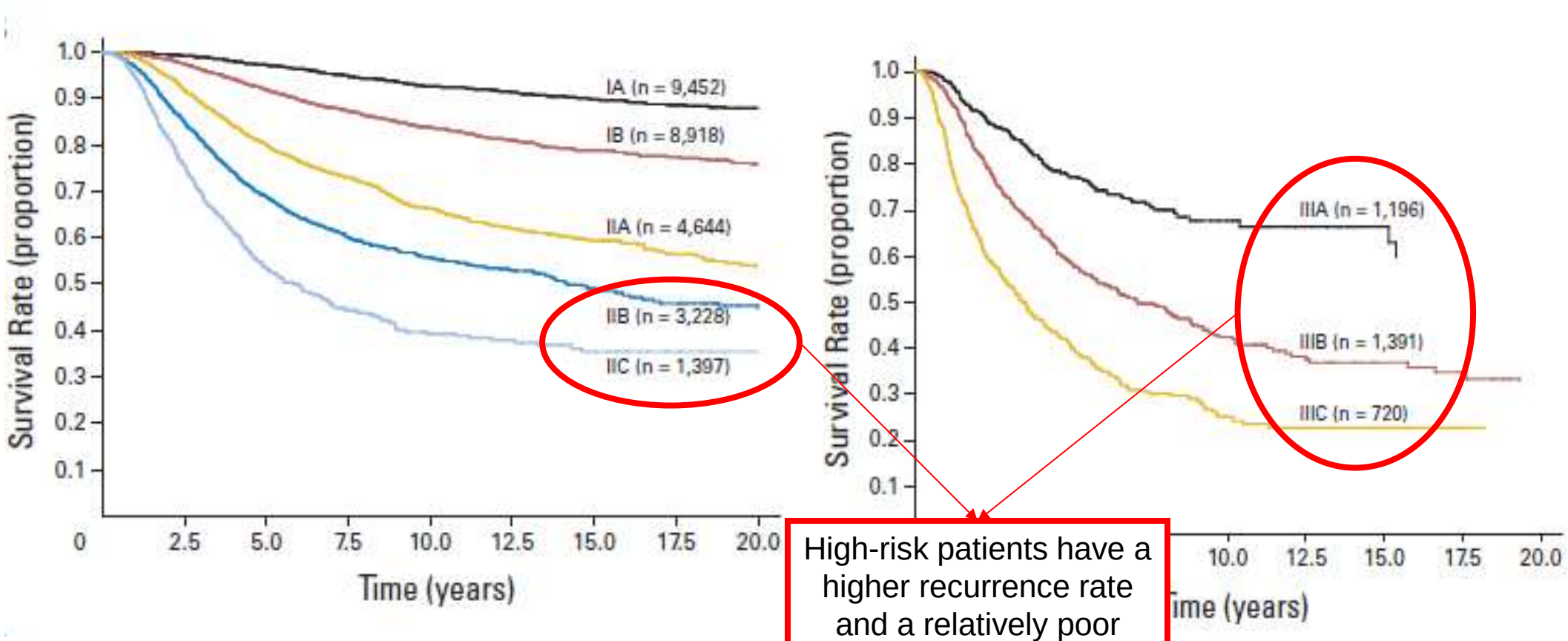
New pathological categories | Change in pathological definition | New stage

AJCC, American Joint Committee on Cancer.

Grob JJ, et al. *Eur J Cancer*. 2017;91:168-170.

High-Risk Melanoma

Comparison of Survival Rates at Stages I, II, and III (AJCC 2009)

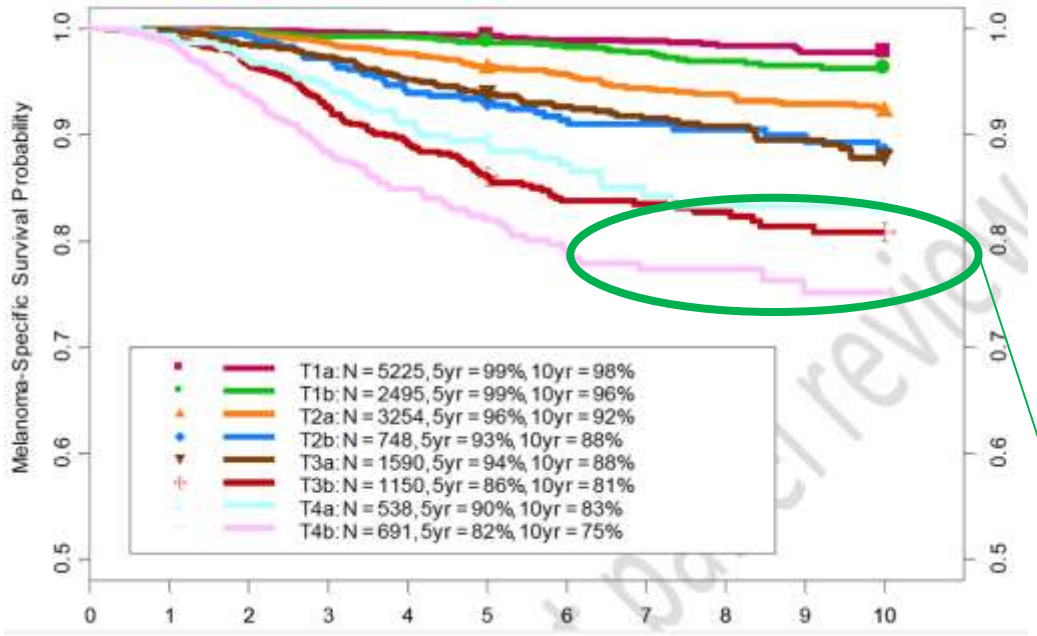


High-risk patients have a higher recurrence rate and a relatively poor survival

Balch et al. *J Clin Oncol* 2009; 27:6199 -6206

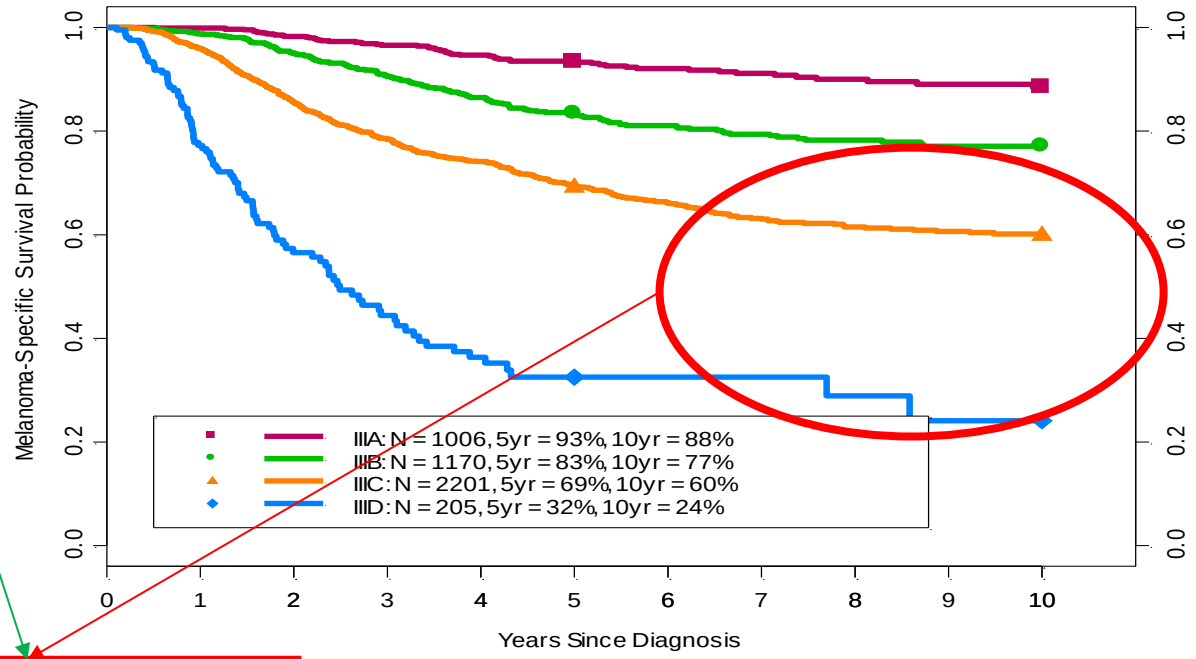
High-Risk Stage I-III Melanoma

Melanoma-Specific Survival by T-category
8th Edition international melanoma database



pT3b 5 yrs = 86%
pT4a 5 yrs = 90%
pT4b 5 yrs = 82%

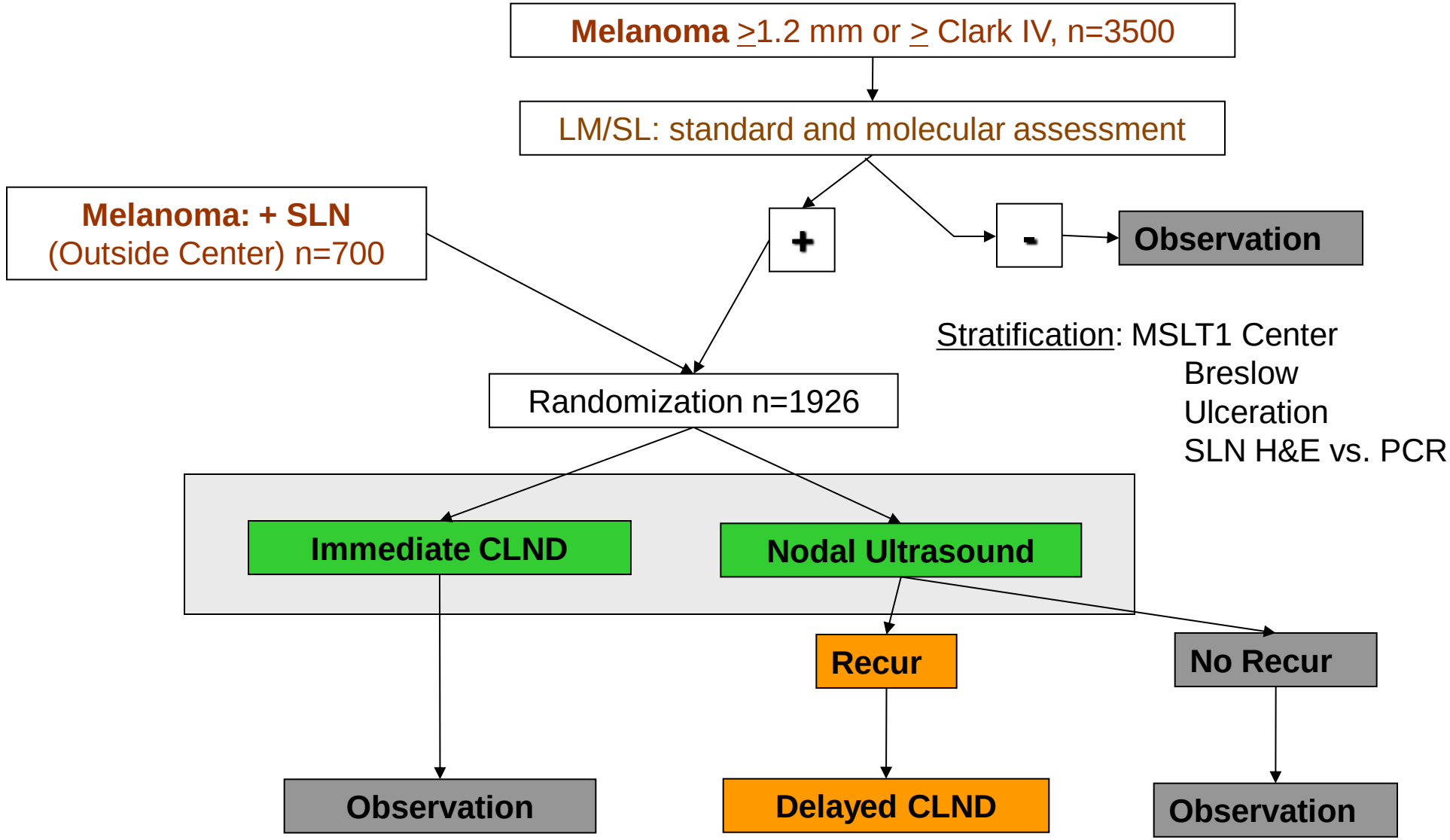
MSS according to Stage III Groups
8th Edition international melanoma database



IIIA 5 yrs = 93%
IIIB 5 yrs = 83%
IIIC 5 yrs = 69%
IIID 5 yrs = 32%

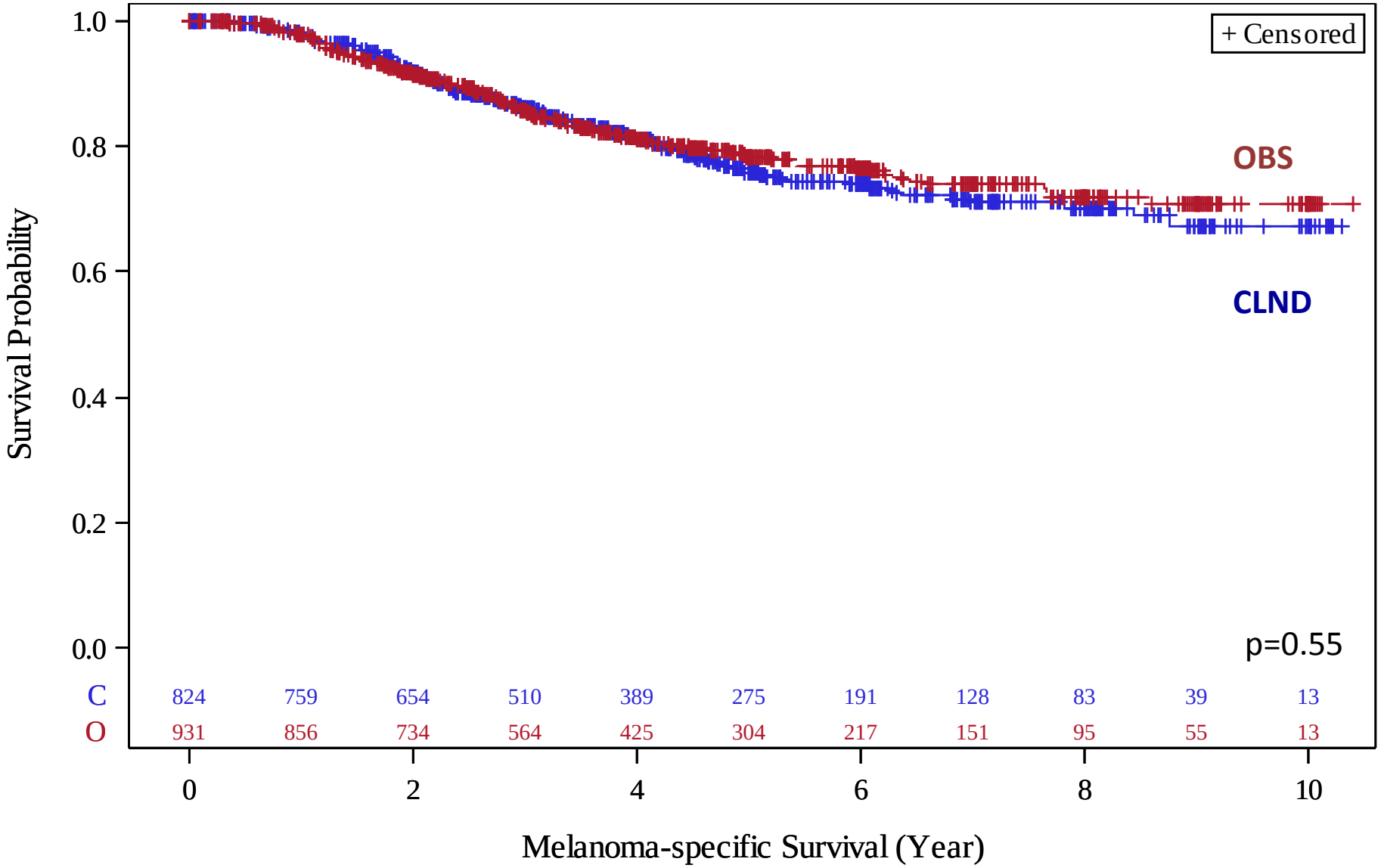
High-risk patients have a higher recurrence rate and a relatively poor survival

MSLT II: Trial Design



Faries MB, et al. N Engl J Med 2017;376:2211-22

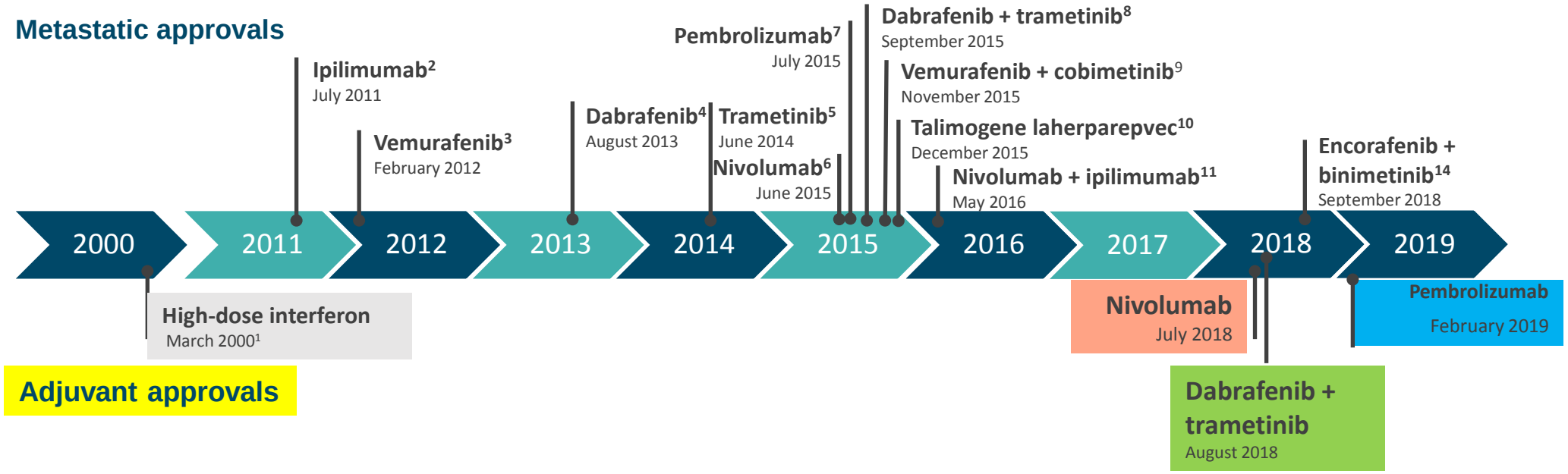
Melanoma-Specific Survival



Faries MB, et al. N Engl J Med 2017;376:2211-22

Therapeutic Landscape 2019 (EUROPE)

- Recent therapeutic and surgical advancements have improved options and outcomes for patients with melanoma but also bring new challenges in patient management



References in slide notes

Adjuvant IFN-α

What Do We Know?

IFN-α

Meta-analysis[1,a]

- DFS significantly improved in 10 of 17 comparisons (HR = 0.82; 95% CI, 0.77–0.87; *P* < 0.001)
- OS significantly improved in 4 of 14 comparisons (HR = 0.89; 95% CI, 0.83–0.96; *P* = 0.002)
- No clear dose effect or treatment duration identified

Phase 3 trials[2]

- Considerable toxicity: dose reduction or delay in ~50% of patients

PEG-IFN (phase 3 trials)

- **EORTC 18991[3]** (stage III vs observation)
  - OS: not significant in overall population
  - Benefit only in ulcerated melanoma (being tested in EORTC 18081[4])
- **DeCOG[5]** (stage IIA-IIIB vs low-dose IFN)
  - No DMFS or OS improvement
  - More treatment-related discontinuations with PEG-IFN
- **EADO study[6]** (PEG-IFN 100 µg QW vs low-dose IFN, ≥1.5 mm thick and N0)
  - Not more effective, but more grade 3/4 AEs and discontinuations

[a]Largest meta-analysis of adjuvant IFN-α trials so far (14 randomized, controlled trials included, involving 17 comparisons of IFN-α versus a comparator agent)

AE, adverse event; DeCOG, Dermatologic Cooperative Oncology Group; DFS, disease-free survival; EADO, European Association of Dermato Oncology; QW, once weekly

1. Mocellin S, et al. *J Natl Cancer Inst* 2010;102:493–501. 2. Davar D, Kirkwood JM. *Cancer Treat Res* 2016;167:181–208. 3. Eggermont AM, et al. *J Clin Oncol* 2012;30:3810–3818. 4. Adjuvant PEG intron in ulcerated melanoma. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT01502696. Accessed May 2017. 5. Eigentler TK, et al. *Ann Oncol* 2016;27:1625–1632. 6. Grob JJ, et al. *Eur J Cancer* 2013;49:166–174.

Goodbye to IFN? except for ulcerated melanoma

Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis

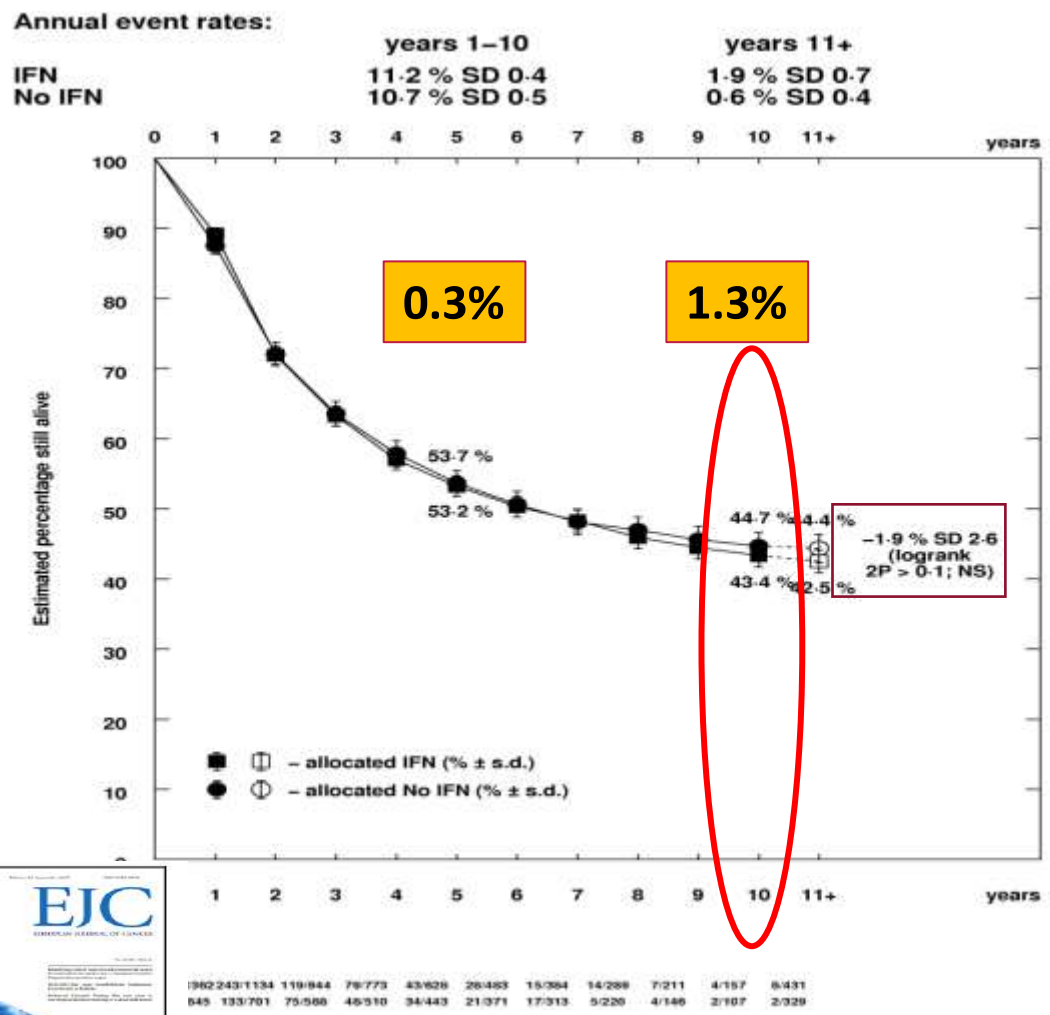
Natalie J. Ives [a], Stefan Suciu [b], Alexander M.M. Eggermont [c], John Kirkwood [d], Paul Lorigan [e], Svetomir N. Markovic [f], Claus Garbe [g], Keith Wheatley [h,*] on behalf of the International Melanoma Meta-Analysis Collaborative Group (IMMCG)

European Journal of Cancer 82 (2017) 171–183

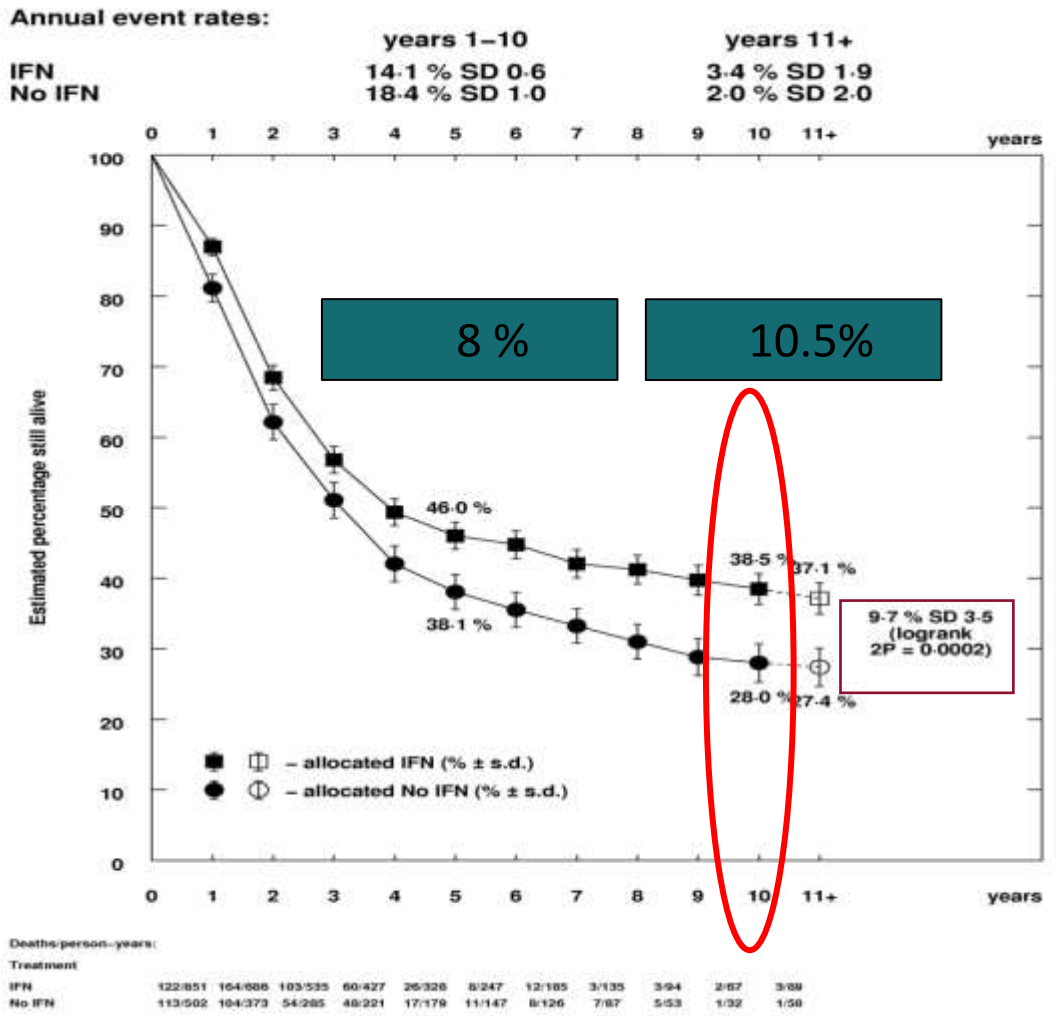
Bristol-Myers Squibb

ULCERATION AND IFN-SENSITIVITY
OVERALL SURVIVAL

Non-ulcerated primary (67%)



Ulcerated primary (33%)



European Journal of Cancer 82 (2017) 171–183

Checkpoint inhibitors

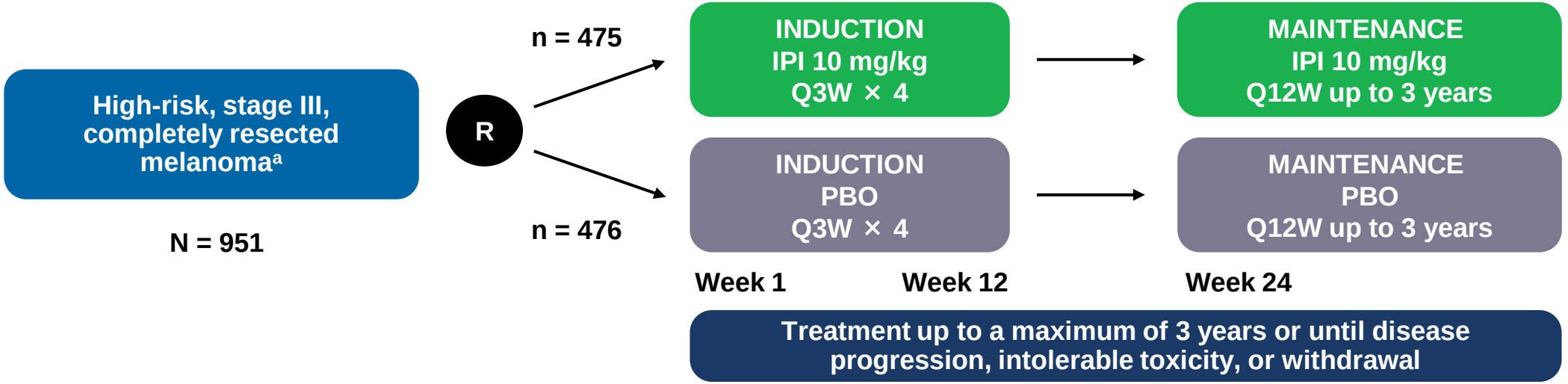
Adjuvant IPI
EORTC 18071/CA184-029

Randomized, double-blind, phase 3 study evaluating the efficacy and safety of IPI in the adjuvant setting for patients with high-risk melanoma

Stratification factors

- **Stage (IIIA vs IIIB vs IIIC [1–3 positive lymph nodes] vs IIIC [≥4 positive lymph nodes])**
- **Regions (North America, European countries, and Australia)**

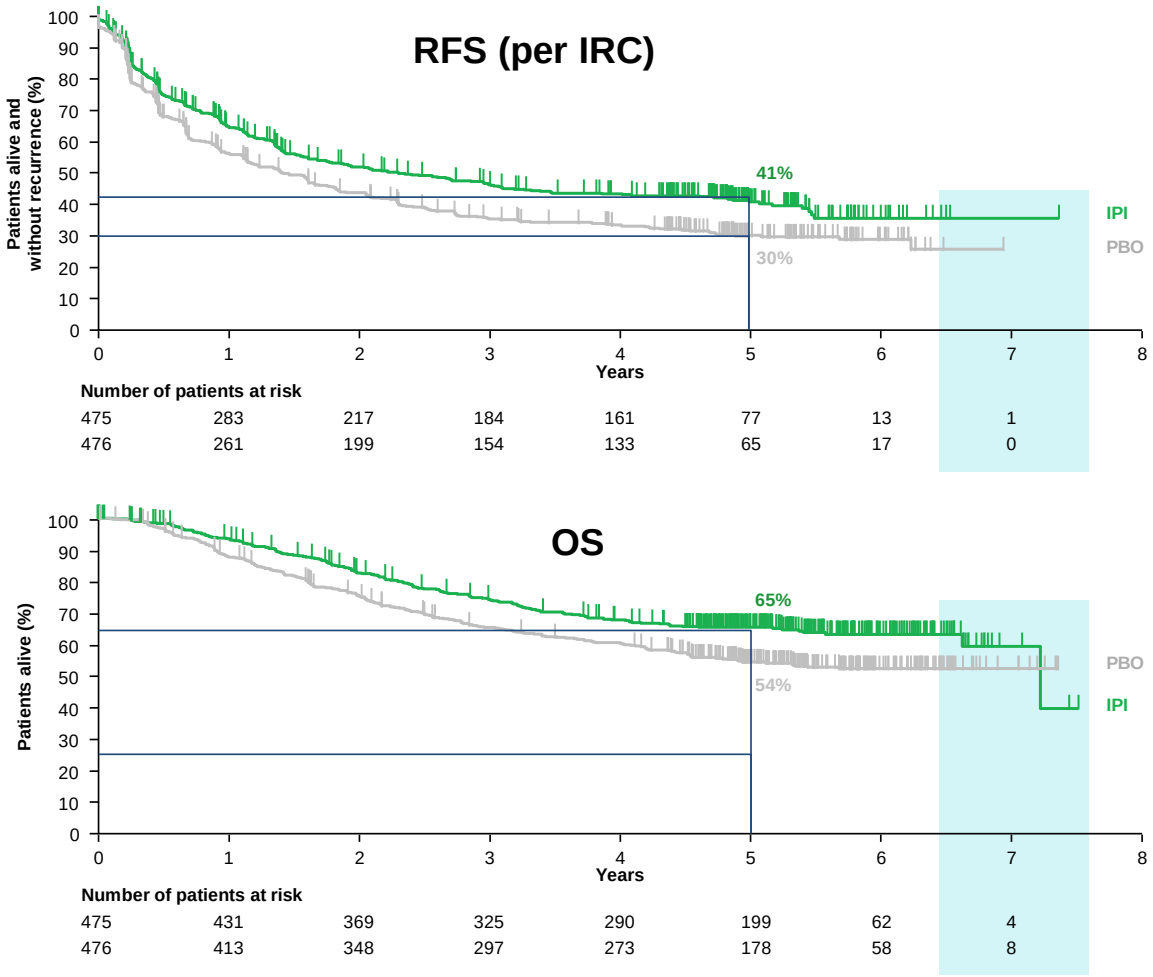
Enrollment period: June 2008 to July 2011



[a]Stage IIIA (if N1a, at least 1 metastasis >1 mm); stage IIIB or IIIC (no in-transit metastasis)

1. Eggermont AM, et al. Presented at ESMO 2016; abstract LBA2_PR. 2. Eggermont AM, et al. *N Engl J Med* 2016;375:1845–1855.

EORTC 18071/CA184-029
Survival



	IPI	PBO
Events/patients	264/475	323/476
HR (95% CI)	0.76 (0.64–0.89)	
Log-rank *P* value	*P* < 0.001	
Median RFS, months (95% CI)	27.6 (19.3–37.2)	17.1 (13.6–21.6)

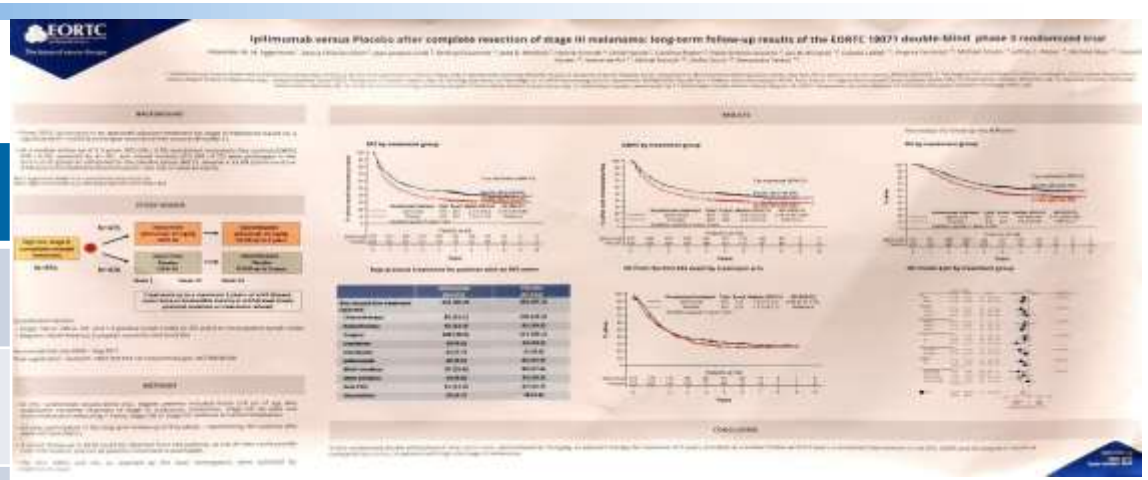
	IPI	PBO
Death/patients	162/475	214/476
HR (95% CI)	0.72 (0.58–0.88)	
Log-rank *P* value	0.001	

IRC, institutional review committee

Adapted from Eggermont AM, et al. *N Engl J Med* 2016;375:1845–1855.

ASCO 2019

	RFS		DMFS		OS	
	IPI	PBO	IPI	PBO	IPI	PBO
No. of events	273	323	247	292	173	223
5-year rate	43.9%	32.5%	49.9%	39.8%	65.2%	54.1%
7-year rate	39.2%	30.9%	44.5%	36.9%	60.0%	51.3%
Median (yrs)	2.7	1.5	5.0	2.4	NR	7.8
HR (95% CI)†	0.75 (0.63-0.88)		0.76 (0.64-0.90)		0.73 (0.60-0.89)	
Log-rank p-value†	0.0004		0.0018		0.0021	



EORTC 18071/CA184-029
Safety[1,2]

	IPI (n = 471)		PBO (n = 474)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.7	54.1	91.1	26.2
TRAE, %	94.1	45.4	59.9	4.0
TRAE leading to discontinuation, %	48.0	32.9	1.5	0.6
Any immune-related AE, %	90.4	41.6	39.7	2.7
Treatment-related deaths, n		5[a]		0

[a]3 patients had colitis (2 with gastrointestinal perforations), 1 patient had myocarditis, 1 patient had multiorgan failure with Guillain-Barré syndrome

1. Eggermont AM, et al. Presented at ESMO 2016; abstract LBA2_PR. 2. Eggermont AM, et al. *N Engl J Med* 2016;375:1845–1855.

ASCO 2019
US Intergroup E1609 Phase 3 Trial[a]

IPI 10 mg/kg and IPI 3 mg/kg versus high-dose IFN for patients with resected stage IIIB/C or stage IV (M1a/M1b) melanoma

OS

	IPI3	HDI	IPI10	HDI
HR	0.78 (0.61-0.99)		0.88 (0.69-1.12)	
P value	0.044		NS	
5-years OS (95%CI)	0.72 (0.68-0.76)	0.67 (0.62-1.72)	0.70 (0.65-0,74)	0.65 (0.60-0.70)

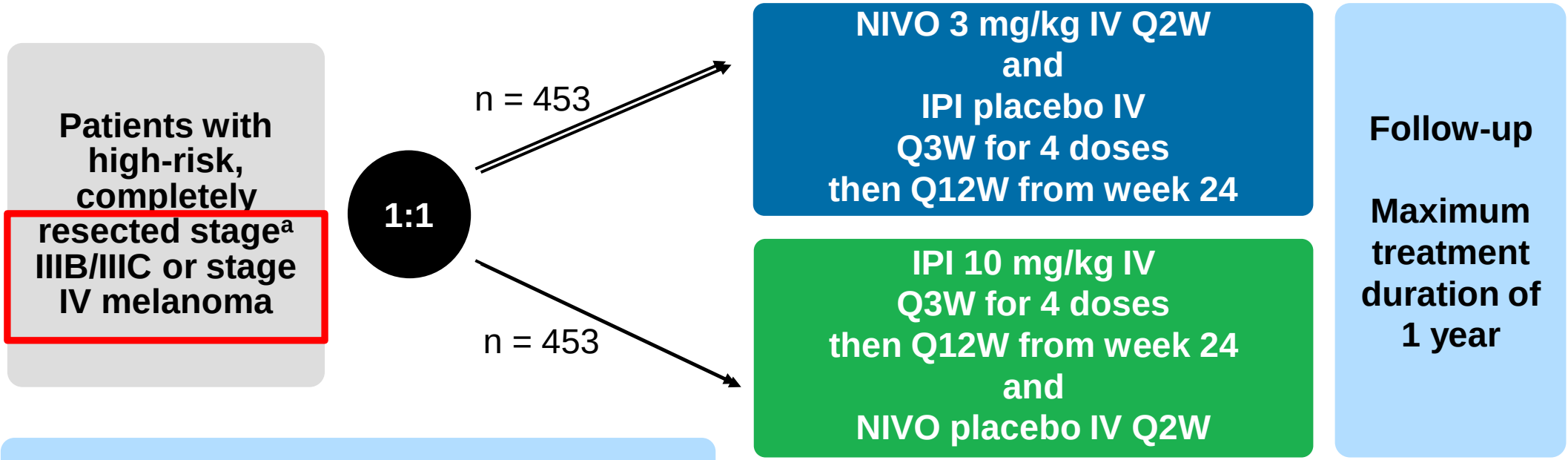
RFS

	IPI3	HDI	IPI10	HDI
HR	0.85 (0.66-1.09)		0.84 (0.65-1.09)	
P value	NS		NS	
Median RFS	4.5 year (2,6-/)	2,5 years (1,7-3,3)	3,9 years (2,9-/)	2,4 years (1,6-3,0)

Treatment related adverse events (AEs) Grade 3 or higher were experienced by 37% pts with ipi3, 79% with HDI and 58% with ipi10, and those of any grade leading to treatment discontinuation were 35% with ipi3, 20% HDI and 54% ipi10.

ASCO meeting 2019, Ahmad A. Tarhini et al. *United States Intergroup E1609: A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon-α2b for resected high-risk melanoma.*

CheckMate 238/CA209-238
Study Design



Stratified by:

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

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

Primary endpoint

- RFS from randomization until first recurrence or death

Secondary endpoints

- OS
- Safety and tolerability
- RFS by PD-L1 tumor expression
- HRQoL

Exploratory endpoint

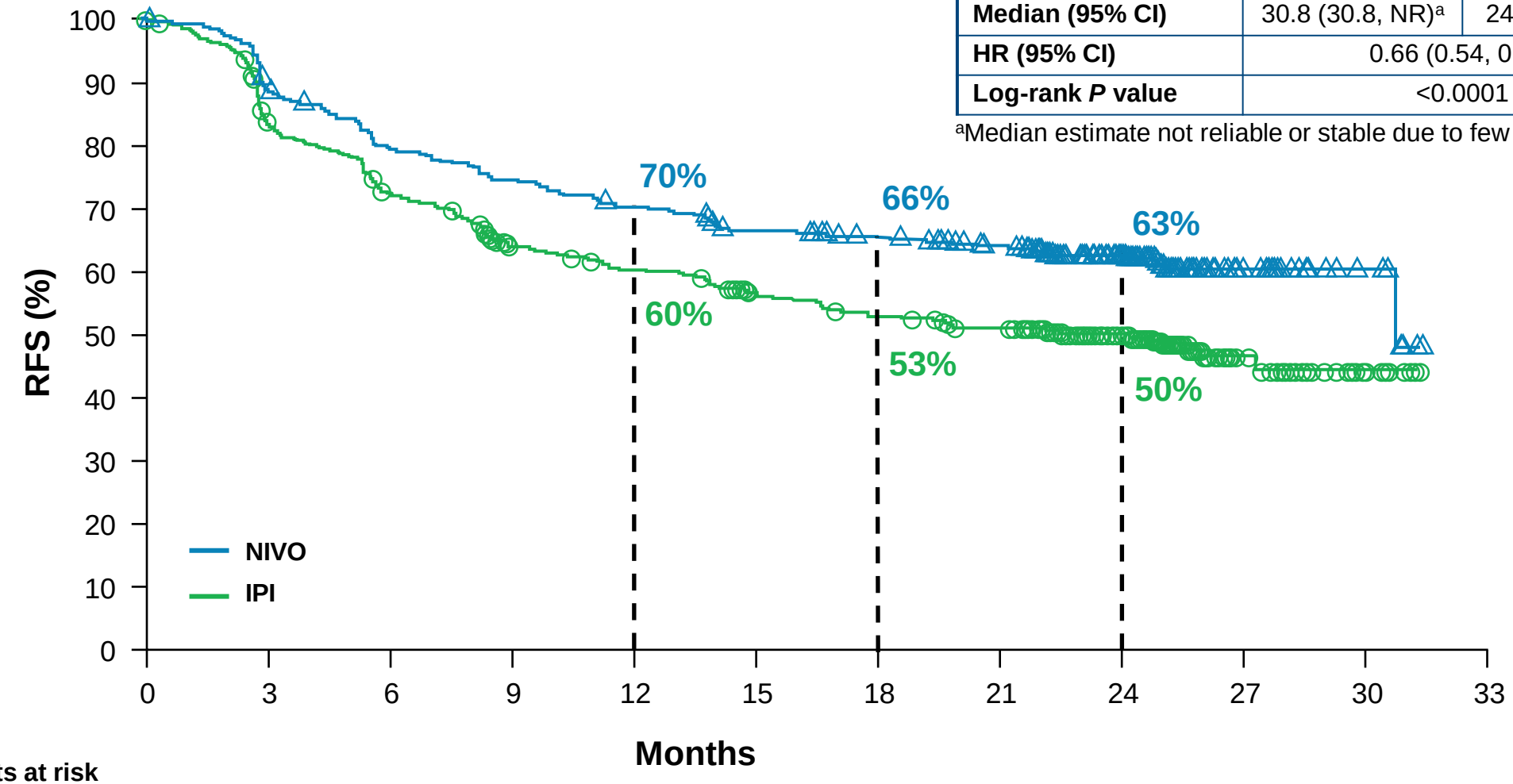
- DMFS

[a]American Joint Committee on Cancer 2009 classification, 7th edition
HRQoL, health related quality of life; PD-L1, programmed death ligand 1
Weber J, et al. ASCO 2018; abstract 9502.

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	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

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

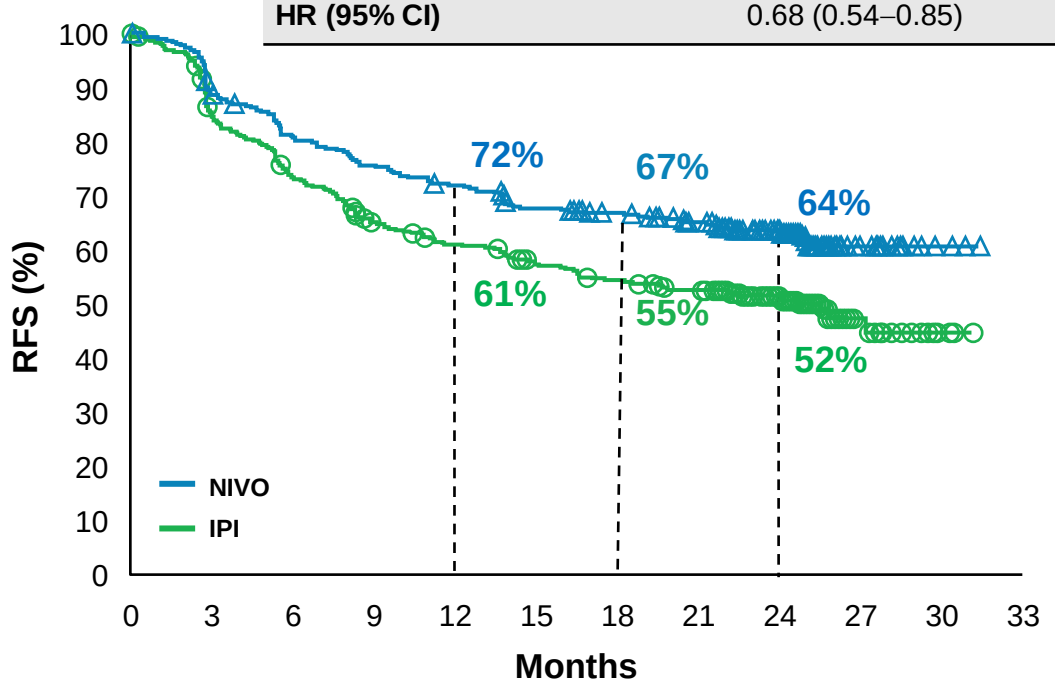
Weber et al. ASCO 2018

Subgroup Analysis of RFS

Disease Stage III and Stage IV

Stage III

	NIVO	IPI
Events/patients	135/368	174/366
Median (95% CI)	NR	25.5 (16.6–NR)
HR (95% CI)	0.68 (0.54–0.85)	

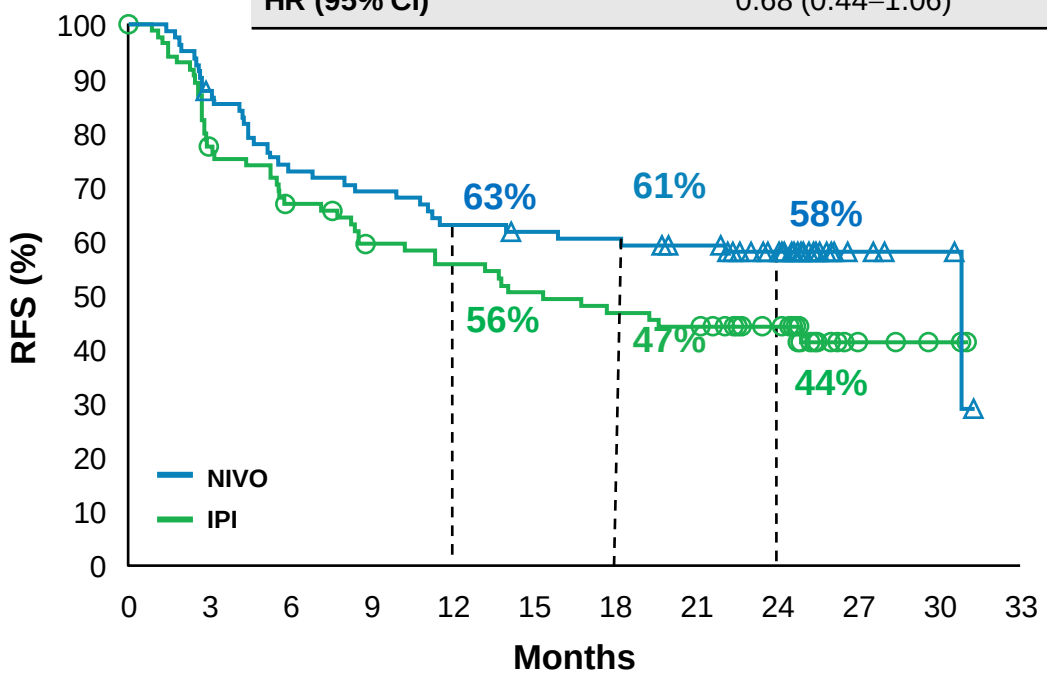


Number of patients at risk

NIVO	368	320	291	272	258	240	230	217	166	22	4	0
IPI	366	298	259	223	207	190	179	169	121	18	3	0

Stage IV

	NIVO	IPI
Events/patients	35/82	47/87
Median (95% CI)	30.8 (15.9–NR)[a]	15.4 (8.5–NR)
HR (95% CI)	0.68 (0.44–1.06)	



Number of patients at risk

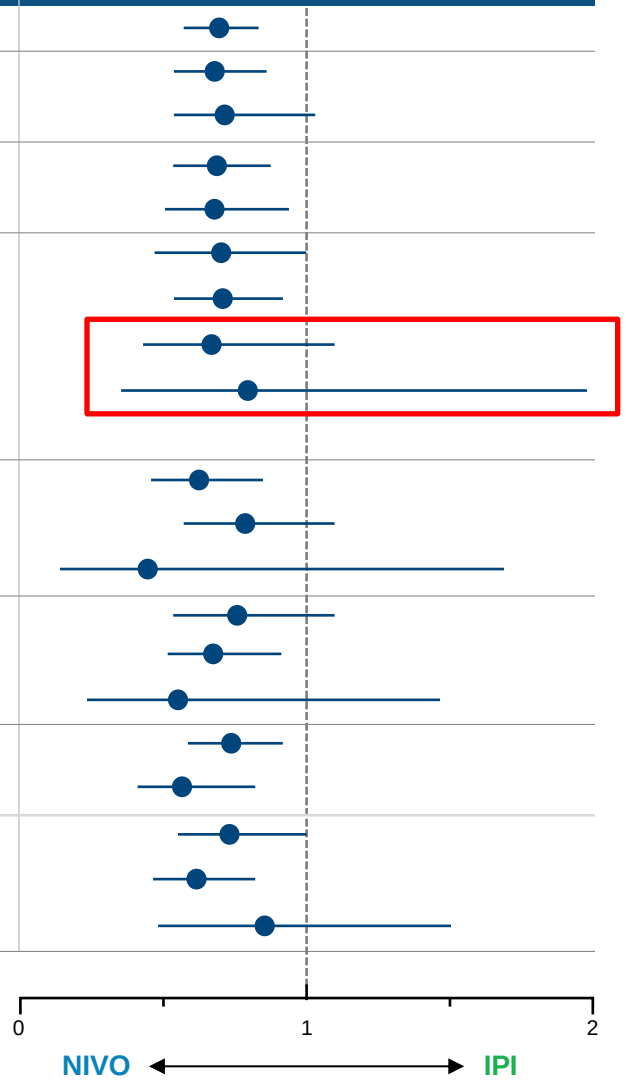
NIVO	82	71	59	56	51	49	48	45	37	6	3	0
IPI	87	65	55	47	44	40	37	35	28	5	2	0

[a]Median estimate not stable due to few patients at risk

Weber J, et al. ASCO 2018; abstract 9502.

RFS: Prespecified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	171/453	221/453	0.68 (0.56, 0.83)
Age	<65 years	117/333	158/339	0.67 (0.53, 0.85)
	≥65 years	54/120	63/114	0.70 (0.49, 1.01)
Sex	Male	106/258	141/269	0.69 (0.53, 0.88)
	Female	65/195	80/184	0.68 (0.49, 0.94)
Stage (CRF)	Stage IIIb	48/165	60/148	0.68 (0.47, 1.00)
	Stage IIIc	87/203	114/218	0.68 (0.52, 0.91)
	Stage IV M1a-M1b	27/62	37/66	0.66 (0.40, 1.08)
	Stage IV M1c	8/20	10/21	0.78 (0.31, 1.99)
	Not reported	1/1	0/0	
Stage III: Ulceration	Absent	64/201	100/216	0.61 (0.44, 0.83)
	Present	68/154	68/135	0.77 (0.55, 1.08)
	Not reported	3/15	6/15	0.42 (0.11, 1.70)
Stage III: Lymph node involvement	Microscopic	46/126	59/134	0.75 (0.51, 1.10)
	Macroscopic	82/219	107/214	0.66 (0.49, 0.88)
	Not reported	7/25	8/18	0.53 (0.19, 1.48)
PD-L1 status	<5%/indeterminate	132/300	157/299	0.73 (0.58, 0.91)
	≥5%	39/152	64/154	0.54 (0.36, 0.81)
***BRAF* mutation status**	Mutant	73/187	95/194	0.73 (0.54, 0.99)
	Wild-type	73/197	107/212	0.61 (0.45, 0.82)
	Not reported	25/69	19/47	0.85 (0.47, 1.55)



Weber et al. ASCO 2018

Safety Summary
(Median Follow-up of 18 Months)

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	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

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

Per protocol, safety analysis was not reported beyond the 18-month median follow-up, given that all patients had been off study treatment >100 days at the time of the 18-month analysis

Weber J, et al. *N Engl J Med* 2017;377:1824–1835.

An Analysis of Nivolumab-Mediated Adverse Events and Association With Clinical Efficacy in Resected Stage III or IV Melanoma (CheckMate 238)

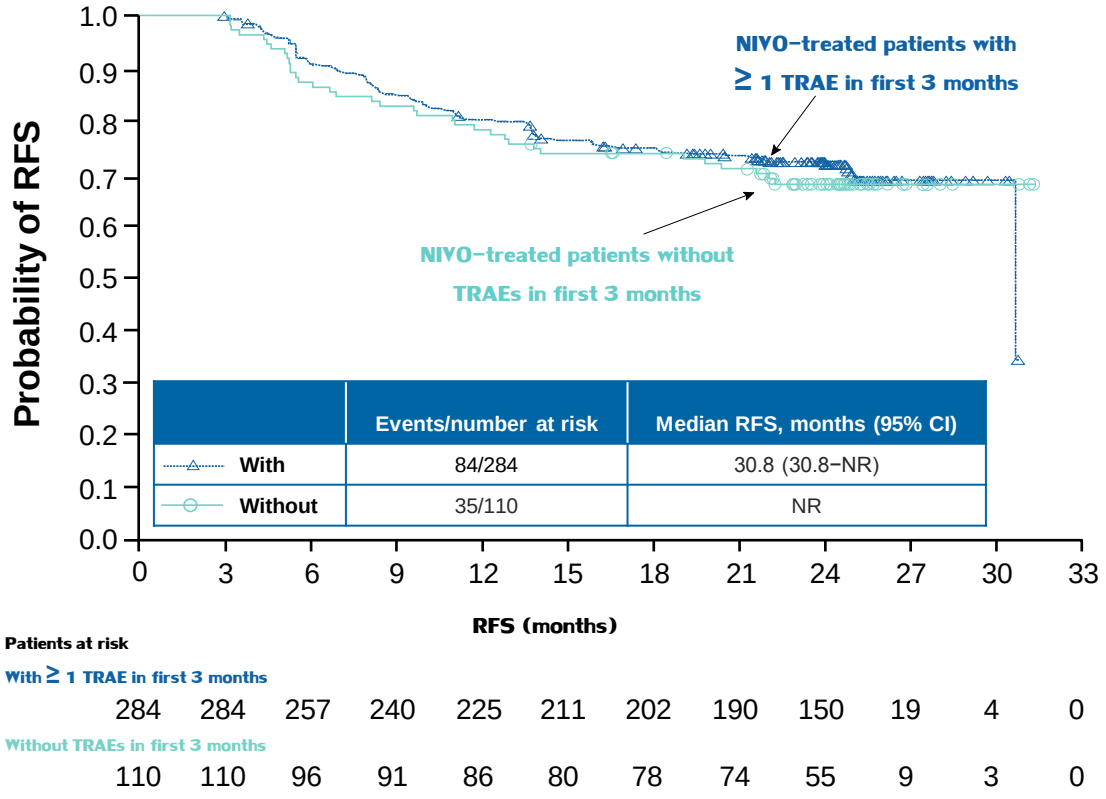
Mario Mandalá,[1] James Larkin,[2] Paolo A. Ascierto,[3] Michele Del Vecchio,[4] Helen Gogas,[5] C. Lance Cowey,[6] Ana Arance,[7] Stéphane Dalle,[8] Michael Schenker,[9] Jean-Jacques Grob,[10] Vanna Chiarion-Sileni,[11] Ivan Marquez-Rodas,[12] Marcus Butler,[13] Anna Maria Di Giacomo,[14] Mark Middleton,[15] Jose Lutzky,[16] Michael Millward,[17] Veerle de Pril,[18] Maurice Lobo,[18] Jeffrey Weber[19]

[1]Papa Giovanni XXIII Hospital, Bergamo, Italy; [2]The Royal Marsden NHS Foundation Trust, London, UK; [3]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [4]Medical Oncology, National Cancer Institute, Milan, Italy; [5]National and Kapodistrian University of Athens, Athens, Greece; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Hospices Civils de Lyon, Pierre Bénite, France; [9]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [10]Hôpital de la Timone, Marseille, France; [11]Oncology Institute of Veneto IRCCS, Padua, Italy; [12]General University Hospital Gregorio Marañón, CIBERONC, Madrid, Spain; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Churchill Hospital, Oxford, UK; [16]Mount Sinai Medical Center, Miami Beach, FL; [17]Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia; [18]Bristol-Myers Squibb, Princeton, NJ; [19]NYU Perlmutter Cancer Center, New York, NY

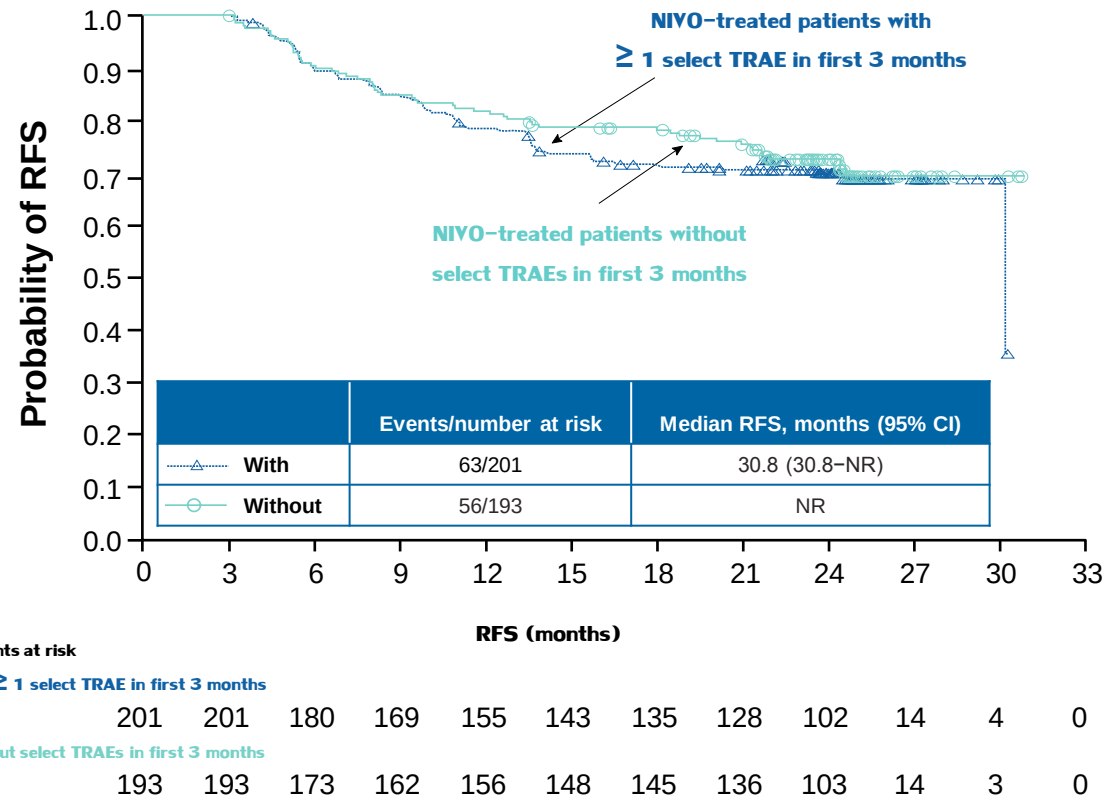
Abstract Number 9584

Three-month landmark analysis of RFS in NIVO-treated patients with and without early TRAEs (A) and with and without early select TRAEs (B)

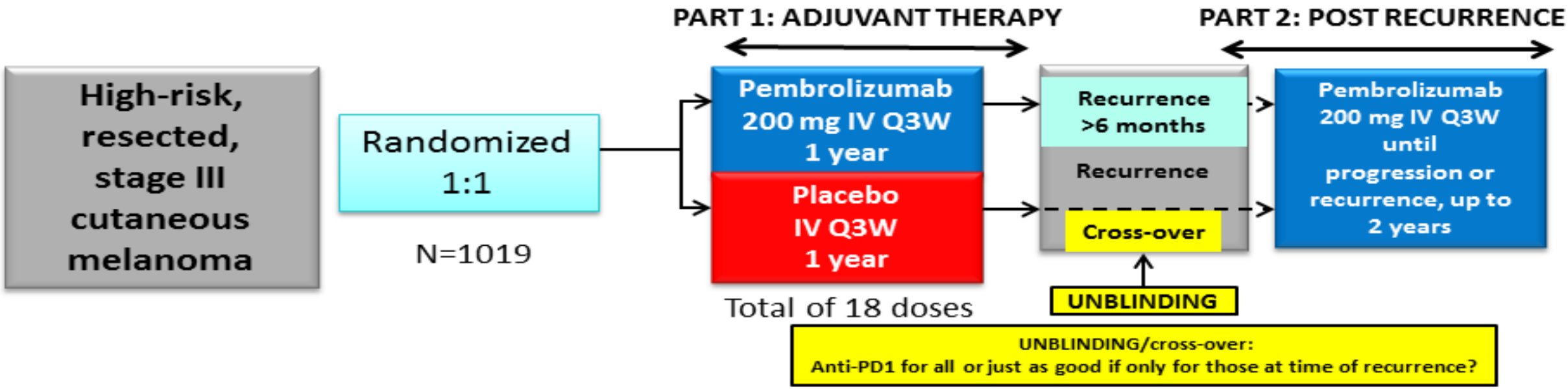
A.



B.



EORTC 1325/KEYNOTE-54: Study Design



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:

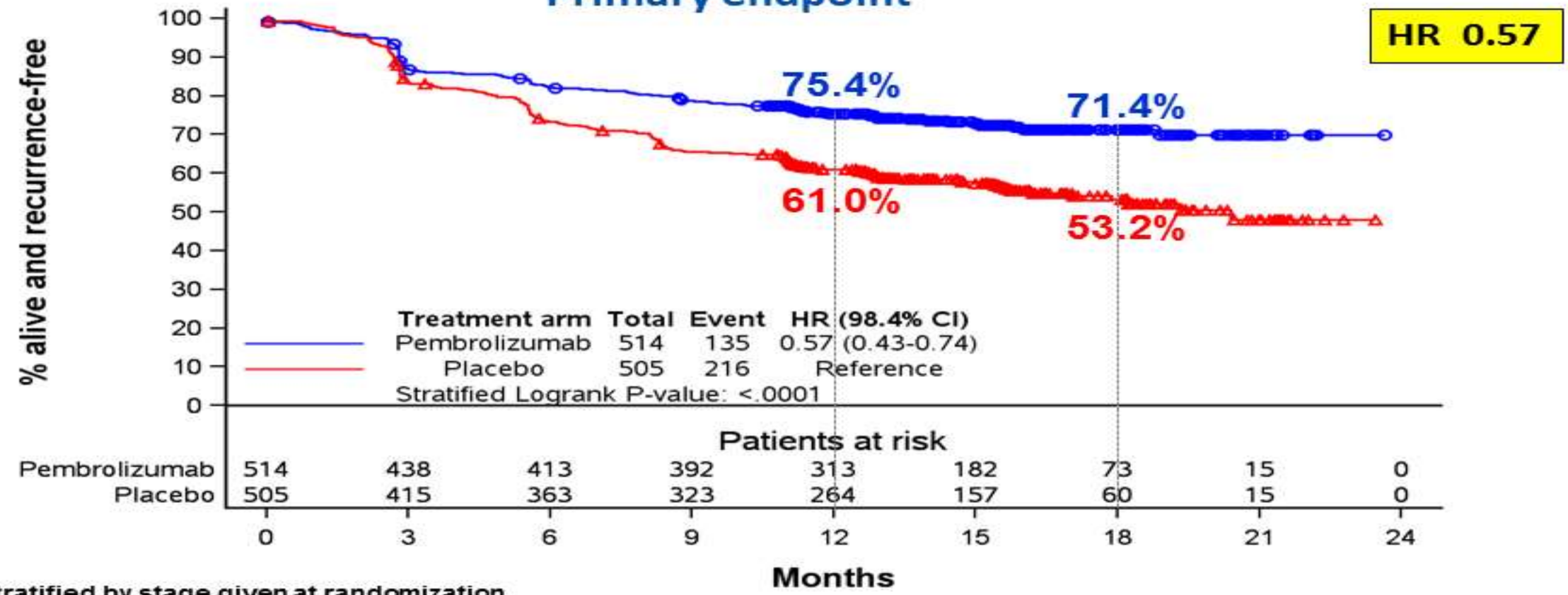
- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

EORTC

L. Eggermont AACR 2018

Recurrence-Free Survival in the ITT Population

Primary endpoint



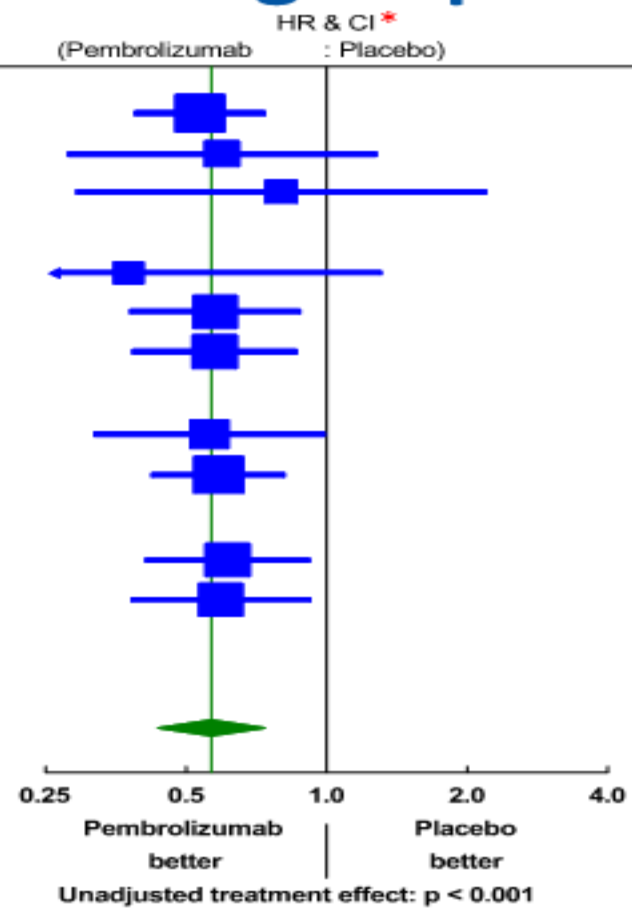
*Stratified by stage given at randomization

EORTC

L. Eggermont AACR 2018

Recurrence-Free Survival: Subgroup Analysis

	Events / Patients Pembrolizumab	Placebo	HR (CI)		Interaction test
PD-L1					
Positive	102 / 428	176 / 425	0.54	(0.39 ; 0.74)	P=0.61
Negative	20 / 59	27 / 57	0.60	(0.28 ; 1.28)	
Indeterminate	13 / 27	13 / 23	0.80	(0.29 ; 2.19)	
AJCC 2009					
Stage IIIA	6 / 77	15 / 76	0.38	(0.11 ; 1.31)	P=0.69
Stage IIIB	62 / 240	97 / 232	0.58	(0.38 ; 0.88)	
Stage IIIC	67 / 197	104 / 197	0.58	(0.38 ; 0.86)	
Type of positive lymph nodes					
Microscopic	35 / 187	50 / 161	0.56	(0.32 ; 0.99)	P=0.86
Macroscopic	100 / 327	166 / 344	0.59	(0.42 ; 0.81)	
BRAF status					
WT	69 / 233	97 / 214	0.61	(0.41 ; 0.92)	P=0.89
V600 E or K mutation	54 / 186	94 / 209	0.59	(0.38 ; 0.92)	
	N missing = 177				
Total	**135 / 514**	**216 / 505**	**0.57**	**(0.43 ; 0.74)**	
	(26.3 %)	**(42.8 %)**			



*98.4% CI for total, 99% CI for subgroups

EORTC

L. Eggermont AACR 2018

General Adverse Events

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any adverse events (AE)	93.3	31.6	90.2	18.5
Any treatment-related AE	77.8	14.7	66.1	3.4
Fatigue/asthenia	37.1	0.8	33.3	0.4
Skin reactions	28.3	0.2	18.3	0
Rash	16.1	0.2	10.8	0
Pruritus	17.7	0	10.2	0
Diarrhea	19.1	0.8	16.7	0.6
Arthralgia	12.0	0.6	11.0	0
Nausea	11.4	0	8.6	0

1 death in pembrolizumab arm due to autoimmune miositis

EORTC

ASCO 2019

Prognostic and predictive value of an immune-related adverse event among stage III melanoma patients included in the EORTC 1325/KEYNOTE-054 pembrolizumab versus placebo trial

Alexander M. M. Eggermont, Michal Kicinski, Christian U. Blank, Mario Mandalà, Georgina V. Long, Victoria Atkinson, Stéphane Dalle, Andrew Mark Haydon, Mikhail Lichinitser, Muhammad Khattak, Matteo S. Carlino, Shahneen Kaur Sandhu, Susana Puig, Paolo Antonio Ascierto, Clemens Krepler, Nageatte Ibrahim, Sandrine Marreaud, Alexander Christopher Jonathan Van Akkooi, Caroline Robert, Stefan Suciu

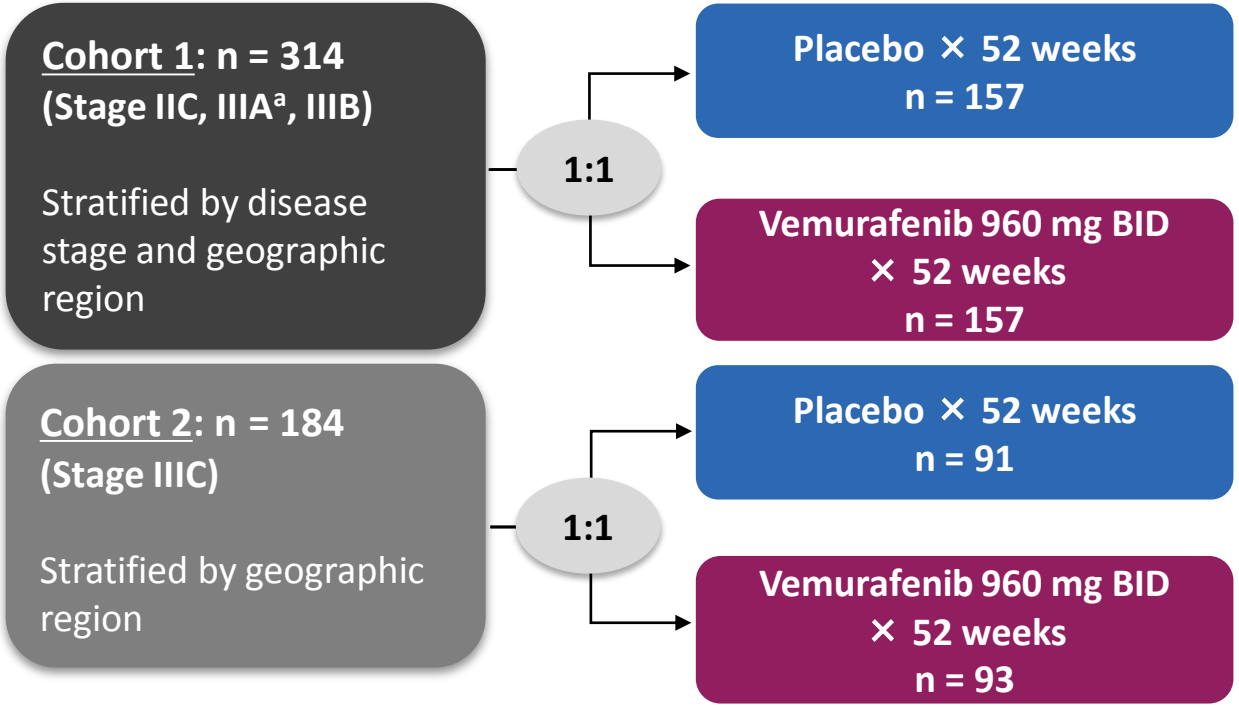
In the EORTC 1325/KEYNOTE-054 study conducted in high-risk stage III melanoma pts, the occurrence of an irAE was strongly associated with a longer RFS in those treated with pembrolizumab, but not with placebo

irAE	Treatment arm and irAE status	HR for RFS (95%CI)	p-value
Any irAE	Placebo Pembrolizumab without/before irAE Pembrolizumab after irAE onset	1 0.62 0.37	0,027
Endocrine adverse events	Placebo Pembrolizumab without/before irAE Pembrolizumab after irAE onset	1 0.60 0.34	0.034
Vitiligo	Placebo Pembrolizumab without/before irAE Pembrolizumab after irAE onset	1 0.57 0.13	0.15
Any severe (G3-4) irAE	Placebo Pembrolizumab without/before irAE Pembrolizumab after irAE onset	1 0.55 0.78	0.43

Target Therapy

BRIM8 STUDY DESIGN

- Phase 3, international, multicenter, double-blind, randomized, placebo-controlled study



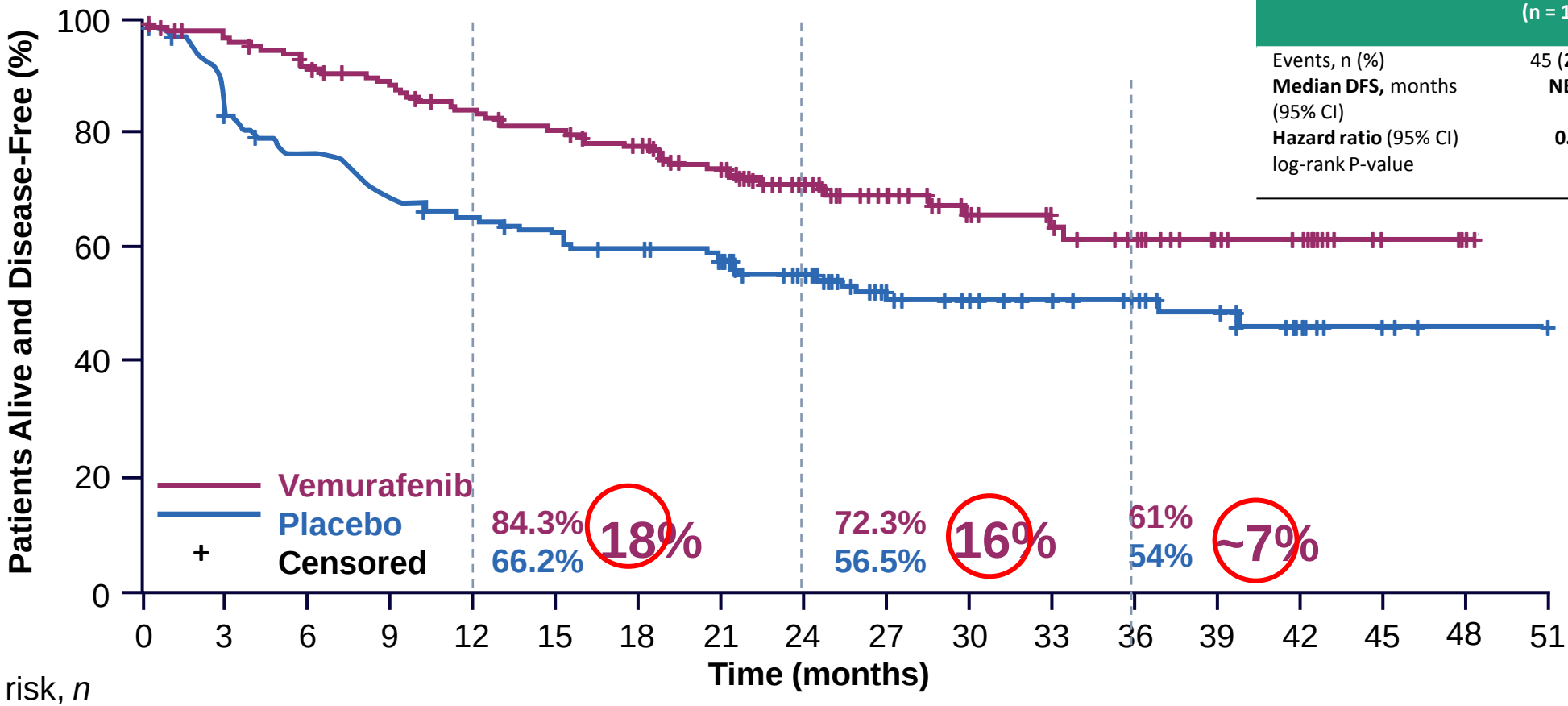
- **Primary endpoint**
  - DFS
- **Secondary endpoints**
  - DMFS
  - OS
  - Safety
  - HRQOL

BID, twice daily; DFS, disease-free survival; DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival.
[a]Patients with stage IIIA melanoma were eligible if they had one or more nodal metastases >1 mm in diameter.

BRIM8: Primary DFS endpoint (Cohort 1, stage IIC–IIIB)

- One year of adjuvant vemurafenib results in 46% DFS risk reduction in stage IIC-IIIB *BRAF*^{V600} melanoma, demonstrating a substantial clinical benefit vs placebo

	Vemurafenib (n = 157)	Placebo (n = 157)
Events, n (%)	45 (**29**)	72 (**46**)
Median DFS, months	**NE**	**36.9**
(95% CI)		(21.4 – NE)
Hazard ratio (95% CI)	**0.54** (0.37 to 0.78)	
log-rank P-value	*p = 0.0010*[a]	



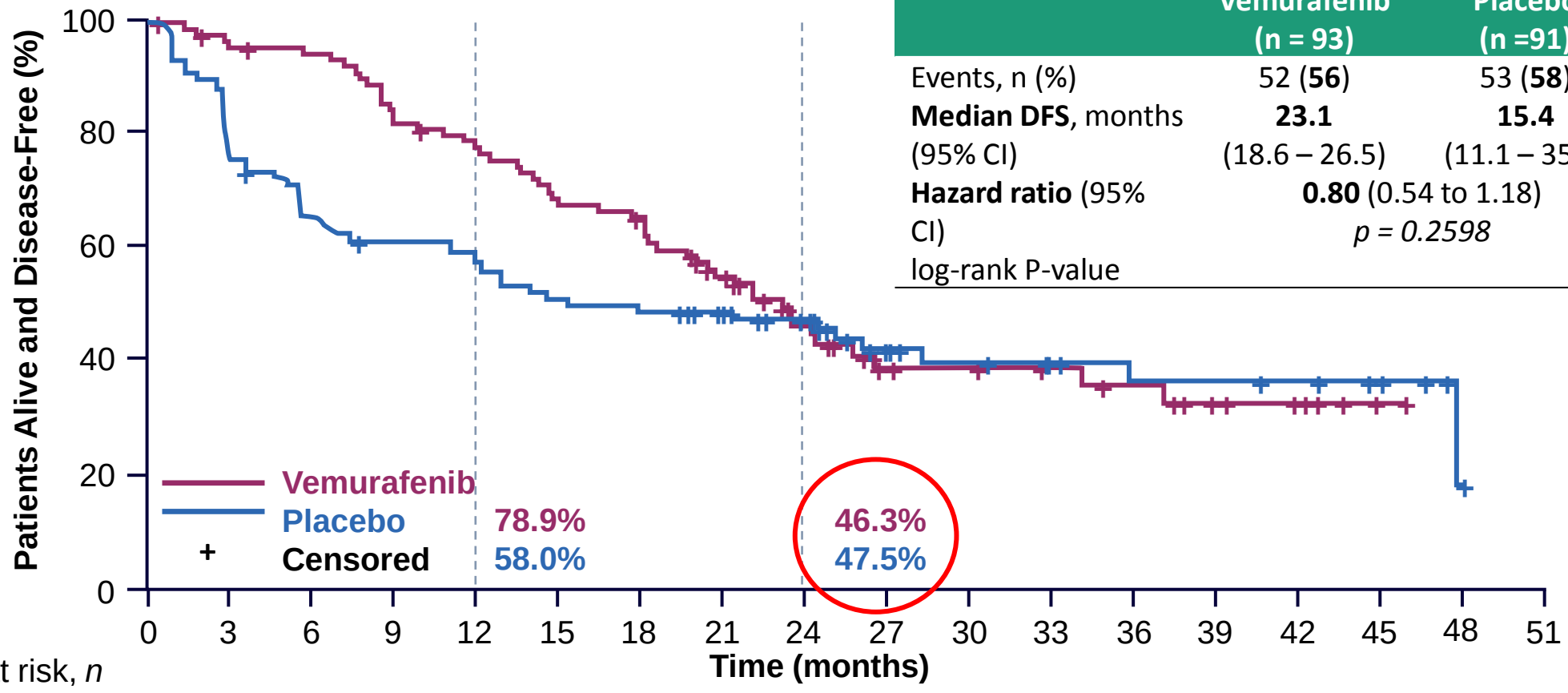
Patients at risk, *n*

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	–

BRIM8: Primary DFS endpoint (Cohort 2, stage IIIC)

- One year of adjuvant vemurafenib increased median DFS vs placebo in stage IIIc *BRAF*^{V600} melanoma demonstrating a biologic effect, however it did not significantly reduce DFS risk

	Vemurafenib (n = 93)	Placebo (n =91)
Events, n (%)	52 (**56**)	53 (**58**)
Median DFS, months	**23.1**	**15.4**
(95% CI)	(18.6 – 26.5)	(11.1 – 35.9)
Hazard ratio (95% CI)	**0.80** (0.54 to 1.18)	
log-rank P-value	*p = 0.2598*	

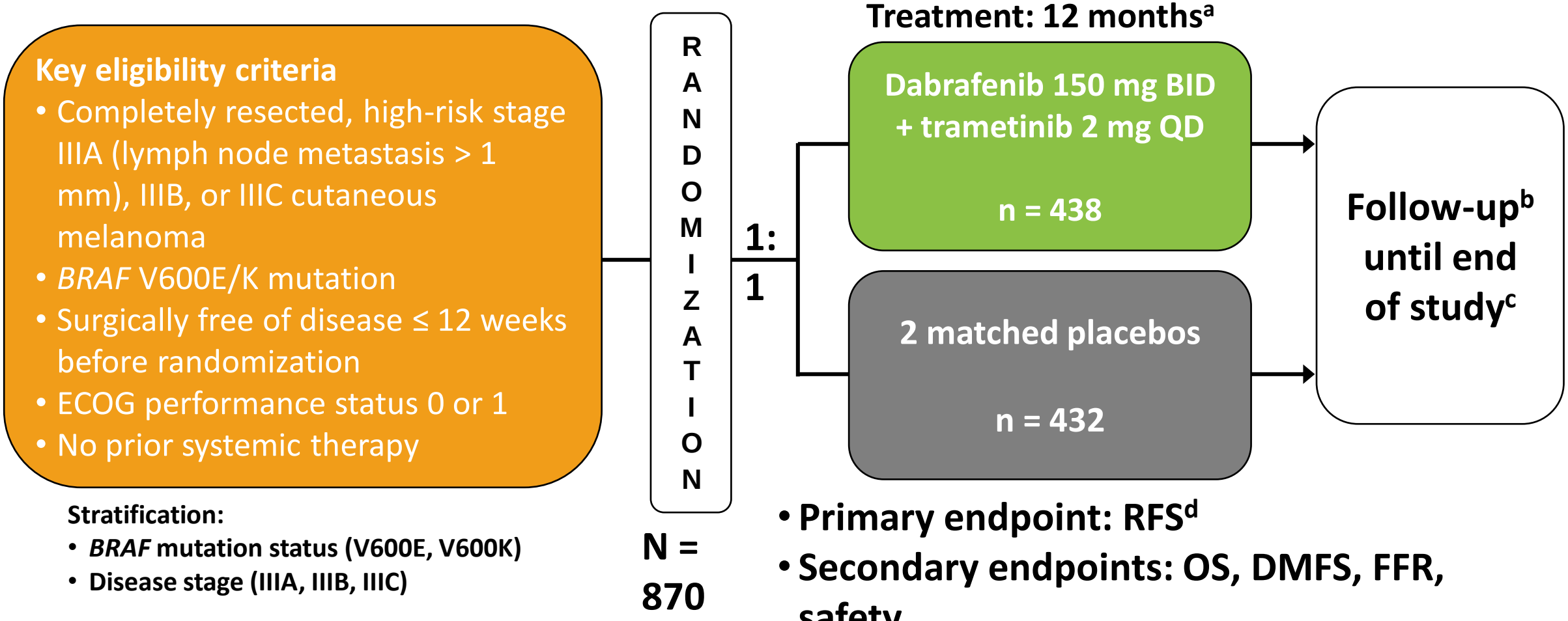


Patients at risk, *n*

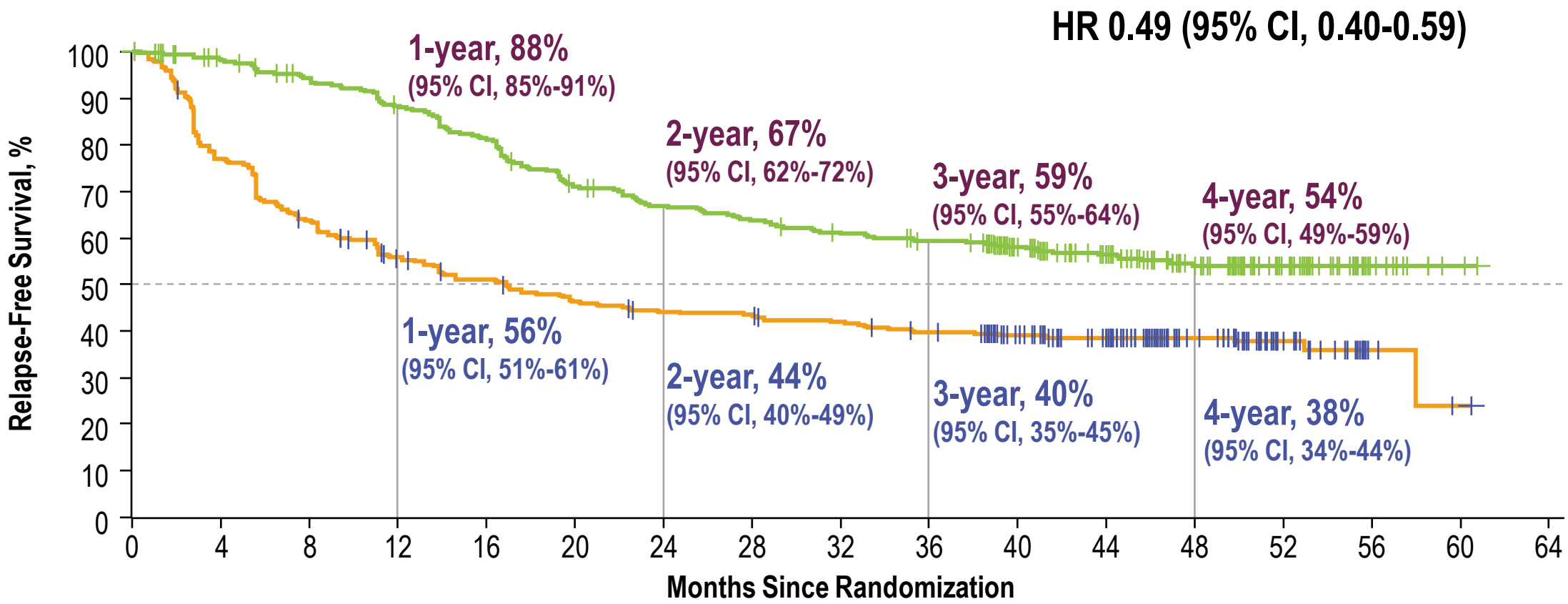
Vemurafenib	93	87	85	76	70	61	57	44	29	16	15	13	11	7	5	1	–	–
Placebo	91	71	59	54	51	45	43	39	31	21	16	13	11	8	7	5	1	–

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio, NE, not estimable.

Combi-AD: Study design



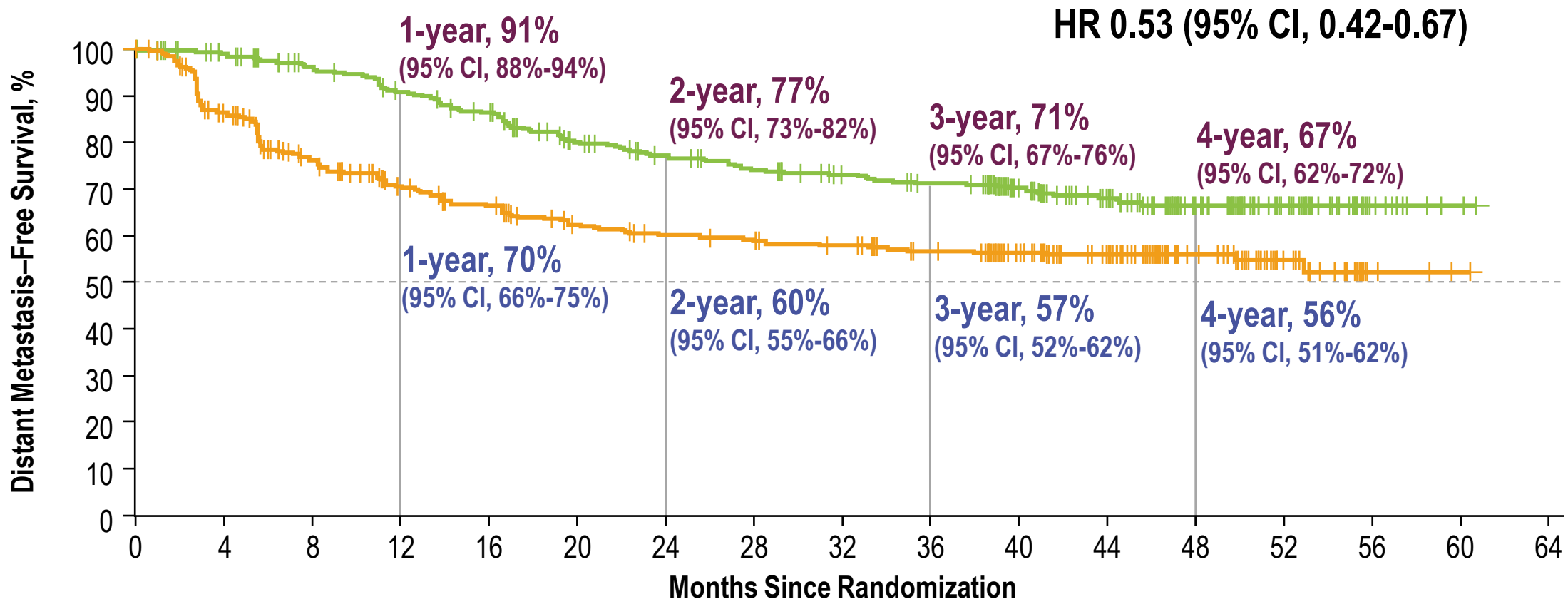
RELAPSE-FREE SURVIVAL



No. at risk																
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

PRESENTED BY GV LONG AT ESMO 2018

DISTANT METASTASIS–FREE SURVIVAL



No. at risk																
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

PRESENTED BY GV LONG AT ESMO 2018

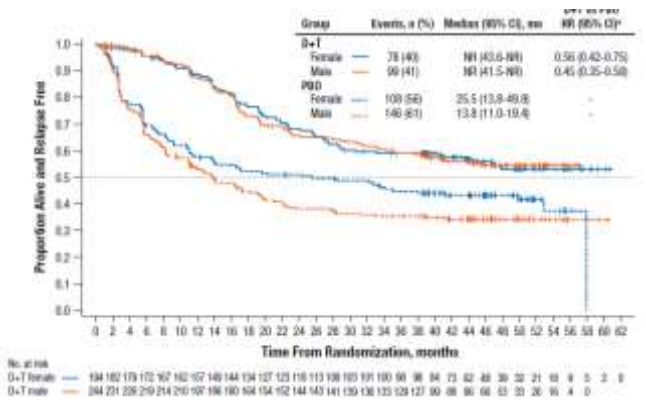
ASCO 2019

Association Between Baseline Disease Characteristics and Relapse-Free Survival in Patients With *BRAF* V600–Mutant Resected Stage III Melanoma Treated With Adjuvant Dabrafenib + Trametinib or Placebo

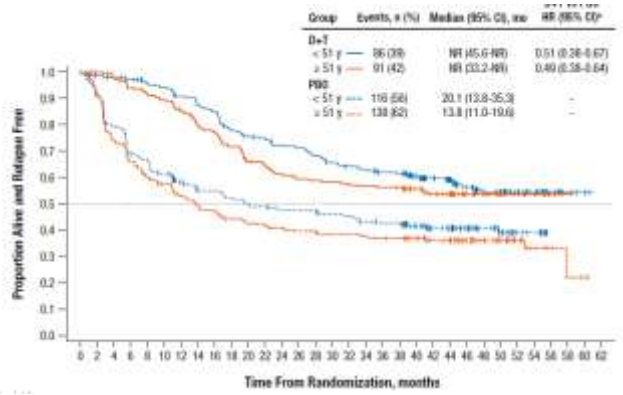
RFS benefit favored dabrafenib + trametinib in patients with completely resected stage III BRAF V600E/K–mutant melanoma vs placebo regardless of the following baseline factors, confirming previous findings1:

Age
Sex
T stage
N stage
Status of in-transit metastasis
Histological subtype

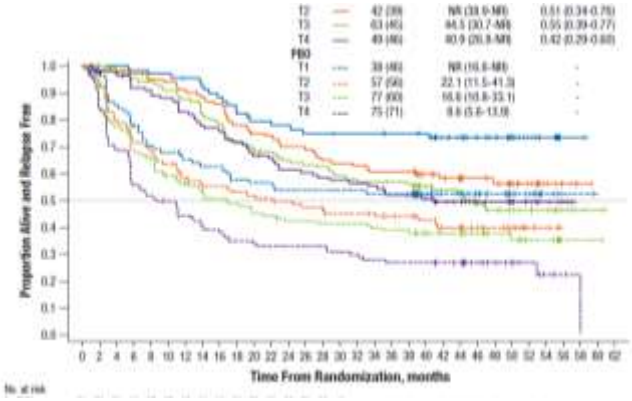
Sex



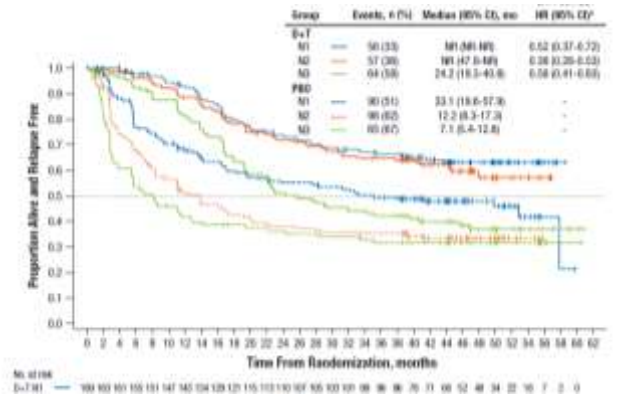
Age



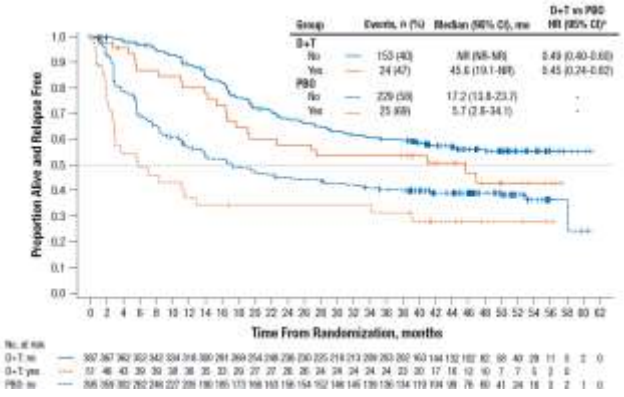
T stage



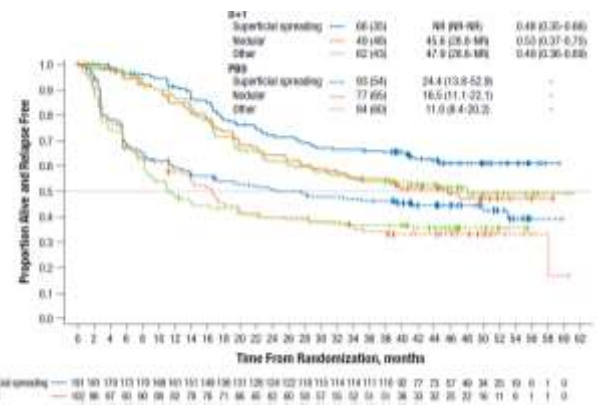
N stage



In transit metastasis



Hystological subtype



Adjuvant Treatment Options in 2019

IFN-α
High-dose IFN-α Low-dose IFN-α (preferred in EU)
PEG–IFN-α

PEMBROLIZUMAB (200 mg Q3W)
In USA: FDA approved for patients with LN involvement / metastases
In Europe: EMA approved for patients with LN involvement / metastases

Observation

IPI (10 mg/kg)
In USA: FDA approved for patients with LN metastases >1 mm

NIVO (240 mg Q2W / 480 mg Q4W)
In USA: FDA approved for patients with LN involvement / metastases
In Europe: EMA approved for patients with LN involvement / metastases

Clinical trial

Dabrafenib + trametinib

In USA: FDA approved for patients with BRAF V600E or V600K mutations
In Europe: EMA approved for patients with BRAF V600E or V600K mutations

EAP

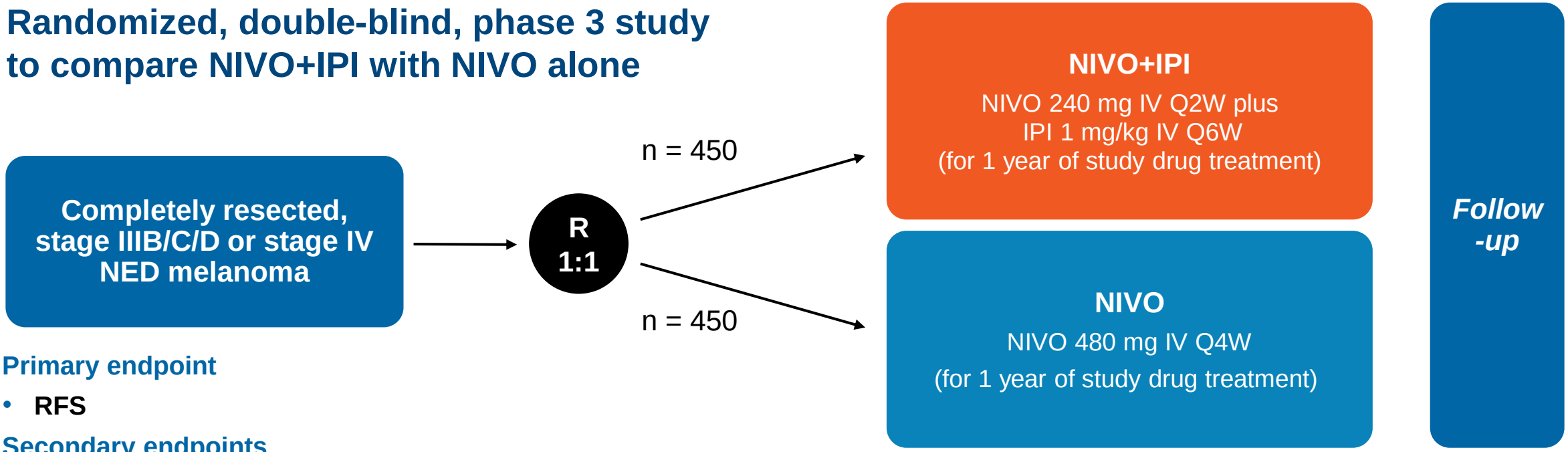
FDA, US Food and Drug Administration; PEG, pegylated

1. Garbe C, et al. *Eur J Cancer* 2016;63:201–217. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma V.1.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed August 10, 2017. 3. McArthur GA. *J Clin Oncol* 2014;32:171–173. 4. MEKINIST US Prescribing Information, April 2018. 5. OPDIVO US Prescribing Information, April 2018.

Ongoing Trial Designs

CheckMate 915
Study Design (Phase 3)[1,2]

Randomized, double-blind, phase 3 study to compare NIVO+IPI with NIVO alone



Primary endpoint

- **RFS**

Secondary endpoints

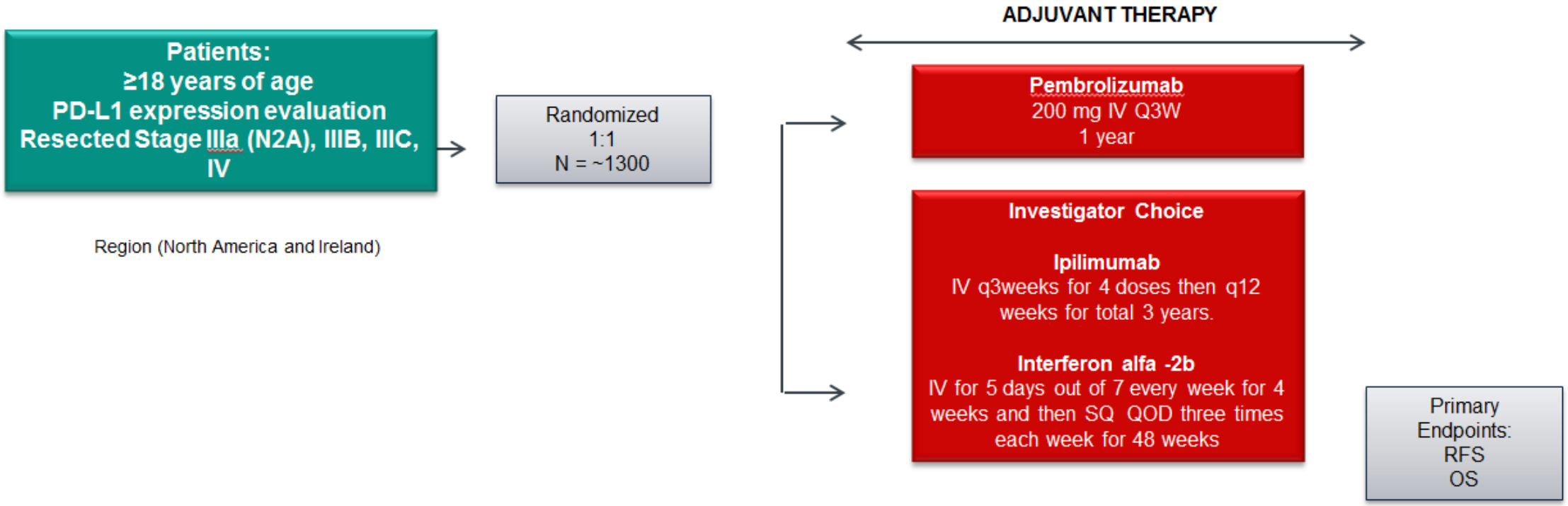
- **OS, association between PD-L1 and RFS**

Estimated enrollment: 900 patients

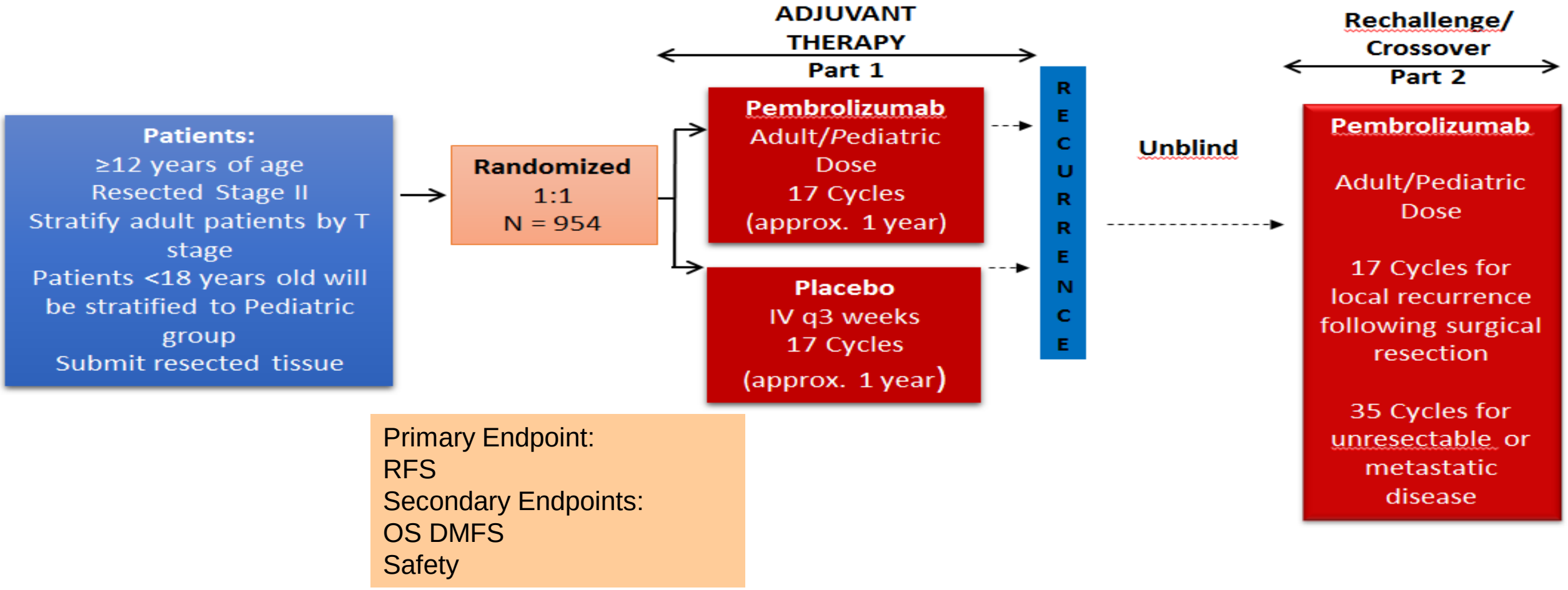
Study start date: April 2017

Estimated primary completion date: December 2020

Keynote053/SWOG S1404



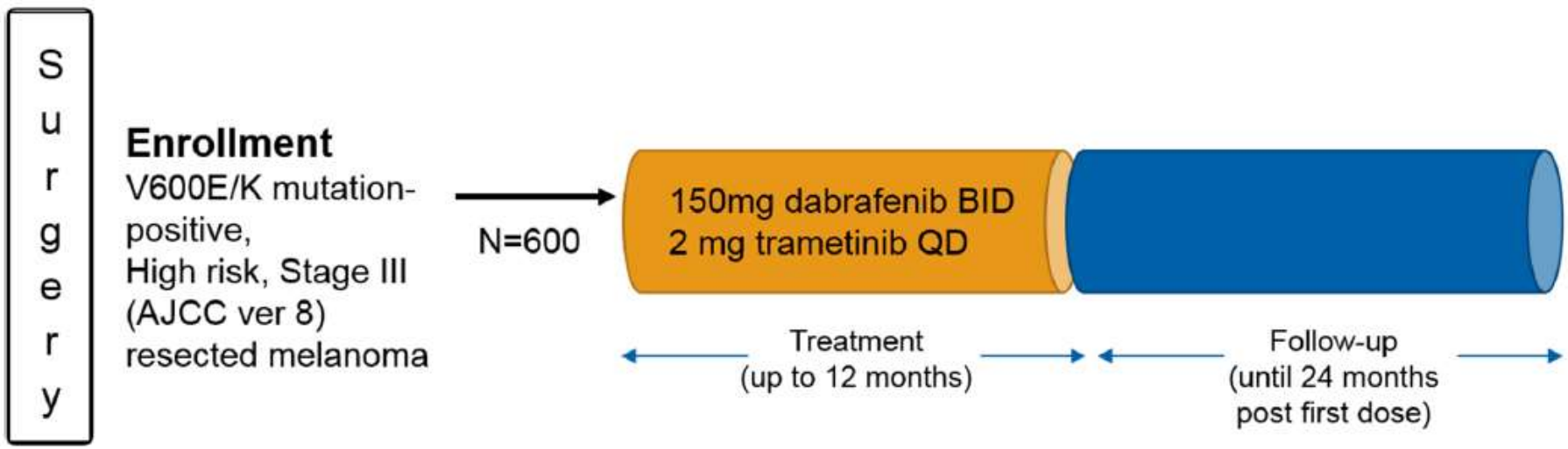
Keynote 716



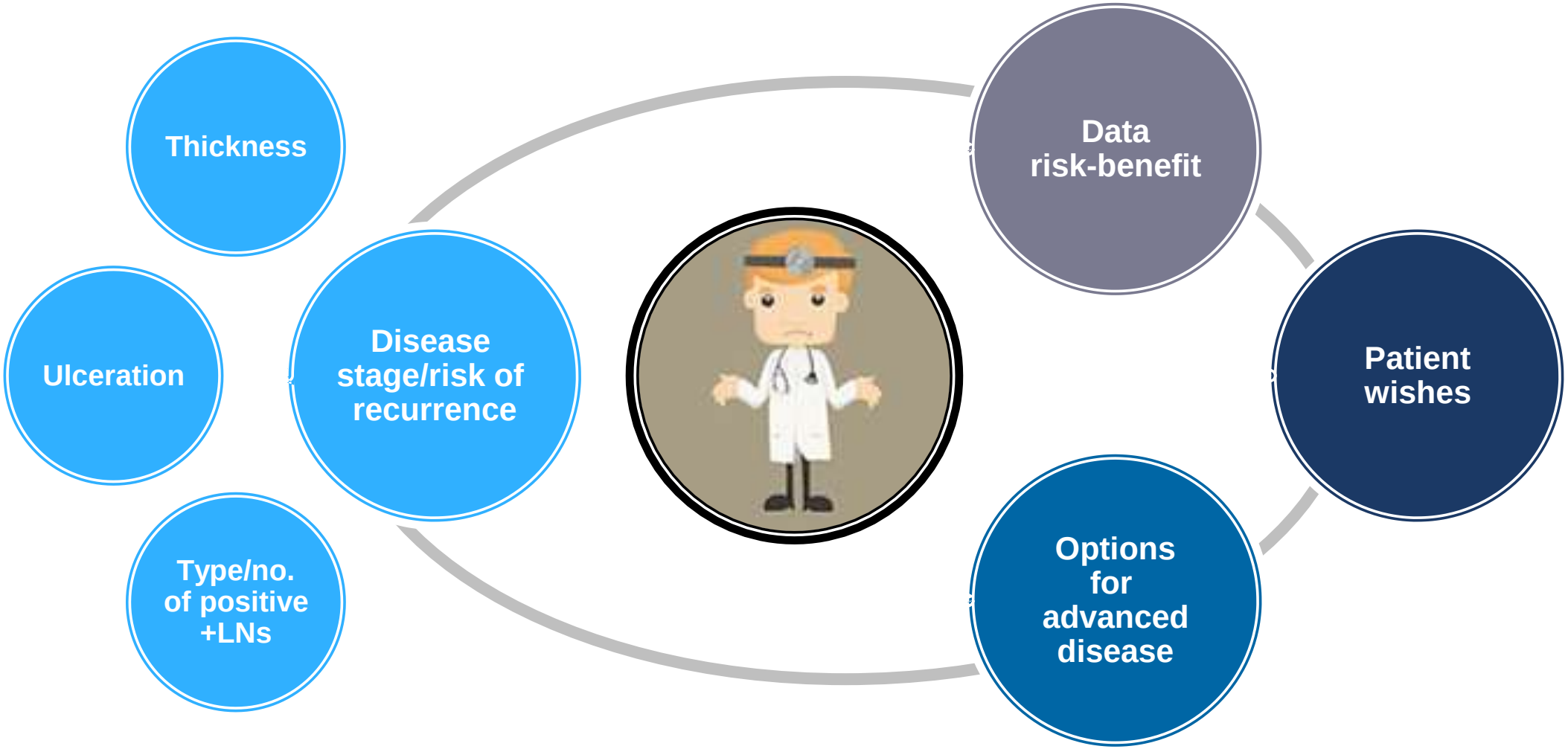
Primary Endpoint:
RFS
Secondary Endpoints:
OS DMFS
Safety

COMBI-APlus: Open-label, phase IIIb study to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm (Plus) with dabrafenib in COMBInation with trametinib in the Adjuvant treatment of high-risk stage III *BRAF* V600 mutation-positive melanoma after complete resection

Figure 4-1 Study Design



Factors for Consideration in Adjuvant Treatment Decisions



Thank you!