



INNOVAZIONE, ACCESSIBILITÀ, SOSTENIBILITÀ, INFORMAZIONE IN ONCOLOGIA

ENNA

1 Marzo 2019

Hotel Federico II

2 Marzo 2019

Aula Magna Ospedale Umberto I



MELANOMA: Trattamento nella fase adiuvante

Dr.ssa Lorenza Di Guardo

*Fondazione IRCCS Istituto Nazionale dei Tumori
Milano*

Oncologia Medica 1 , SS Oncologia Melanomi

lorenza.diguardo@istitutotumori.mi.it



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

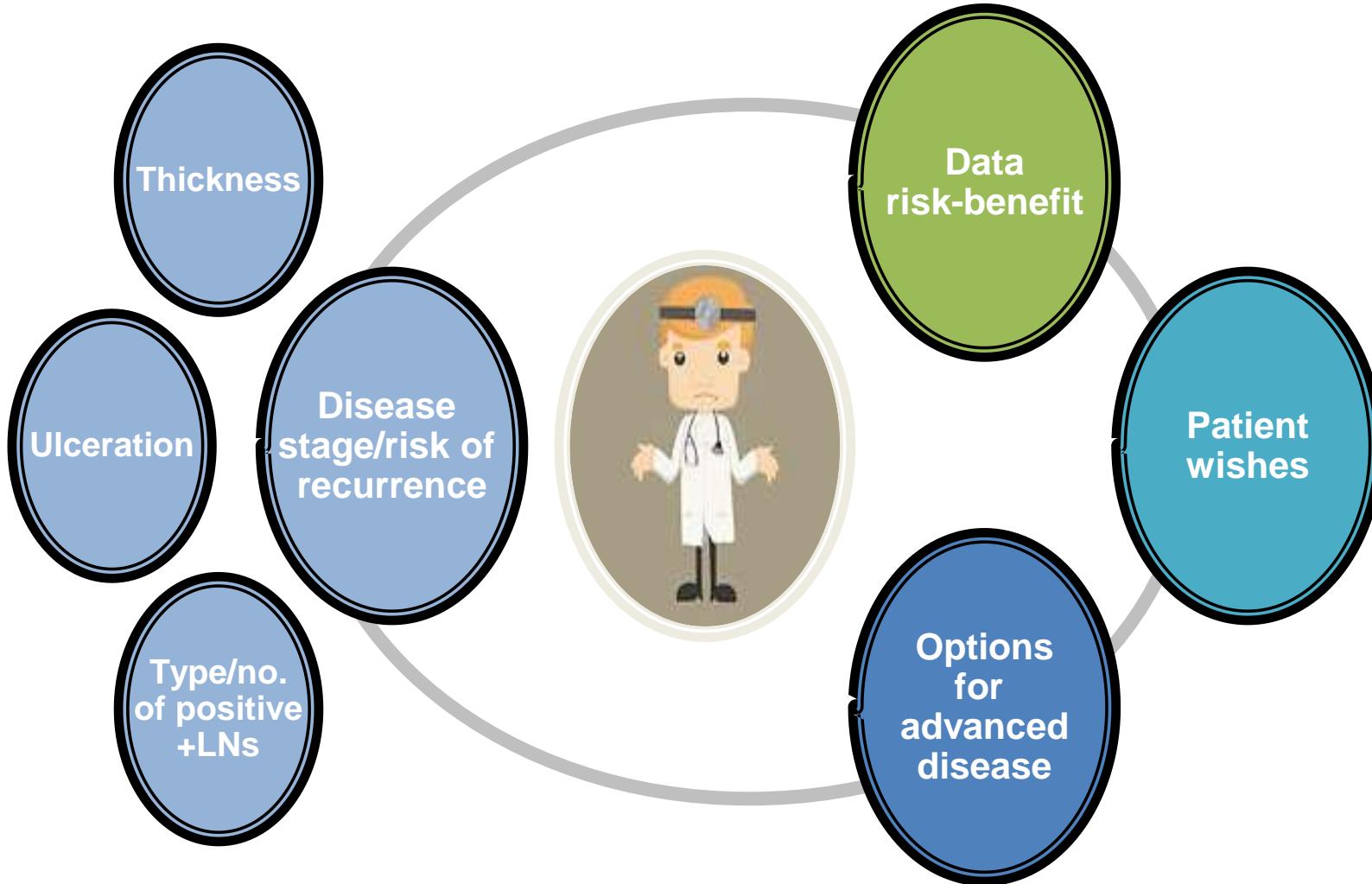
(included in the 7th, but not 8th, edition of AJCC staging manual)^{a2,3}

^aRemoved 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

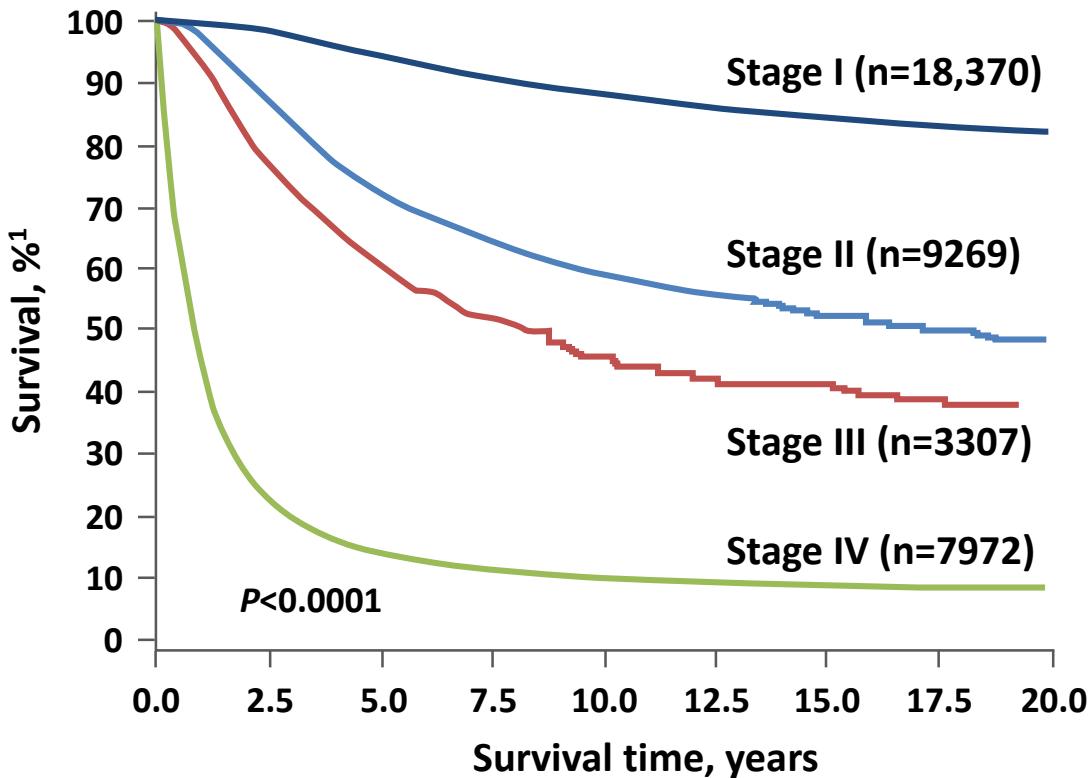
AJCC, American Joint Committee on Cancer

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.

Factors for Consideration in Adjuvant Treatment Decisions



Patient Survival Decreases as Melanoma Disease Stage Increases



The 5-year relative survival with metastatic disease is 18%²

1. American Joint Committee on Cancer (AJCC) Cancer Staging System, 7th ed. Compton CC, ed. New York: Springer; 2010. 2. American Cancer Society. Cancer Facts & Figures 2015. <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2017/index>. 2015. Accessed July 19, 2017.
AJCC, American Joint Committee on Cancer

Goals of Adjuvant Treatment^{1–4}

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.

USA Adjuvant Treatment Options in 2018^{1–5}

IFN- α

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

Dabrafenib + trametinib

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

IPI (10 mg/kg)

*In USA: FDA approved for
patients with LN metastases
>1 mm*

Observation

NIVO (240 mg Q2W / 480 mg Q4W)

*In USA: FDA approved for
patients with LN
involvement / metastases*

Clinical trial

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.

ITALY

Adjuvant Treatment Options in 2018^{1–5}

IFN- α

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

Dabrafenib + trametinib

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

IPI (10 mg/kg)

*In USA: FDA approved for
patients with LN metastases
>1 mm*

Observation

NIVO (240 mg Q2W / 480 mg Q4W)

*In USA: FDA approved for
patients with LN
involvement / metastases*

Clinical trial

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.

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 trials²

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

PEG-IFN (phase 3 trials)

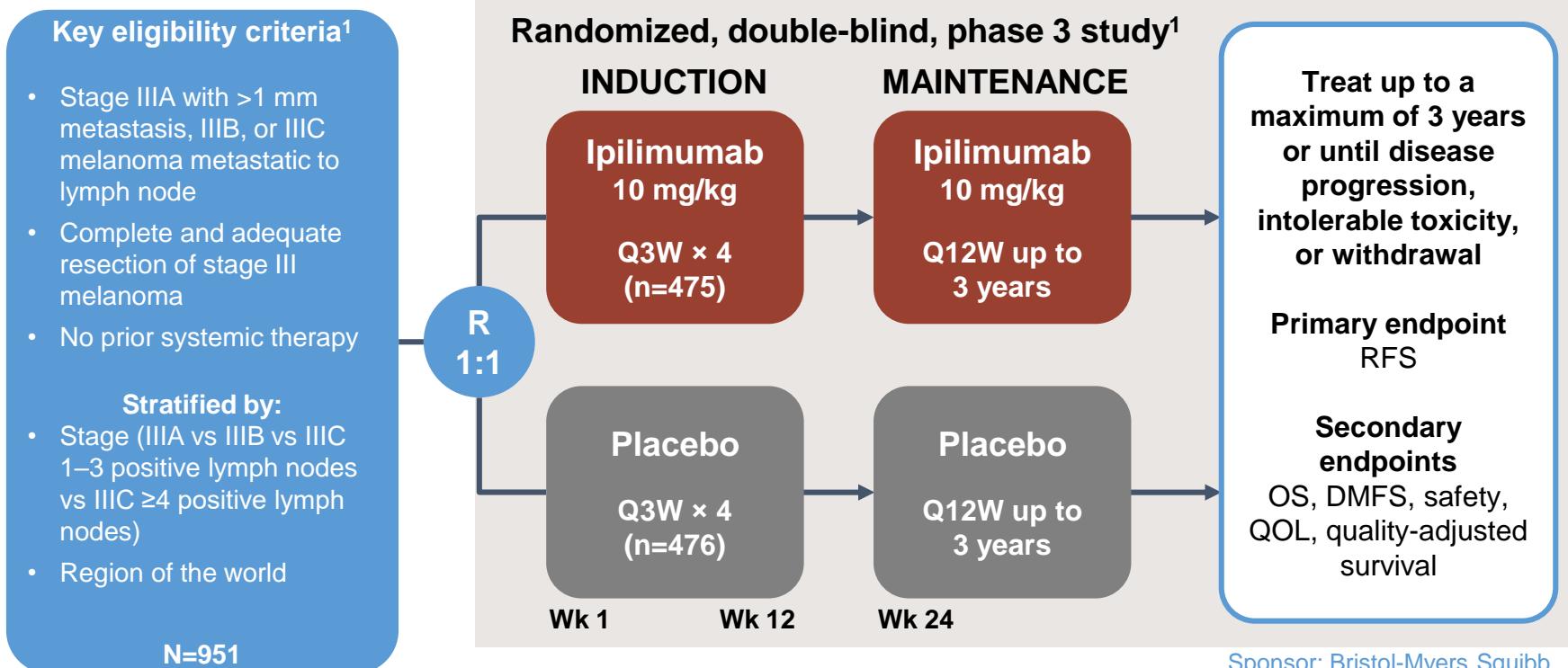
- EORTC 18991³ (stage III vs observation)
 - **OS: not significant in overall population**
 - Benefit only in ulcerated melanoma (being tested in EORTC 18081⁴)
- DeCOG⁵ (stage IIA-IIIB vs low-dose IFN)
 - No DMFS or OS improvement
 - More treatment-related discontinuations with PEG-IFN
- EADO study⁶ (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

^aLargest 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.

EORTC 18071: Adjuvant Ipilimumab vs Placebo

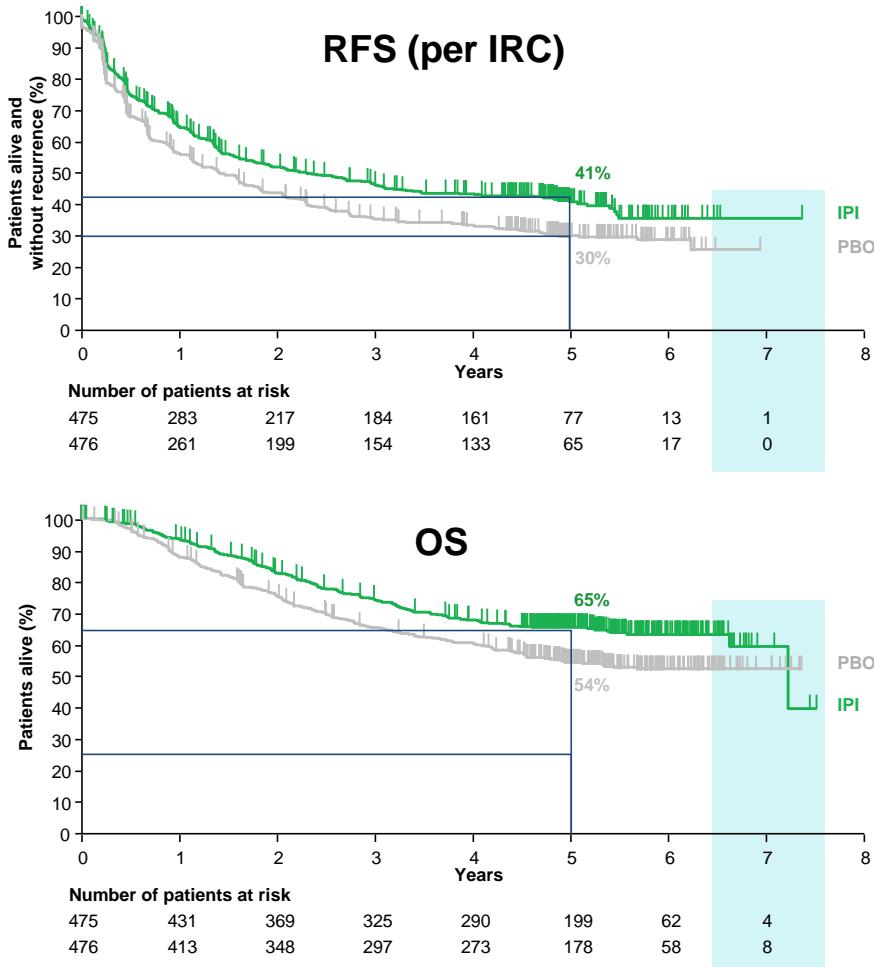


1. Eggermont AMM et al. *Lancet Oncol* 2015;16:522–530; 2. ClinicalTrials.gov. NCT00636168. Available at: <https://www.clinicaltrials.gov/ct2/show/NCT00636168>. Accessed July 17, 2017.

DMFS, distant metastases-free survival; EORTC, European Organisation for Research and Treatment of Cancer; R, randomization; RFS, recurrence-free survival.

EORTC 18071/CA184-029

Survival



	IPI	PBO
Events/patients	264/475	323/476
HR (95% CI)	0.76 (0.64–0.89)	
Log-rank <i>P</i> value		<i>P</i> < 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 <i>P</i> value		0.001

IRC, institutional review committee

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

EORTC 18071 (Ipilimumab):Toxicity

Event	Ipilimumab (N=471)				Placebo (N=474)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Any immune-related adverse event	426 (90.4)	169 (35.9)	27 (5.7)	5 (1.1)	188 (39.7)	12 (2.5)	1 (0.2)	0
Any dermatologic event	298 (63.3)	20 (4.2)	0	0	99 (20.9)	0	0	0
• Rash	161 (34.2)	5 (1.1)	0	0	52 (11.0)	0	0	0
Any gastrointestinal event	217 (46.1)	70 (14.9)	6 (1.3)	3 (0.6)	85 (17.9)	3 (0.6)	1 (0.2)	0
• Diarrhea	194 (41.2)	46 (9.8)	0	0	80 (16.9)	2 (0.4)	0	0
• Colitis	73 (15.5)	32 (6.8)	4 (0.8)	3 (0.6)	7 (1.5)	1 (0.2)	1 (0.2)	0
Any endocrine system event	178 (37.8)	34 (7.2)	3 (0.6)	0	38 (8.0)	1 (0.2)	0	0
• Hypophysitis	77 (16.3)	20 (4.2)	1 (0.2)	0	1 (0.2)	0	0	0
Any hepatic event	115 (24.4)	38 (8.1)	13 (2.8)	0	20 (4.2)	1 (0.2)	0	0
• increase in liver-enzyme levels	83 (17.6)	14 (3.0)	6 (1.3)	0	18 (3.8)	0	0	0
Any neurologic event	21 (4.5)	5 (1.1)	4 (0.8)	0	9 (1.9)	0	0	0
Other	111 (23.6)	34 (7.2)	2 (0.4)	2 (0.4)	23 (4.9)	8 (1.7)	0	0

Eggermont AMM et al. *N Engl J Med* 2016;375:1845–1855.

EORTC, European Organisation for Research and Treatment of Cancer.

Despite a High Risk of Recurrence, the Rate of Adjuvant Treatment Can Be Low

- Recurrence and treatment rates prior to the approval of nivolumab and dabrafenib + trametinib

Recurrence rate^a in stage III¹

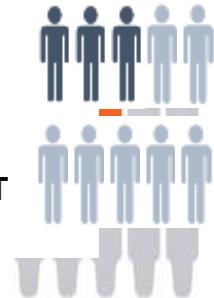
Stage III
melanoma

60%

48% (stage IIIA)
71% (stage IIIB)
85% (stage IIIC)

Treatment rate in stage III^{2,3}

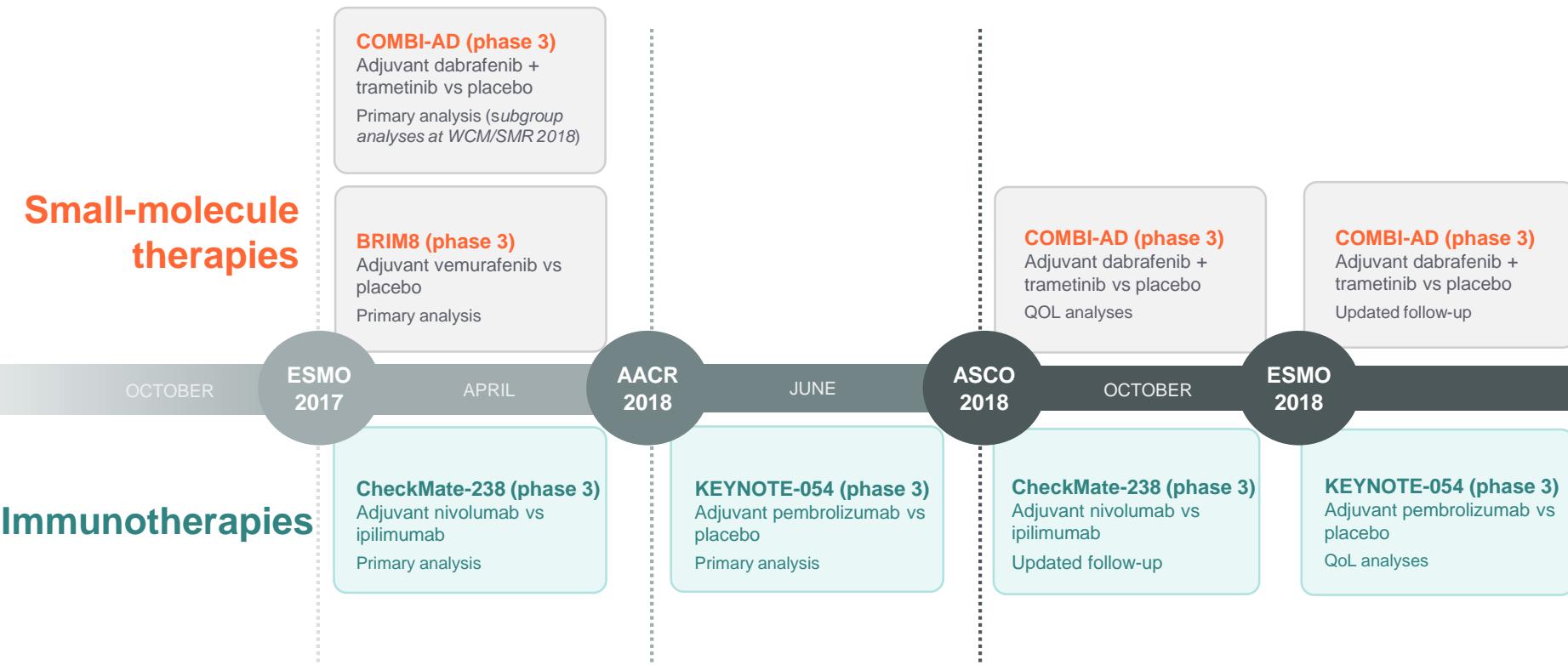
APPROXIMATELY
3 out of **10**
RECEIVE ADJUVANT
THERAPY



^aRetrospective review of clinical records at Memorial Sloan Kettering Cancer Center between 1992 and 2004¹

1. Romano E, et al. *J Clin Oncol* 2010;28:3042–3047. 2. Harlan LC, et al. *Melanoma Res* 2011;21:547–554. 3. Mohr P (discussant). Presented at ASCO 2017.

Key Advances in the Adjuvant Setting



ASCO, American Society of Clinical Oncology; EORTC, European Organisation for Research and Treatment of Cancer; SMR, Society for Melanoma Research; QOL, quality of life; WCM, World Congress of Melanoma.

UPDATED RELAPSE-FREE SURVIVAL AND BIOMARKER ANALYSIS IN THE COMBI-AD TRIAL OF ADJUVANT DABRAFENIB + TRAMETINIB IN PATIENTS WITH RESECTED *BRAF* V600–MUTANT STAGE III MELANOMA

Georgina V. Long, Axel Hauschild, Mario Santinami, Victoria Atkinson, Mario Mandalà, Vanna Chiarion-Sileni, James Larkin, Caroline Robert, Dirk Schadendorf, Kohinoor Dasgupta, Mark Shilkrut, James Garrett, Jan C. Brase, Richard Kefford, John M. Kirkwood, Reinhard Dummer

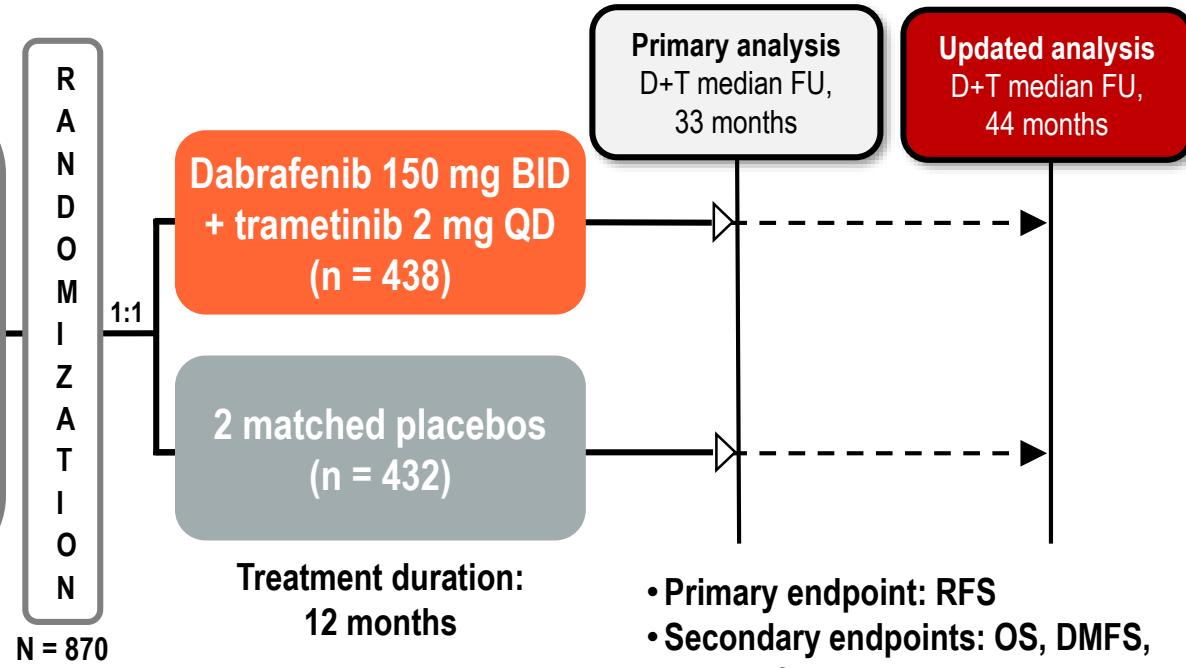
COMBI-AD: STUDY DESIGN—EXTENDED FOLLOW-UP ANALYSIS

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)

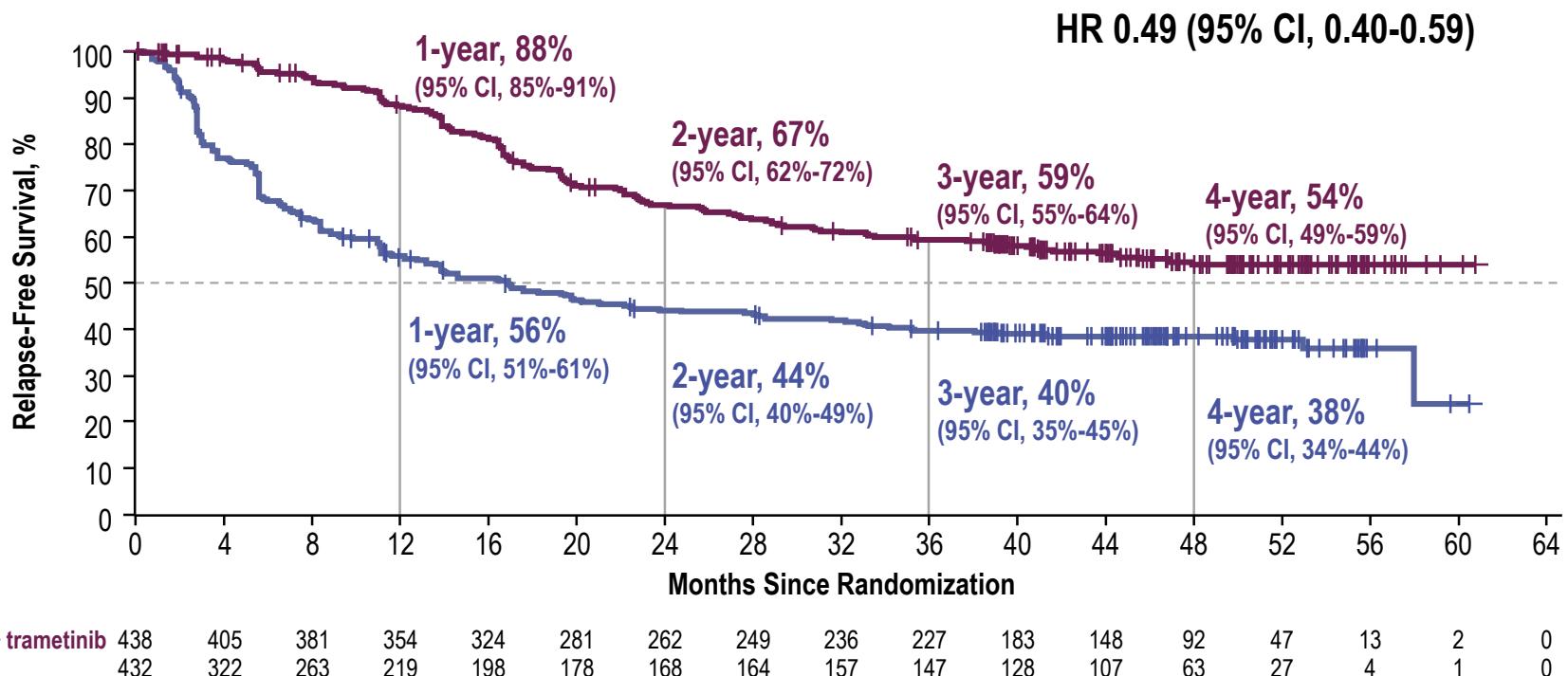


- Primary endpoint: RFS
- Secondary endpoints: OS, DMFS, FFR, safety

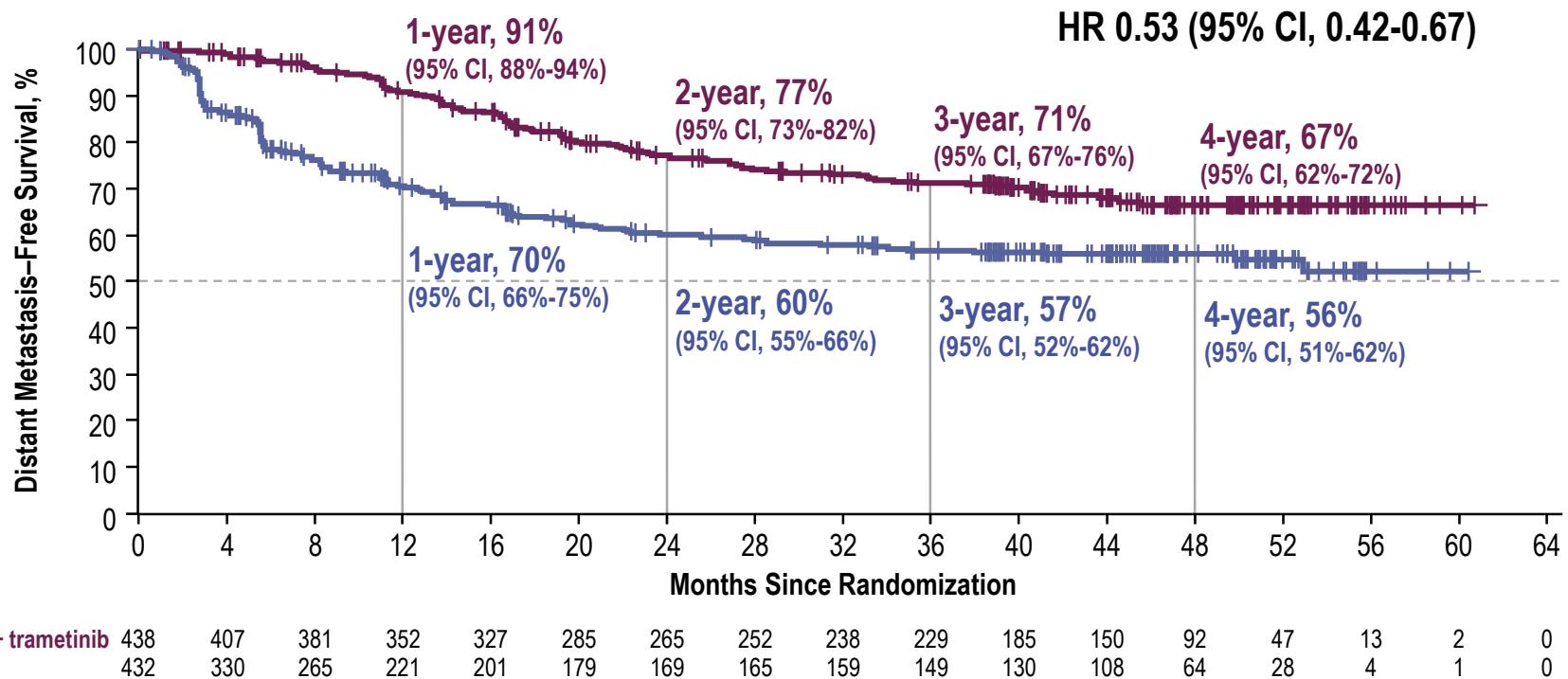
BID, twice daily; DMFS, distant metastasis-free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

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

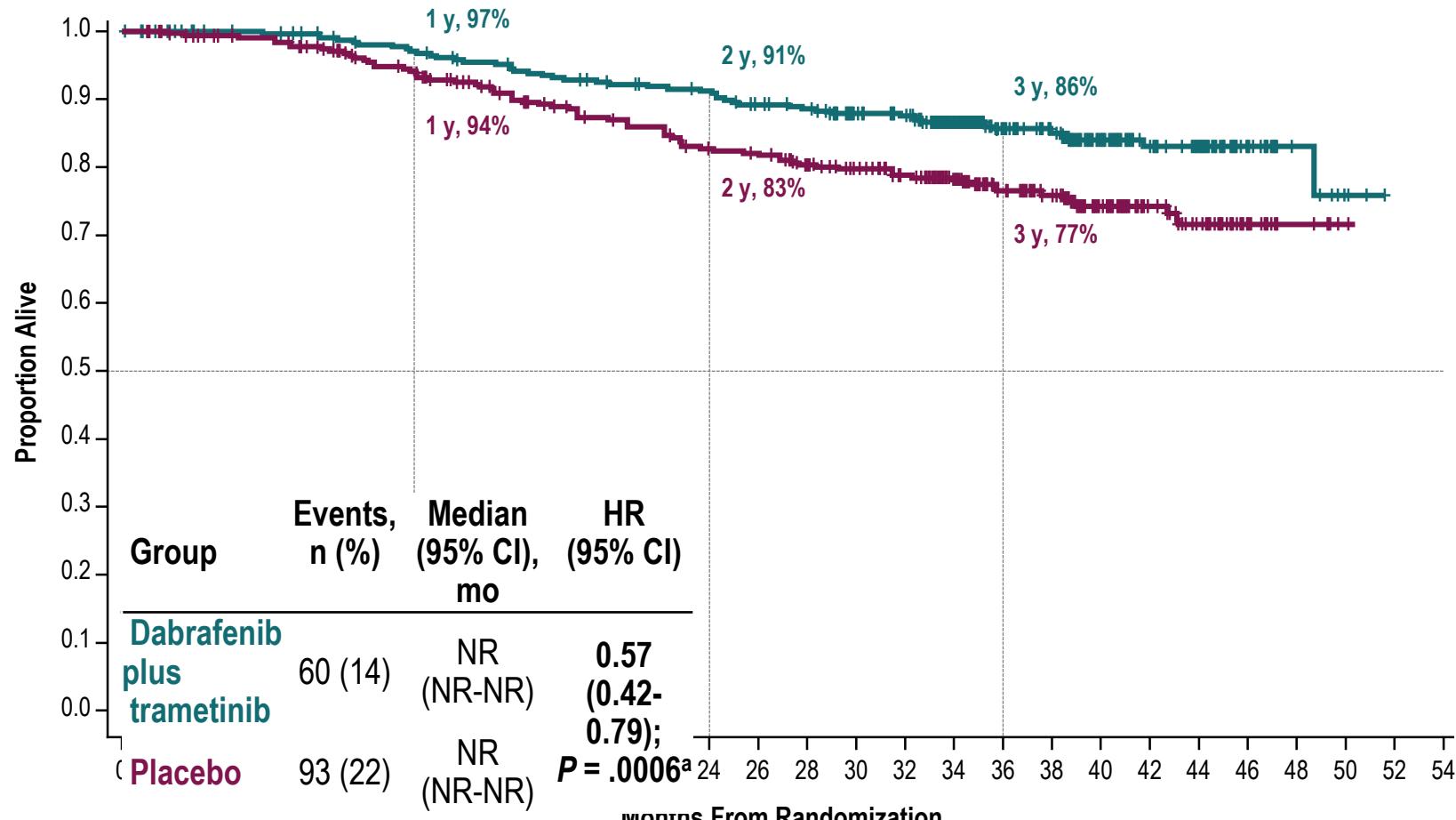
RELAPSE-FREE SURVIVAL



DISTANT METASTASIS-FREE SURVIVAL



OVERALL SURVIVAL (FIRST INTERIM ANALYSIS)



^a Prespecified significance boundary ($P = .000019$).

RESULTS

- The most common AE reported in patients who received dabrafenib plus trametinib was pyrexia (63%; **Table 1**)
 - Of patients with pyrexia, 28% had one occurrence, 20% had 2 occurrences, and 52% had 3 or more occurrences

Table 1. Common AEs ($\geq 15\%$ of patients)⁶

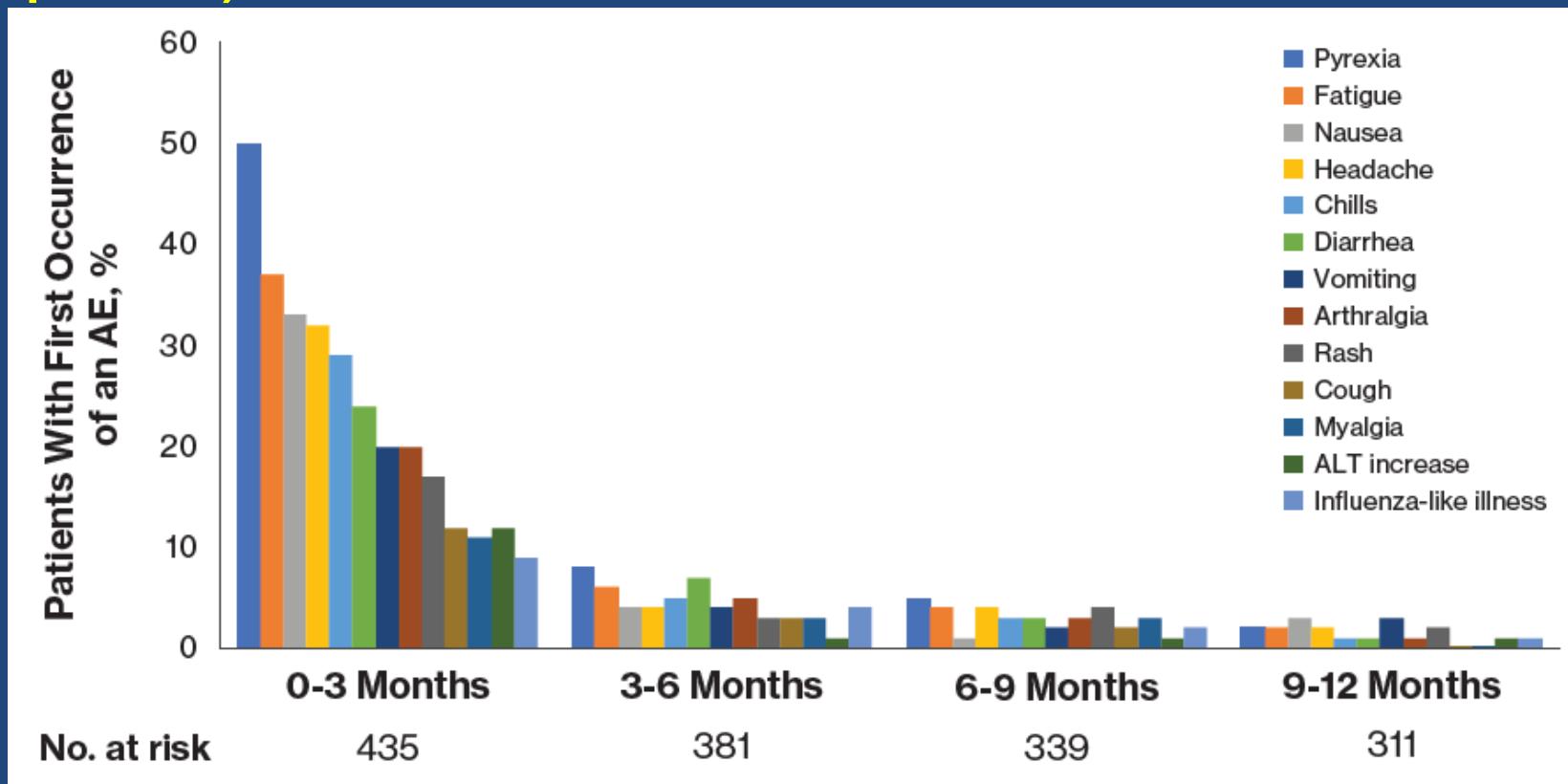
AEs, n (%)	Dabrafenib + Trametinib n = 435		Placebo n = 432	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE ^a	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (< 1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (< 1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	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

^a All cause.

RESULTS (cont)

- The peak onset of all AEs occurring in $\geq 15\%$ of patients in the dabrafenib plus trametinib arm occurred within the first 3 months of treatment (**Figure 2** and **Table 3**)

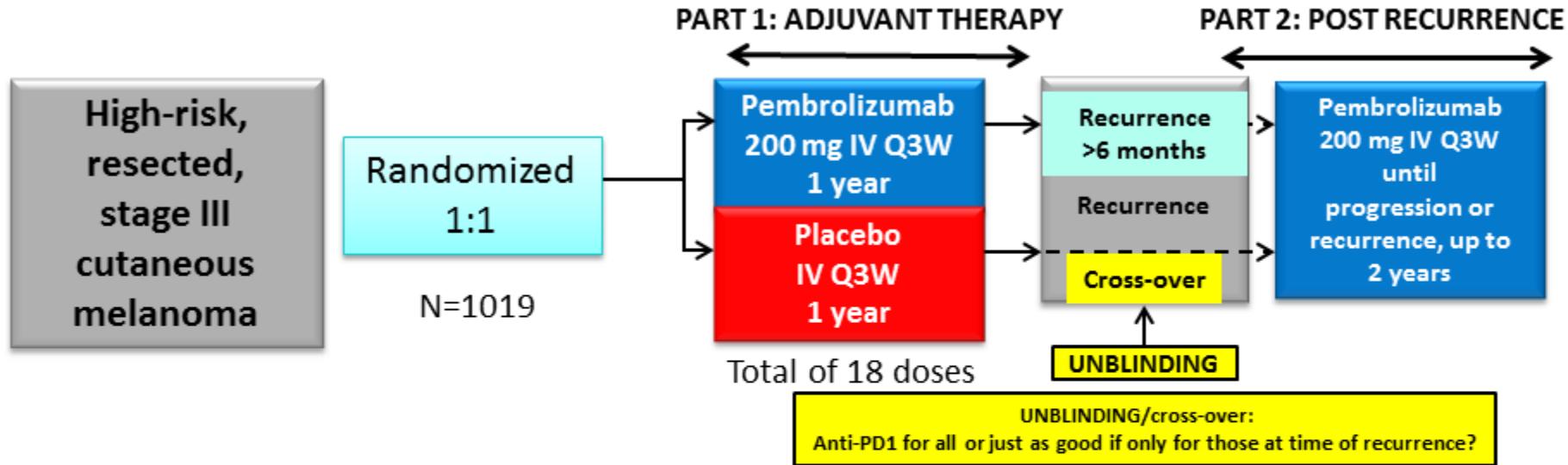
Figure 2. First Occurrence (exposure-adjusted) of AEs ($\geq 15\%$ of patients) in Patients Who Received Dabrafenib Plus Trametinib



AE, adverse event

EORTC 1325/KEYNOTE-54: Study Design

High-risk,
resected,
stage III
cutaneous
melanoma



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:

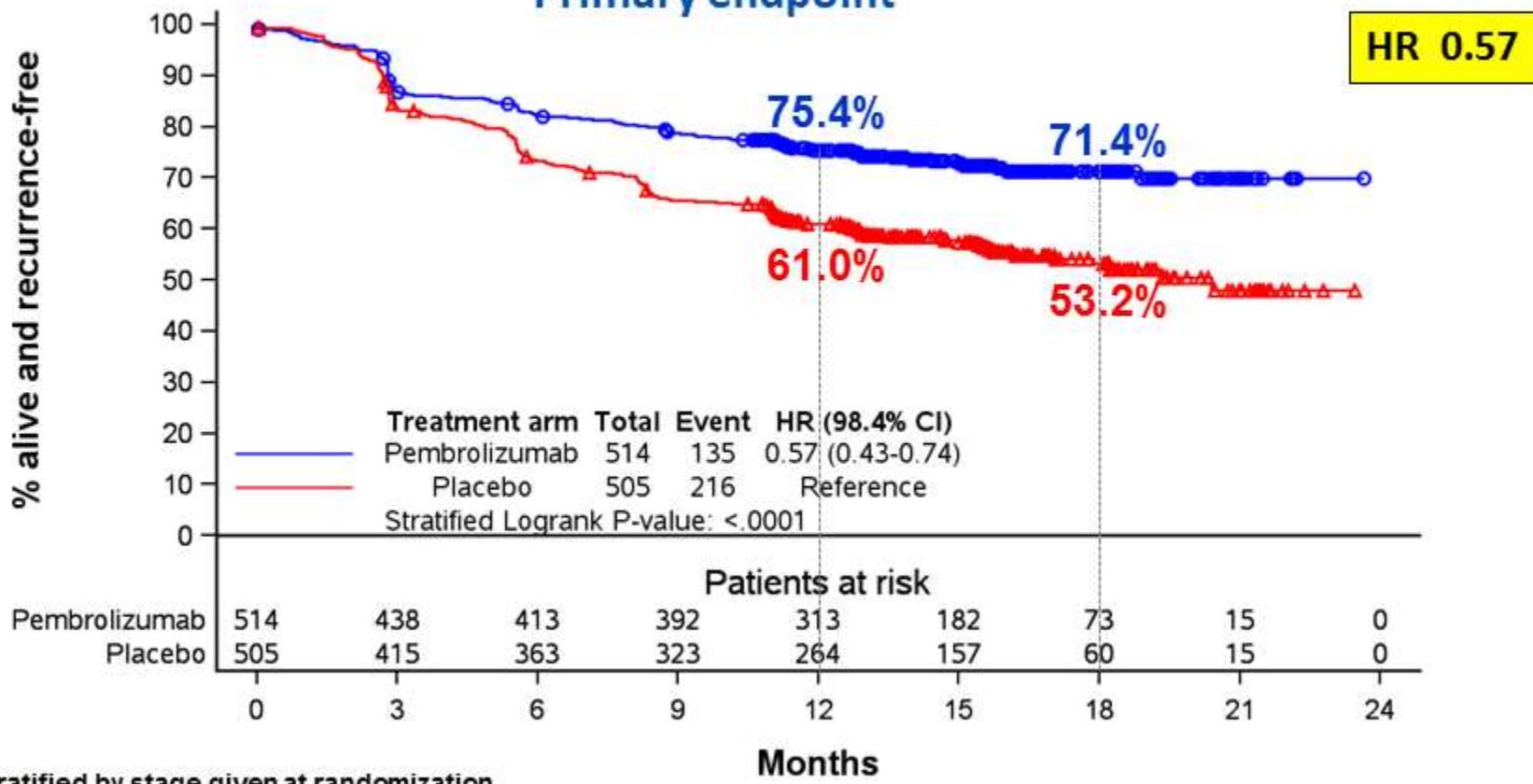
- RFS (per investigator) in overall population, and RFS in patients with PD-L1-positive tumors

Secondary Endpoints:

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

Recurrence-Free Survival in the ITT Population

Primary endpoint

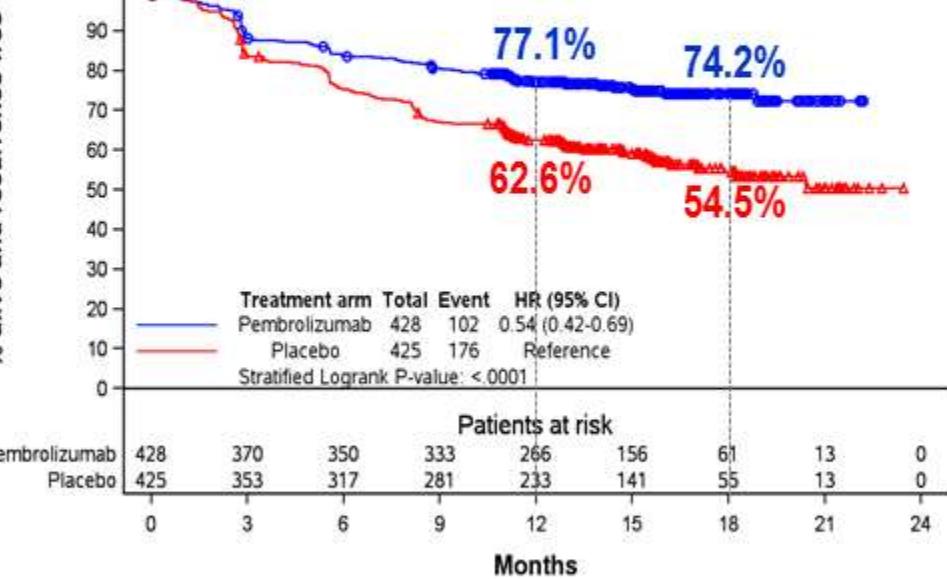


*Stratified by stage given at randomization

Recurrence-Free Survival

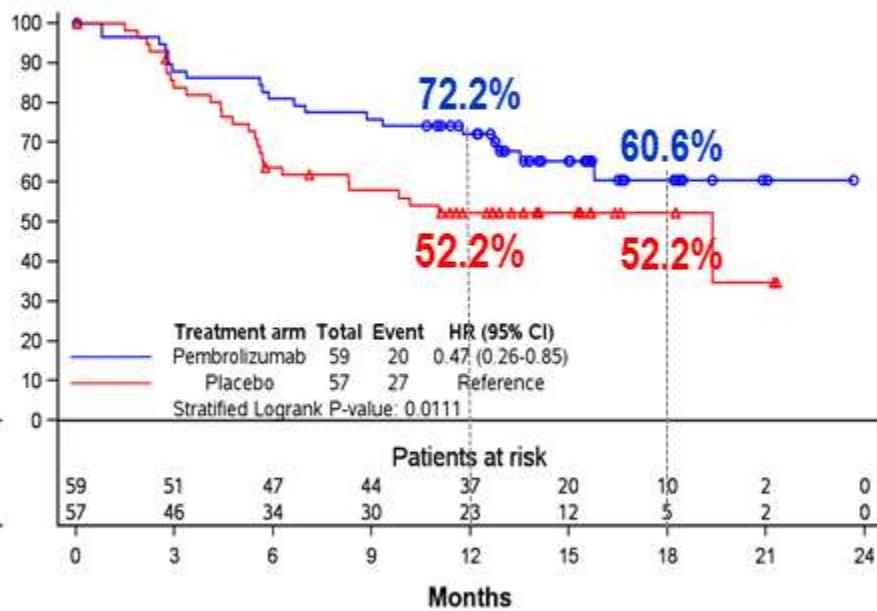
PD-L1+

HR 0.54



PD-L1-

HR 0.47

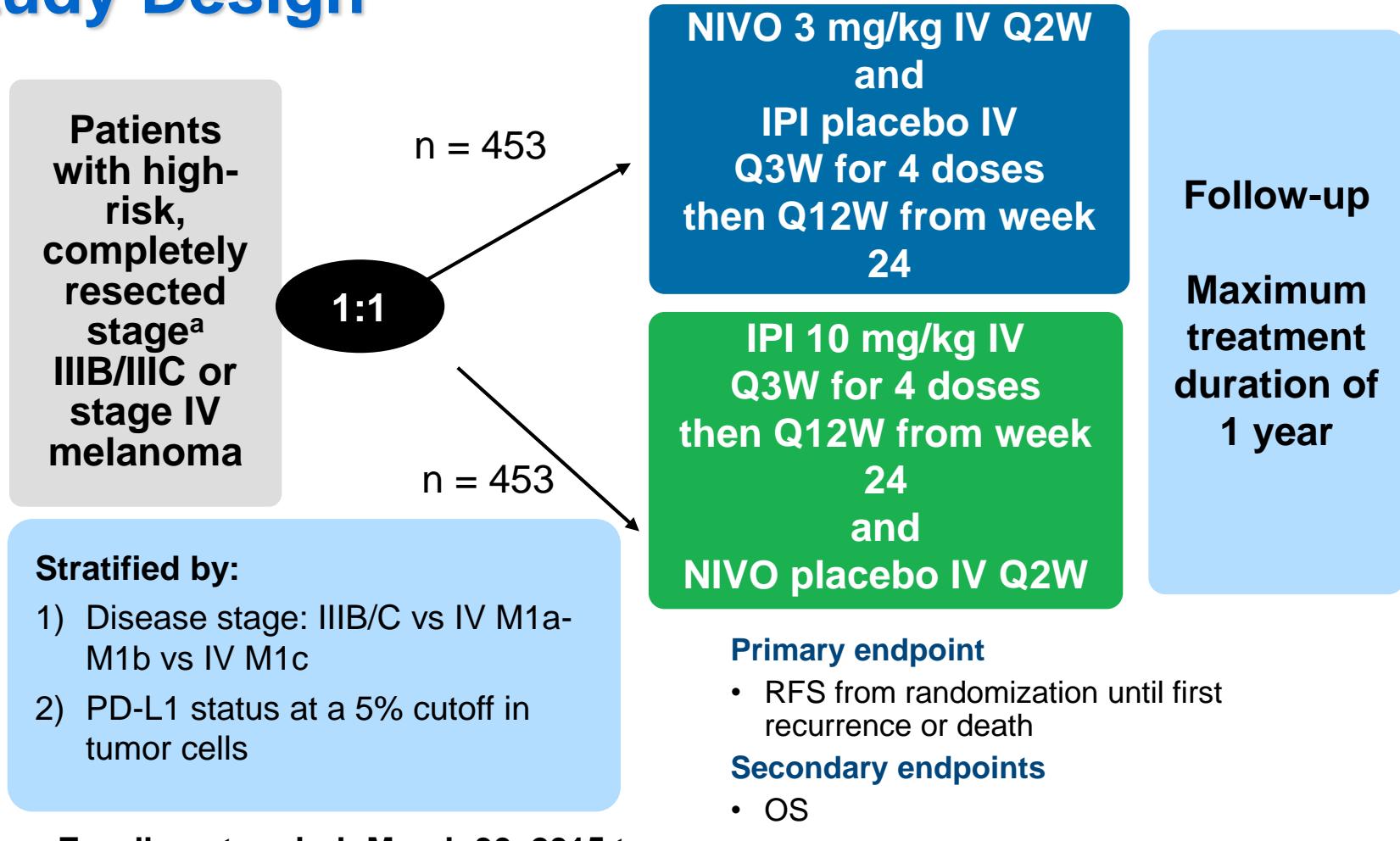


*Stratified by stage given at randomization

Immune-Related Adverse Events

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any irAE	37.3	7.1	9.0	0.6
Endocrine disorders	23.4	1.8	5.0	0
Hypothyroidism	14.3	0	2.8	0
Hyperthyroidism	10.2	0.2	1.2	0
Thyroiditis	3.1	0	0.2	0
Hypophysitis/hypopituitarism	2.2	0.6	0.2	0
Type I diabetes mellitus	1.0	1.0	0	0
Adrenal insufficiency	1.0	0.2	0.8	0

CheckMate 238/CA209-238 Study Design



^aAmerican 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 from randomization until first recurrence or death

Secondary endpoints

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

Exploratory endpoint

- DMFS

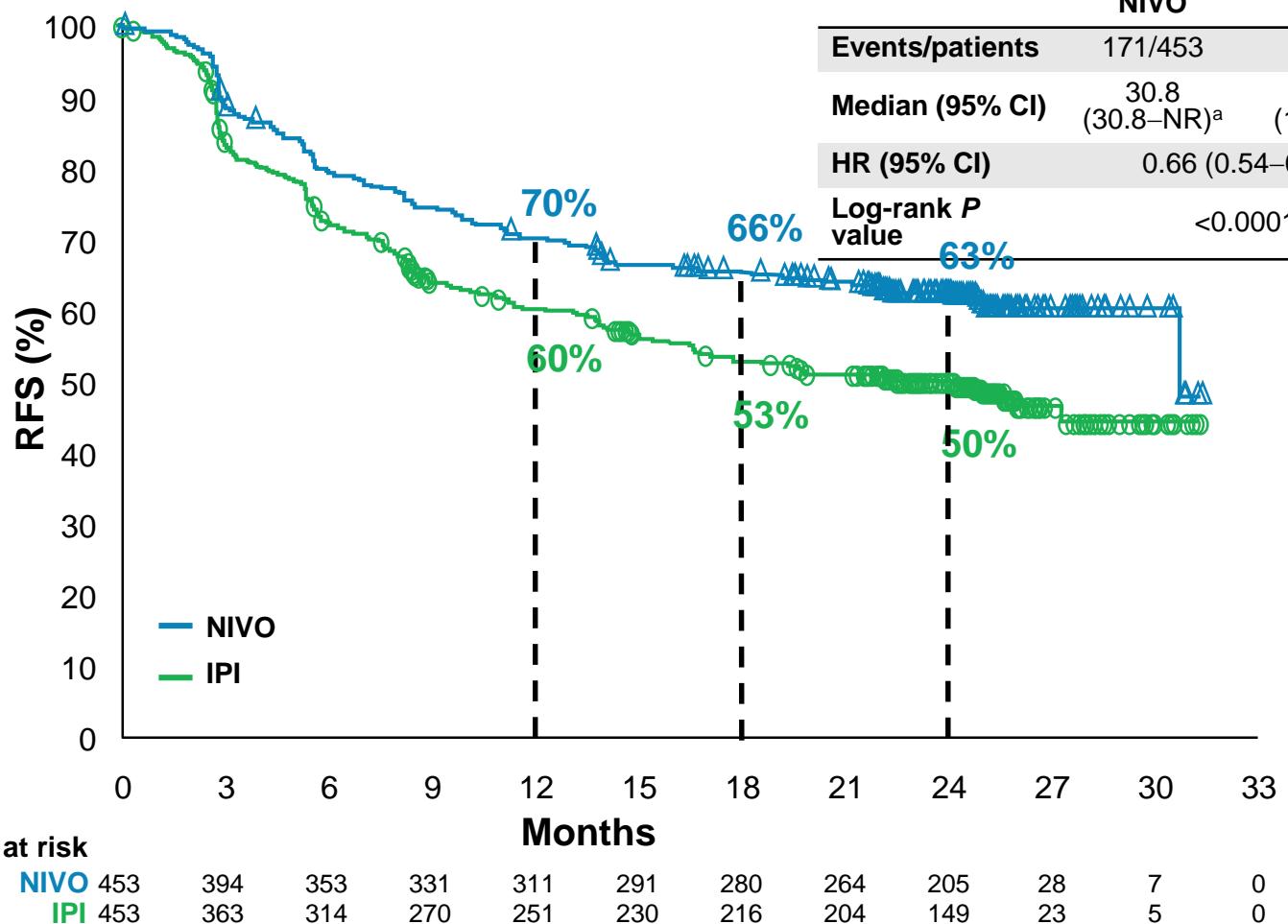
Baseline Patient Characteristics and Treatment Summary

	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 ≥5%, %	34	34
BRAF mutation, %	41	43
LDH ≤ ULN, %	91	91
Melanoma subtype, %		
Cutaneous	86	83
Mucosal	4	3
Acral	4	4

- All patients were off treatment as of the 18-month analysis, with median doses of 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

LDH, lactate dehydrogenase; ULN, upper limit of normal. Weber J, et al. ASCO 2018; abstract 9502.

Primary Endpoint RFS in All Patients

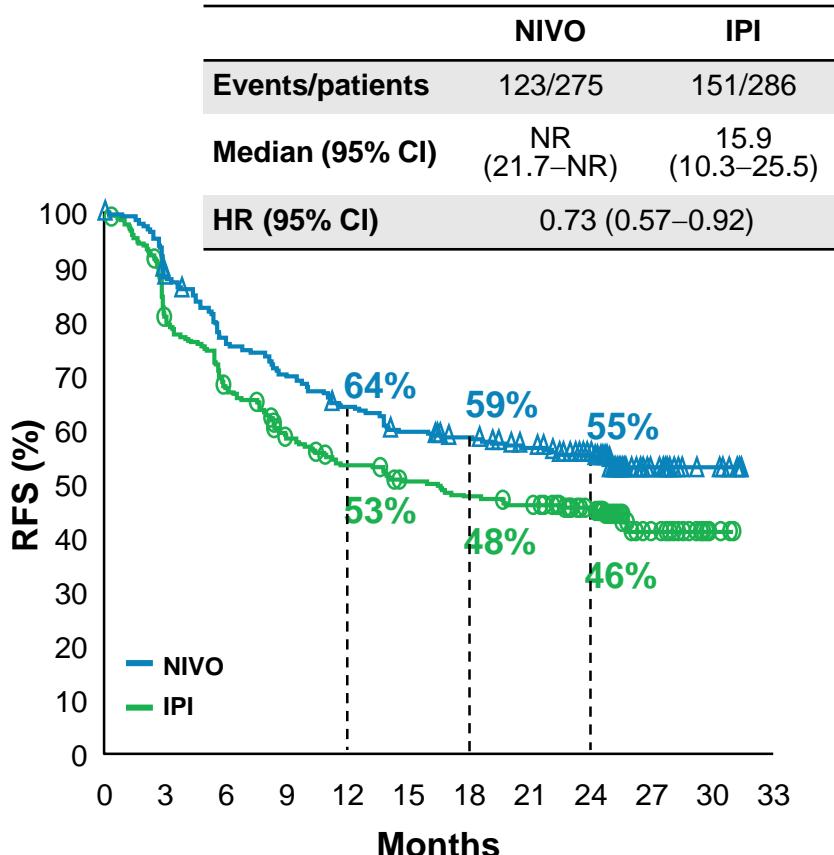


^aMedian estimate not stable due to few patients at risk

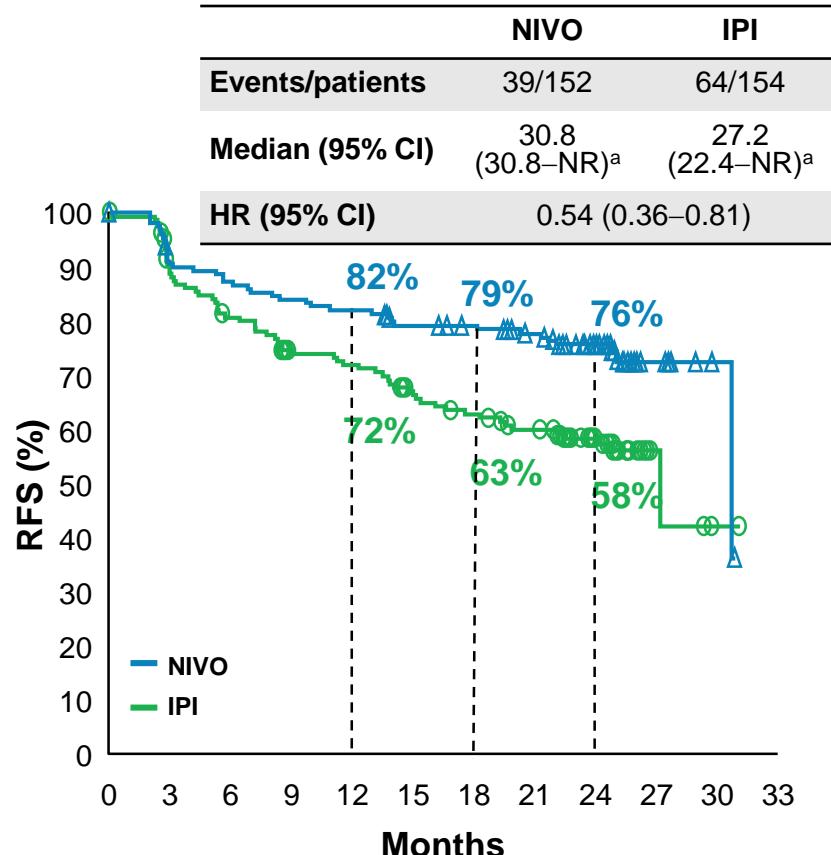
Weber J, et al. ASCO 2018; abstract 9502.

Subgroup Analysis of RFS 5% PD-L1 Expression Level

PD-L1 <5%



PD-L1 ≥5%



Number of patients at risk

NIVO	275	238	204	188	171	158	151	141	108	17	5	0
IPI	286	218	184	154	139	128	121	116	83	17	3	0

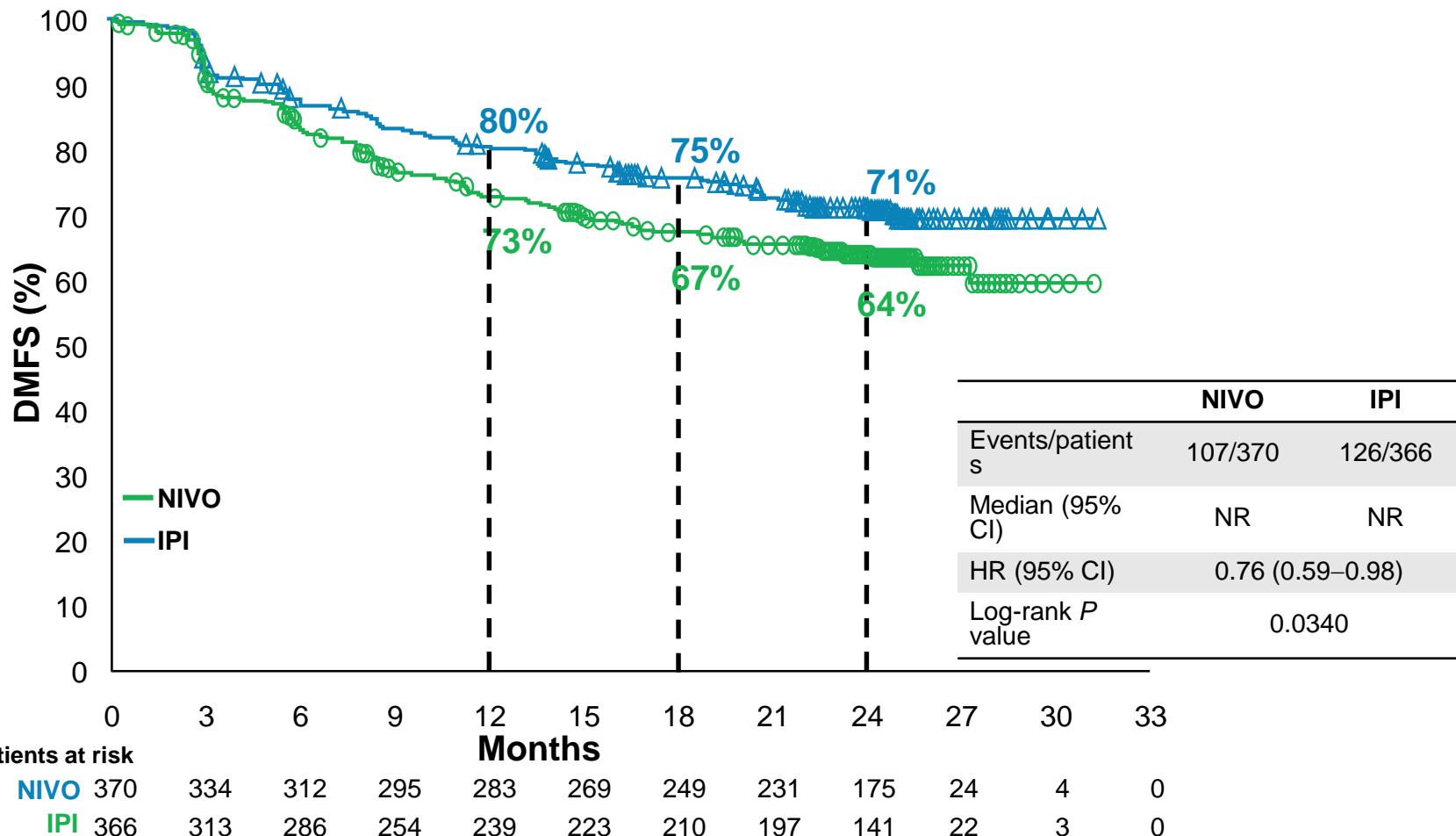
Number of patients at risk

NIVO	152	135	130	125	122	115	112	106	87	10	2	0
IPI	154	133	120	108	104	94	88	81	61	4	1	0

^aMedian estimate not stable due to few patients at risk. NR, not reached

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

Exploratory Endpoint DMFS for Stage III Patients



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)

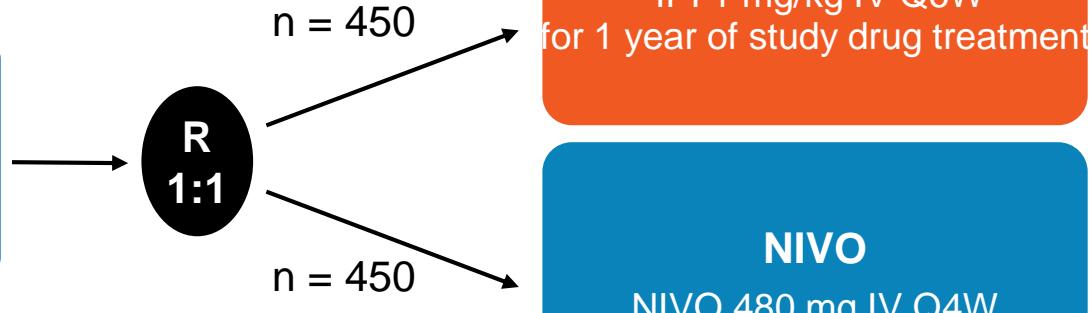
Per protocol, safety analysis was not reported beyond the 18-month median follow-up, given that all patients had been off study treatment >100 days at the time of the 18-month analysis

Backup: Ongoing Trials

CheckMate 915 Study Design (Phase 3)^{1,2}

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

**Completely
resected, stage
IIIB/C/D or stage IV
NED melanoma**



Primary endpoint

- RFS

Secondary endpoints

- OS, association between PD-L1 and RFS

Estimated enrollment: 900 patients

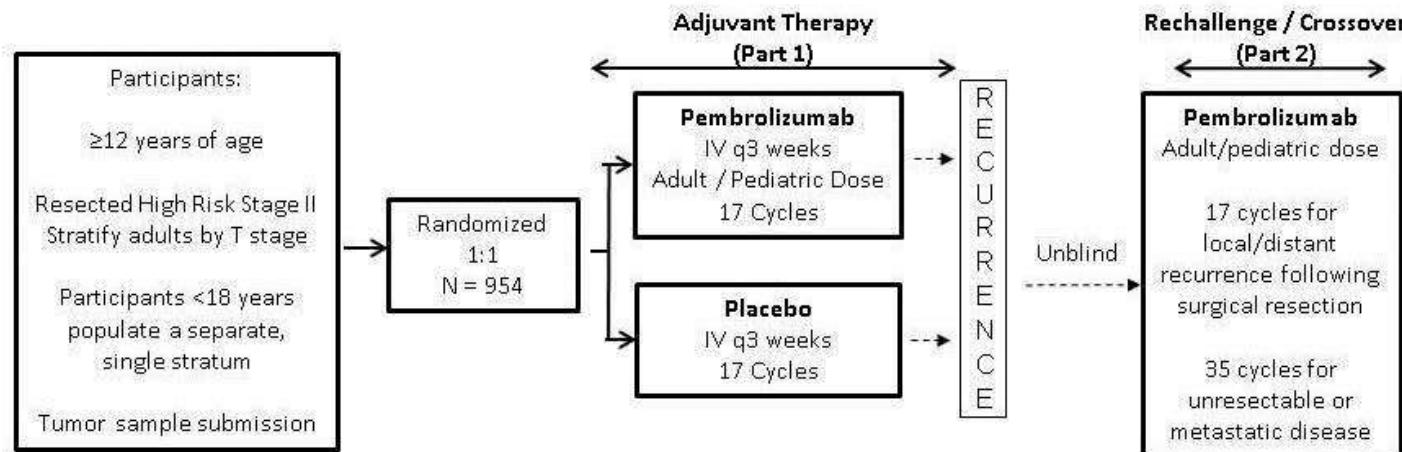
Study start date: April 2017

Estimated primary completion date:
December 2020

**Follow-
up**

Adjuvant Therapy with Pembrolizumab versus Placebo in Resected Highrisk

Stage II Melanoma: A Randomized, Double-blind Phase 3 Study (KEYNOTE 716)



Compassionate use trials



Costi & Sostenibilità

dabrafenib 75mg 120 cp + trametinib 2mg 30 cp	mese	€ 6.949,25	anno	€ 83.391,00
dabrafenib 50mg 120 cp + trametinib 0,5mg 60 cp	mese	€ 4.208,55	anno	€ 50.502,60
pembrolizumab 200mg	3 settimane	€ 5.656,20	anno (17 cicli)	€ 96.155,40
nivolumab 480mg	mese	€ 5.322,90	anno	€ 63.874,80

prezzi praticati alla Fondazione secondo gara regionale compresa iva 10%

al netto di accordi MEA



THANK YOU