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Advances in Melanoma Adjuvant Therapy: Implications for Clinical Practice and Future Research

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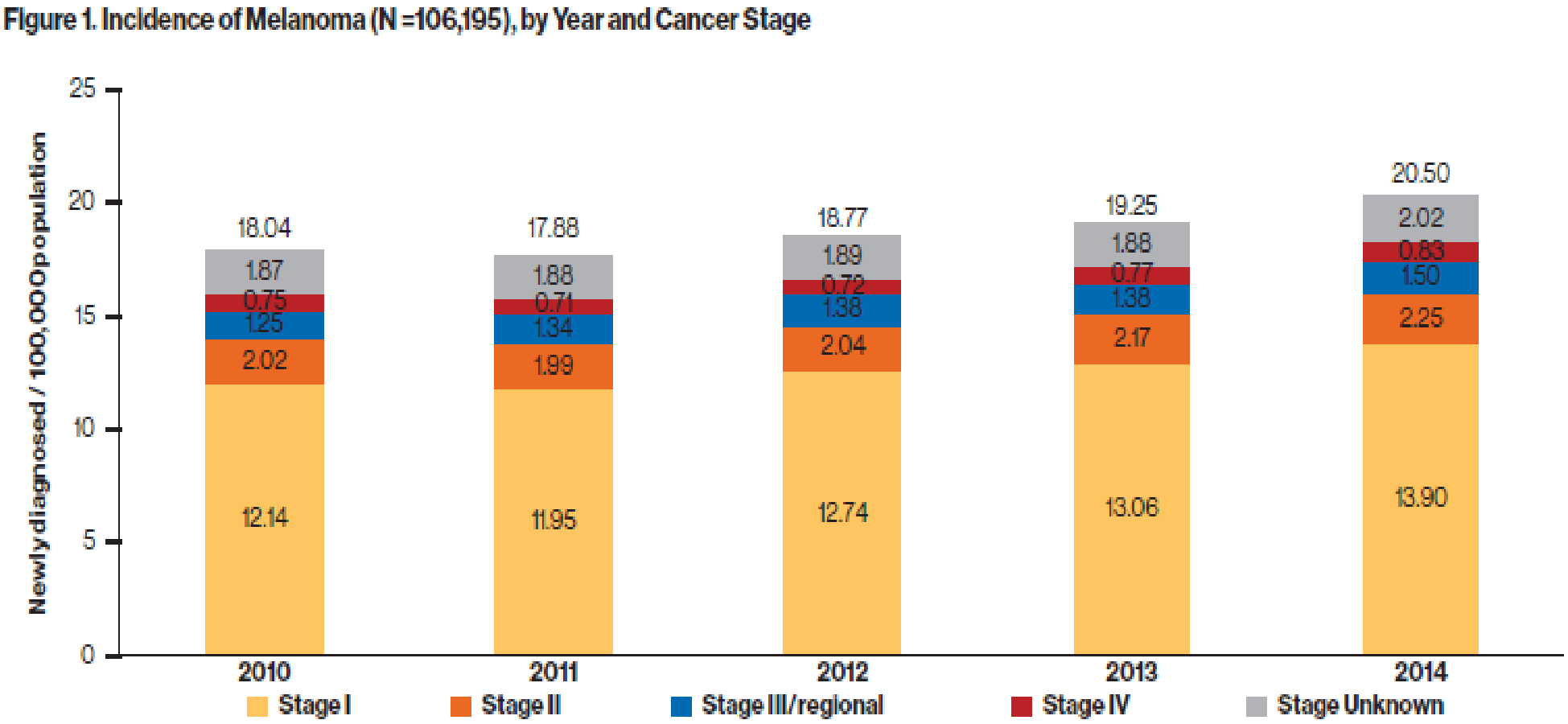
Disclosures

- Consultant Role: Novartis, Sanofi-Genzyme/Regeneron, BioNTech, Array Biopharma
- Contracted Research: OncoSec, Clinigen, BMS, Merck, Novartis, Genentech

Rising Incidence of Melanoma in the U.S.



Tarhini at al. Melanoma Research 2018

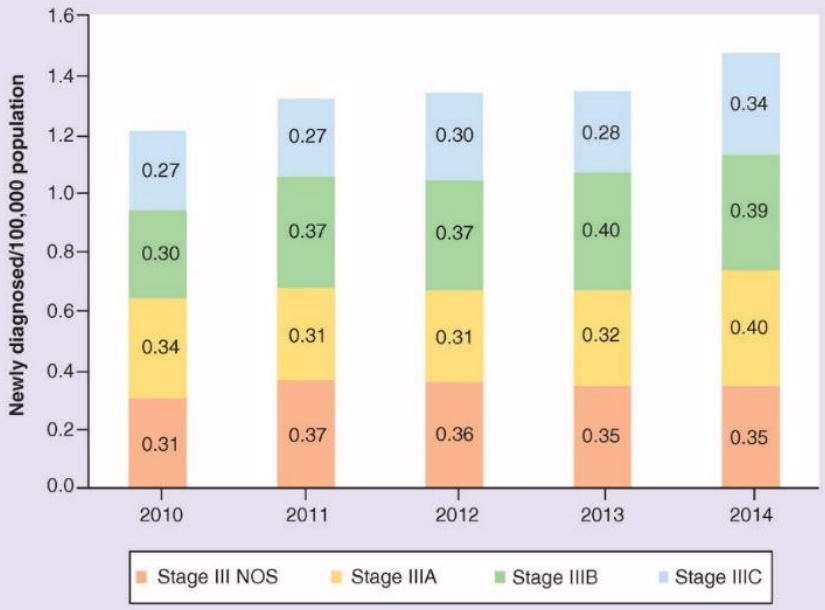
Incidence of Stage III melanoma 2010-2014 stratified by AJCC7 (A) & AJCC8 (B) groups & year of diagnosis

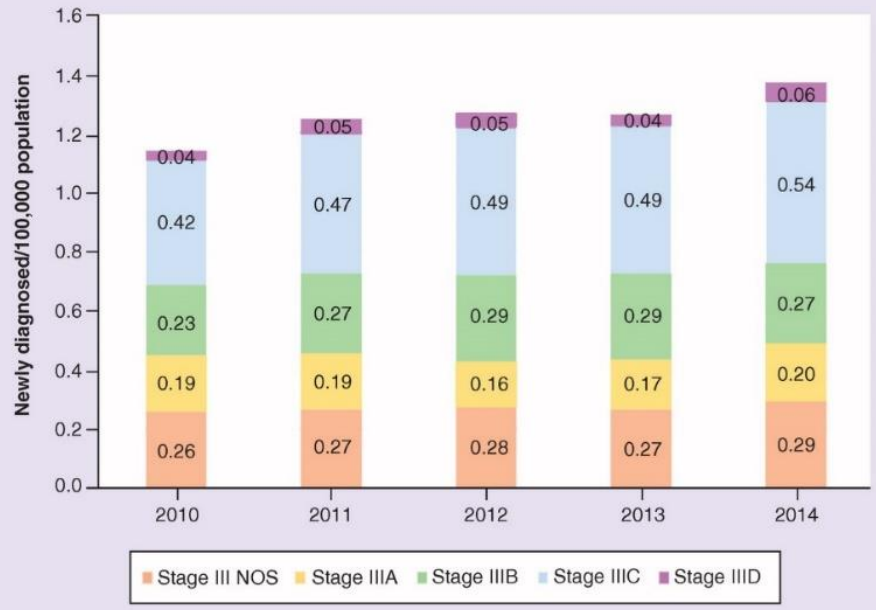
Ⓐ

	Incidence [95% CI]			
Year	III NOS	IIIA	IIIB	IIIC
2010	0.31 [0.28; 0.34]	0.34 [0.30; 0.37]	0.30 [0.27; 0.33]	0.27 [0.24; 0.30]
2011	0.37 [0.34; 0.41]	0.31 [0.28; 0.35]	0.37 [0.34; 0.41]	0.27 [0.24; 0.30]
2012	0.36 [0.33; 0.40]	0.31 [0.28; 0.35]	0.37 [0.34; 0.41]	0.30 [0.27; 0.33]
2013	0.35 [0.32; 0.39]	0.32 [0.29; 0.36]	0.40 [0.36; 0.44]	0.28 [0.25; 0.31]
2014	0.35 [0.32; 0.38]	0.40 [0.36; 0.43]	0.39 [0.36; 0.43]	0.34 [0.31; 0.37]

Ⓑ

	Incidence [95% CI]				
Year	III NOS	IIIA	IIIB	IIIC	IIID
2010	0.26 [0.23; 0.29]	0.19 [0.16; 0.22]	0.23 [0.21; 0.26]	0.42 [0.38; 0.46]	0.04 [0.03; 0.05]
2011	0.27 [0.24; 0.30]	0.19 [0.16; 0.21]	0.27 [0.24; 0.30]	0.47 [0.43; 0.51]	0.05 [0.04; 0.07]
2012	0.28 [0.25; 0.31]	0.16 [0.13; 0.18]	0.29 [0.26; 0.32]	0.49 [0.45; 0.53]	0.05 [0.04; 0.07]
2013	0.27 [0.24; 0.30]	0.17 [0.15; 0.19]	0.29 [0.26; 0.32]	0.49 [0.45; 0.54]	0.04 [0.03; 0.05]
2014	0.29 [0.26; 0.33]	0.20 [0.17; 0.22]	0.27 [0.24; 0.30]	0.54 [0.50; 0.59]	0.06 [0.05; 0.08]





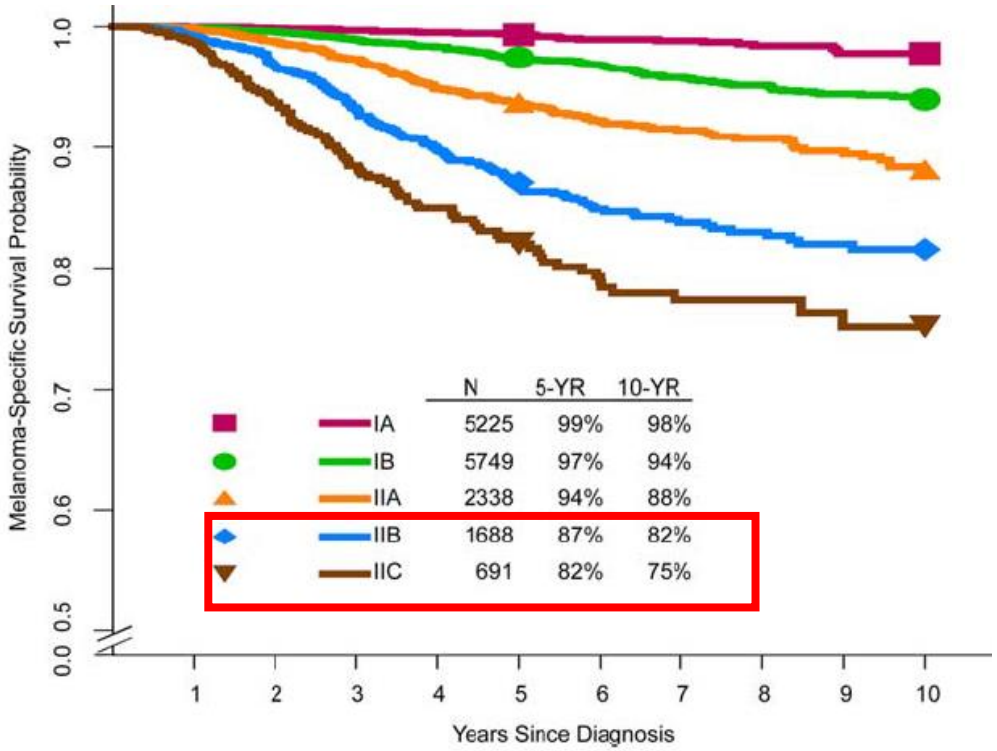
30% of pts with AJCC7 Stage III were reclassified in a higher Stage III group by AJCC8

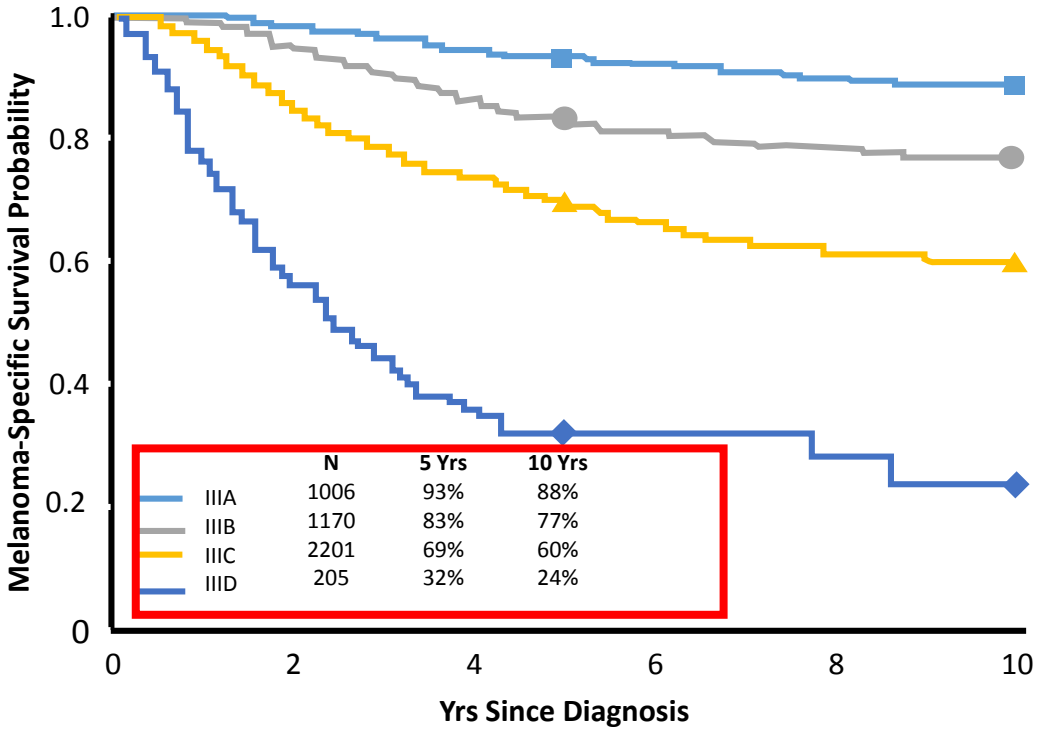
vs. 7% in lower stage group

Tarhini et al. Future Oncol. 2019
Tarhini et al. J Comp Eff Res. 2019

High-Risk Surgically Resected Melanoma

KM Melanoma-Specific Survival Curves According to Stage I, II, III Subgroups





5-year RFS for Stage III groups (AJCC7)[2]:

IIIA: 63%

IIIB: 32%

IIIC: 11%

Adjuvant therapy provides an opportunity to reduce the risk of relapse, improve survival and CURE

RFS and OS with Adjuvant HDI, PegIFN and Ipi10

Study	Stage	N	Regimen	Median Follow up (year)	RFS (HR)	OS (HR)
E1684	T4, N+	287	HD-IFN Vs. Observation	6.9 – 12.6	0.61–0.72	0.67–0.82*
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	3.8	0.82	-
				7.6	0.87	-
EORTC 18071	N1,2,3	951	Ipilimumab 10 mg/kg vs. Placebo	5.3	0.76	0.72

*NS: non-significant at the median follow-up of 12.6 years.

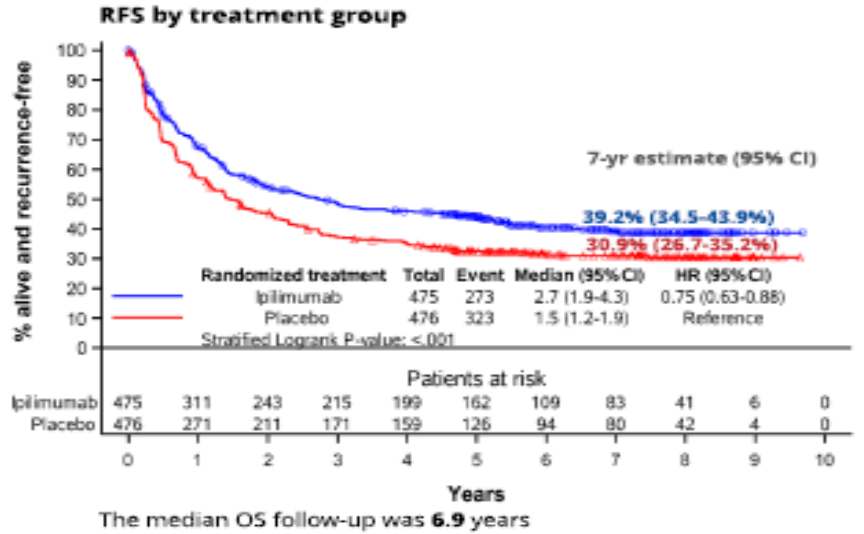
HD-IFN: IFN-α2b 20 MU/m^2/day IV for 1 month then 10 MU/m^2 SC TIW for 11 months

EORTC 18071: Ipilimumab 10 mg/kg IV every 21 days x4 then every 12 weeks for 3 years

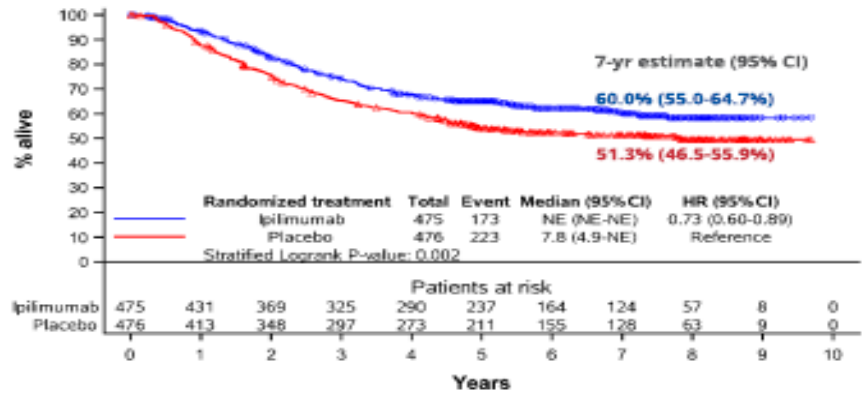
Kirkwood 1996, 1999, 2000, 2004; Eggermont 2007, 2011

EORTC 18071: Ipilimumab 10 mg/kg vs. Placebo in Stage III Long-term Follow-up Results

Median follow up:
6.9 years



The median OS follow-up was **6.9** years



Safety Summary

	Ipilimumab (n = 471)	
	Any Grade	Grade 3/4
Any AE, %	98.7	54.1
Treatment-related AE, %	94.1	45.4
Treatment-related AE leading to discontinuation, %	48.0	32.9
Any immune-related AE, %	90.4	41.6

Deaths due to drug-related AEs

- 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

Eggermont et al. ASCO 2019; Eur J Cancer. 2019

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North American Intergroup E1609 - A Phase III Study of Adjuvant Ipilimumab (3 or 10 mg/kg) versus High-Dose Interferon-α2b for Resected High-Risk Melanoma

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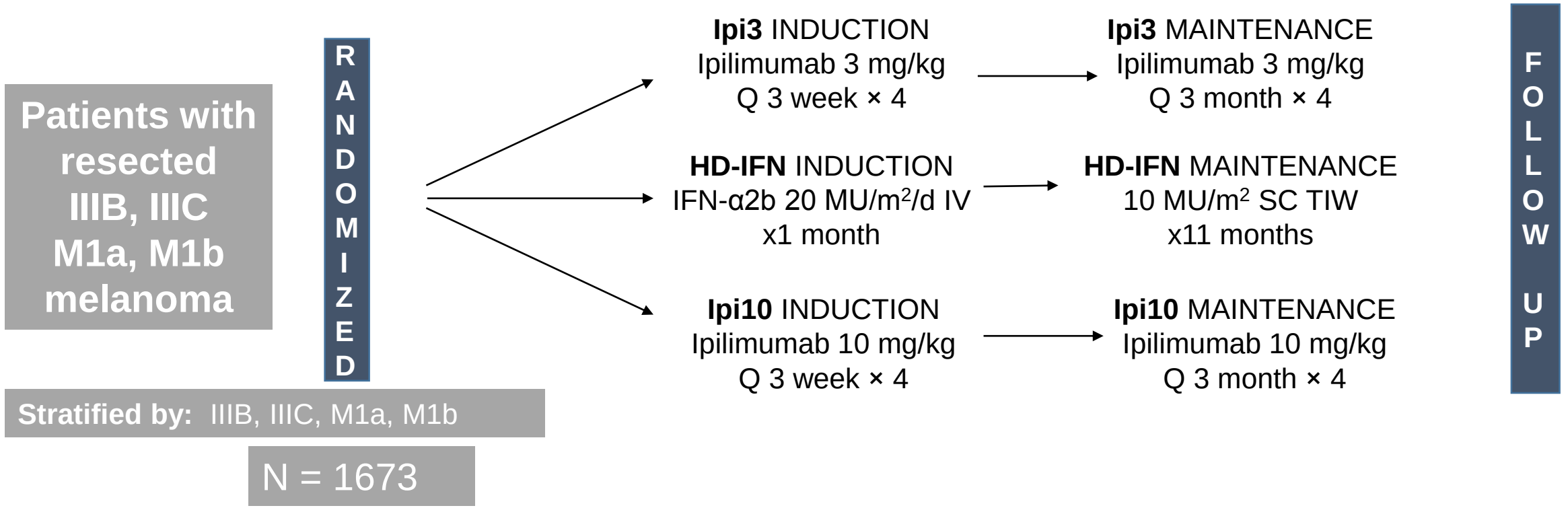
Intergroup E1609: Study Design and Accrual

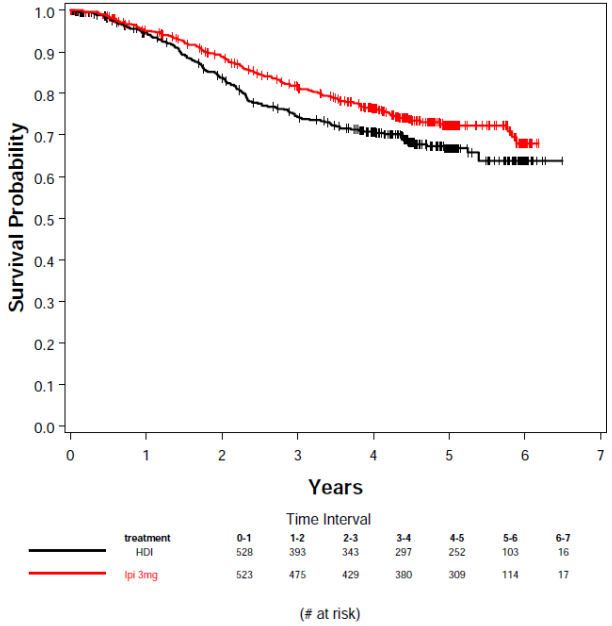


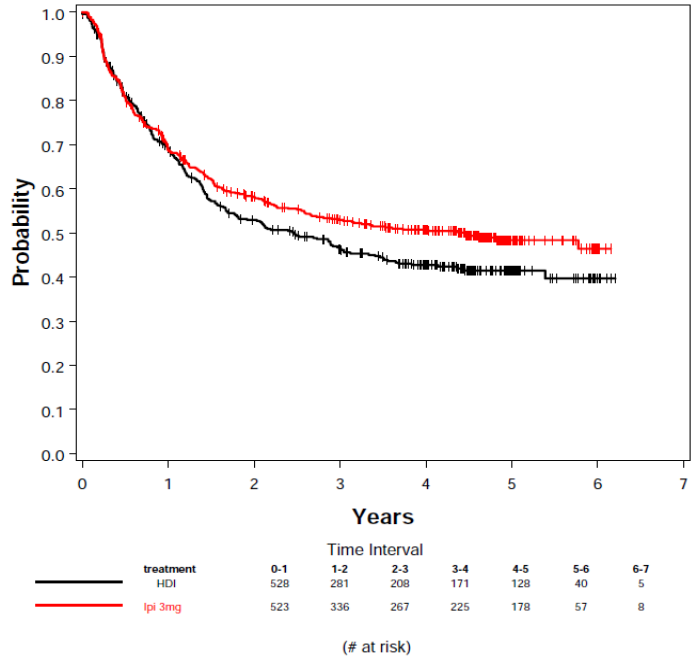
Tarhini AA, et al. ASCO 2019

First-step comparison of Ipi3 versus HDI: OS & RFS

OS	Ipi3	HDI
HR (95.6% RCI)	0.78 (0.61, 0.99)	
Log-rank P value	0.044	
5-yr OS (95% CI)	72% (68%, 76%)	67% (62%, 72%)

RFS	Ipi3	HDI
HR (99.4% CI)	0.85 (0.66, 1.09)	
Log-rank P value	0.065	
Median (95% CI)	4.5 years (2.6, -)	2.5 years (1.7, 3.3)

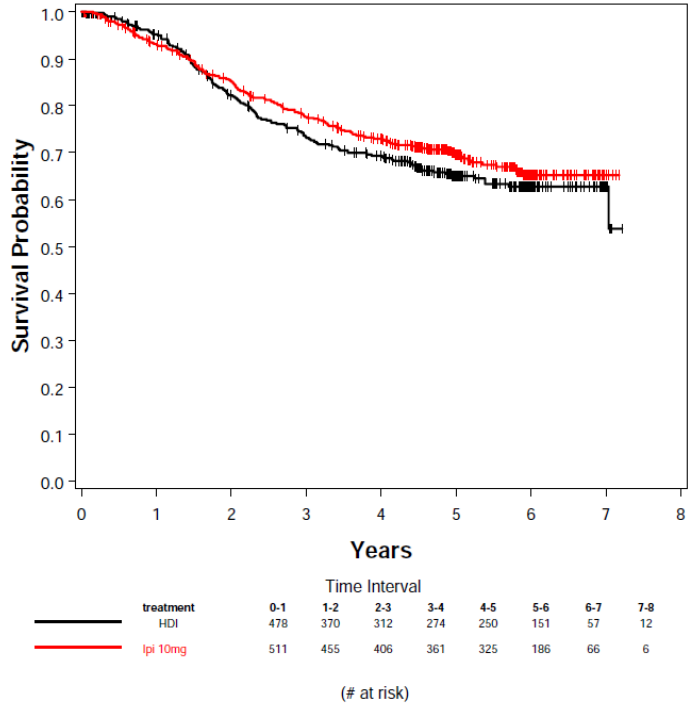


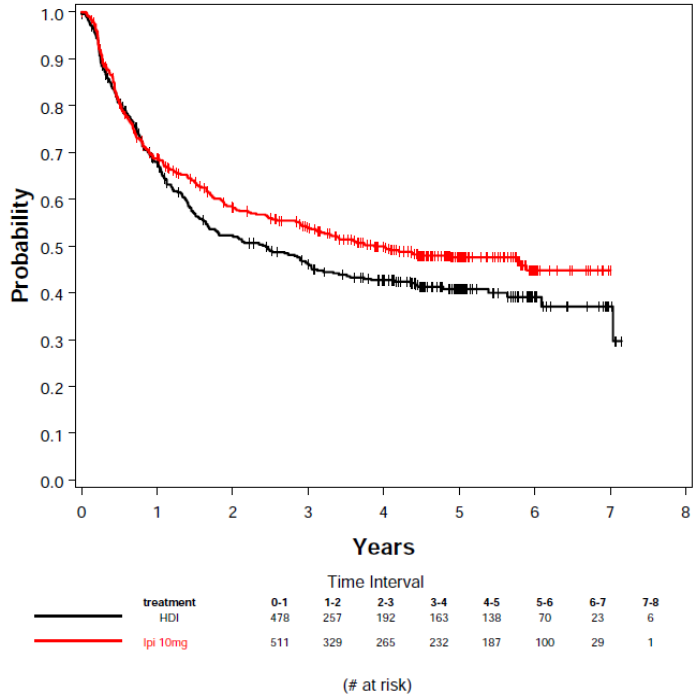


Second-step comparison of Ipi10 versus HDI: OS & RFS

OS	Ipi10	HDI
HR (95.6% RCI)	0.88 (0.69, 1.12)	
Log-rank P value	NS	
5-yr OS (95% CI)	70% (65%, 74%)	65% (60%, 70%)

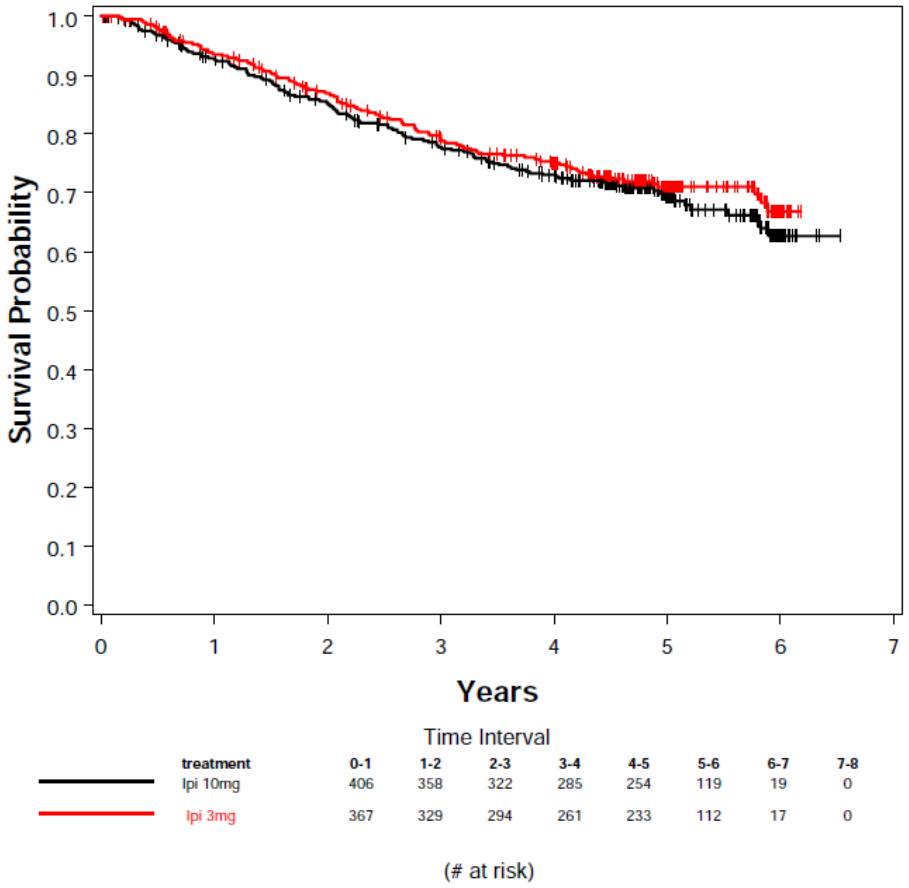
RFS	Ipi10	HDI
HR (99.4% CI)	0.84 (0.65, 1.09)	
Log-rank P value	NS	
Median (95% CI)	3.9 years (2.9, -)	2.4 years (1.6, 3.0)



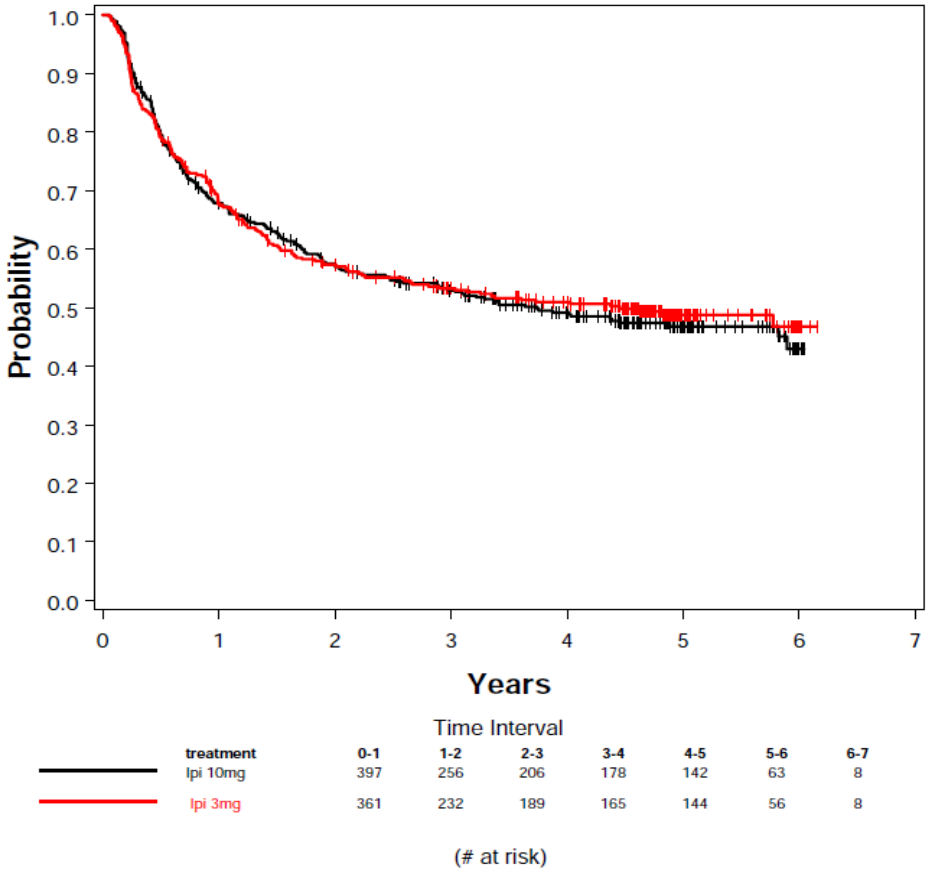


Exploratory Analysis of OS and RFS with Ipi3 vs. Ipi10

OS



RFS



Tarhini AA, et al. ASCO 2019

E1609: Safety Summary of Ipi3 and Ipi10

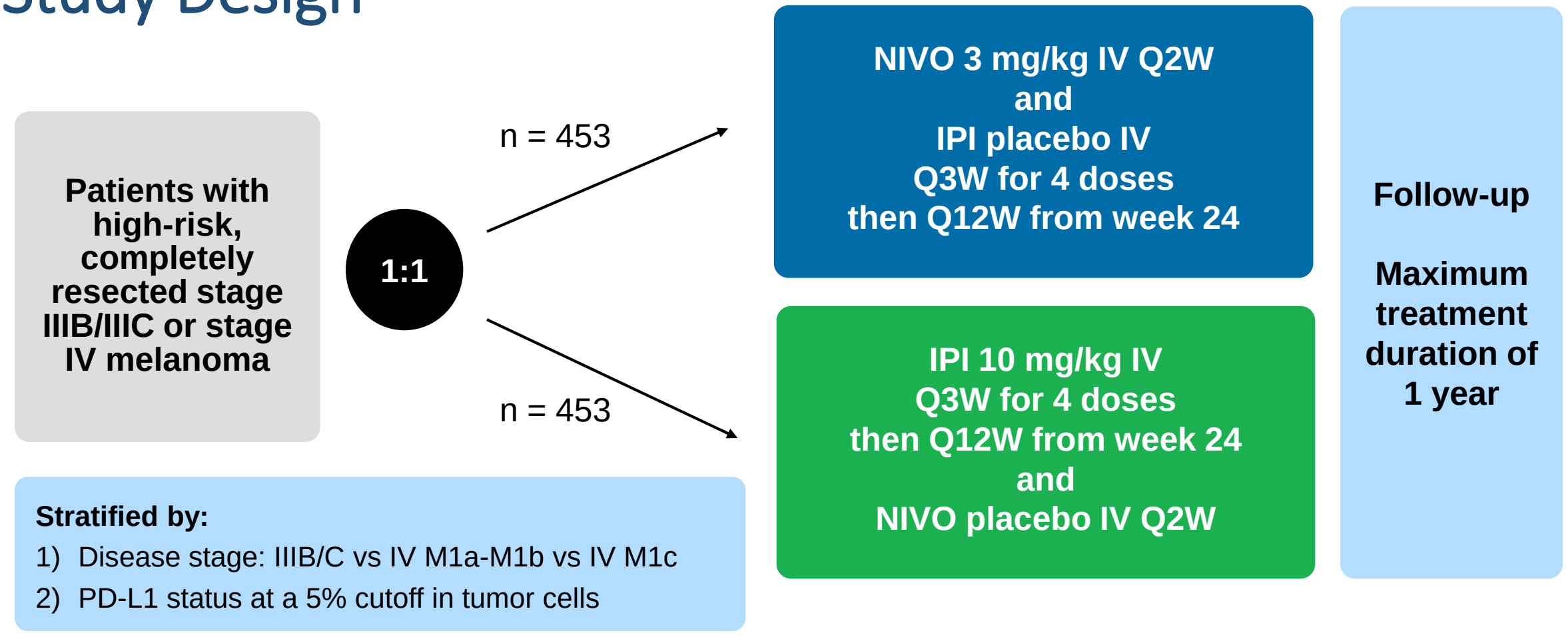
	Ipilimumab 3 mg/kg (n = 516)		Ipilimumab 10 mg/kg (n = 503)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	508 (98.4)	277 (53.7)	503 (100)	337 (67.0)
Treatment-related AE, %	495 (95.9)	197 (38.2)	497 (98.8)	285 (56.7)
Treatment-related AE leading to discontinuation, %	180 (34.9)	129 (25.0)	272 (54.1)	216 (42.9)
Any immune-related AE, %	383 (74.2)	98 (18.9)	438 (87.1)	171 (34.0)
Grade 5 AE, n (%); type (n)	**3 (0.6)** colitis (1), death NOS after consent withdrawal (1), cardiac arrest (1)		**8 (1.6)** colitis (5), pneumonitis (1), thromboembolic event/ hypopituitarism (1), cardiac arrest (1)	

Tarhini AA, et al. ASCO 2019

E1609 Discussion

- Differences in OS and RFS with ipi10 vs. HDI were not statistically significant
  - Increased toxicity with ipi10 may have affected efficacy outcomes
  - Protocol had strict toxicity-specific criteria for treatment delay and discontinuation; less treatment exposure and higher discontinuation rates with ipi10 compared to ipi3
  - Fewer patients received salvage therapy following ipi10
  - Salvage use of anti-PD1/PDL1, BRAFi, MEKi, ipilimumab & combinations
    - 70% after ipi3
    - 86% after HDI
    - 52% after ipi10
- Adjuvant ipi3 is significantly less toxic than ipi10 and at least as effective in terms of RFS and OS outcomes
- The data support the use of ipi3 over HDI based on improved survival and similar RFS, and comparable toxicity
- In cases where adjuvant therapy with ipilimumab represents an option, ipi3 has an advantage over approved dosage of ipi10

CA209-238 – Adjuvant Nivolumab Vs. Ipilimumab: Study Design

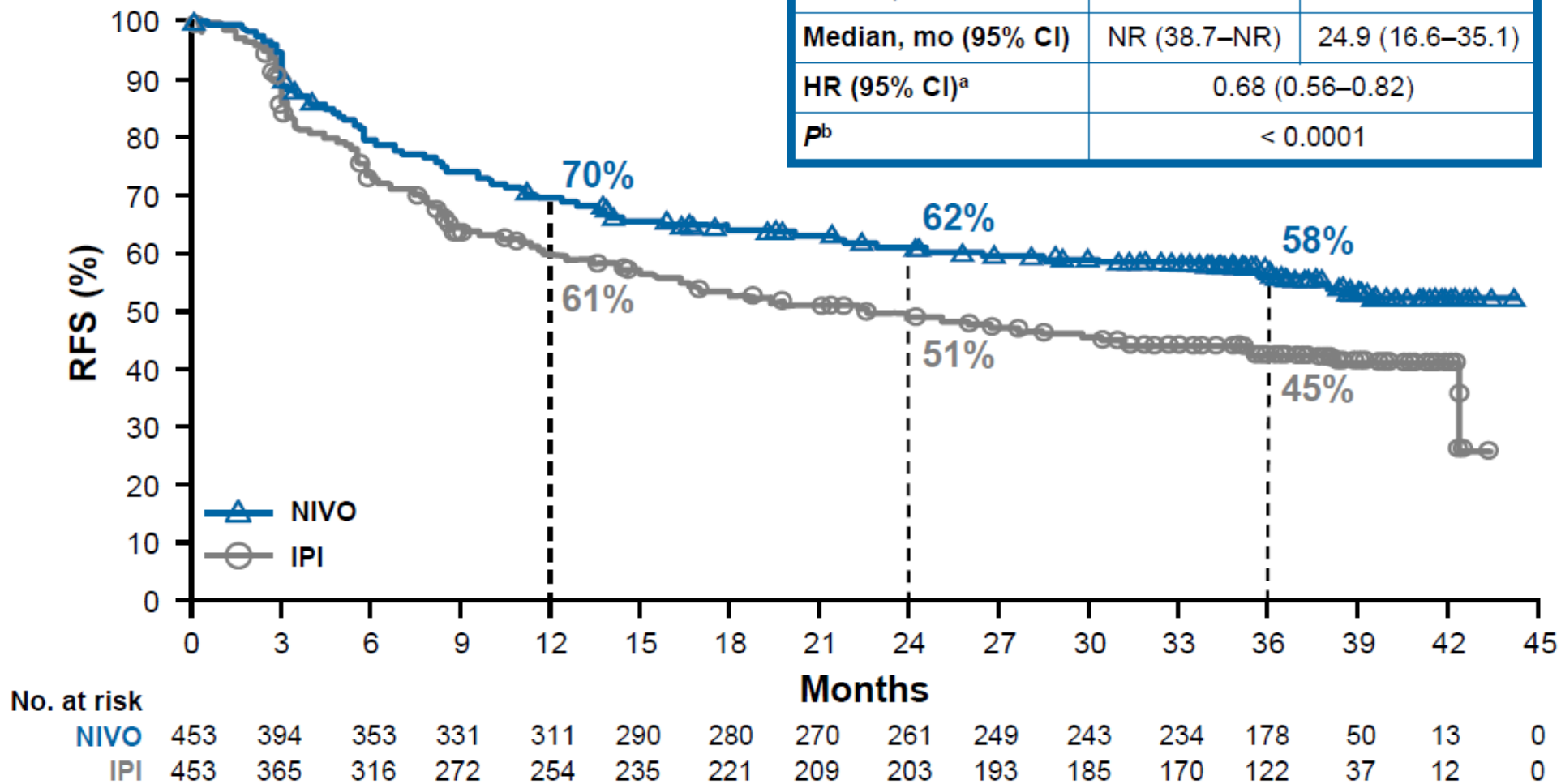


Enrollment period: March 30, 2015 to November 30, 2015

Weber et al. ESMO 2017; NEJM 2017; ESMO 2019

Primary Endpoint: RFS in All Patients

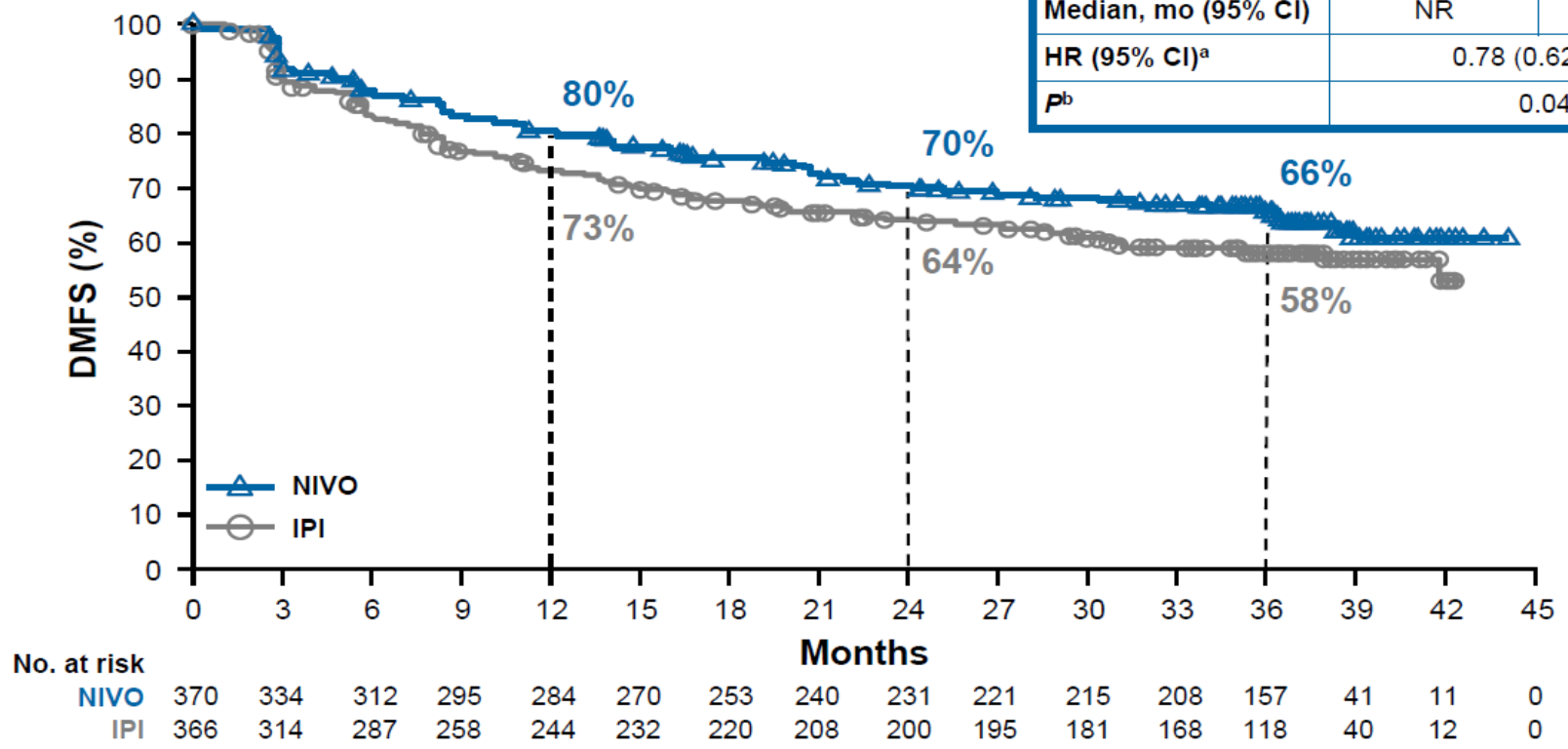
	NIVO (n = 453)	IPI (n = 453)
Events, n	188	239
Median, mo (95% CI)	NR (38.7–NR)	24.9 (16.6–35.1)
HR (95% CI)[a]	0.68 (0.56–0.82)	
P[b]	< 0.0001	



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

Exploratory Endpoint: DMFS in Stage III Disease

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



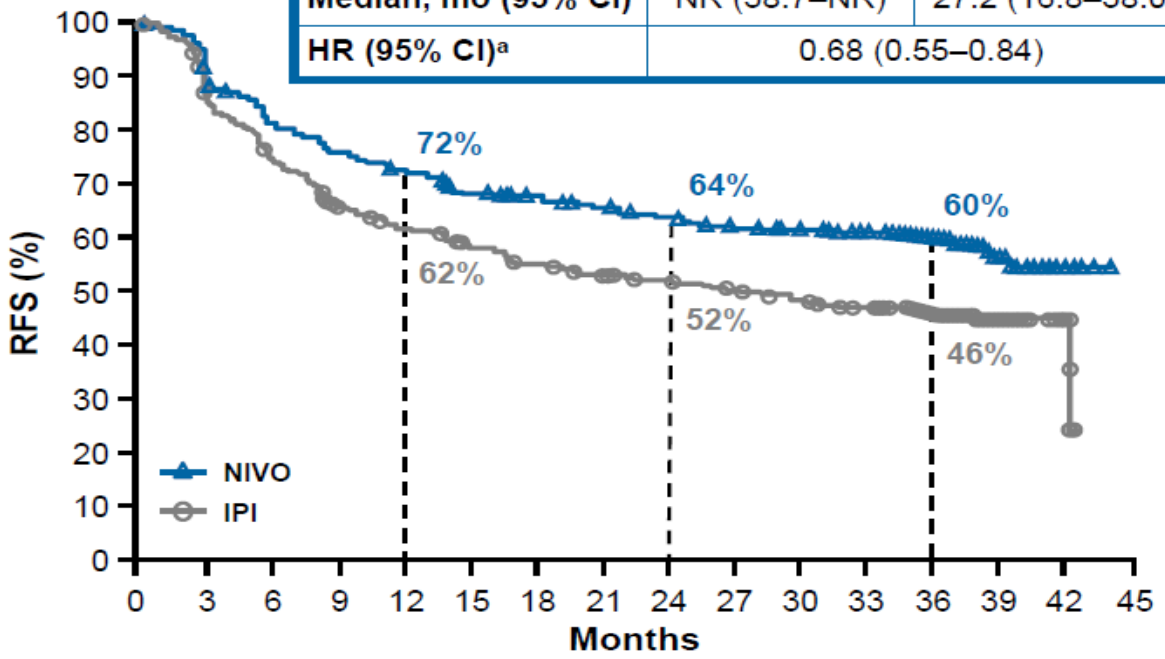
[a]Stratified; [b]Log-rank test.

Weber et al. ESMO 2017; NEJM 2017; ESMO 2019

Subgroup Analysis of RFS: Disease Stage III and IV

Stage III

	NIVO (n = 370)	IPI (n = 366)
Events, n	149	190
Median, mo (95% CI)	NR (38.7–NR)	27.2 (16.8–38.0)
HR (95% CI)[a]	0.68 (0.55–0.84)	



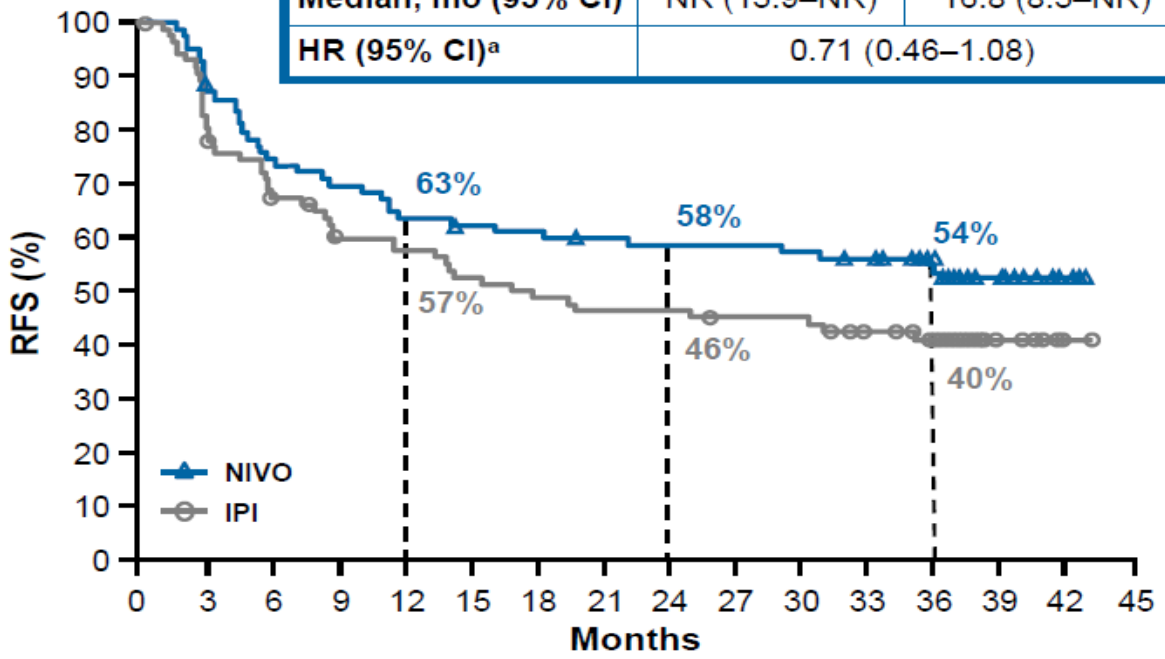
No. at risk

NIVO	370	322	293	274	260	241	232	224	216	204	199	192	147	39	10	0
IPI	366	300	261	225	209	194	183	173	167	159	151	141	100	31	11	0

[a]Unstratified.

Stage IV

	NIVO (n = 82)	IPI (n = 87)
Events, n	38	49
Median, mo (95% CI)	NR (15.9–NR)	16.8 (8.5–NR)
HR (95% CI)[a]	0.71 (0.46–1.08)	



No. at risk

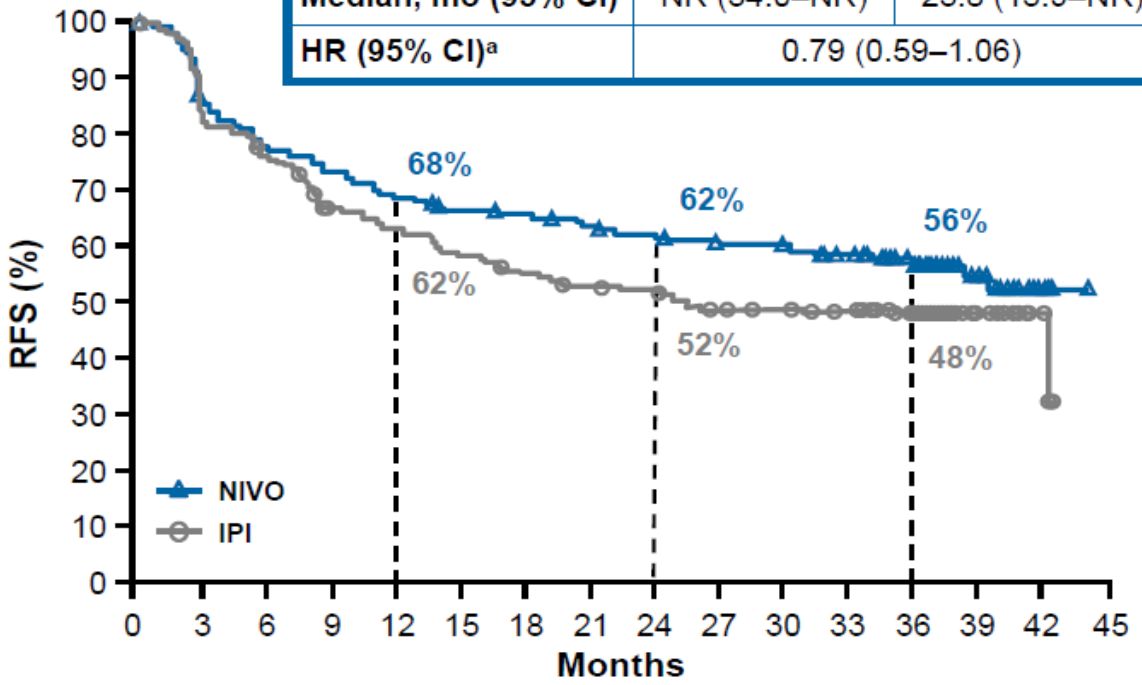
NIVO	82	71	59	56	51	49	48	46	45	45	44	42	31	11	3	0
IPI	87	65	55	47	45	41	38	36	36	34	34	29	22	6	1	0

Weber et al. ESMO 2017; NEJM 2017; ESMO 2019

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

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

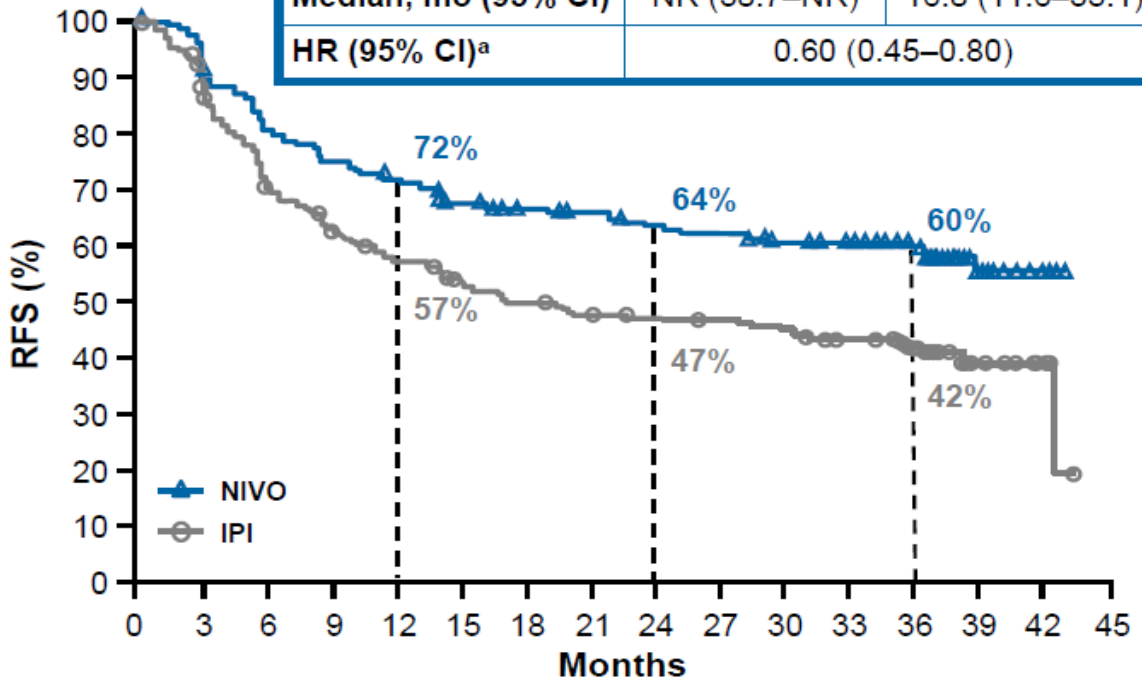


No. at risk

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

BRAF Wild-type

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



No. at risk

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

Safety Summary

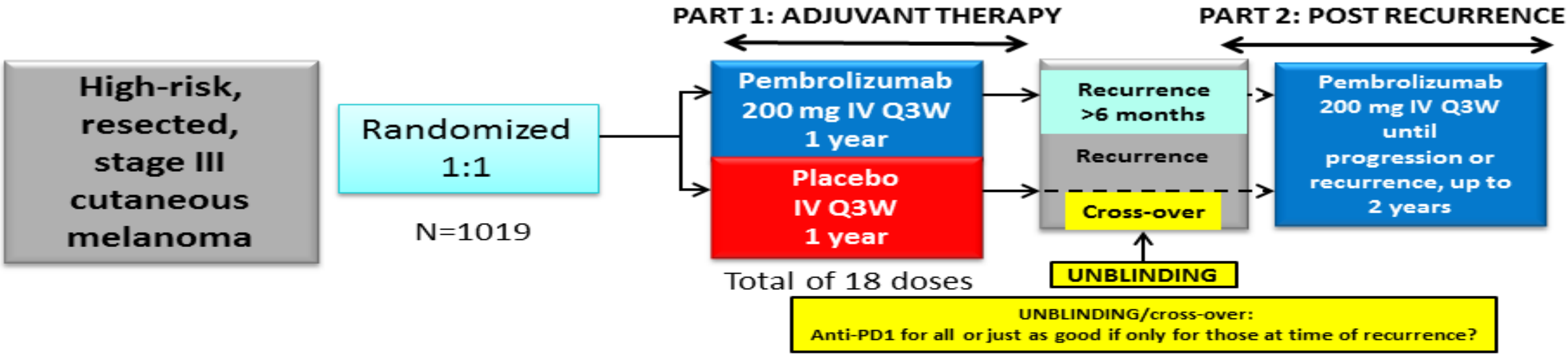
AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)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

Weber et al. ESMO 2017; NEJM 2017; ESMO 2019

L. Eggermont AACR 2018

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

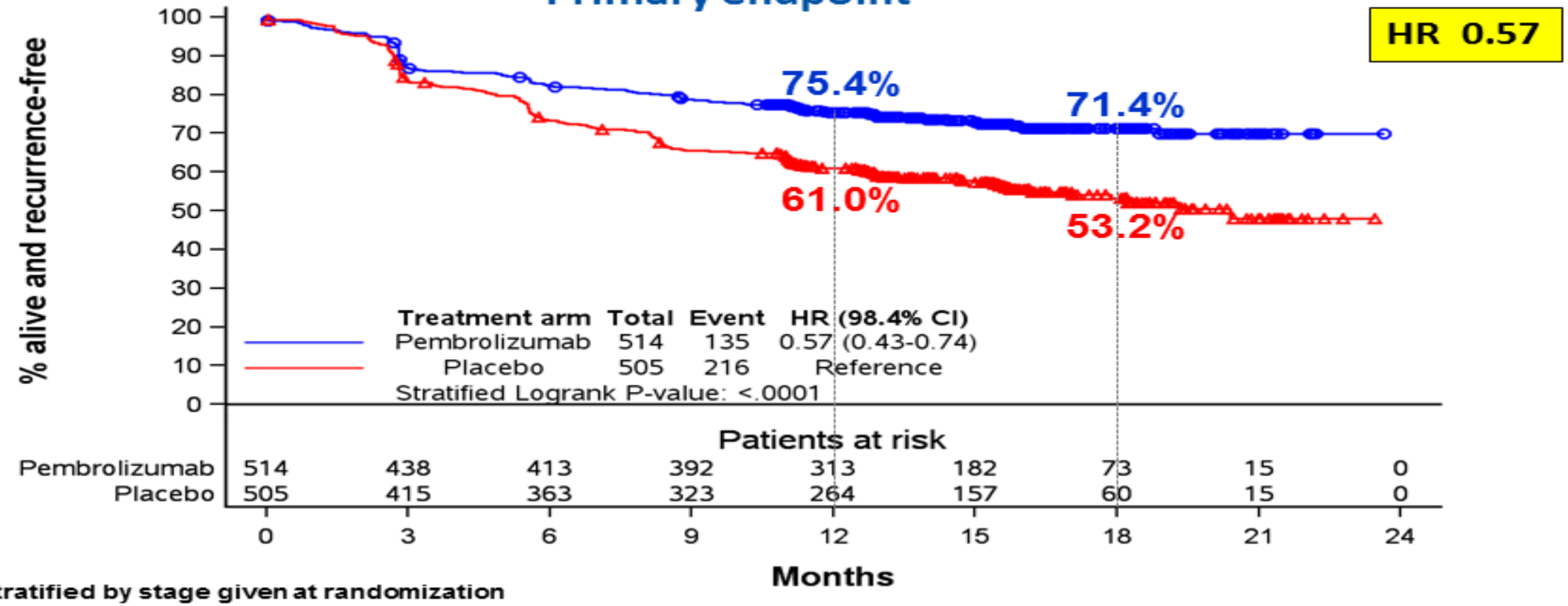
The future of cancer therapy

Eggermont et al. AACR 2018; NEJM 2018

L. Eggermont AACR 2018

Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

Pr Proprietary

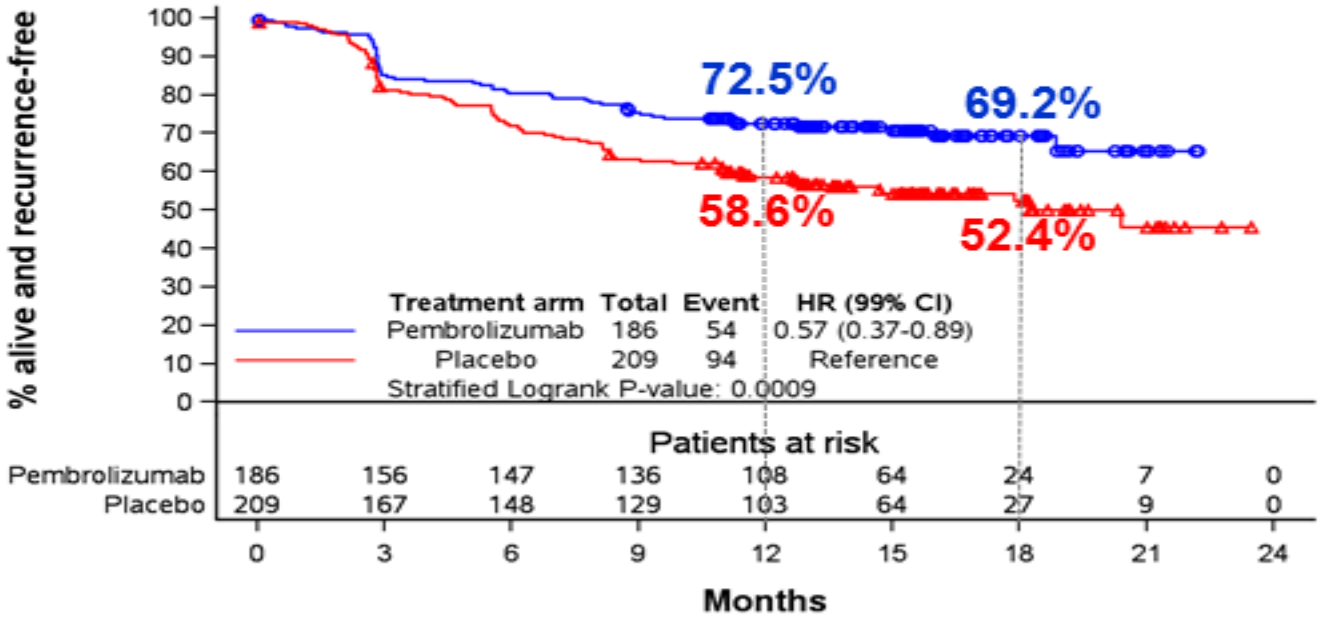
Eggermont et al. AACR 2018; NEJM 2018

L. Eggermont AACR 2018

Recurrence-Free Survival

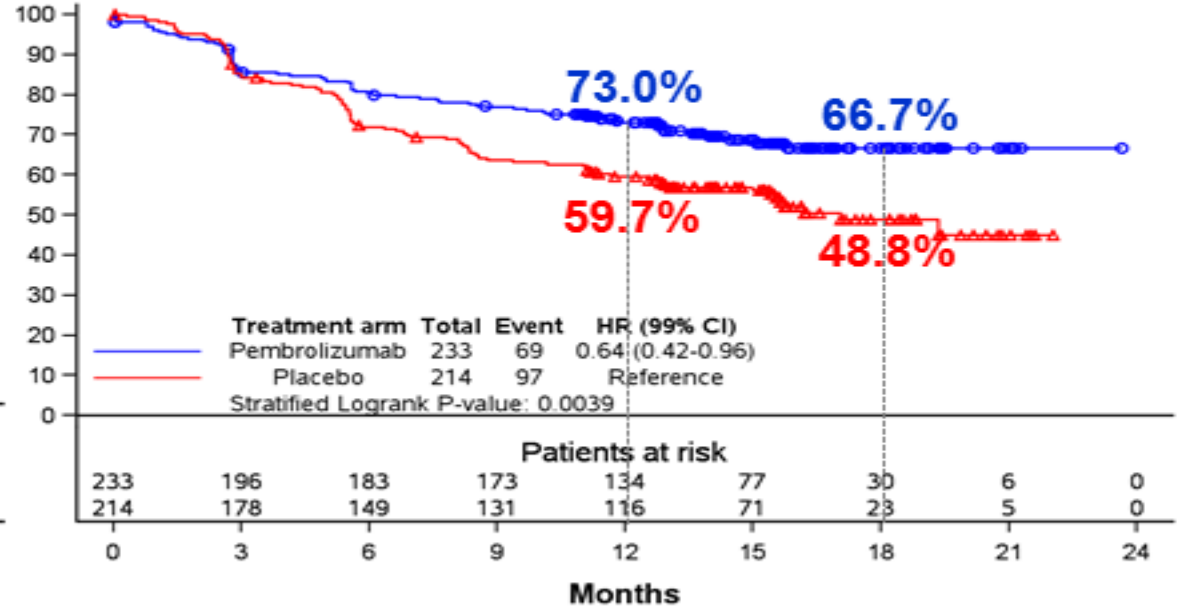
BRAF V600E/K

HR 0.57



BRAF WT

HR 0.64



*Stratified by stage given at randomization

EORTC

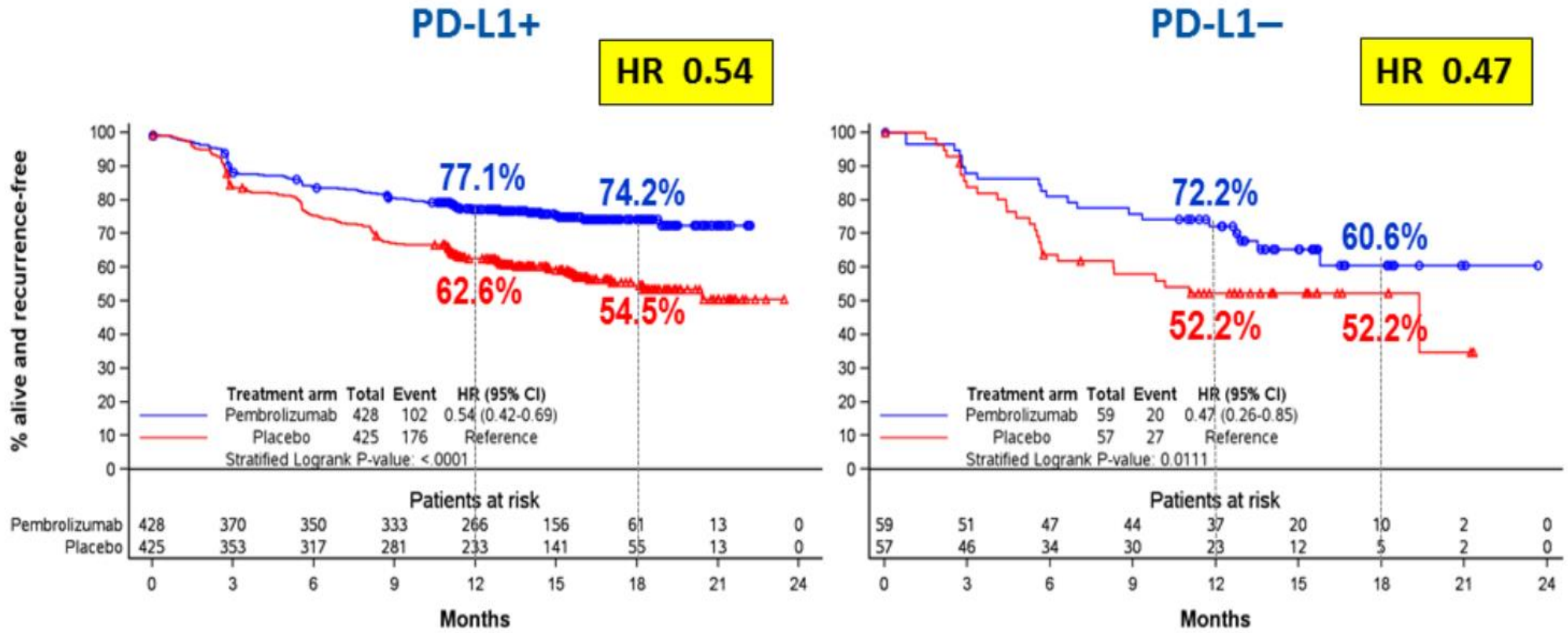
The future of cancer therapy

Proprietary

Eggermont et al. AACR 2018; NEJM 2018

L. Eggermont AACR 2018

Recurrence-Free Survival



*Stratified by stage given at randomization

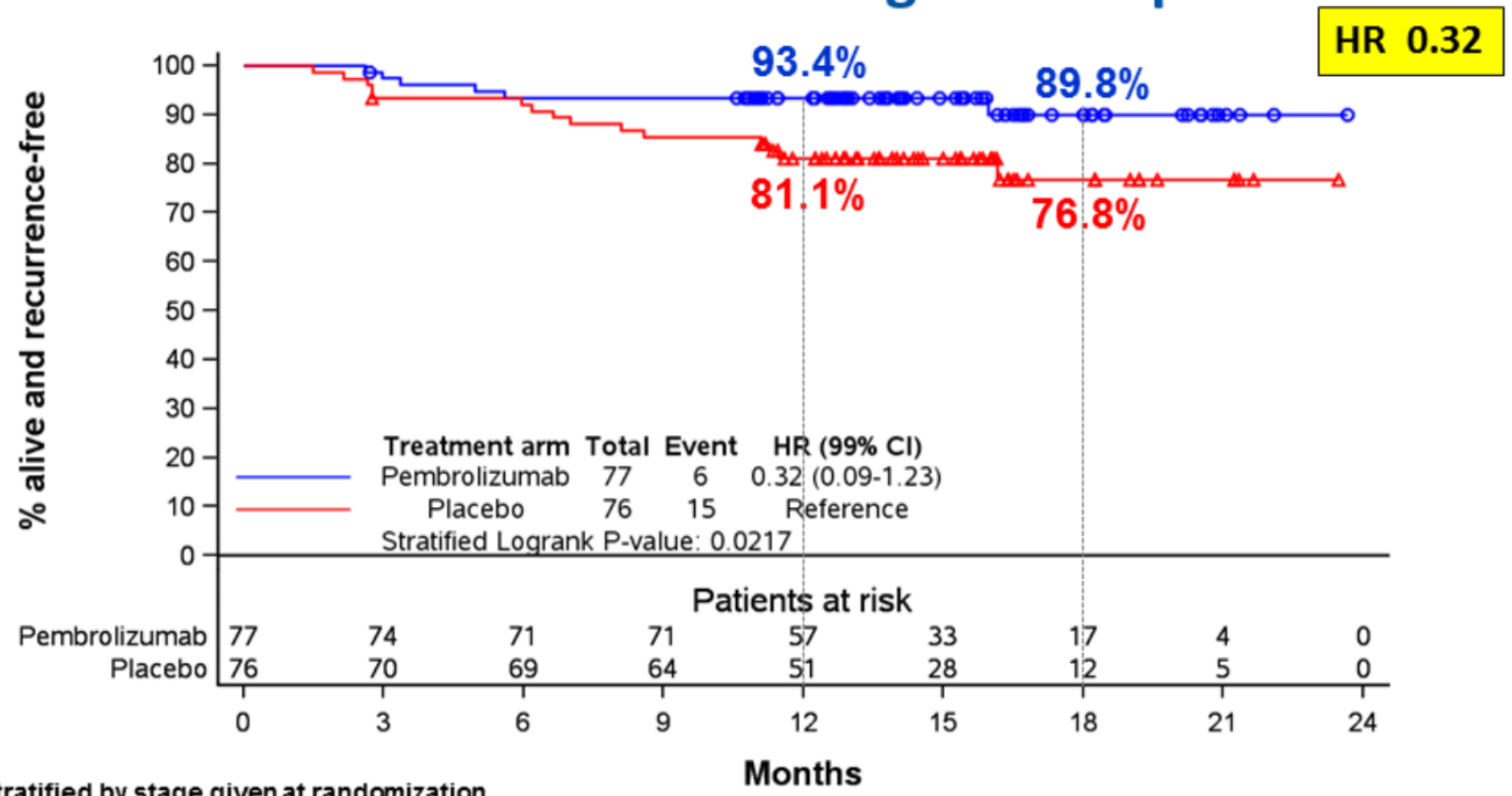
EORTC

The future of cancer therapy

Eggermont et al. AACR 2018; NEJM 2018

L. Eggermont AACR 2018

Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

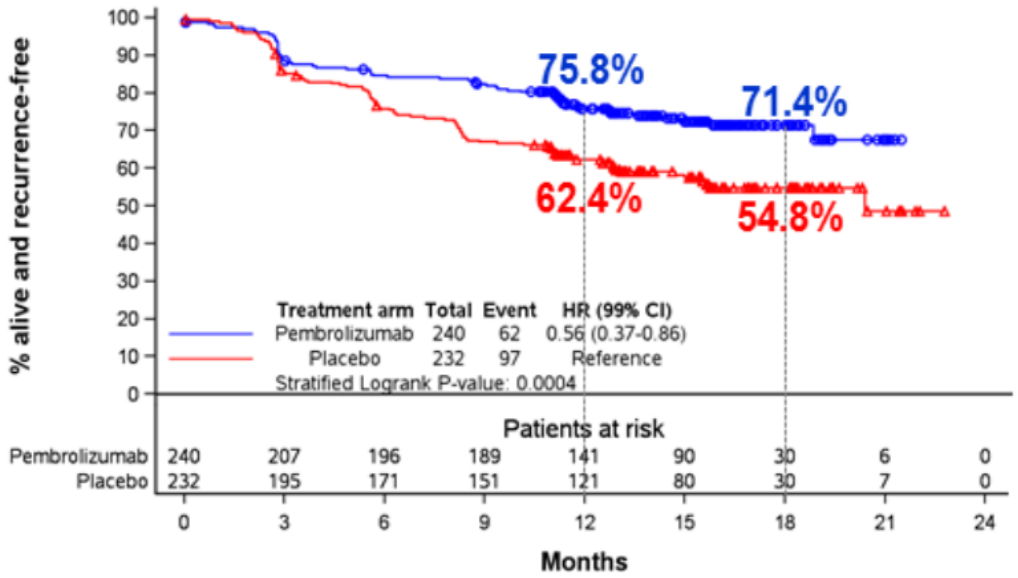
Eggermont et al. AACR 2018; NEJM 2018

L. Eggermont AACR 2018

Recurrence-Free Survival

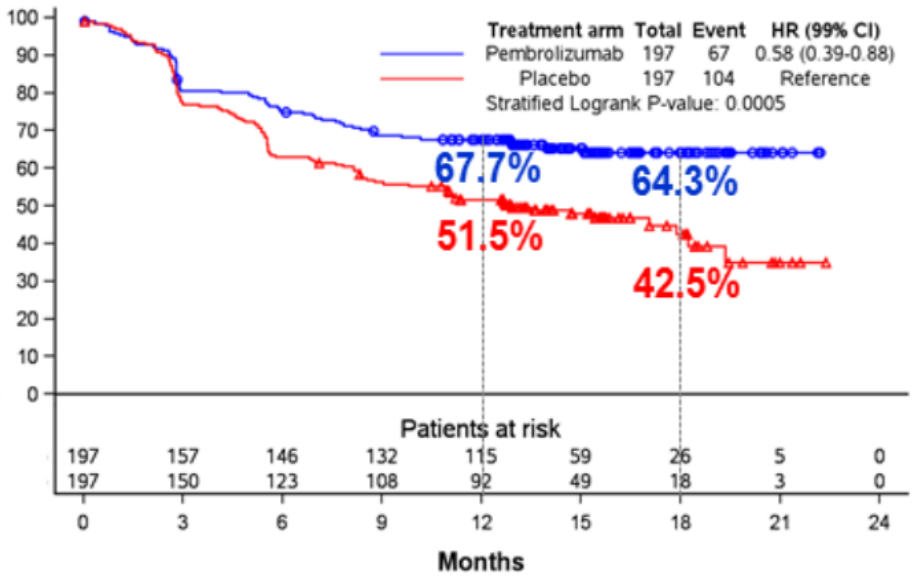
Stage IIIB

HR 0.56



Stage IIIC

HR 0.58



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

Eggermont et al. AACR 2018; NEJM 2018

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

EORTC

The future of cancer therapy

Eggermont et al. AACR 2018; NEJM 2018

Combi-AD: Study design

Key eligibility criteria

- Completely resected, high-risk stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- Surgically free of disease ≤ 12 weeks before randomization
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy

Stratification

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

RANDOMIZATION

N = 870

1:1

Treatment: 12 months[a]

Dabrafenib 150 mg BID + trametinib 2 mg QD

(n = 438)

2 matched placebos

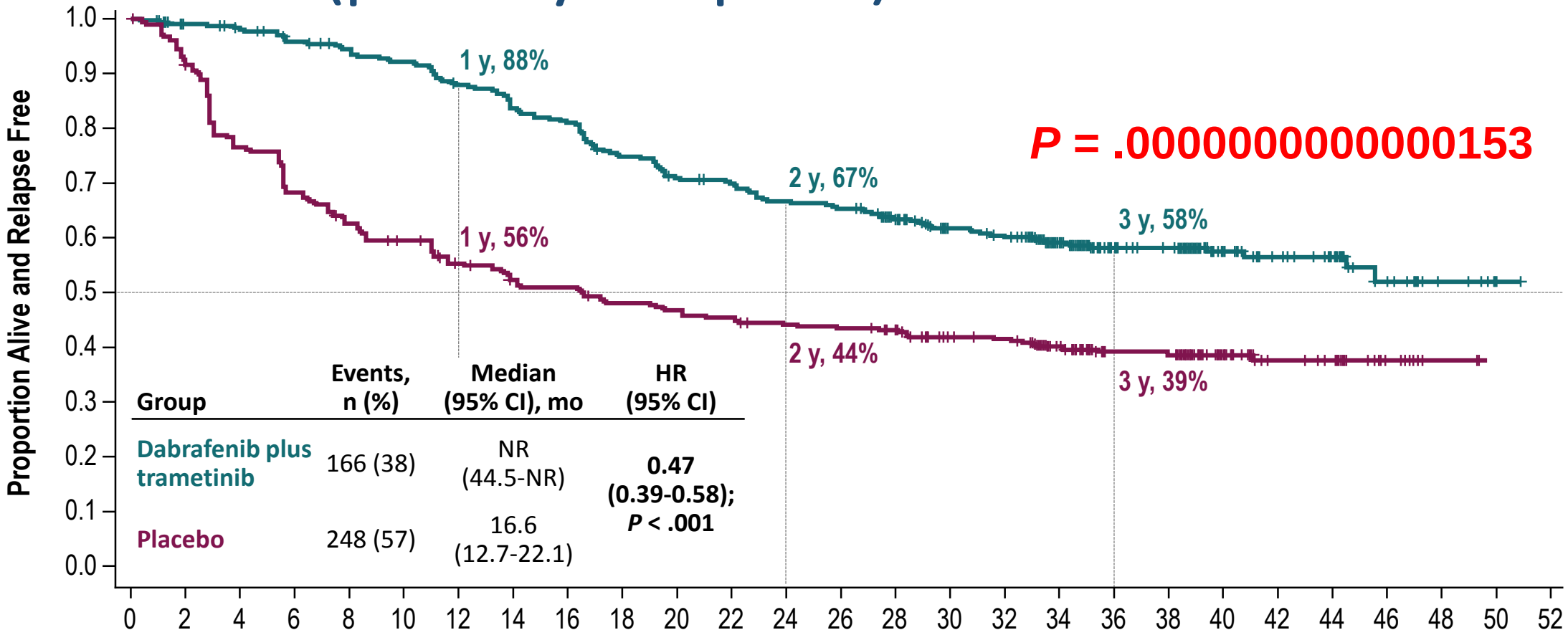
(n = 432)

Follow-up[b] until end of study[c]

- **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.

COMBI-AD: Relapse Free Survival (primary endpoint)

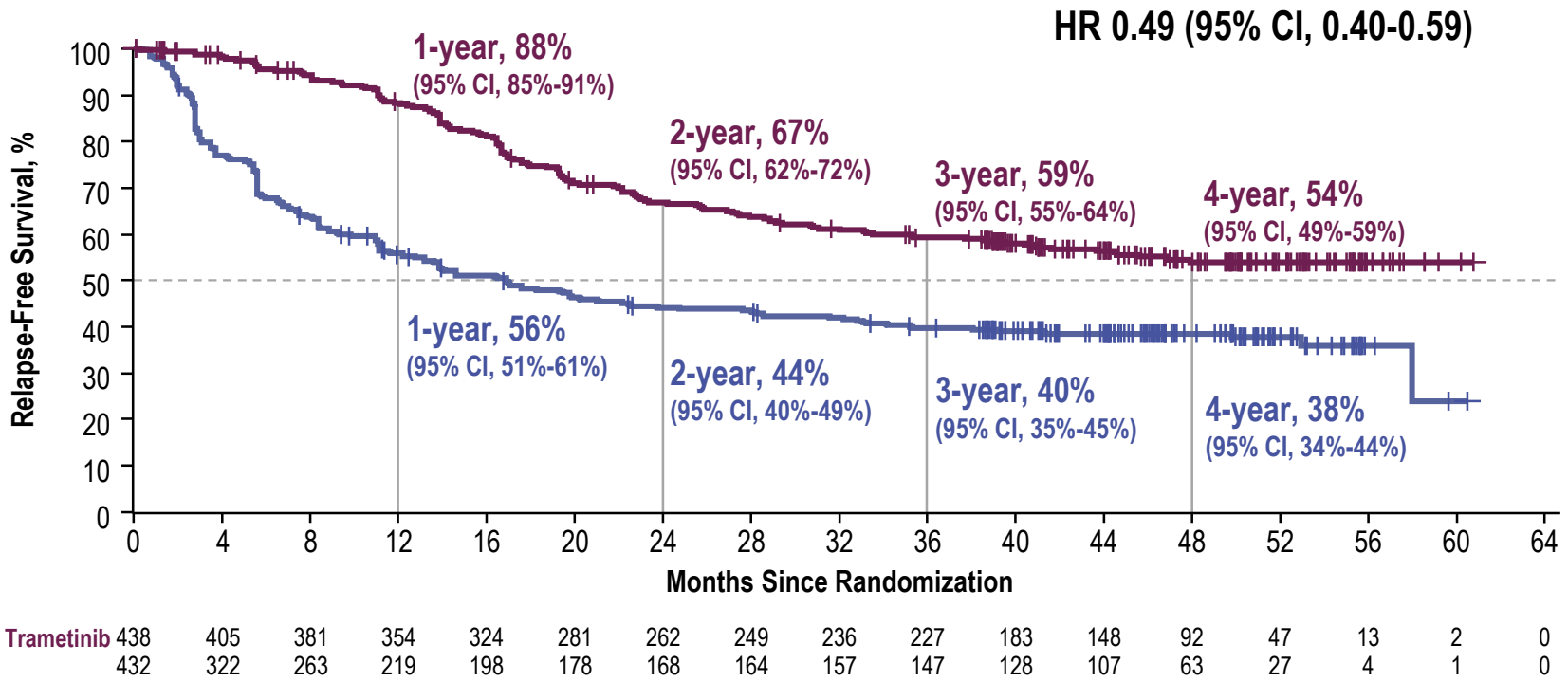


No. at Risk																										
Dabrafenib plus trametinib	438	413	405	392	382	373	355	336	325	299	282	276	263	257	233	202	194	147	116	110	66	52	42	19	7	2	0
Placebo	432	387	322	280	263	243	219	203	198	185	178	175	168	166	158	141	138	106	87	86	50	33	30	9	3	0	0

NR, not reached.

COMBI-AD: Updated Relapse-Free Survival[a]

Median Follow-Up: 44 months (Minimum: 40 Months)

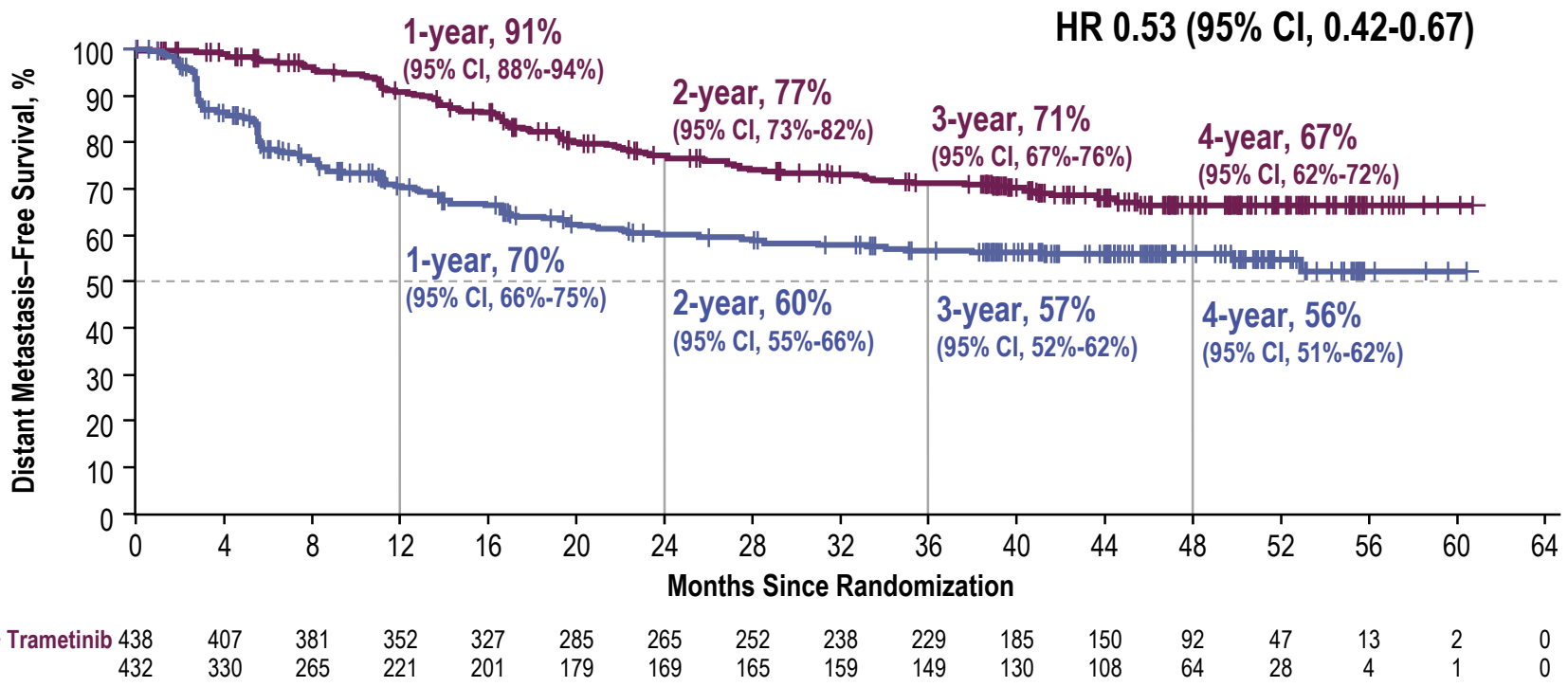


[a] At median follow-up of 44 months (data cutoff: April 30, 2018).

Long GV, et al. ESMO 2018 LBA. 2. Hauschild A, et al, *J Clin Oncol* 2018

COMBI-AD: Distant Metastasis-Free Survival[a]

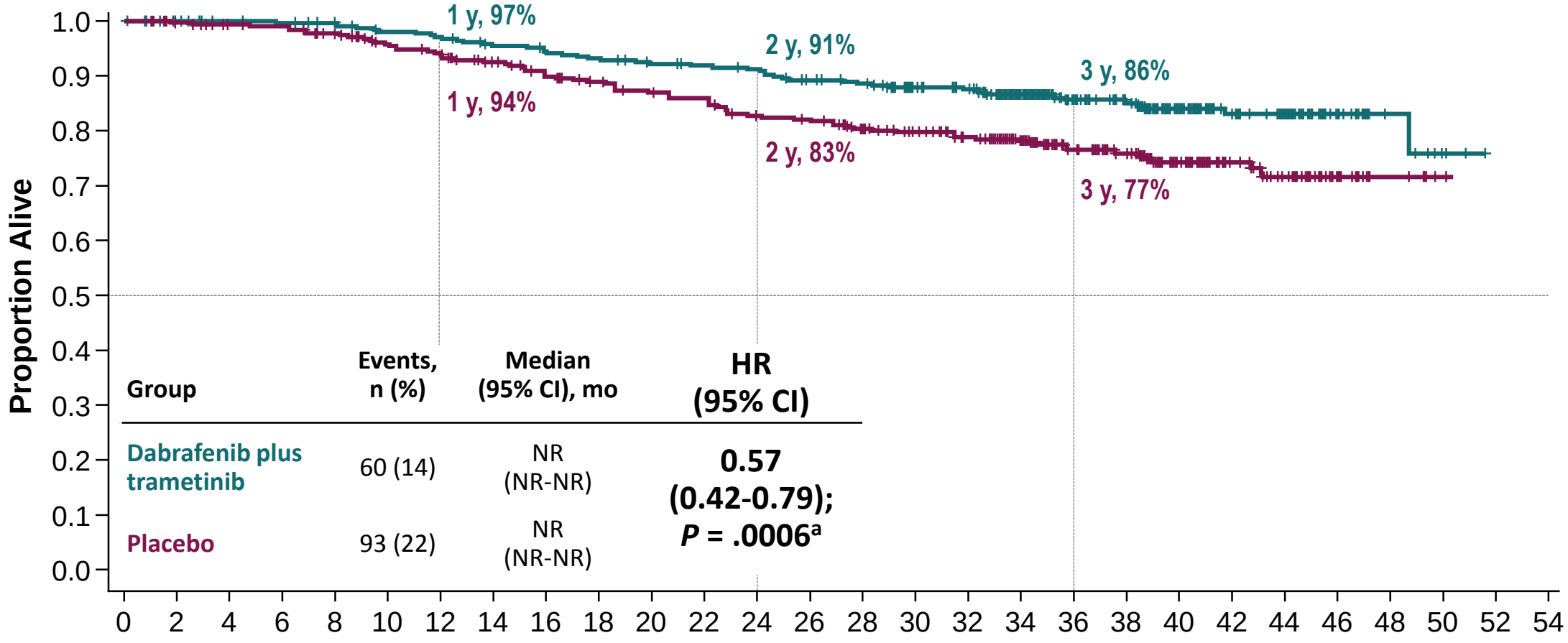
Median Follow-Up: 44 months (Minimum: 40 Months)



[a] At median follow-up of 44 months (data cutoff: April 30, 2018).

Long GV, et al. ESMO 2018 LBA. 2. Hauschild A, et al, *J Clin Oncol* 2018

Overall survival
(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

[a] Prespecified significance boundary (*P* = .000019).

MADRID 2017 ESMO congress

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[a]	114 (26)	12 (3)

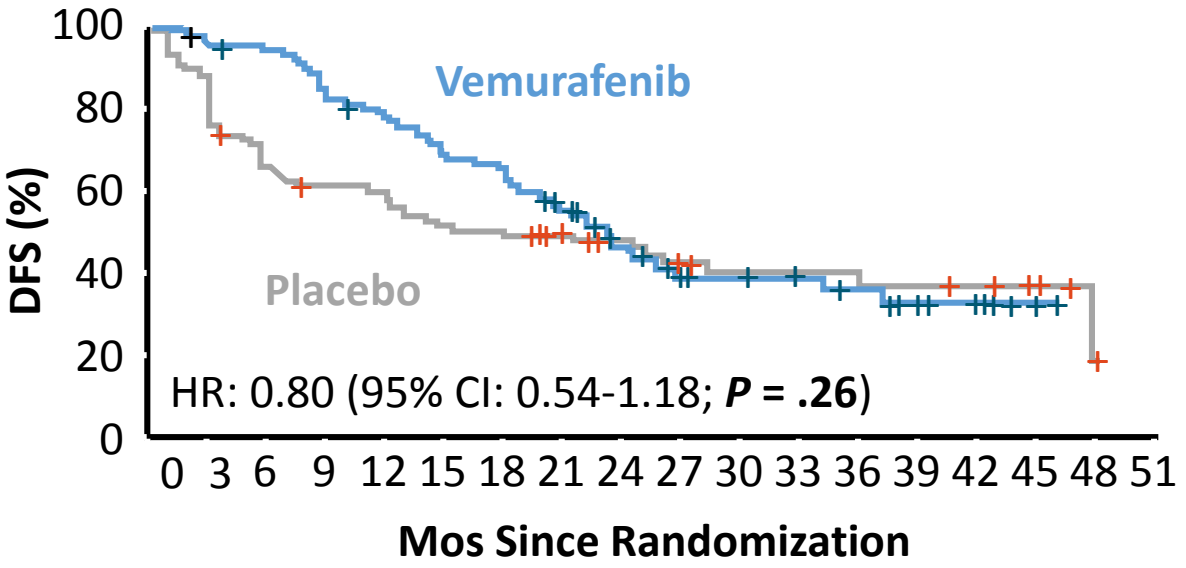
AE, adverse event; SAE, serious adverse event.

[a] Most common AEs leading to treatment discontinuation in the dabrafenib plus trametinib arm were pyrexia (9%) and chills (4%).

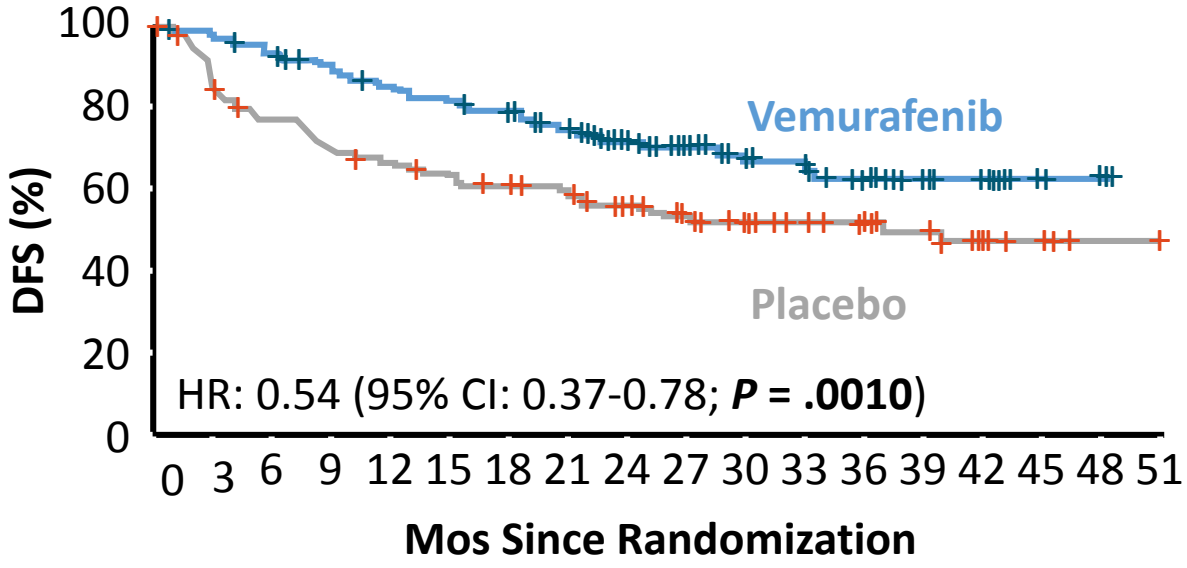
BRIM8: Adjuvant Vemurafenib vs Placebo in Resected Stage III Melanoma

Randomized, double-blind phase III study of adjuvant **vemurafenib** vs **placebo** for 1 yr in patients with resected stage IIC-IIIC, *BRAF* mutation–positive melanoma (N = 498)

DFS, Stage IIIC (Cohort 2)



DFS, Stage IIC-IIIB (Cohort 1)



Maio. Lancet Oncol. 2018;19:510

Major Ongoing Adjuvant Trials in Melanoma

Study	No of Patients	TNM Stage	Therapy	Primary Endpoint
US Intergroup S1404	1240	**IIIA (N2), IIIB, IIIC, IV**	**Pembrolizumab vs. HD-IFN or Ipilimumab 10 mg/kg**	**RFS & OS**
CheckMate 915	1125	**IIIB, IIIC, IIID, IV**	**Ipilimumab-Nivolumab vs. Ipilimumab or Nivolumab**	**RFS**
KEYNOTE 716	954	**IIB, IIC**	**Pembrolizumab vs. Placebo (cross over)**	**RFS**
CheckMate76K	1000	**IIB, IIC**	**Nivolumab Vs. Placebo**	**RFS**

Clinicaltrials.Gov

Issues in Melanoma Adjuvant Therapy

- Not all patients benefit from treatment
- Who is predisposed to BENEFIT?
  - Need to apply and further investigate prognostic and predictive biomarkers in the adjuvant setting
    - Treat only those who will relapse
    - Treat only those who have the capacity to respond
  - Future adjuvant studies should integrate biomarkers into the study design (integral biomarkers)
- Allowing cross-over as an integral plan of the study design is important (Early vs. Late)
- Need to avoid tendencies to include lower stages of disease in adjuvant trials in the absence of a credible prognostic biomarker

Conclusions:

- Ipilimumab improves RFS compared to placebo and OS compared to placebo and HDI, albeit with a high toxicity and discontinuation rate
- In cases where adjuvant therapy with ipilimumab represents an option, ipi3 has an advantage over approved dosage of ipi10
- Nivolumab and pembrolizumab prolong RFS compared to ipilimumab or placebo, respectively
- For BRAF mutant melanoma, dabrafenib and trametinib prolong RFS compared to placebo in resected high-risk melanoma
- Need to incorporate prognostic and predictive biomarkers to better select patients