Adjuvant Treatment of Melanoma; worth the wait.

Dr Andrew Haydon

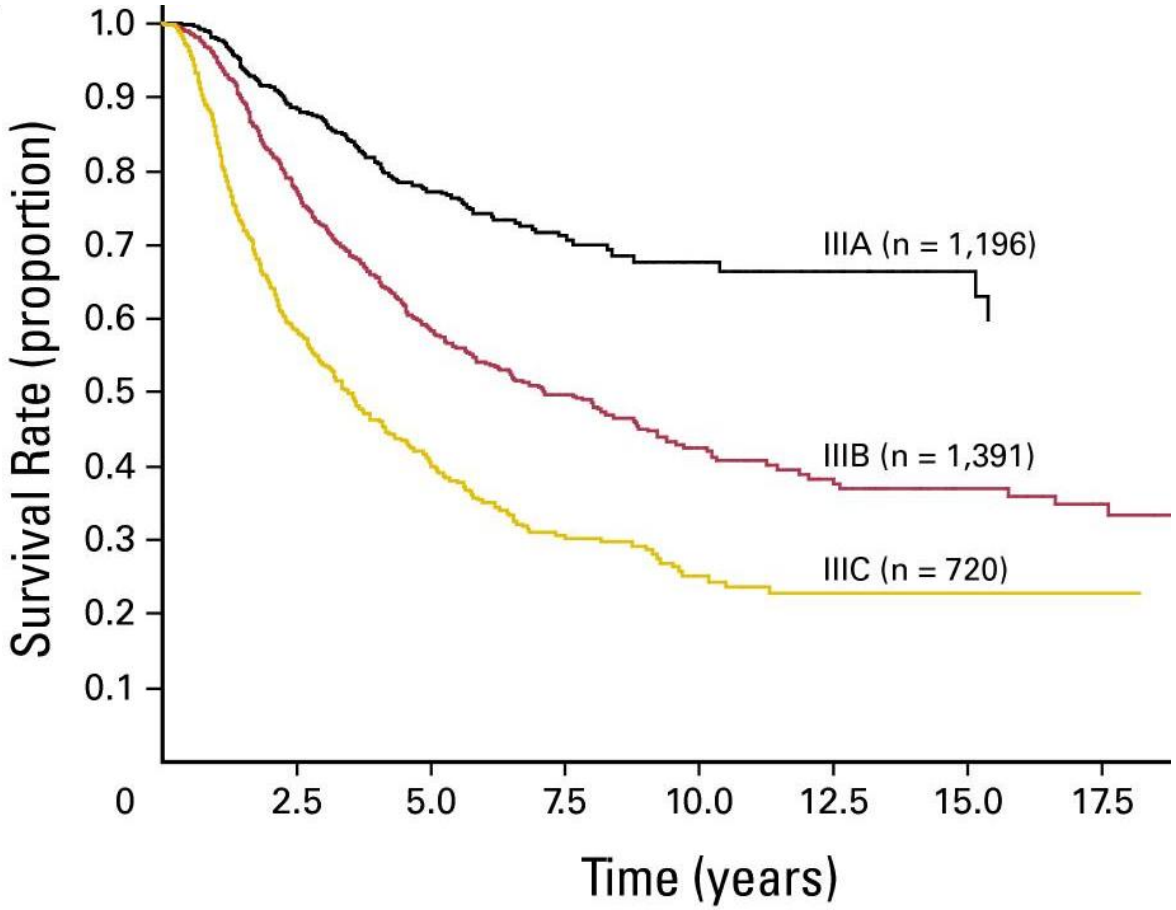
Alfred Health

What is Adjuvant treatment?

- Treatment (usually chemotherapy) given in addition to surgery
- Aimed to eliminate microscopic residual cancer
  - Reduce the risk of cancer recurrence (either locally or at more distant sites)
  - Aimed to improve the chance of cure.
- Used in many different cancers
  - Breast 1976
  - Bowel 1990
  - Oesophagus 2002
  - Lung 2004
  - Pancreas 2004
  - Bladder 2005

Melanoma specific survival for stage 3 Melanoma

AJCC 7th edition



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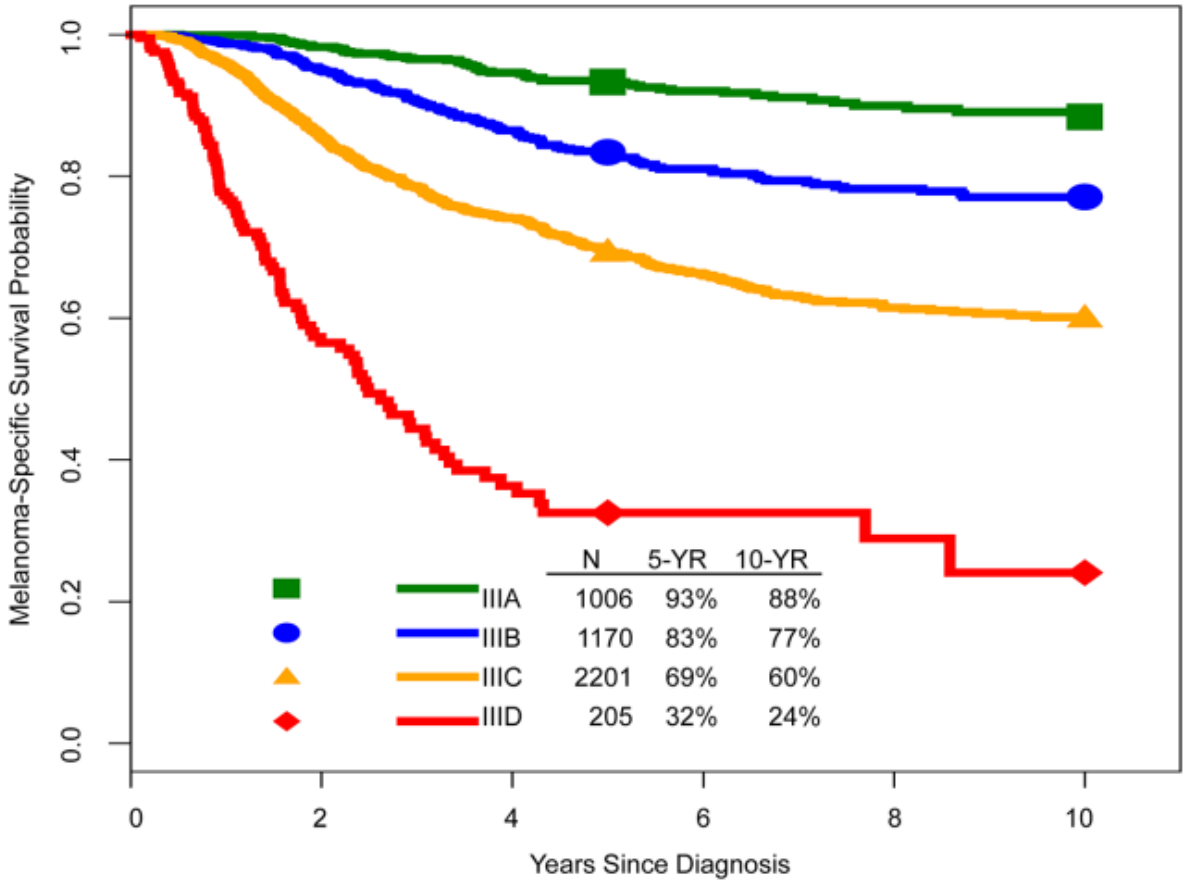


Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual, Volume: 67, Issue: 6, Pages: 472-492, First published: 13 October 2017, DOI: (10.3322/caac.21409)

Adjuvant therapy for melanoma pre 2017

- Chemotherapy
  - Doesn’t work
- Interferon
  - Some activity
  - Very little improvement in overall survival
  - Very Toxic
- Ipilimumab
  - 10% survival improvement
  - >50% serious side effects
  - Prohibitively costly

Significant progress in the last 9 months

- New drugs that have proven benefit in stage 4 disease have now been tested in stage 3 disease.
- 3 new large randomized trials in stage 3 melanoma
  - Dabrafenib + Trametinib vs Placebo in Braf mutant melanoma
  - Nivolumab vs Ipilimumab
  - Pembrolizumab vs Placebo
- Treatment was given for 12 months and was generally well tolerated
- Data is immature, but showing consistent, clinically meaningful benefits.

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 systemic therapy

Stratification:

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

N = 870

RANDOMIZATION

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**

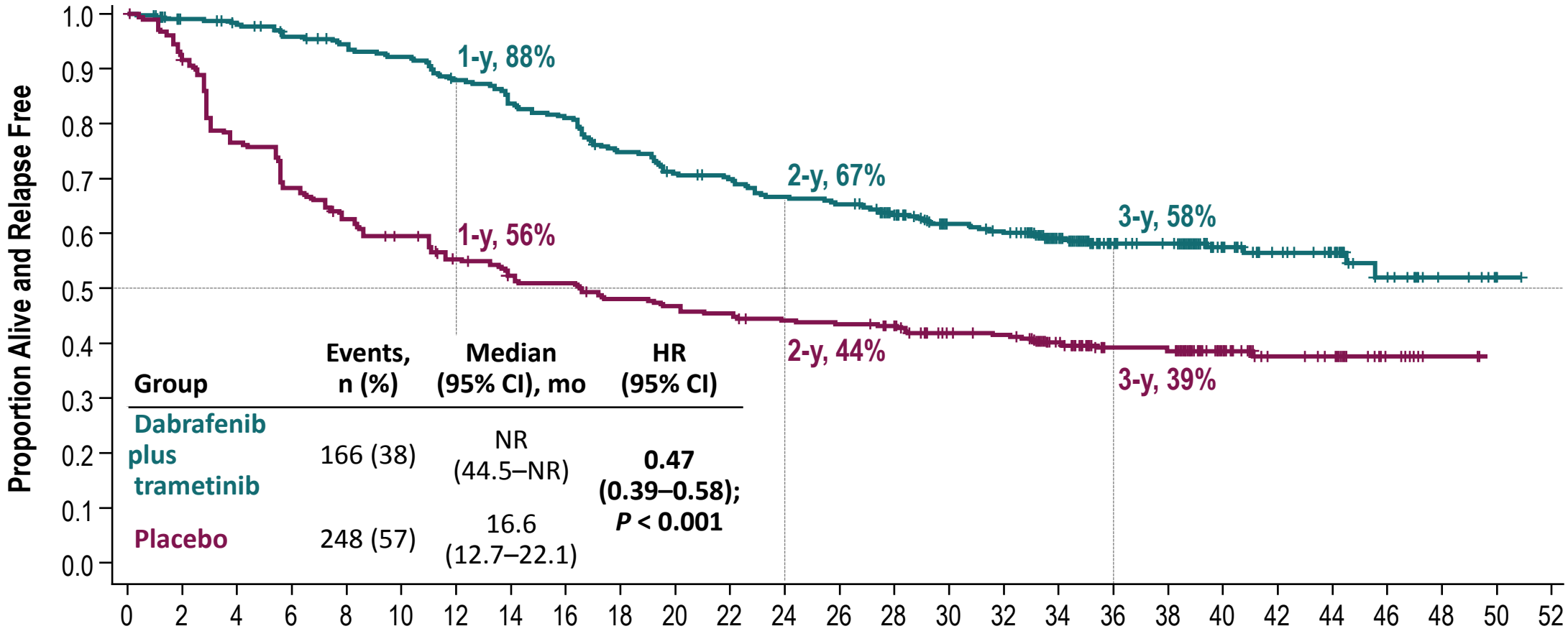
BID, twice daily; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival. [a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b] Patients were followed for disease recurrence until the first recurrence and thereafter for survival; [c] The study will be considered complete and final survival analysis will occur when ≈ 70% of randomized patients have died; [d] New primary melanoma considered as an event.

Common adverse events

	Dabrafenib Plus Trametinib (n = 435)		Placebo (n = 432)	
AEs, n (%)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Any AE[a] (> 20% with dabrafenib plus trametinib)	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)

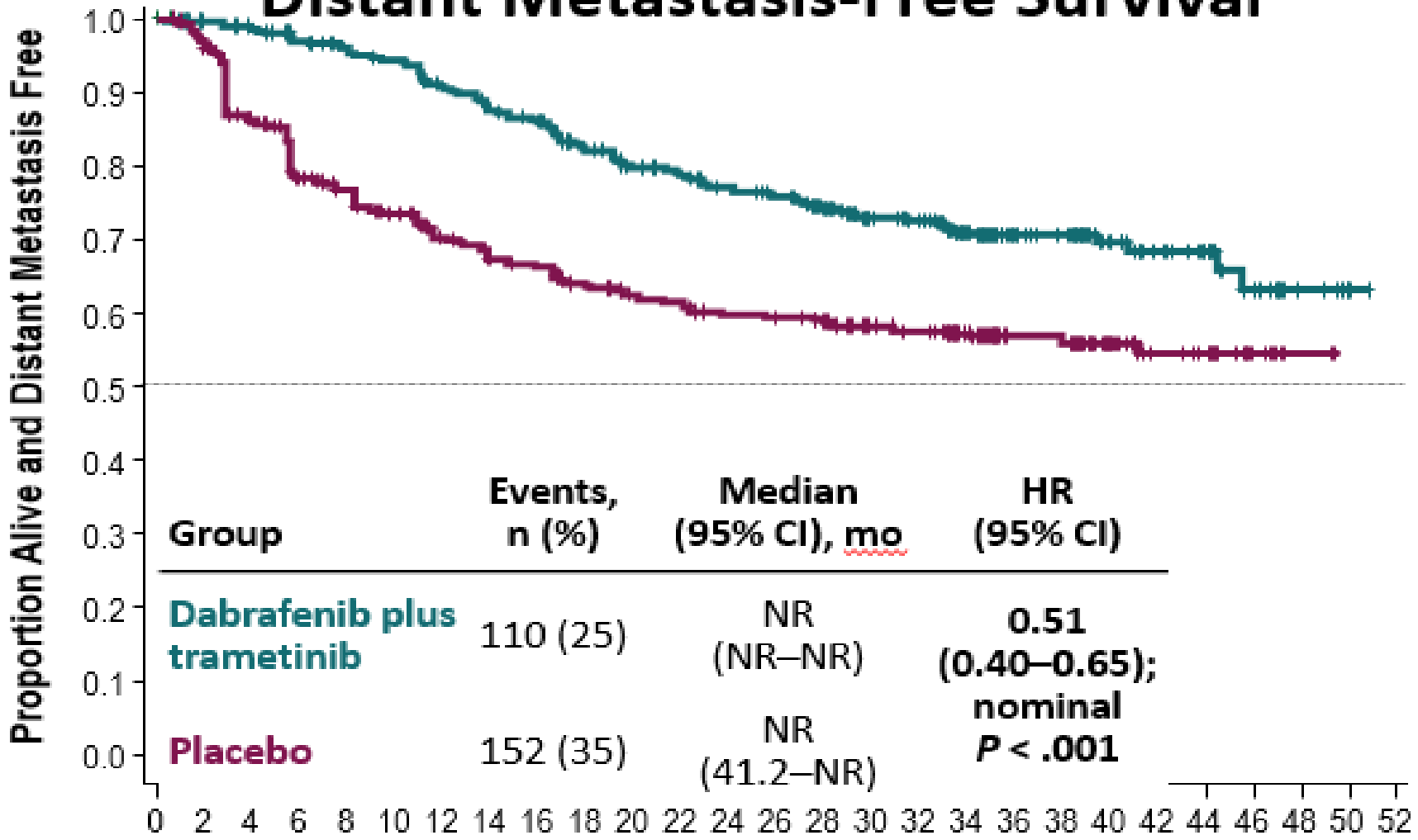
[a] 11 (3%) patients in the treatment arm and 10 (2%) patients in the placebo arm had new primary melanomas, 8 (2%) and 7 (1%), respectively, had cutaneous squamous cell carcinoma/keratoacanthoma, 19 (4%) and 14 (3%), respectively, had basal cell carcinoma, and 10 (2%) and 4 (1%), respectively, had non-cutaneous malignancies.

Relapse-free survival



NR, not reached.

Distant Metastasis-Free Survival



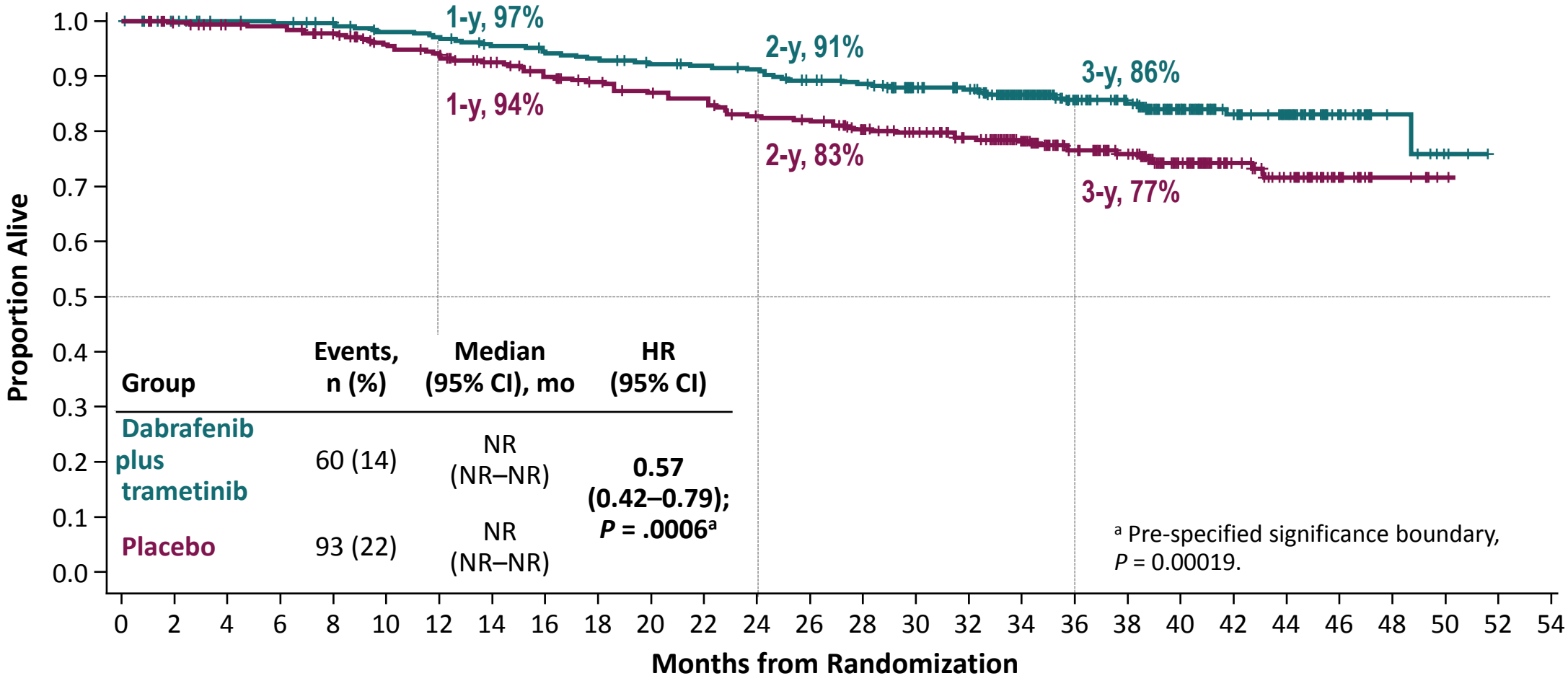
Group	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Dabrafenib plus trametinib	110 (25)	NR (NR–NR)	0.51 (0.40–0.65); nominal *P* < .001
Placebo	152 (35)	NR (41.2–NR)	

No. at Risk

D+T	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

D+T, dabrafenib plus trametinib.

Overall survival



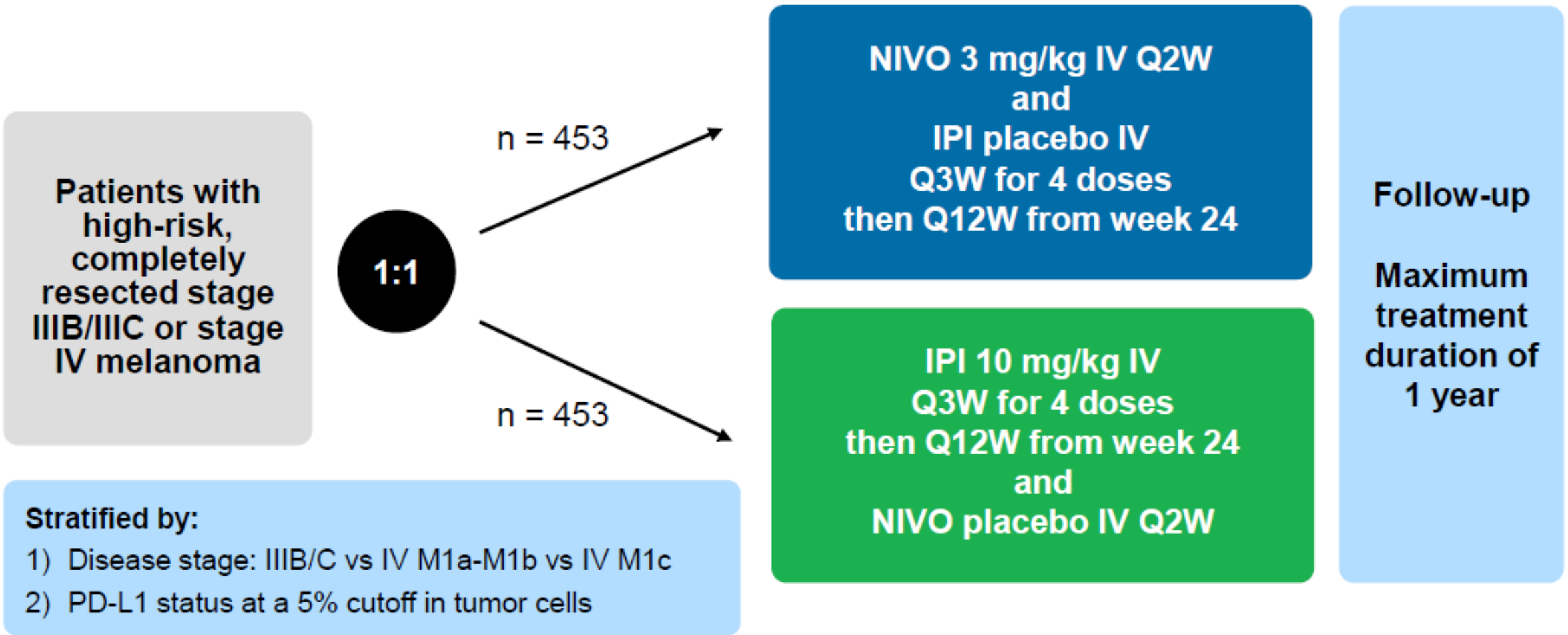
No. at Risk

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

Conclusions from COMBI-AD

- 12 months of Dabrafenib plus Trametinib (Braf + MEK inhibitors) following surgical resection in stage 3 Melanoma significantly reduces the risk of Melanoma recurrence and improves overall survival.
  - Halves to rate of recurrence (absolute reduction of 20% at 3 years)
  - Increases the chance of being alive at 3 years by 10%
- 26% patients were unable to complete 12 months of treatment
  - Main side effects were fever/pyrexia syndrome
  - No long term side effects

CA209-238: Study Design



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

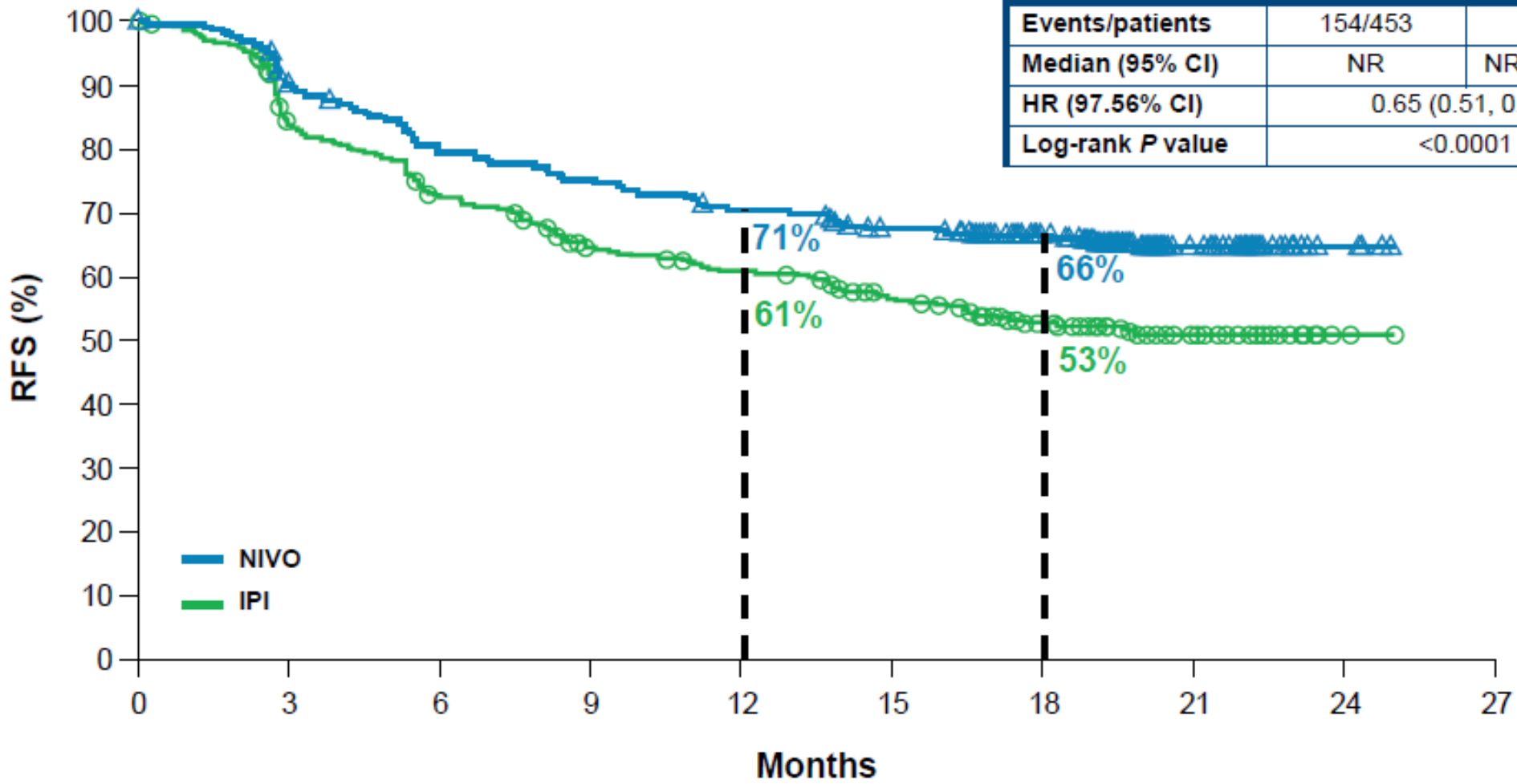
Safety Summary

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

Primary Endpoint: RFS

	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	



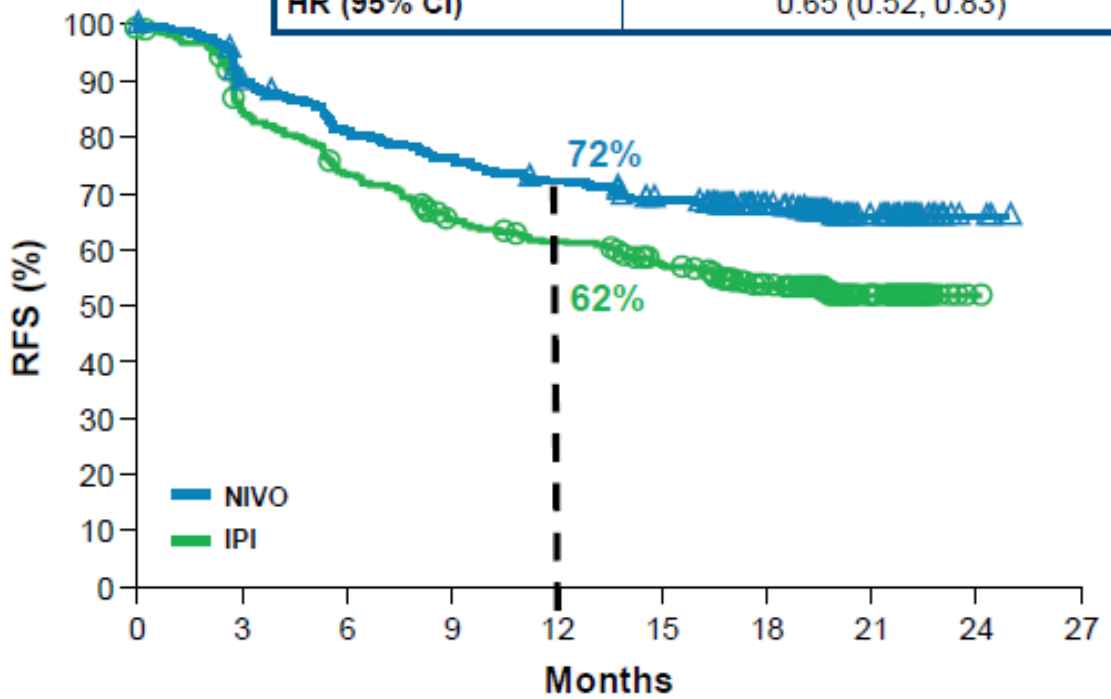
Number of patients at risk

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

Subgroup Analysis of RFS: 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)	

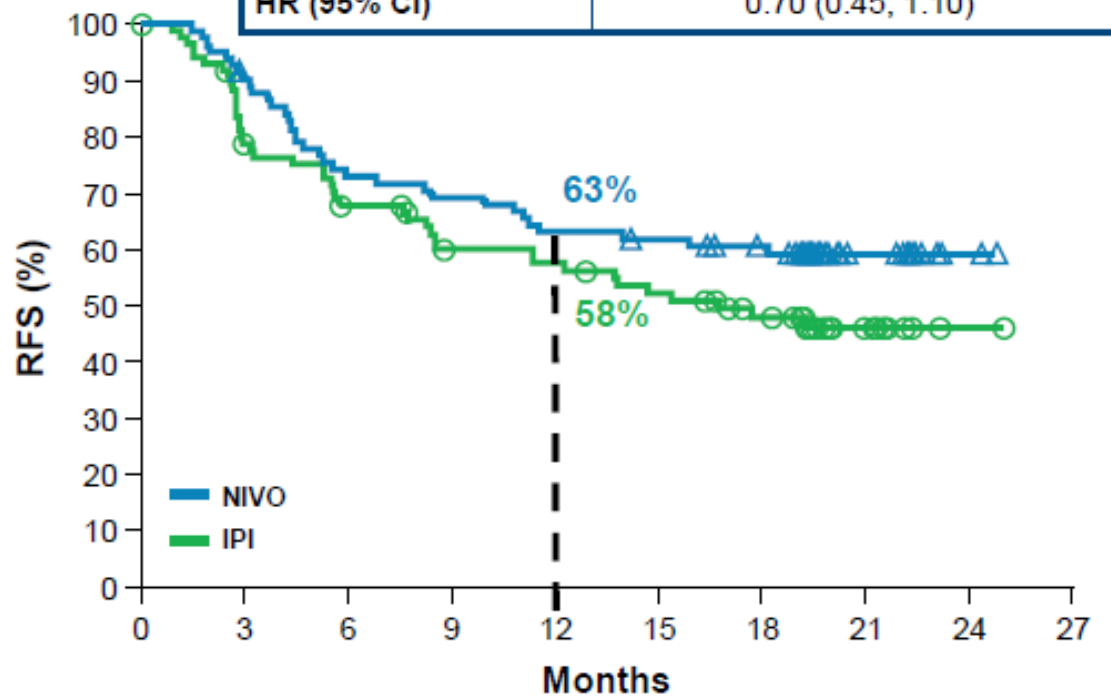


Number of patients at risk

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)	

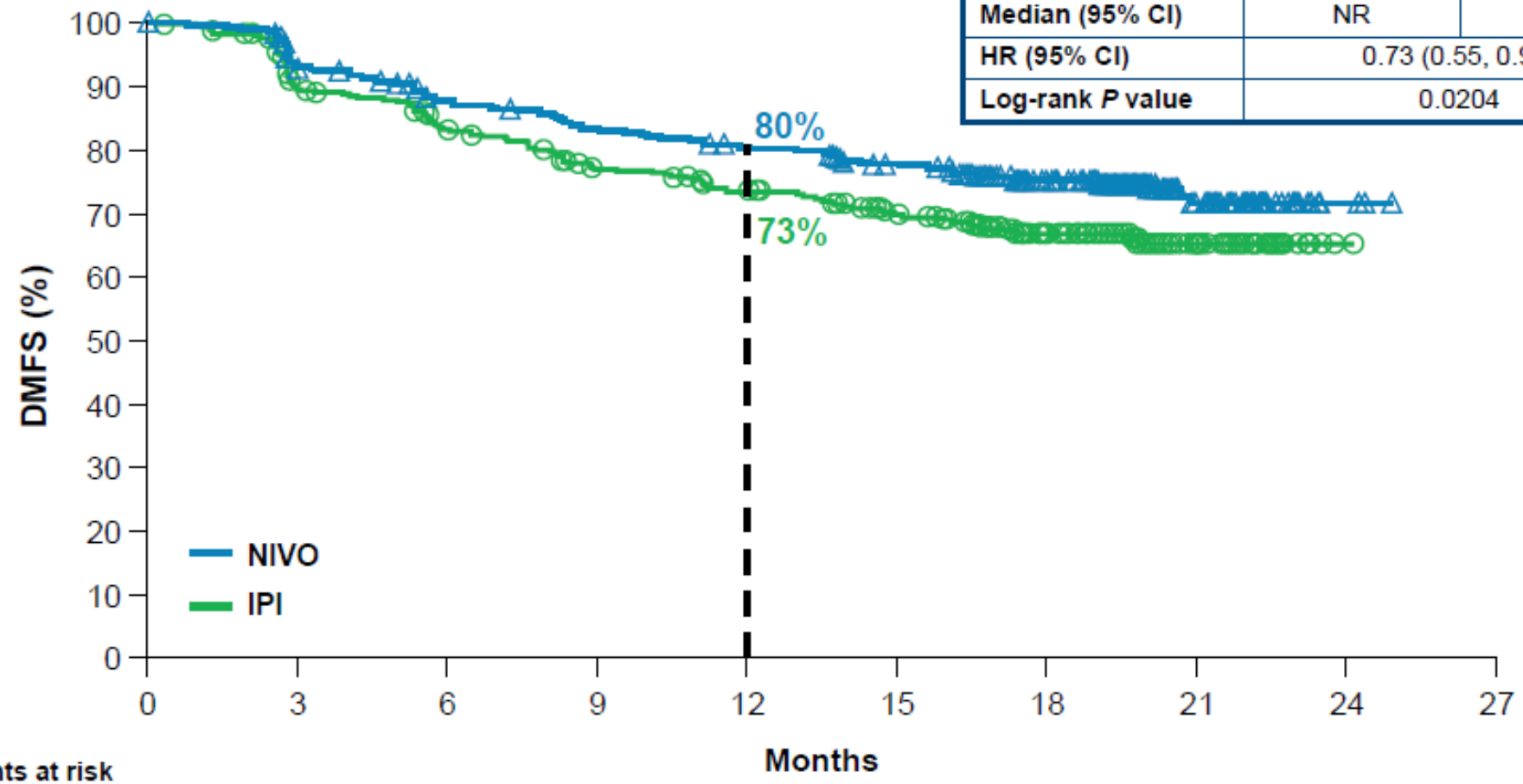


Number of patients at risk

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

Exploratory Endpoint: 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

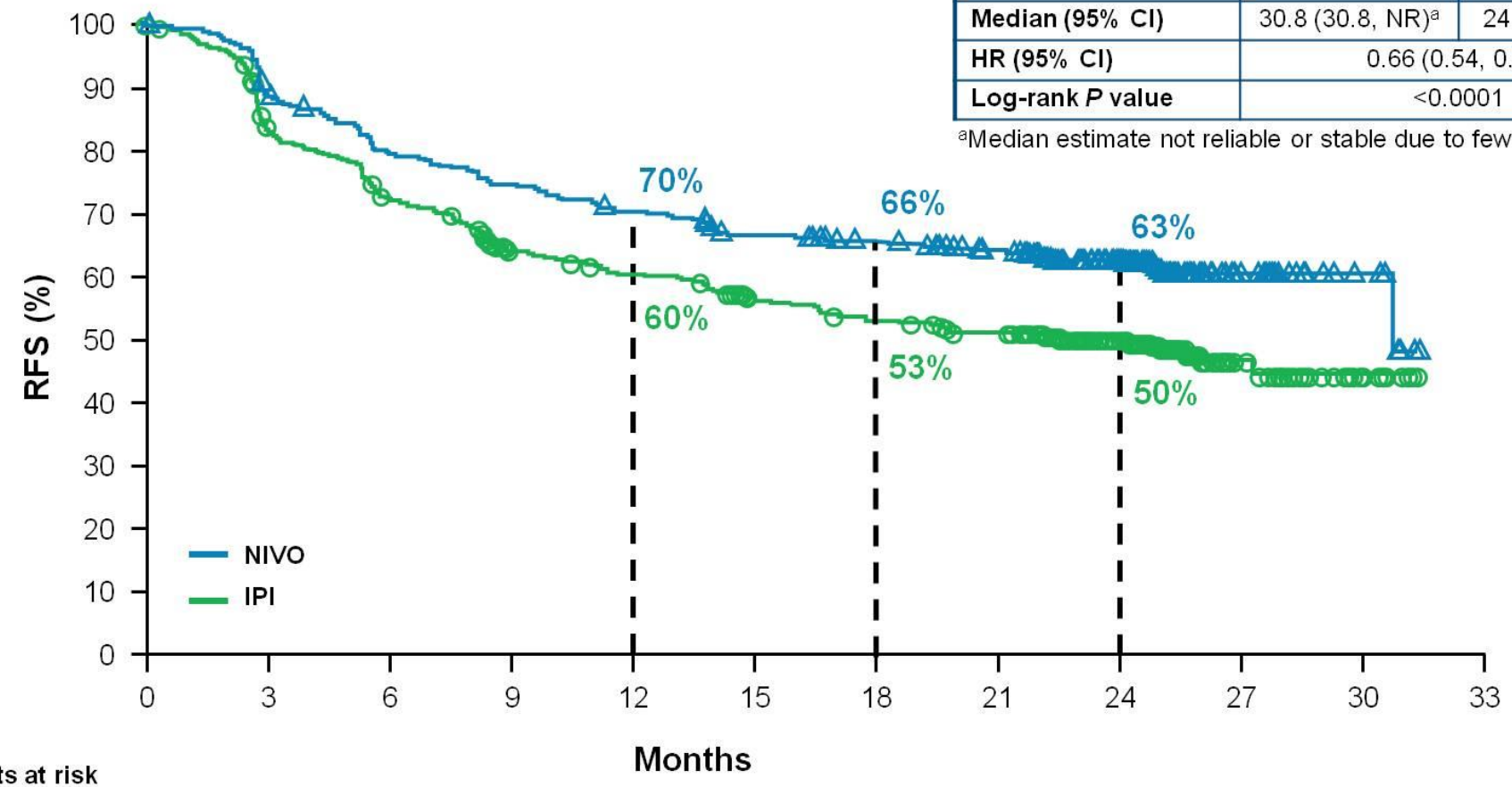
Updated Results from 2 weeks ago

CheckMate 238: 24-Month Follow-Up

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

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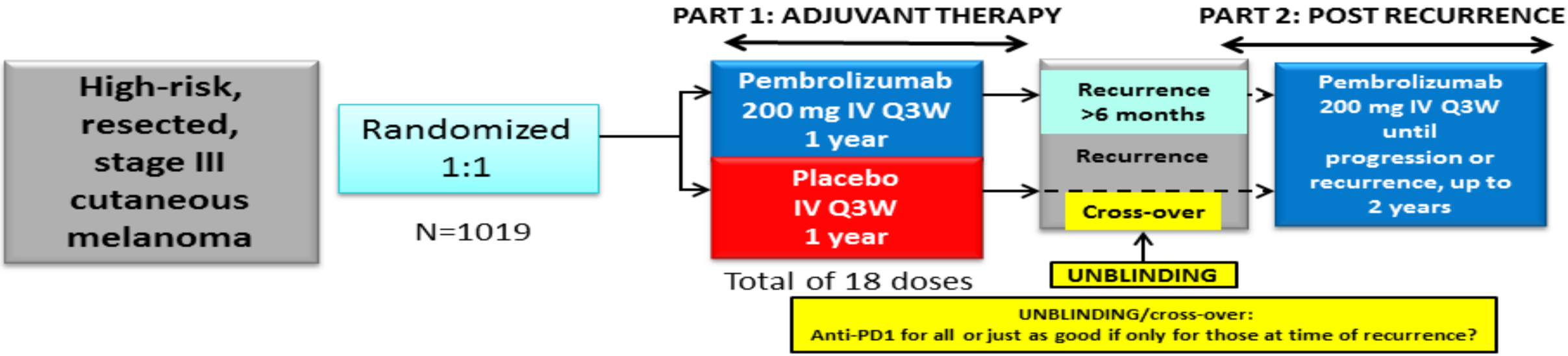
EORTC 1325/KEYNOTE-54: Study Design



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

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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

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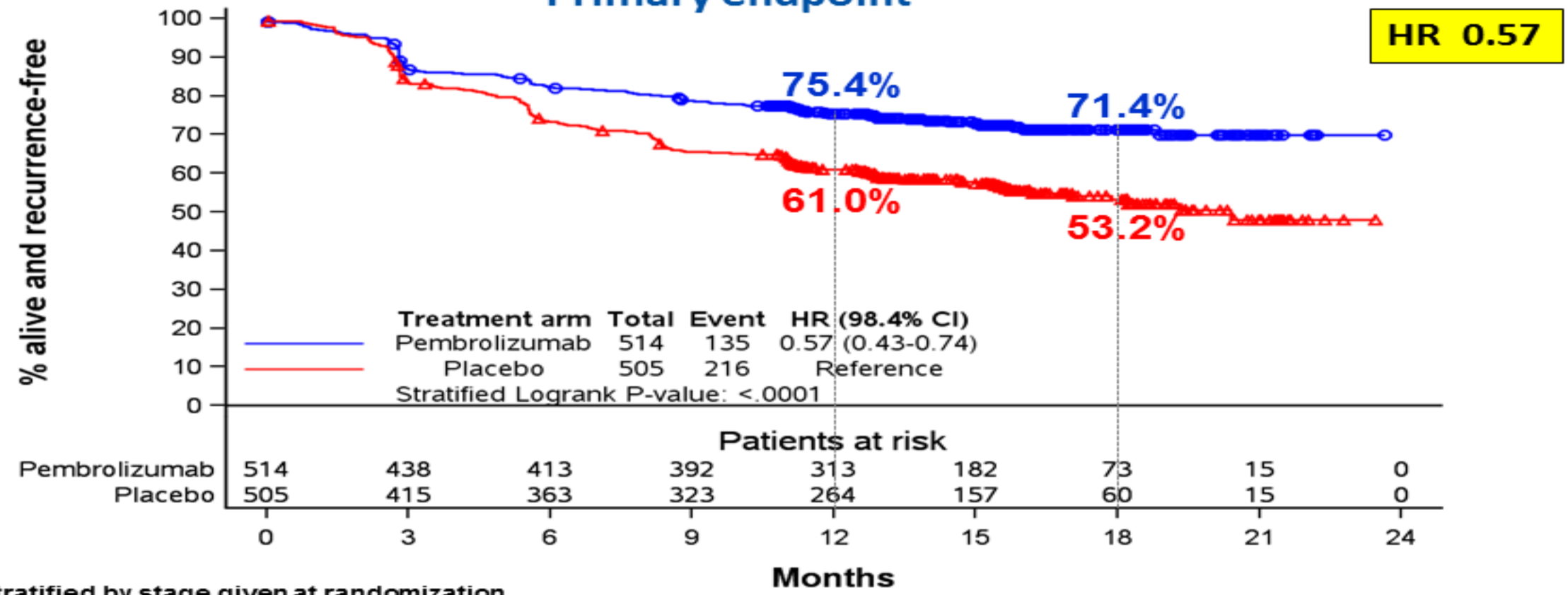
Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

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The future of cancer therapy

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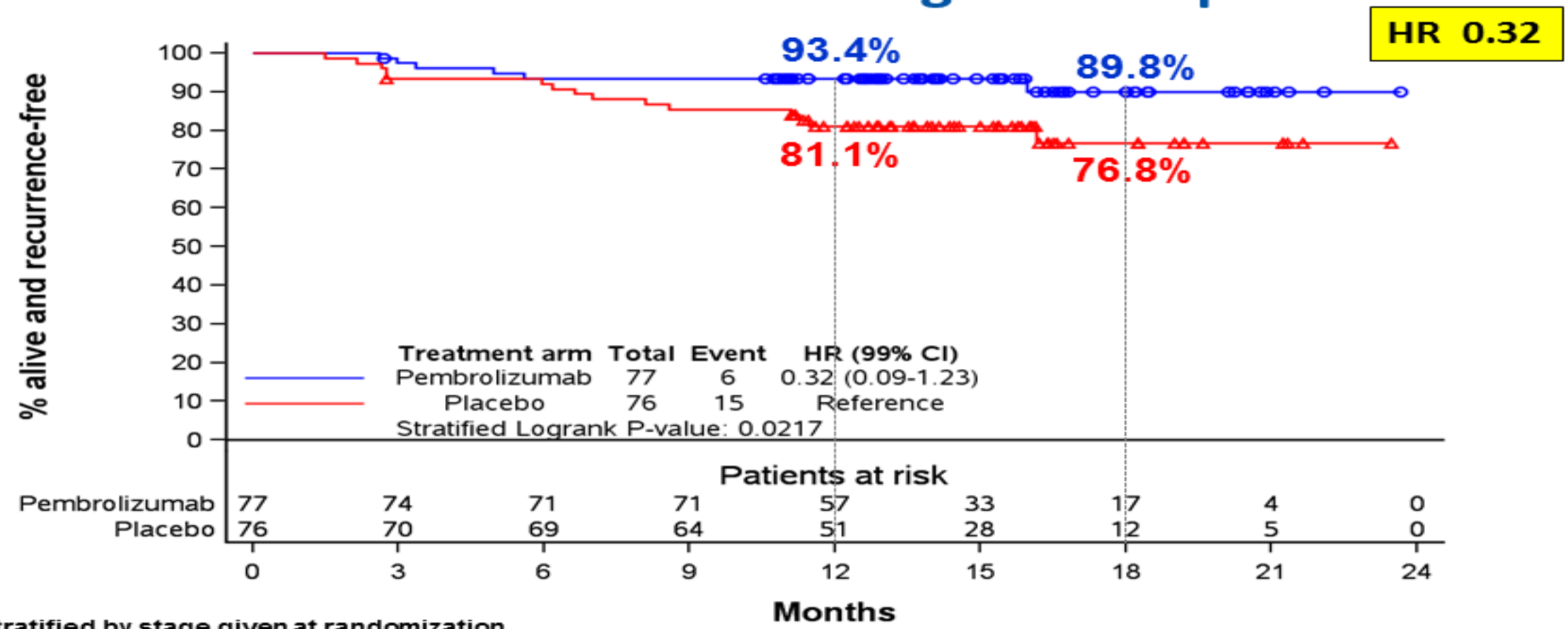
Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

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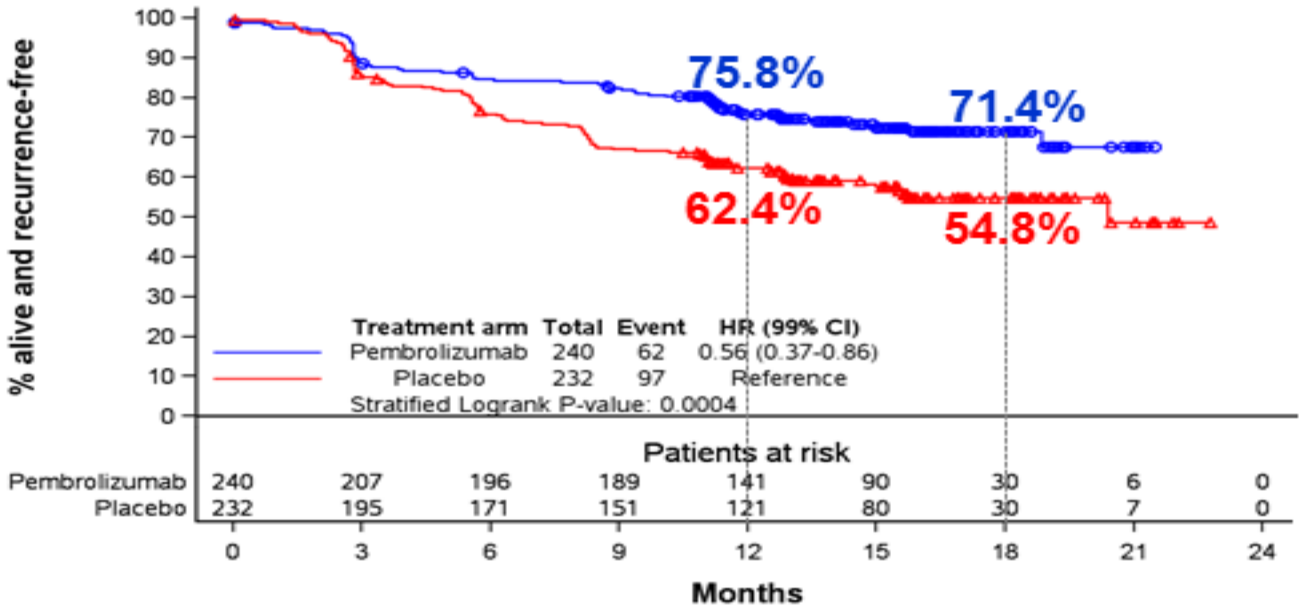
Recurrence-Free Survival

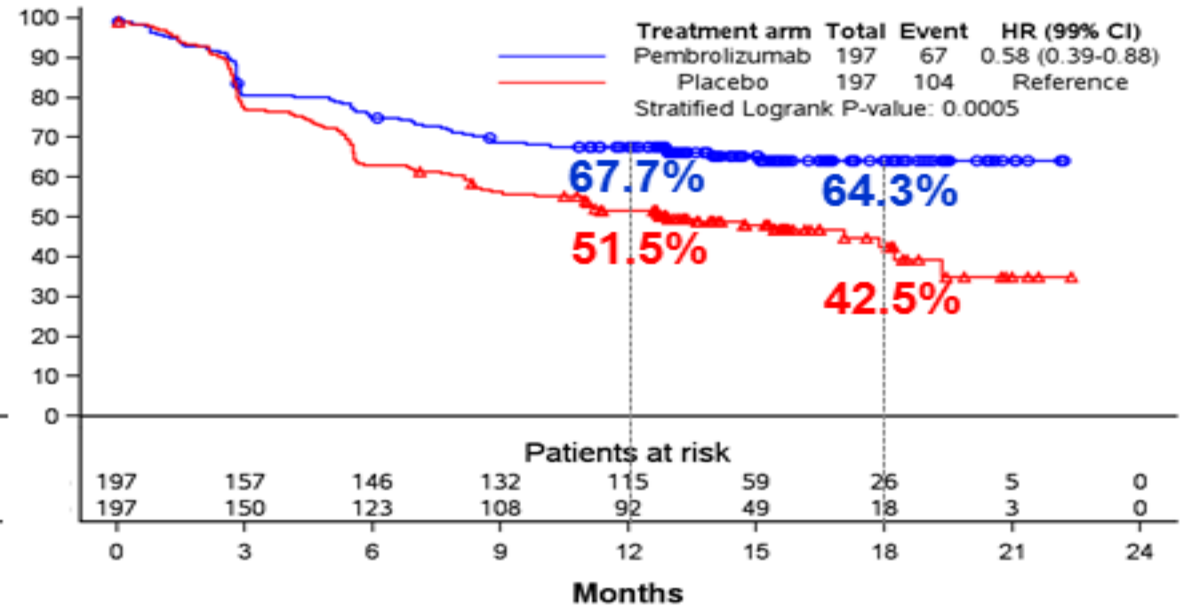
Stage IIIB

HR 0.56



Stage IIIC

HR 0.58



*Stratified by stage given at randomization

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The future of cancer therapy

Conclusions from 238 and 054

- 12 months of Anti PD-1 therapy (Pembrolizumab or Nivolumab) following surgical resection of stage 3 melanoma significantly reduces the risk of Melanoma recurrence.
- No data yet on overall survival.
- Treatments were generally very well tolerated
  - 10-15% moderate to severe side effects
  - 5-10% had to stop treatment because of a side effect
  - Very small risk of a significant long term side effect.

What these trials have told us.

- Adjuvant therapy reduces the relative risk of recurrence by 40-50%
- 15-25% absolute reduction
  - Reduction of both local and distant recurrence
- Overall survival data are immature
  - Significant survival benefit seen with adjuvant Dab/Tram in Braf mutant melanoma
- Treatments are generally well tolerated
  - More short-term toxicity with Dab/Tram
  - Small risk of permanent toxicity with immunotherapy

What we don't yet know

- Will immunotherapy improve overall survival?
  - Is it better to give adjuvant immunotherapy, or treat only once stage 4 disease has developed?
- If a patient is Braf mutant, should we use Targeted therapy or immunotherapy?
- Who will pay for these treatments?
  - Will they get onto the PBS?

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Abstract Submission Deadline – **Sunday 22nd July**

Early Bird Registration Closes – **Sunday 5th August**

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