

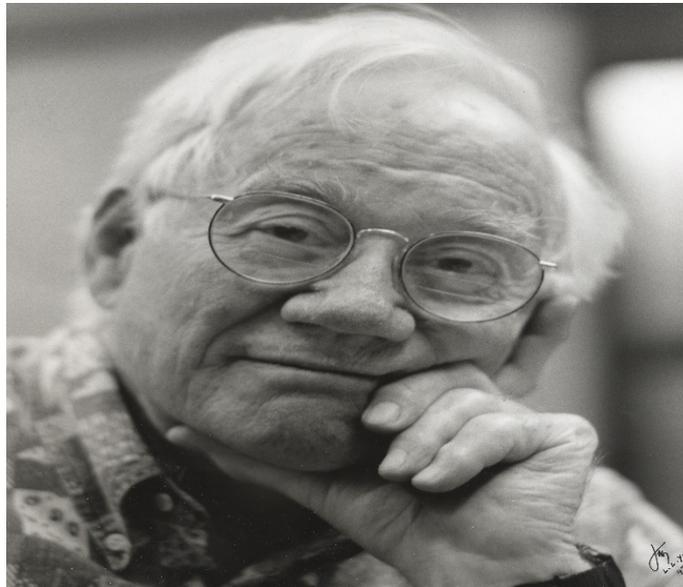


Penn Medicine

# Adjuvant Therapy of Melanoma: Head Spinning Progress

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**2018 Clark Lectureship  
November 16, 2018  
Lynn Schuchter, MD**

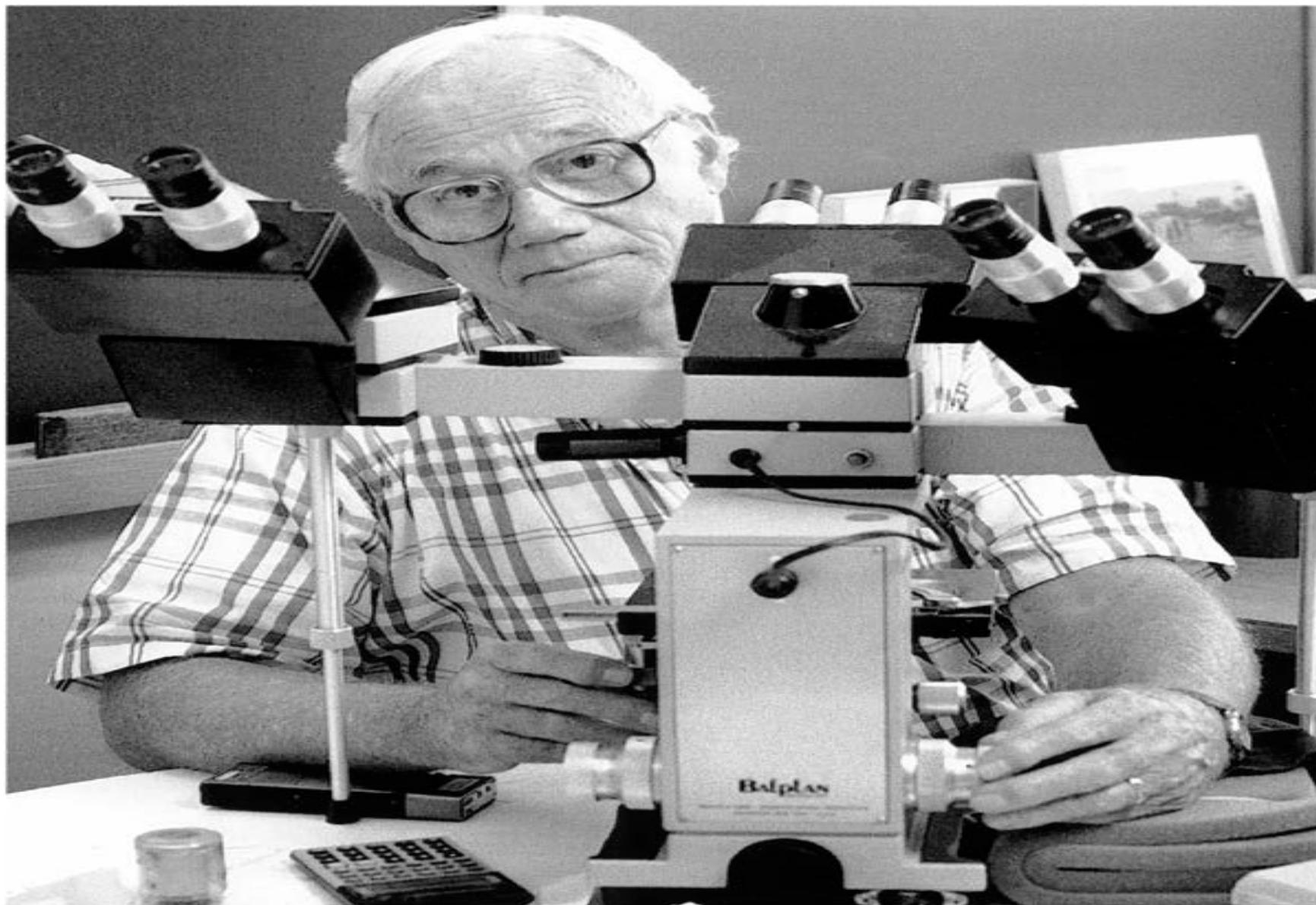


# Disclosures

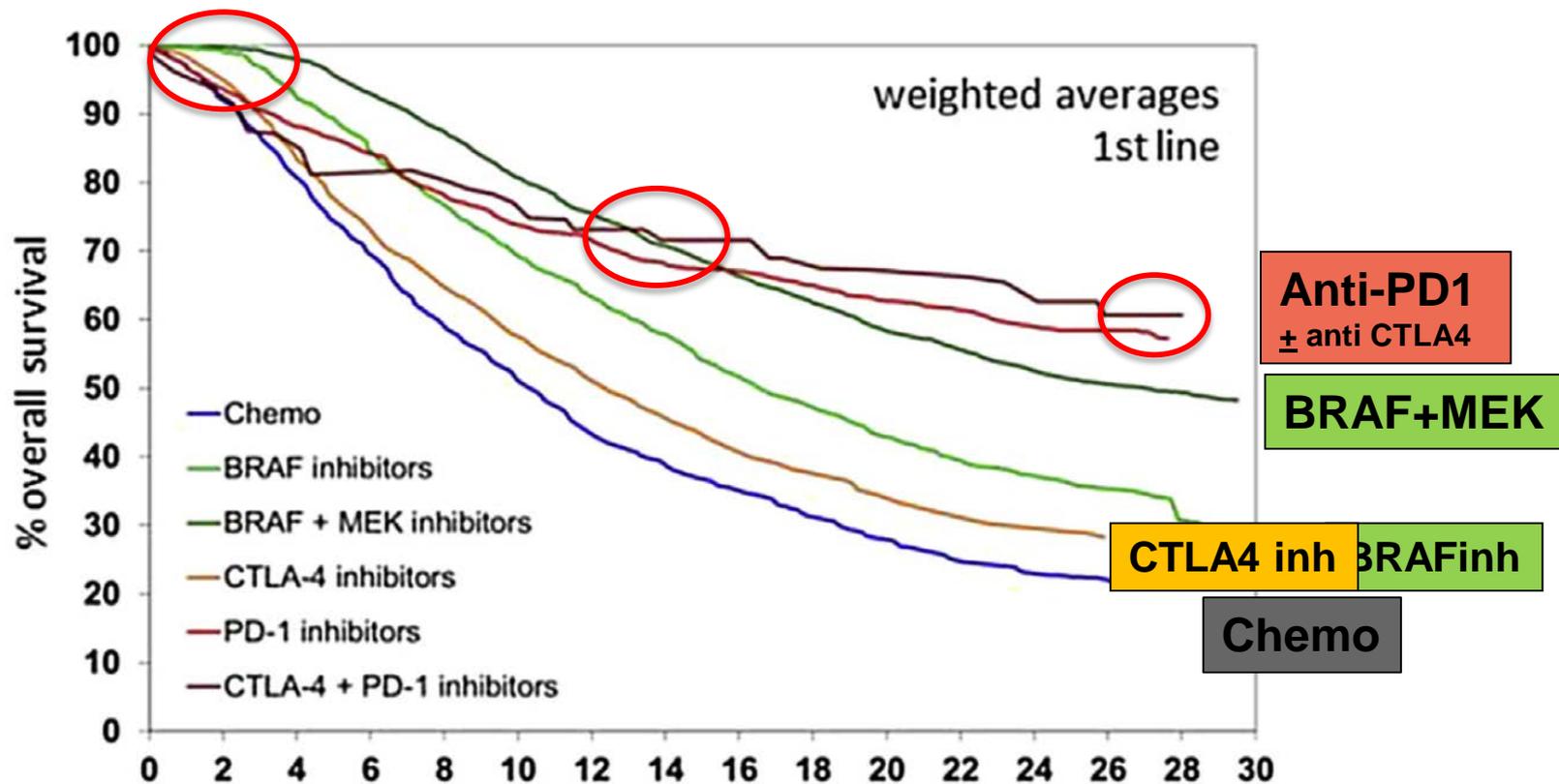
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- ◆ Incyte- Advisory Board

# Wallace Clark, MD



# Effective Drugs in Advanced Melanoma



Ugurel S, et al. *Eur J Cancer* 2017;83:247-57.



# Effective Drugs in Advanced Melanoma

- Remarkably active drugs in Stage IV melanoma.
- Now evidence for direct translation of efficacy of drugs in Stage IV melanoma into the adjuvant setting.
- The best performers in Stage IV disease are best performers in the adjuvant setting.



**Meet Ann**

# THE OLD AND NEW ERA

## Approved drugs for the adjuvant therapy of stage III melanoma

### Old Era (1996–2009)

- High-Dose Interferon (IFN)- $\alpha$ 2b (US, EU), Low-Dose IFN- $\alpha$ 2a (EU), pegylated IFN- $\alpha$ 2b (US)<sup>1</sup>

### New Era (2015–2018)

		Stage	FDA
<b>Ipilimumab (US)<sup>2</sup></b>	HR <sub>RFS</sub> (Ipilimumab vs. Placebo)= 0.75	III	2015
<b>Nivolumab<sup>3</sup></b>	HR <sub>RFS</sub> (Nivolumab vs. Ipil)= 0.65	IIIB/IV	2017
<b>Dabrafenib plus Trametinib<sup>4</sup></b>	HR <sub>RFS</sub> (Dab+Tra vs. Placebo)= 0.47	II	2018
<b>Pembrolizumab<sup>5</sup></b>	HR <sub>RFS</sub> (Pembro vs. Placebo)=0.57	III	(Exp/2018)

<sup>1</sup>Eggermont AM, et al. *Lancet* 2014;383:816-27; <sup>2</sup>Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30; <sup>3</sup>Weber J, et al. *N Engl J Med* 2017;377:1824-35;

<sup>4</sup>Long GV, et al. *N Engl J Med* 2017;377:1813-23; <sup>5</sup>Eggermont AM, et al. *N Engl J Med* 2018;375:1845-55: 15 March; <sup>6</sup>Romano E, et al. *J Clin Oncol* 2010;28:3042-7.

# Adjuvant Ipilimumab in Stage III Melanoma RFS in 2015 and OS in 2016

## Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial

*Alexander M M Eggermont, Vanna Chiarion-Sileni, Jean-Jacques Grob, Reinhard Dummer, Jedd D Wolchok, Henrik Schmidt, Omid Hamid, Caroline Robert, Paolo A Ascierto, Jon M Richards, Céleste Lebbé, Virginia Ferraresi, Michael Smylie, Jeffrey S Weber, Michele Maio, Cyril Kontos, Axel Hoos, Veerle de Pril, Ravichandra Karra Gununath, Gaetan de Schaezen, Stefan Suci, Alessandro Testori*

**Lancet Oncol.** 2015 May;16(5):522-30.

*The NEW ENGLAND JOURNAL of MEDICINE*

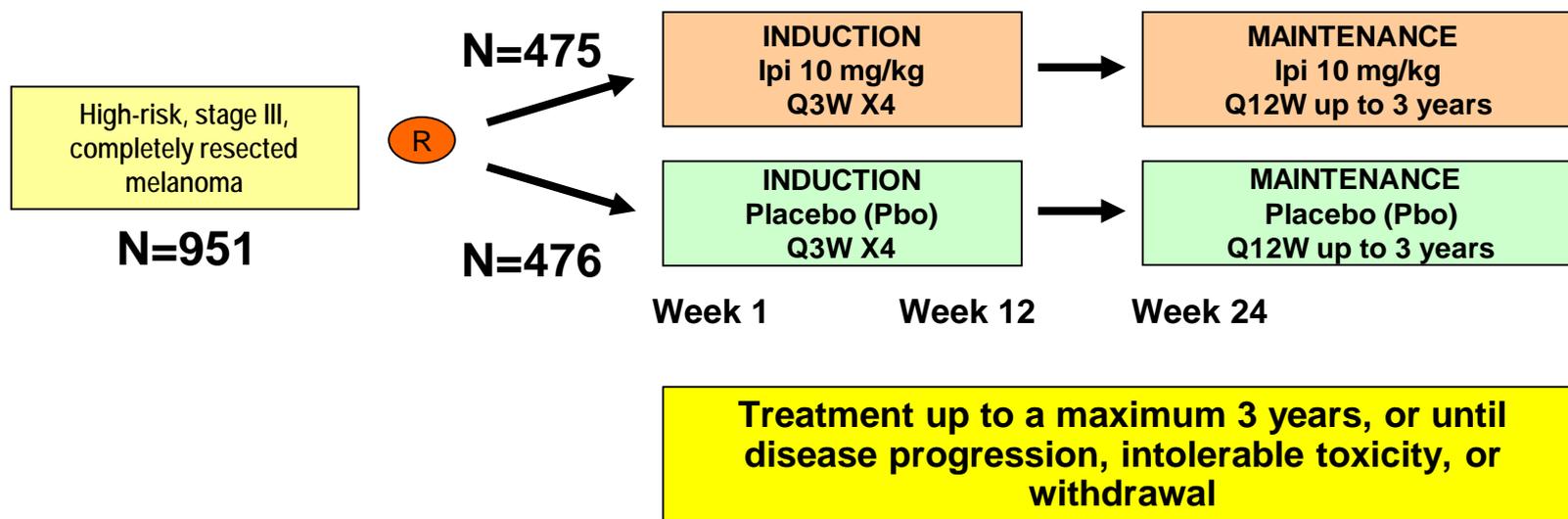
ORIGINAL ARTICLE

## Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaezen, S. Suci, and A. Testori

**NEJM**, 2016 Nov 10;375(19):1845-1855

# EORTC 18071/CA184-029: Study Design

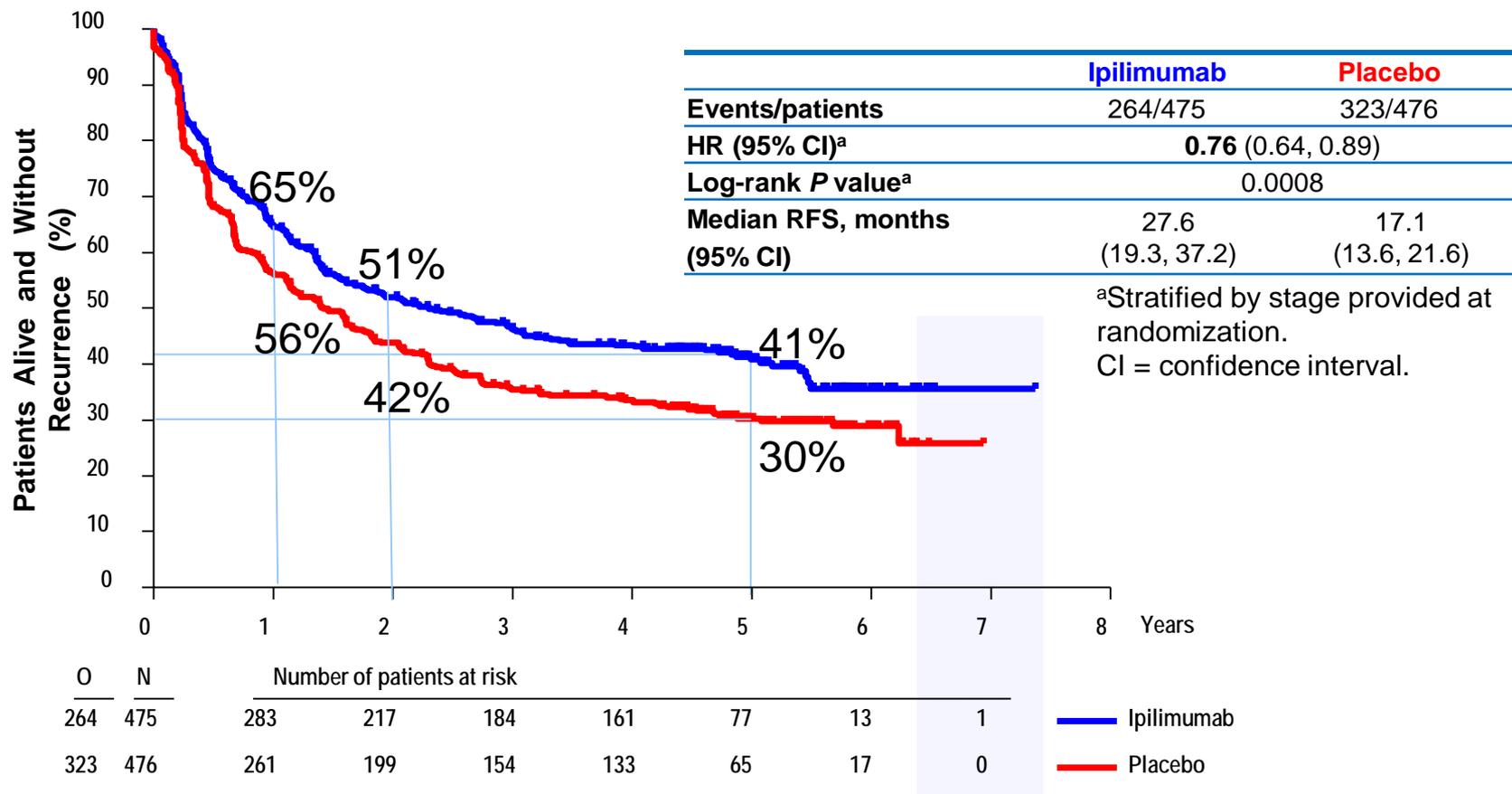


Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC  $\geq 4$  positive lymph nodes)
- Regions (North America, European countries and Australia)

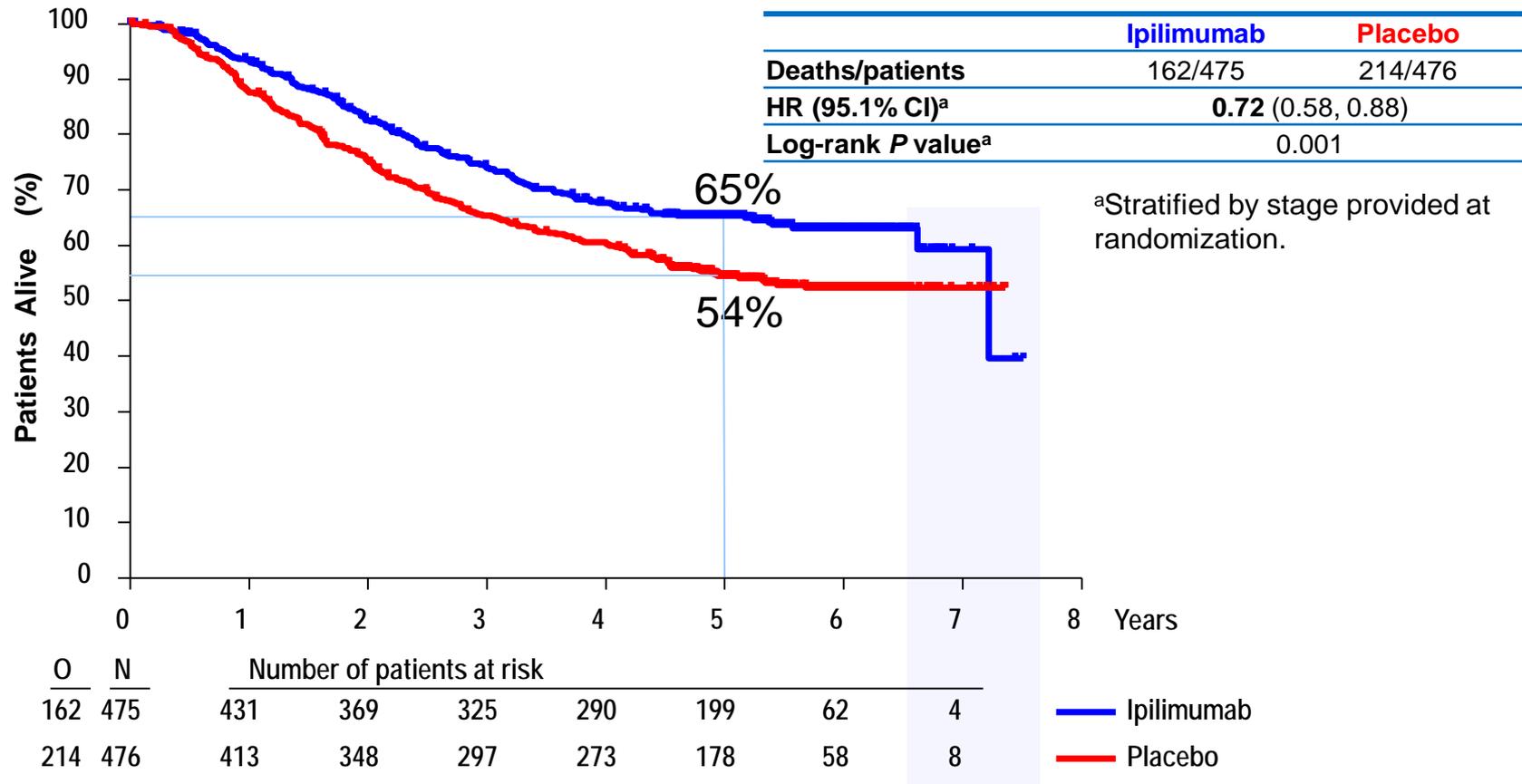
# EORTC 18071 adjuvant ipilimumab

## RFS @ (median FU 5.3 yrs)



# Overall Survival Adjuvant Ipilimumab in Stage III melanoma

OS



# PROBLEM: Immune-Related Adverse Events Ipilimumab Any grade – grade 3-4 (%)

**Skin**  
63.4 – 4.5



**5 GRADE 5 1.1 %**  
3 colitis  
1 myocarditis  
1 Guillain-Barré

**GI 46.3 – 14.9**  
Diarrhea 41.4 - 9.6  
Colitis 15.9 – 7.6



**Pulmonary**  
2.4 – 1.0

**Myocarditis**  
0.2 – 0.2

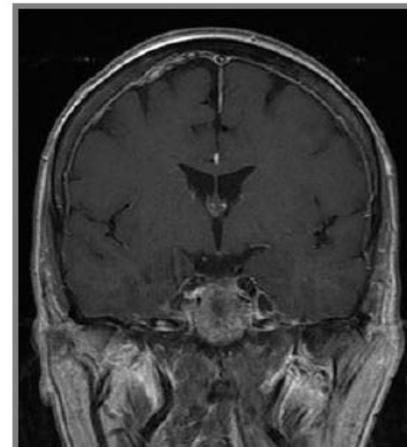
**Hepatitis**  
25.1 – 7.9

**Endocrine**  
37.6 – 7.9

**Hypophysitis**  
18.3 – 5.1

**Thyroid**  
8.9 – 0.2

**Neurologic**  
4.5 – 1.1



ORIGINAL ARTICLE

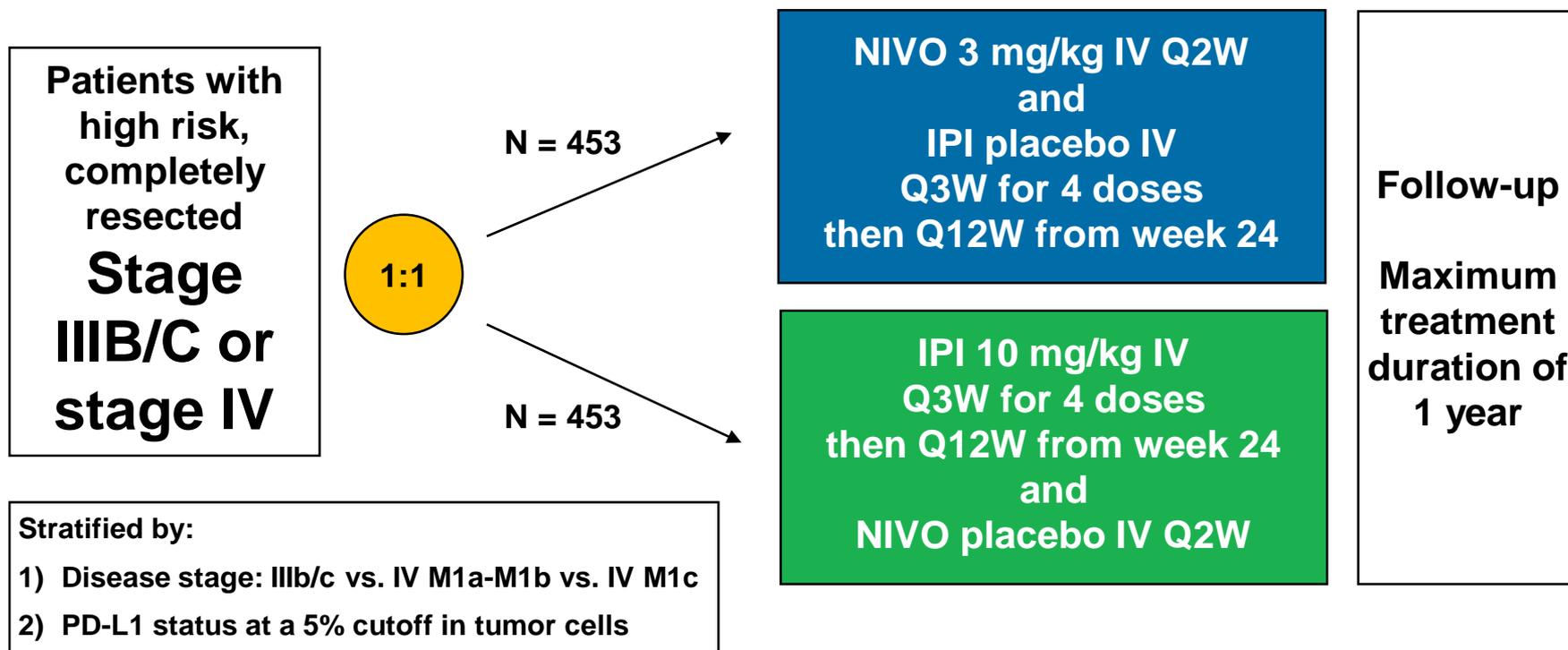
# Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators\*

University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; <sup>15</sup>Gallipoli Medical Research Foundation and Princess Alexandra Hospital, and University of Queensland, Queensland, Australia; <sup>16</sup>IRCCS San Martino-IST, Genova, Italy; <sup>17</sup>Bristol-Myers Squibb, Princeton, NJ, USA; <sup>18</sup>Royal Marsden Hospital, London, UK; <sup>19</sup>Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; \*Contributed equally to this study.

*N Engl J Med* 2017;377:1824-35

# CHECKMATE-238: Study Design



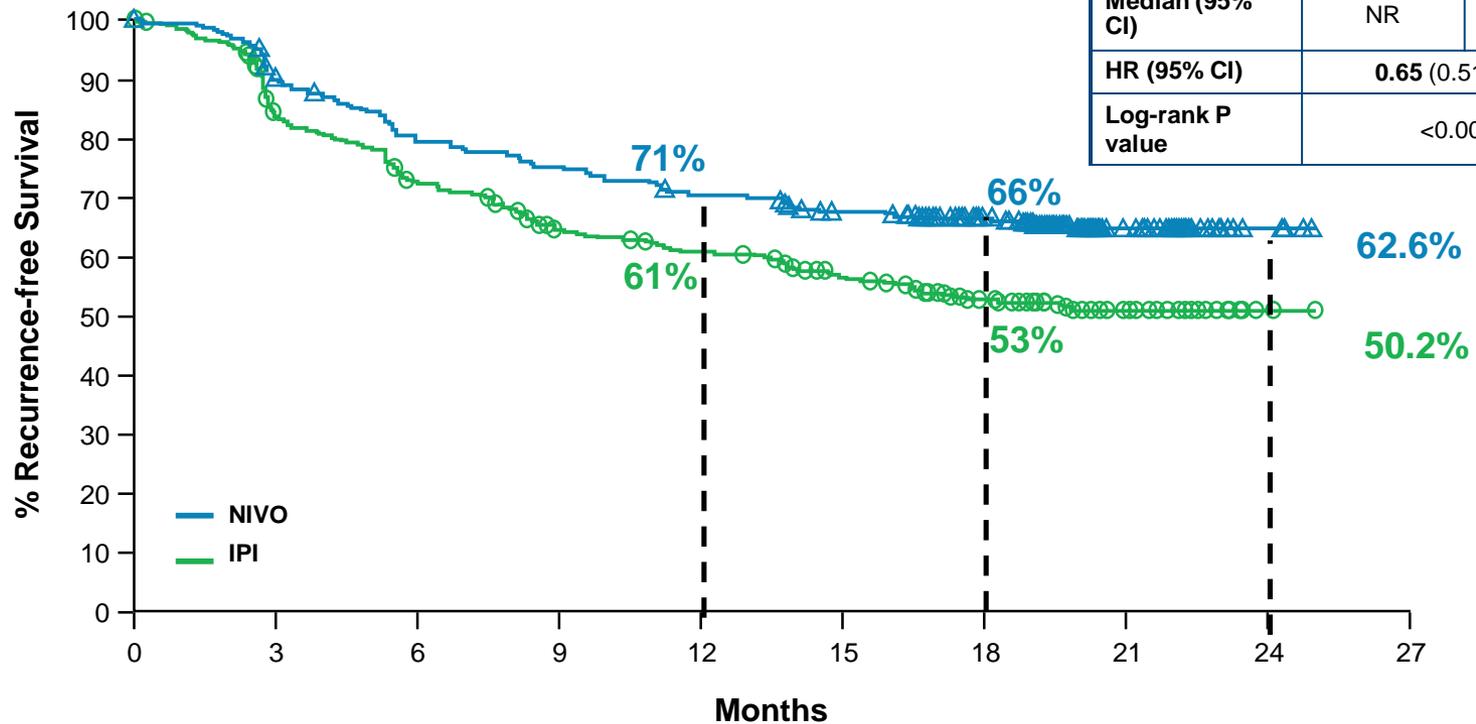
**Enrollment period:** March 30, 2015 to November 30, 2015

IPI, ipilimumab; Mel, melanoma;  
NIVO, nivolumab; QXW, every X weeks

# Adjuvant Nivolumab vs Ipilimumab

## Primary Endpoint: RFS

**RFS**



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

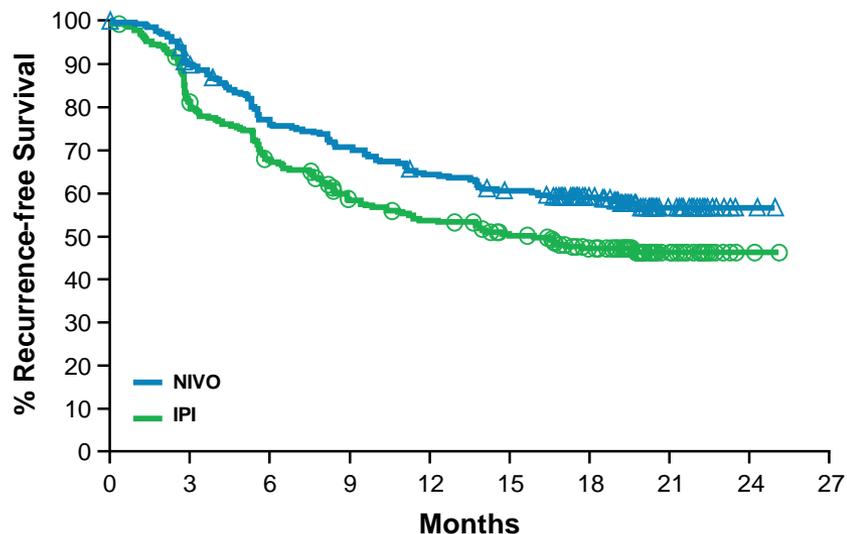
Number of patients at risk

	0	3	6	9	12	15	18	21	24	27
<b>NIVO</b>	453	399	353	332	311	291	249	71	5	0
<b>IPI</b>	453	364	314	269	252	225	184	56	2	0

# Subgroup Analysis of RFS: PD-L1 Expression Level

## PD-L1 Expression Level <5%

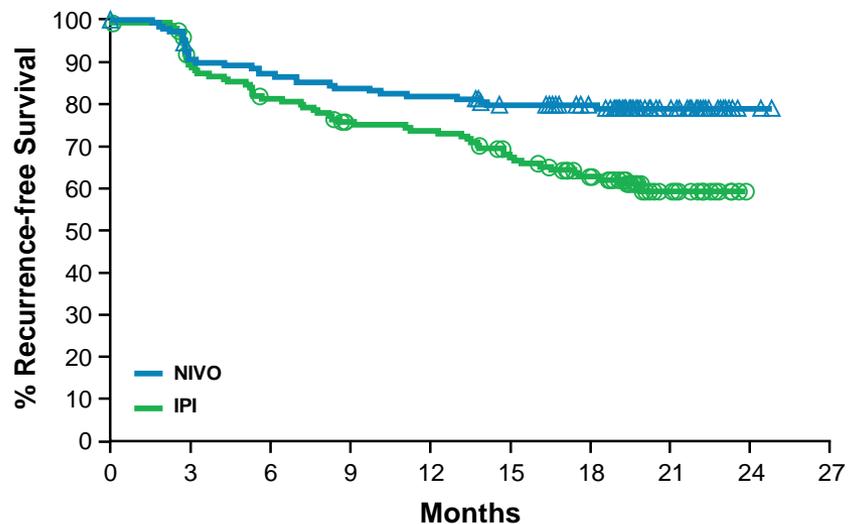
	NIVO	IPI
Events/patients	114/275	143/286
Median (95% CI)	NR	15.9 (10.4, NR)
HR (95% CI)	0.71 (0.56, 0.91)	



	0	3	6	9	12	15	18	21	24	27
NIVO	275	242	204	189	171	159	129	41	3	0
IPI	286	219	184	153	139	124	100	31	2	0

## PD-L1 Expression Level ≥5%

	NIVO	IPI
Events/patients	31/152	57/154
Median (95% CI)	NR	NR
HR (95% CI)	0.50 (0.32, 0.78)	



	0	3	6	9	12	15	18	21	24	27
NIVO	152	135	130	125	122	114	105	26	2	0
IPI	154	133	120	108	105	93	78	21	0	0

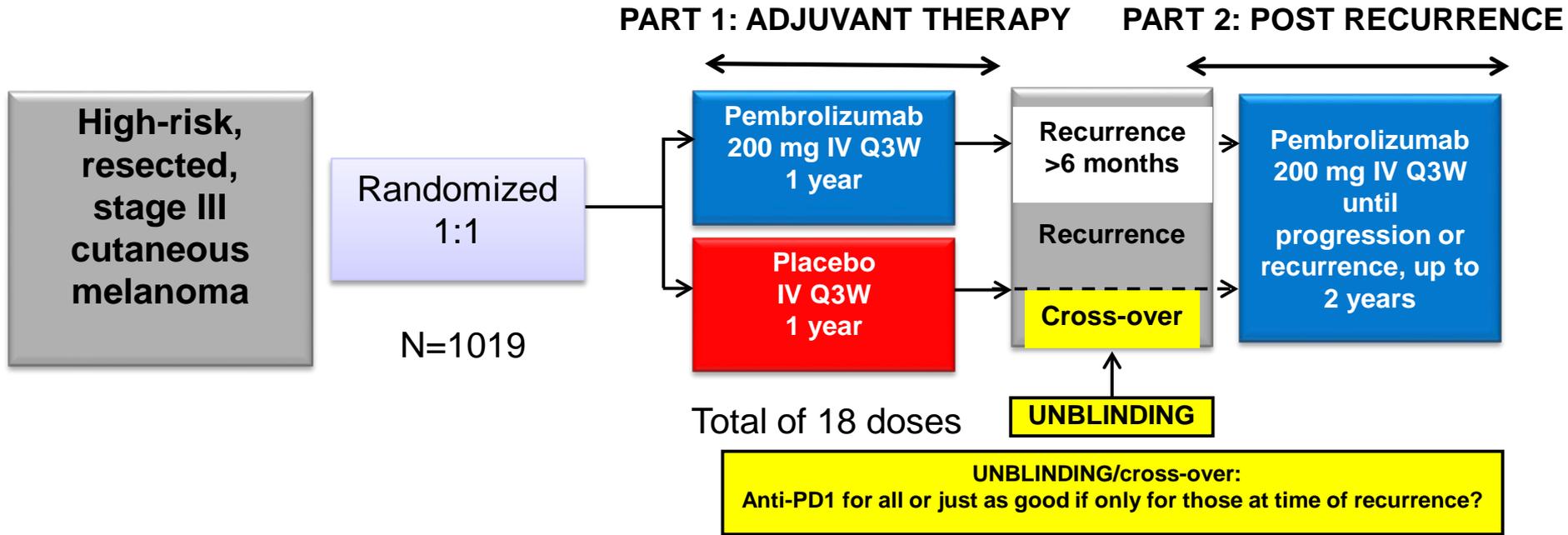
ORIGINAL ARTICLE

# Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D.,  
Mario Mandala, M.D., Georgina V. Long, M.D., Ph.D., Victoria Atkinson, M.D.,  
Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D.,  
Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D.,  
James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D.,  
Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D.,  
Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D.,  
Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D.,  
Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D.,  
Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciú, Ph.D.,  
and Caroline Robert, M.D., Ph.D.

*N Engl J Med* 2018;375:1845-55

# 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

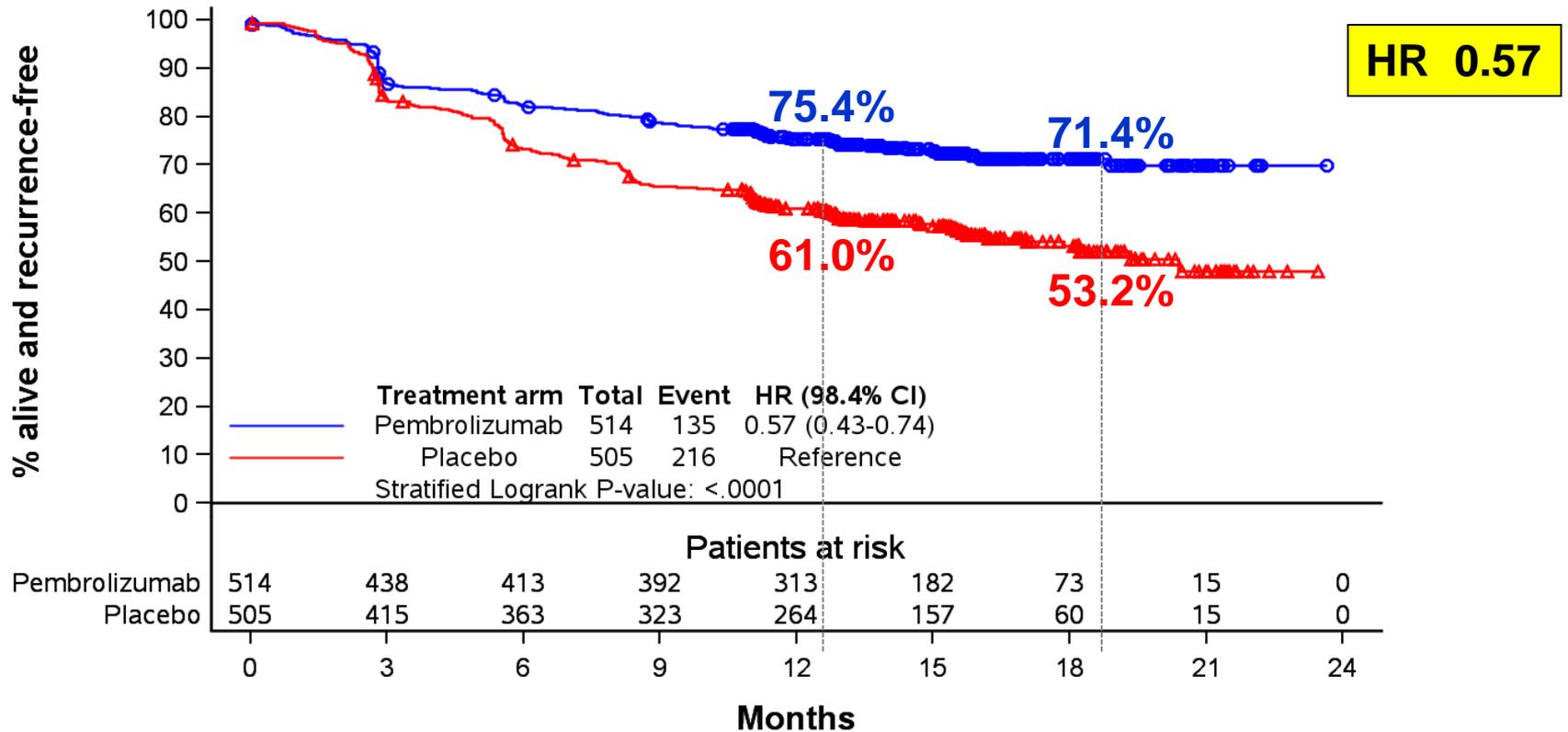
## Primary Endpoints:

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

## Secondary Endpoints:

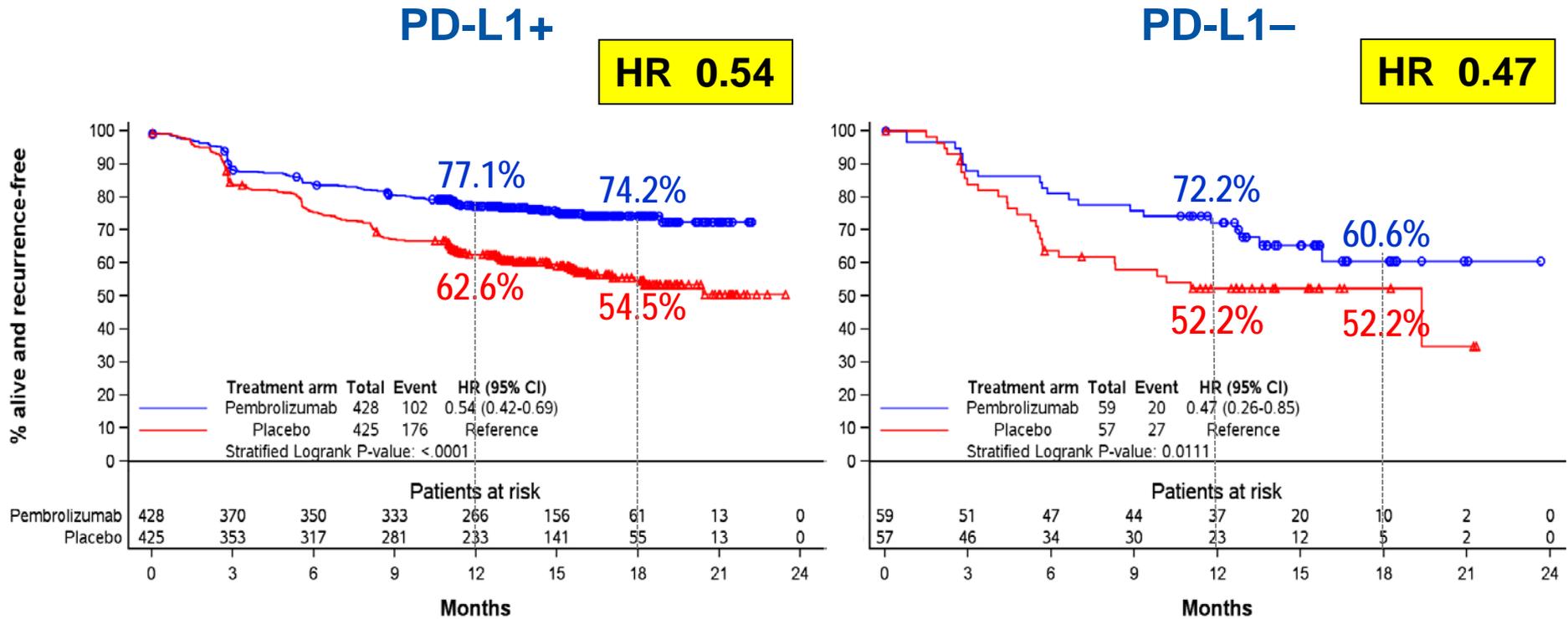
- DMFS and OS in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

# Pembrolizumab vs Placebo ITT Population : RFS Primary endpoint



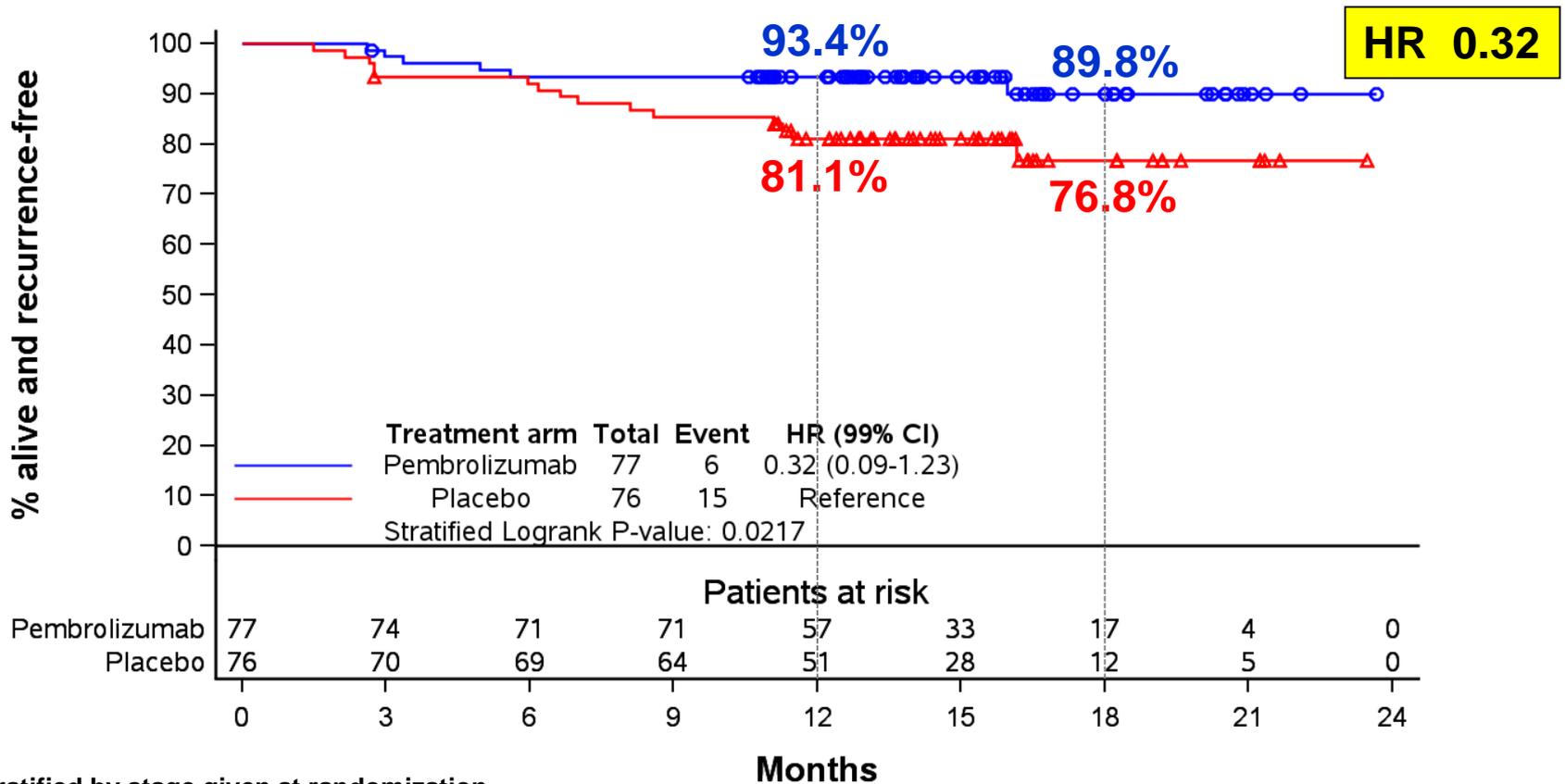
\*Stratified by stage given at randomization

# Recurrence-Free Survival PDL+ vs PL1-



\*Stratified by stage given at randomization

# Recurrence-Free Survival in Stage IIIA

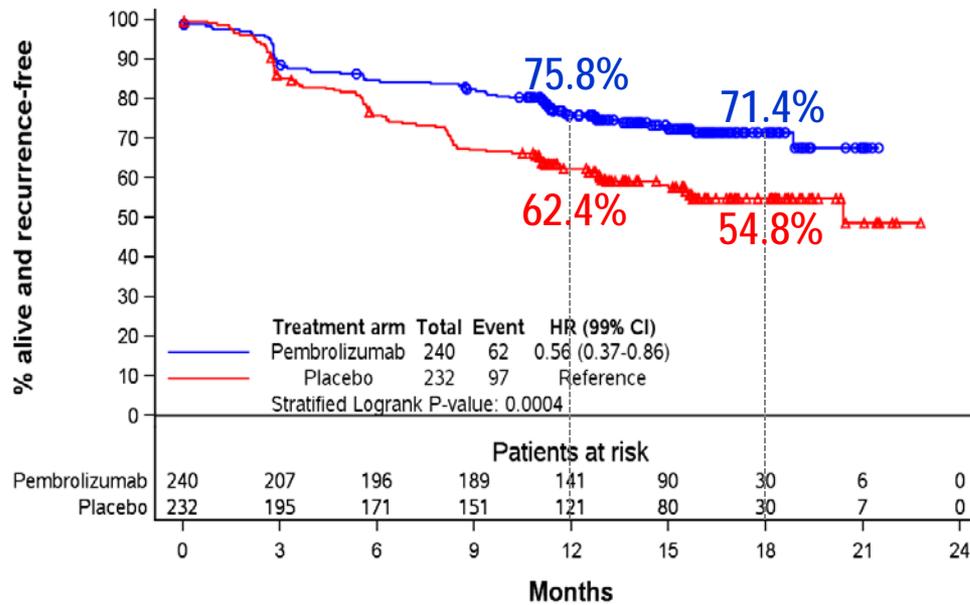


\*Stratified by stage given at randomization

# Recurrence-Free Survival in IIIB and IIIC

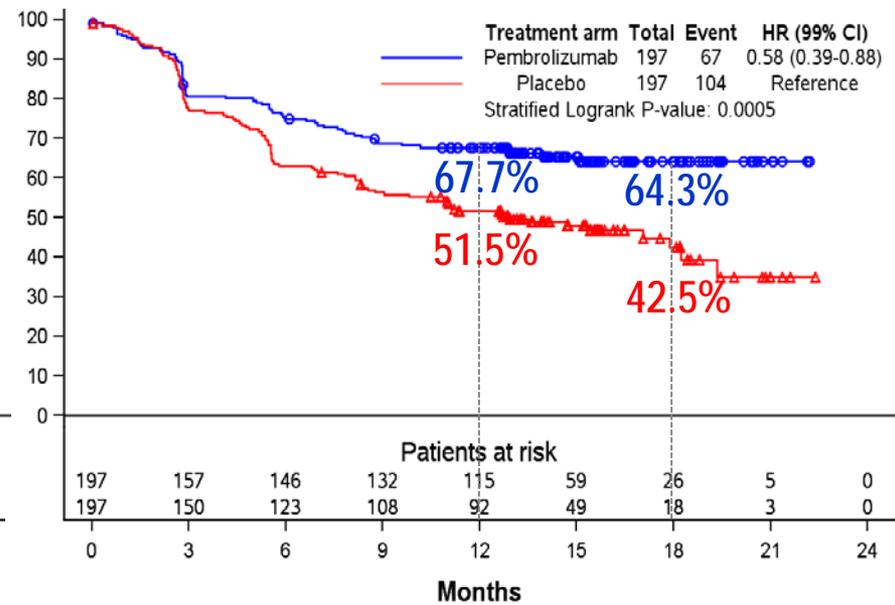
## Stage IIIB

**HR 0.56**



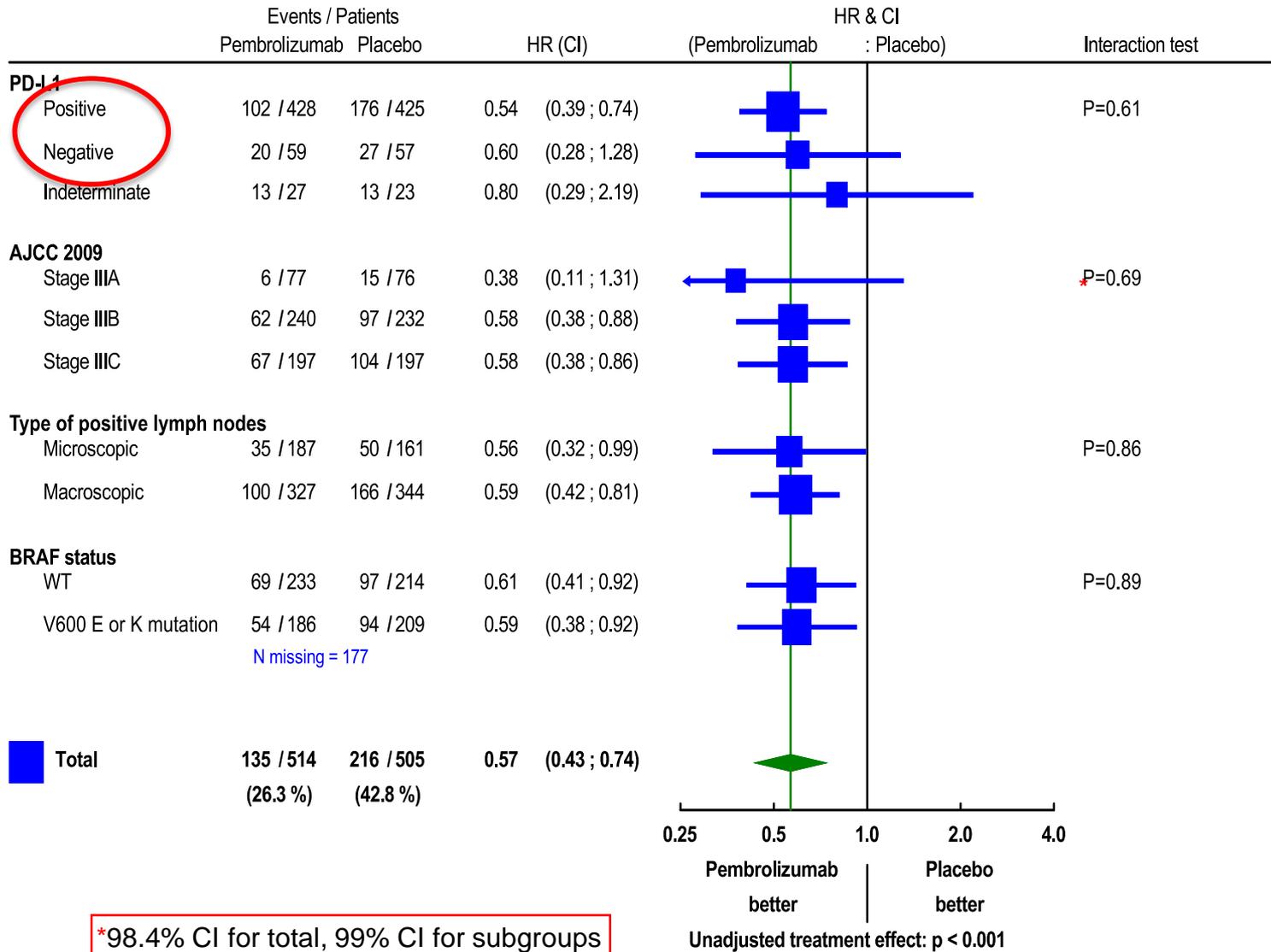
## Stage IIIC

**HR 0.58**



\*Stratified by stage given at randomization

# RFS: Subgroup Analysis (non-stratified)



# Immune-Related Adverse Events Anti-PD1 Adjuvant Tx

Any grade – grade 3-4 (%) (0.2% = 1 patient)

(0.2% = 1  
patient)

**Skin**  
5.3 – 0.6

**Myositis\***  
(grade 5)  
0.2 – 0.2

**Pancreatitis**  
0.4 – 0.2

**Colitis**  
3.7 – 2.0



**Pneumonitis**  
3.3 – 0.8

**Myocarditis**  
0.2 – 0.2

**Hepatitis**  
1.8 – 1.4

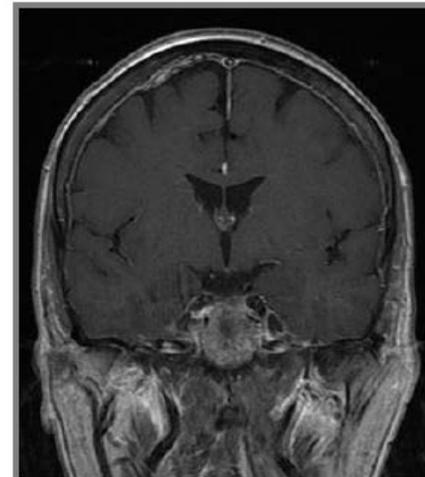
**Nephritis**  
0.4 – 0.4

**Thyroid**  
20.8 – 0.2

**Hypophysitis**  
2.2 – 0.6

**Diabetes**  
1.0 – 1.0

**Adrenal**  
1.0 – 0.2



ORIGINAL ARTICLE

# Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà,  
V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert,  
L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang,  
B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

*N Engl J Med* 2017;377:1813-23

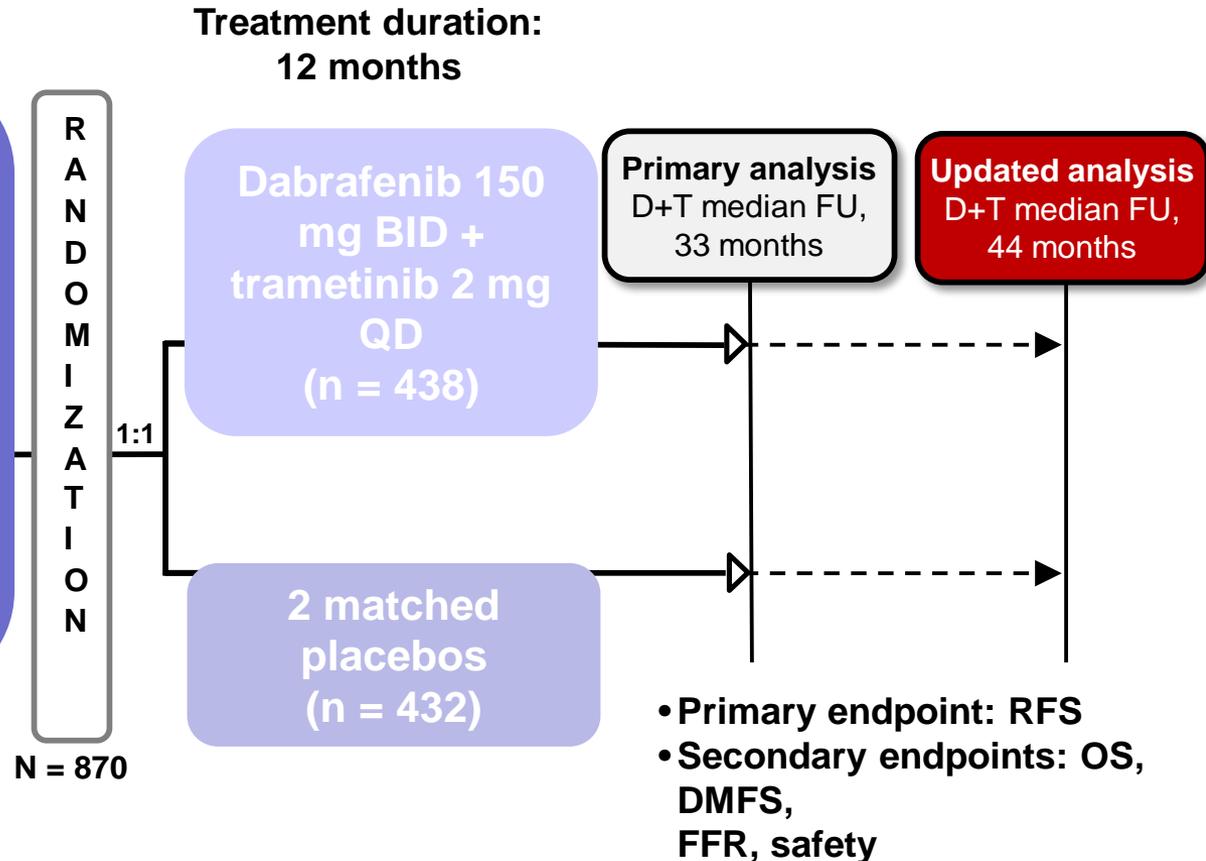
# COMBI-AD: STUDY DESIGN

## 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

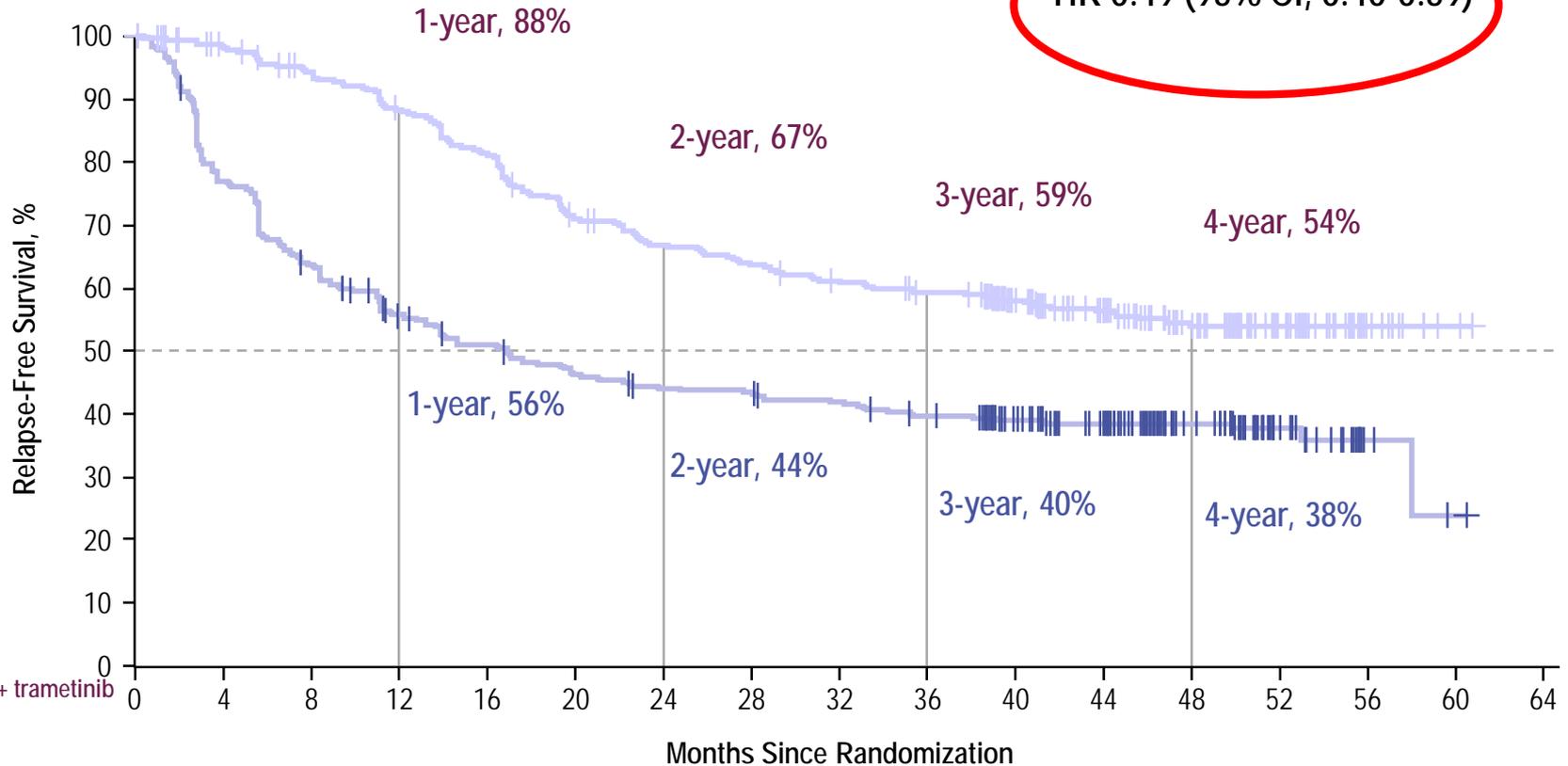
## Stratification

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



# Dabrafenib + Trametinib vs Plac Stage III Relapse Free Survival

HR 0.49 (95% CI, 0.40-0.59)

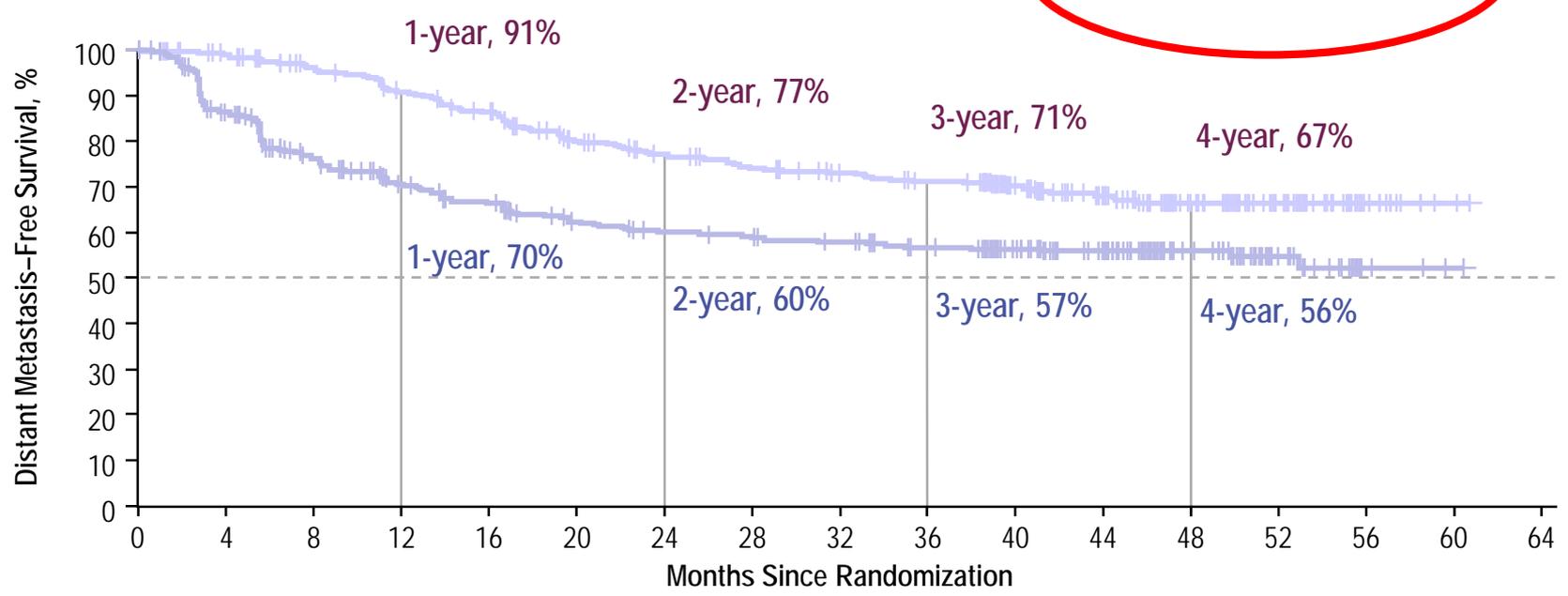


No. at risk  
Dabrafenib + trametinib  
Placebo

438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

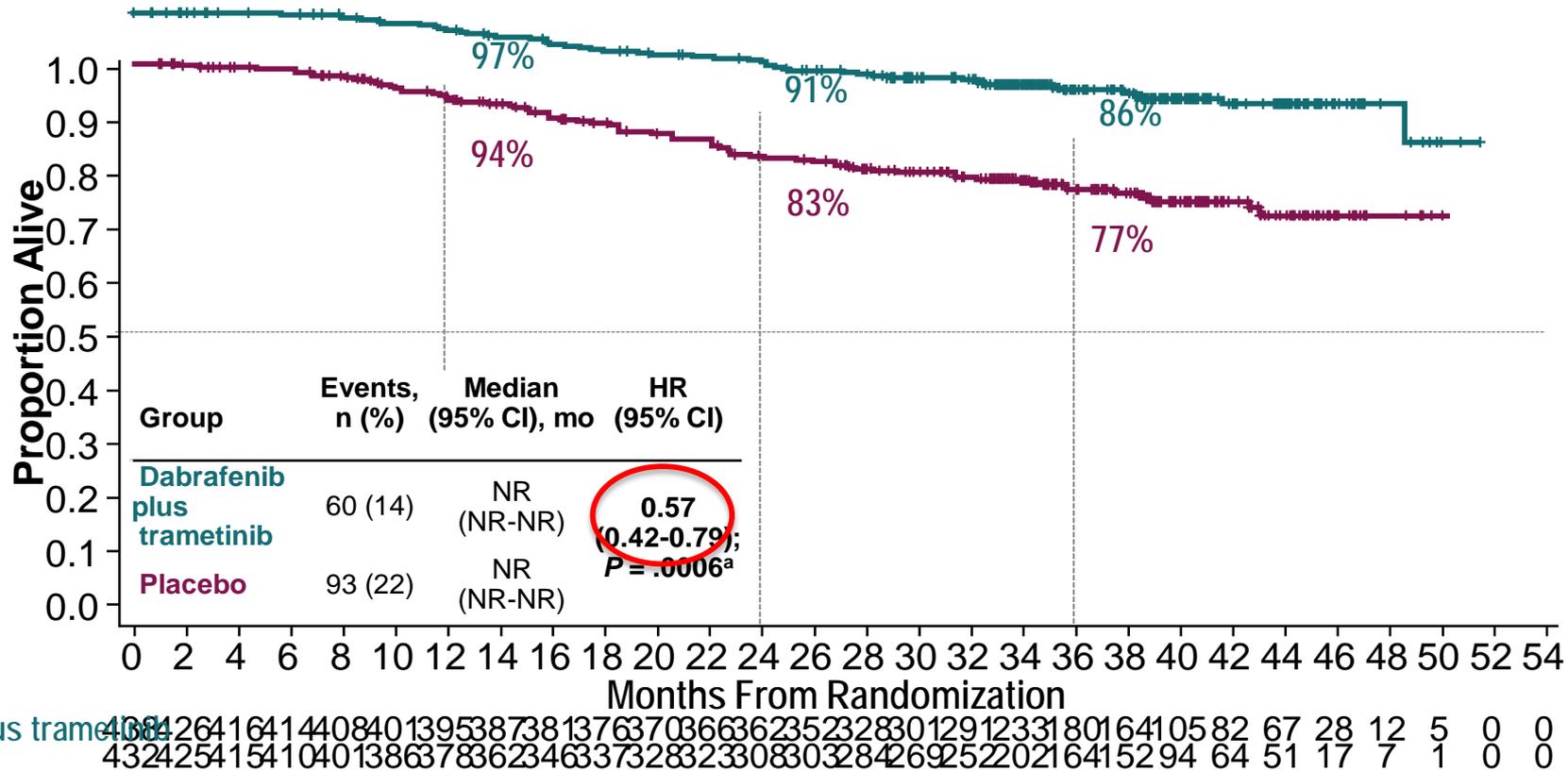
# Dabrafenib + Trametinib vs Plac Stage III Distant Metastasis Free Survival

HR 0.53 (95% CI, 0.42-0.67)



No. at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
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

# D+T vs Placebo: Overall Survival (1st interim analysis)



<sup>a</sup> Prespecified significance boundary (P = .000019).

# Targeted Therapy Side Effects

- Rash, hand-foot,
- Arthralgias
- LFTs abnormalities
- Pyrexia
- Second Malignancies: SCC-  
20%



# COMBI-AD: Safety summary

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

# TOXICITY in perspective

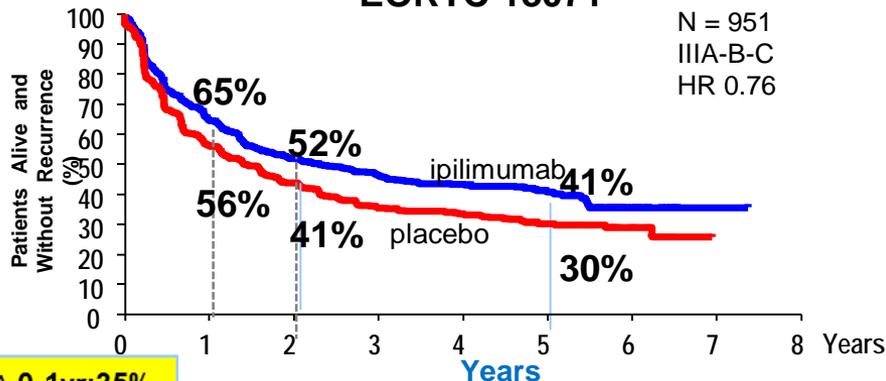
## Ipilimumab - Dabraf+Tramet - Nivo/Pembro

### Toxicities leading to Treatment Discontinuation

- **Ipilimumab** **49%**
- **Dabrafenib/Trametinib** **26%**
- **Nivolumab/Pembrolizumab** **14%**  
*(endocrinopathies chronic)*

# Improvement in RFS in high risk melanoma

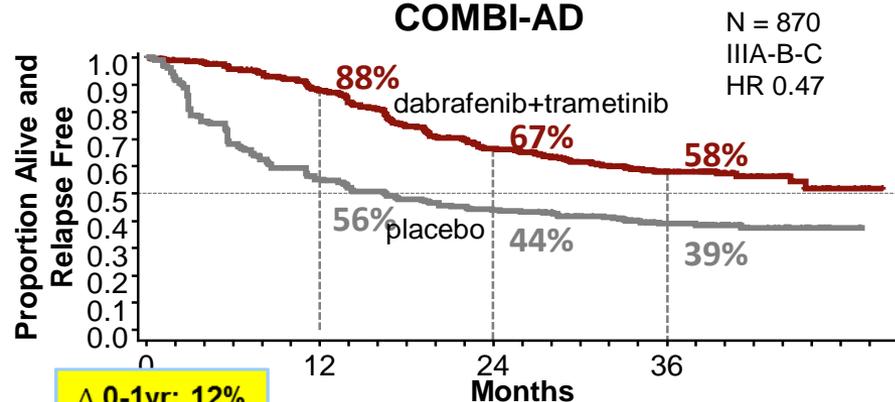
## EORTC 18071



Δ 0-1yr: 35%  
Δ 1-2yr: 13%

Eggermont *et al.* NEJM 2016

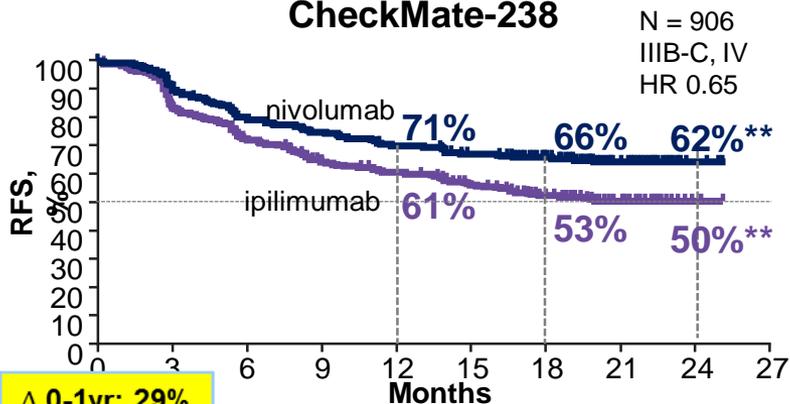
## COMBI-AD



Δ 0-1yr: 12%  
Δ 1-2yr: 21%

Long *et al.* NEJM 2017

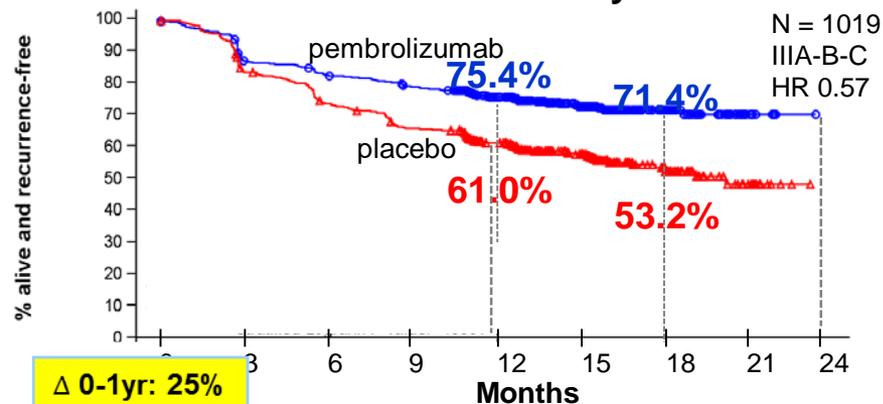
## CheckMate-238



Δ 0-1yr: 29%  
Δ 1-2yr: 9%

Weber *et al.* NEJM 2017

## EORTC 1325-MG/Keynote 054



Δ 0-1yr: 25%  
Δ 1-2yr: 6%?

Eggermont *et al.* NEJM 2018

**2018**  
**New ERA**  
**Adjuvant Therapy**

**END OF IFN**

**END OF IPILIMUMAB**

## Take Home Points

- With highly effective and well tolerated adjuvant therapy, SLN mapping for all patients with melanomas  $> 1$  mm and for some with melanomas  $< 1$  mm.
- Stage III patients- somatic mutation testing for BRAF is standard of care.
- Adjuvant therapy for most patients with stage III melanoma (node positive or intransit disease).

# Selection of Adjuvant Therapy for Patients with Stage III Melanoma

- Which treatment?
  - In general, we choose adjuvant anti- PD-1 therapy, nivolumab or pembrolizumab even in BRAF mutant melanoma (but that could change)
- Duration?
  - One year of therapy
- Dose/Schedule
  - Nivolumab- 240 mg q 2 weeks or 480 mg q 4 weeks
  - Pembrolizumab- 200 mg q 3 weeks
- Monitor closely for side effects
- Scans every 6 months for 5 years

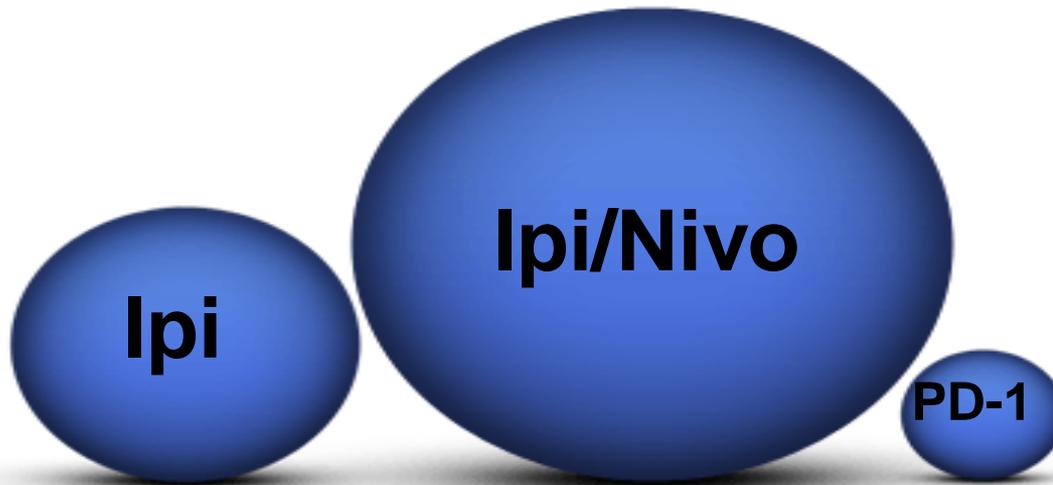


**Ann is doing well.**

# Future Direction

- Longer term follow up to know best approach
- Neoadjuvant therapy- hot topic
- Biomarkers to shape the selection of Rx
- High risk stage II
- Incorporating other agents ( i.e. Imlygic (TVEC), new vaccines)
- Ipi/Nivo-cautiously

# Other immunotherapy strategies



(Nivo or Pembro)

# Lessons from Dr. Wallace Clark

- Love what you do
- Lifelong curiosity, think outside the box
- Challenge the status quo
- Team based philosophy in everything you do
- Everyone's voice matters
- Zest for life
- Mentors matter, and great mentors matter even more

