Department of Soft Tissue/Bone Sarcoma and Melanoma

Perioperative therapy of melanoma

Piotr Rutkowski 3/2019

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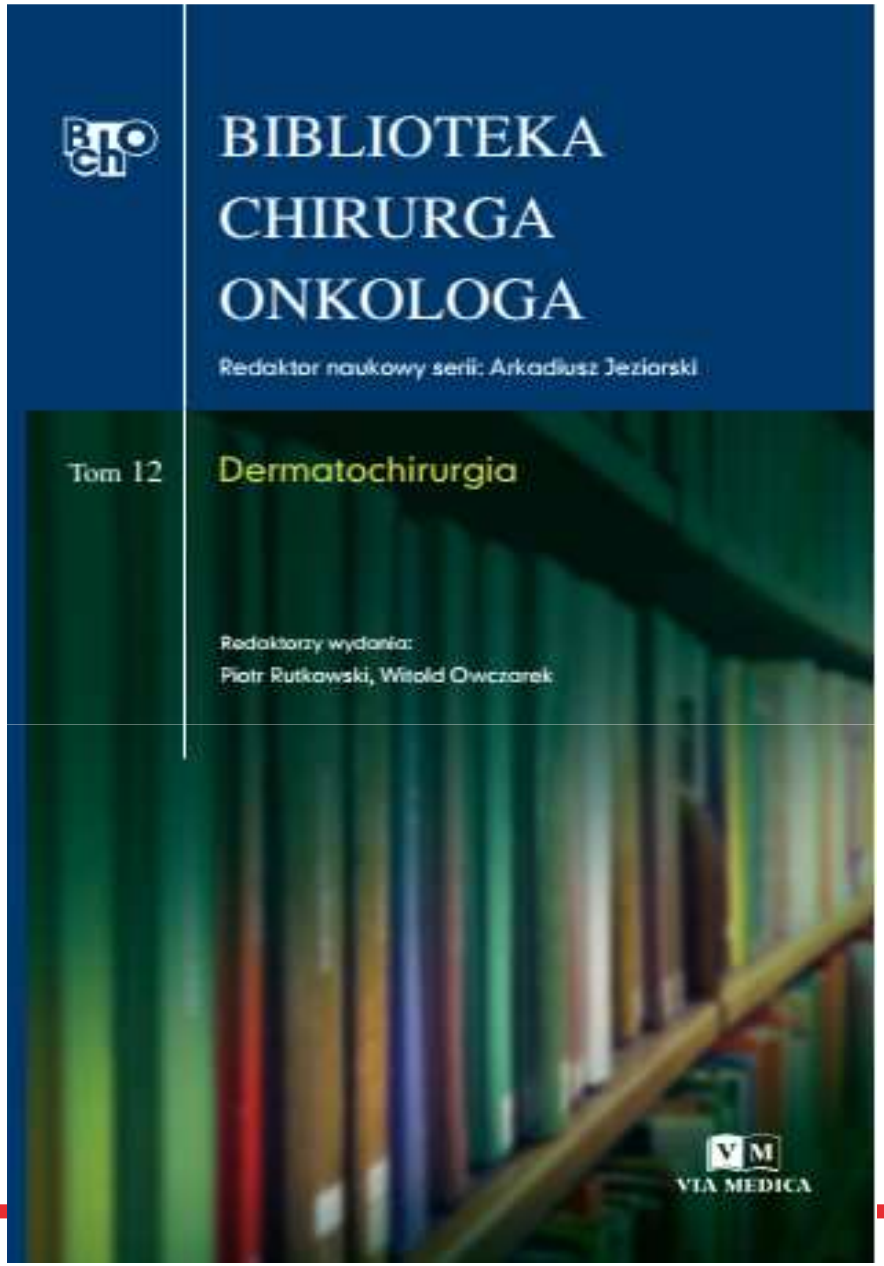
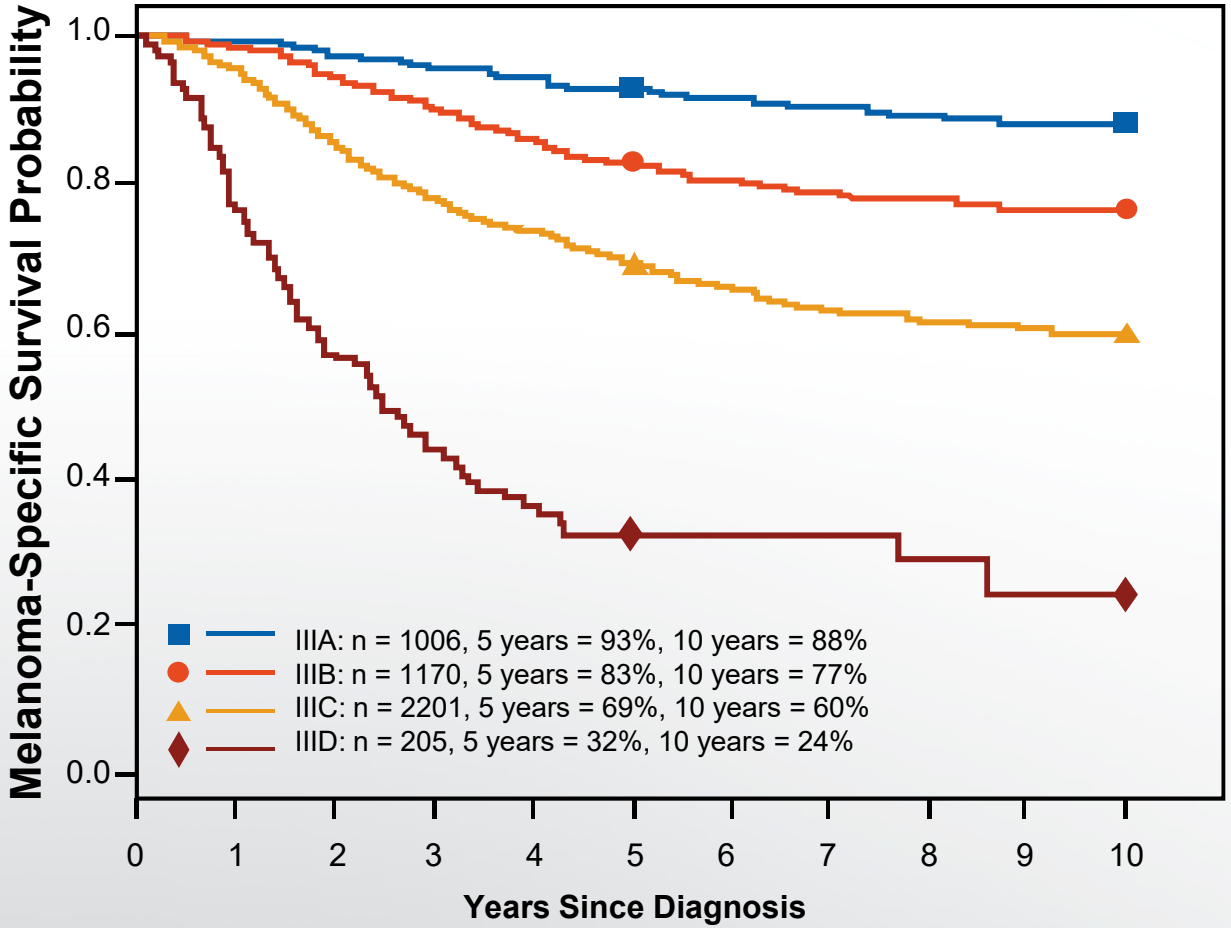
Potential conflicts of interest:

- Advisory board: Novartis, MSD, BMS, Roche, Bayer, Pierre Fabre, Blueprint Medicines
- Honoraria: Novartis, Pfizer, MSD, Roche, BMS, Pierre Fabre, GSK, Amgen
- Travle grants: Novartis, Orphan Drugs



Melanoma-Specific Survival by Resectable Stage
HETEROGENNE ROKOWANIE



Stage, 5-year OS

IIIA, 93%

IIIB, 83%

IIIC, 69%

IIID, 32%

1. Gershenwald J, et al. Oral presentation at SMR 2016; 2. Long GV. Clinical symposium at ECCO 2017.

N stage

7 edycja

Cecha N	Charakterystka	
Nx	nie można ocenić reg. w. chł.	
N0	nie ma przerzutów	
N1	1 mets w. chł.	a: mikroprzerzut
		b: makroprzerzut
N2	2-3 mets w. chł.	a: mikroprzerzut
		b: makroprzerzut
		c: in transit (bez mets w.chł)
N3	4 ≥ mets w.chł, /pakiet/meta in transit (z zajętymi nowotorowo w.chł)	

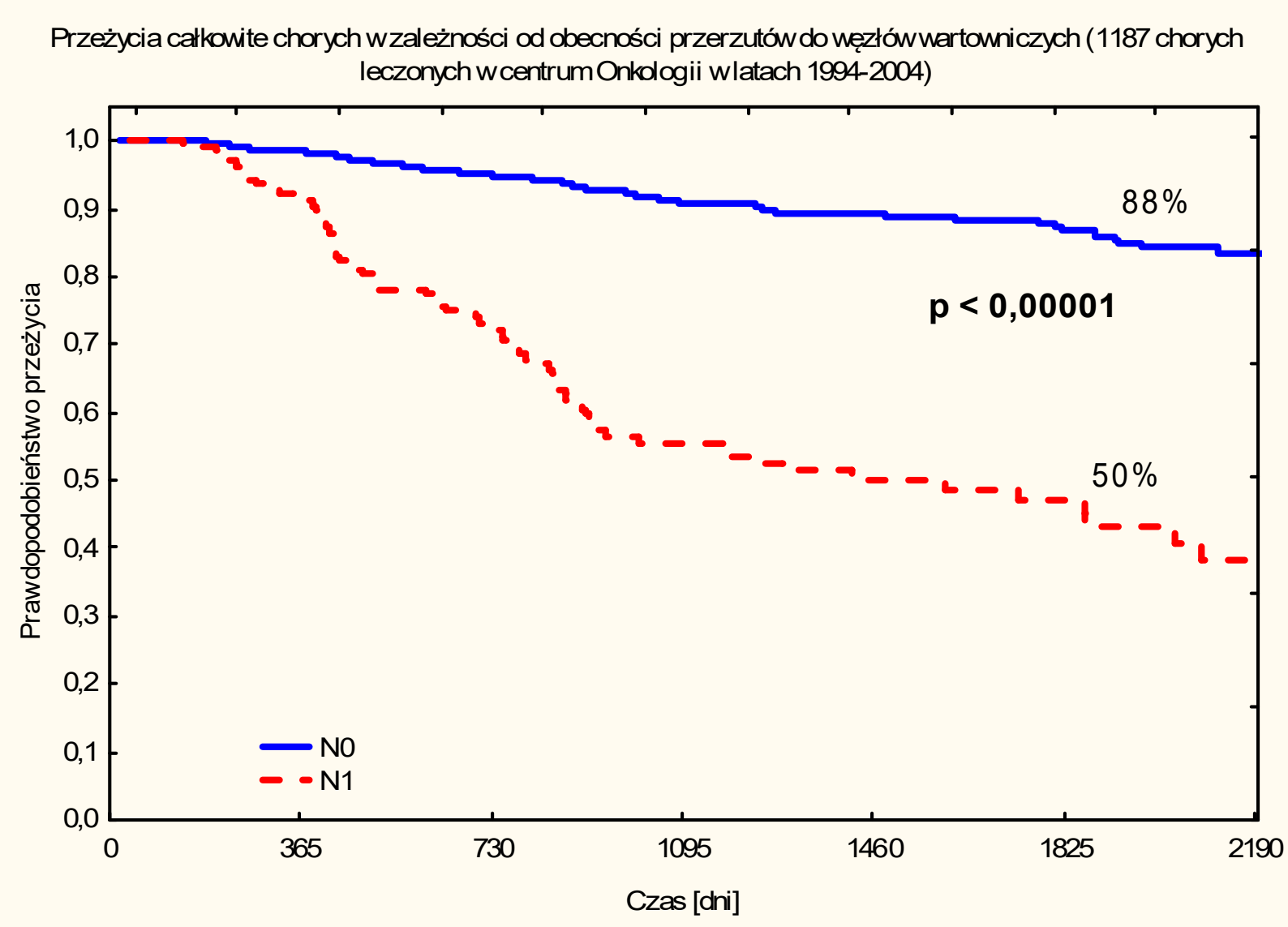
8 edycja

Cecha N	Przerzuty w.chł	In transit/ guzki satelit.
N0	Brak przerzutó w.chł.	
N1	a: 1 niejawny (mikroprzerzut)	nie
	b: 1 jawny (makroprzerzut)	nie
	Nie!	c: tak
N2	a: 2-3 niejawne	nie
	b: 2-3 w tym 1 jawny	nie
	c: 1 jawny/niejawny	c: tak
N3	a: ≥ 4 niejawne	nie
	b:≥ 4 w tym 1 jawny	nie
	c:2 jawne/niejawne	c: tak

Extent of regional lymph node and/or lymphatic metastasis		
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception:** pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	

Extent of regional lymph node and/or lymphatic metastasis		
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Overall survival according to metastases to sentinel lymph nodes



- Micrometastases → Macrometastases
- Prognosis better for micrometastases

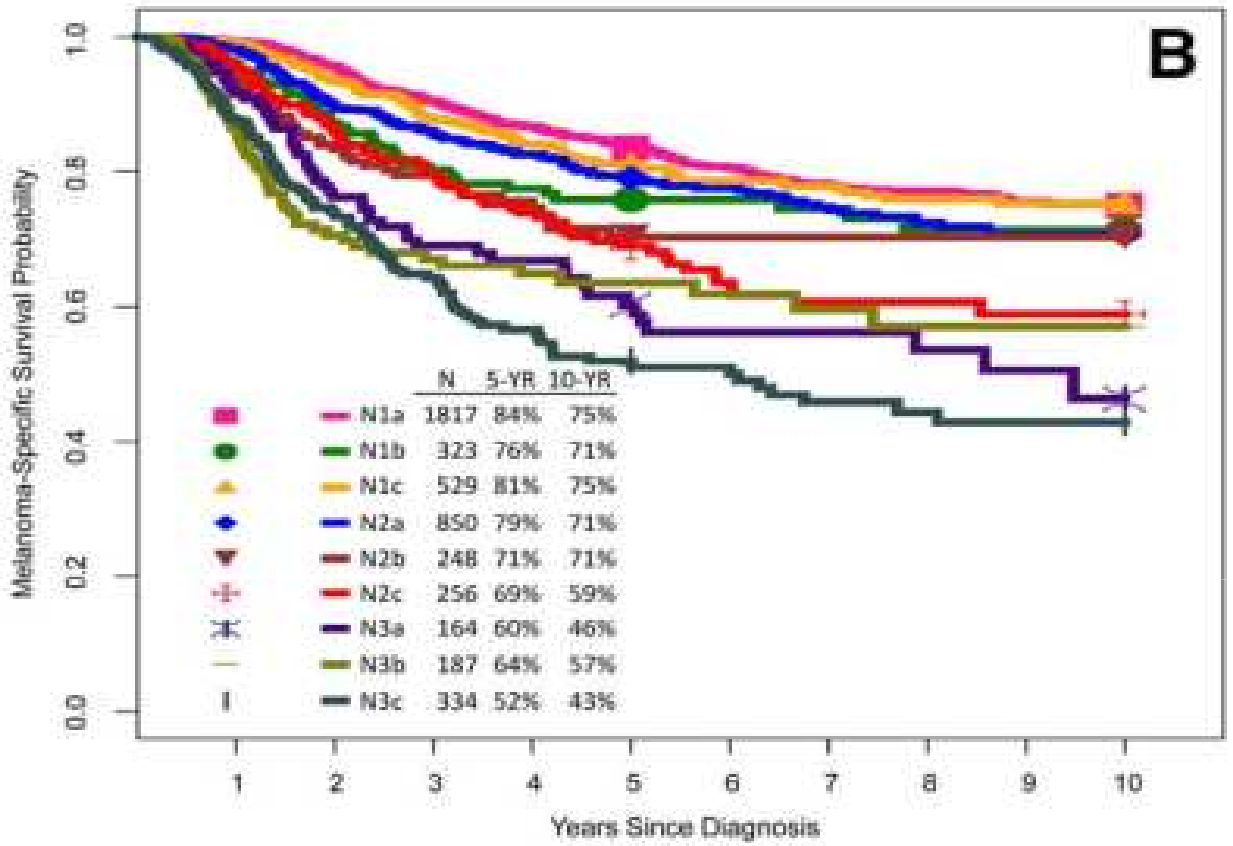
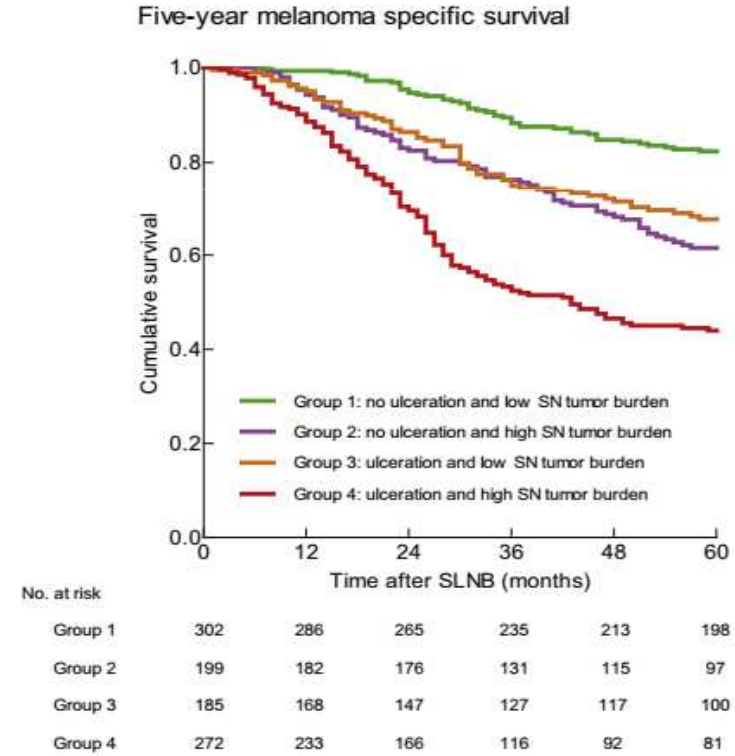


FIGURE 3. Kaplan-Meier Melanoma-Specific Survival Curves According to (A) N Categories and (B) Subcategories From the Eighth Edition International Melanoma Database.

Risk stratification of sentinel node–positive melanoma patients defines surgical management and adjuvant therapy treatment considerations

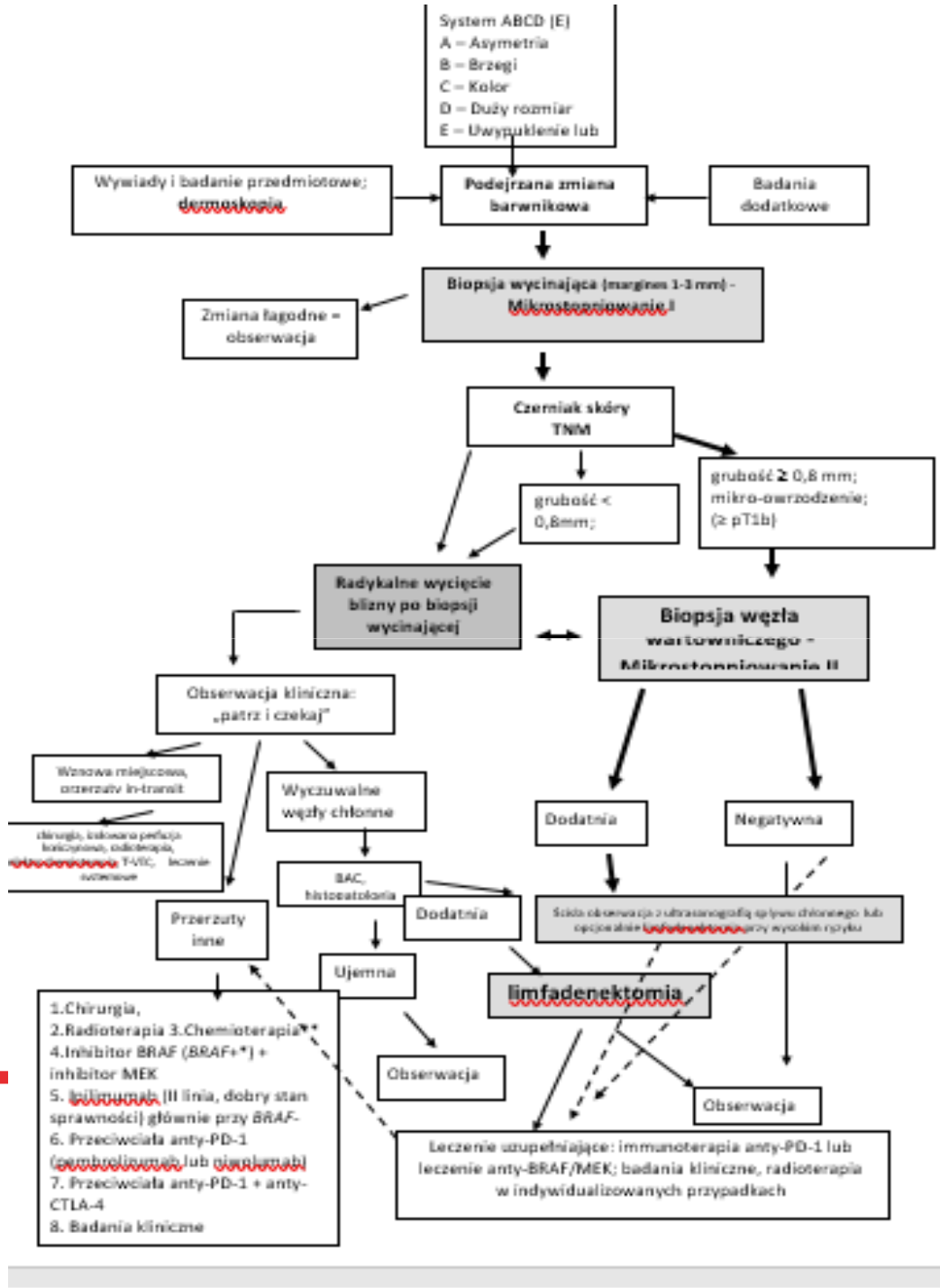
European Journal of Cancer 96 (2018) 25–33

Daniëlle Verver [a,*], David van Klaveren [b], Alexander C.J. van Akkooi [c], Piotr Rutkowski [d], Barry W.E.M. Powell [e], Caroline Robert [f], Alessandro Testori [g], Barbara L. van Leeuwen [h], Astrid A.M. van der Veldt [i], Ulrich Keilholz [j], Alexander M.M. Eggermont [k], Cornelis Verhoef [a], Dirk J. Grünhagen [a]



No. at risk						
Group 1	302	286	265	235	213	198
Group 2	199	182	176	131	115	97
Group 3	185	168	147	127	117	100
Group 4	272	233	166	116	92	81

Fig. 1. Five-year melanoma-specific survival per positive SN group. SN, sentinel node.



VIA MEDICA
WYTYCZNE POSTĘPOWANIA DIAGNOSTYCZNO-TERAPEUTYCZNEGO

Czerniaki skóry

Cutaneous melanomas

Redakcja:
Piotr Rutkowski, Piotr J. Wysocki

Zespół autorski:
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CLINICAL/ PATHOLOGIC STAGE	WORKUP[e]	PRIMARY TREATMENT	ADJUVANT TREATMENT
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or core, incisional, or excisional biopsy • Imaging[j] for baseline staging and to evaluate specific signs or symptoms	Wide excision of primary tumor[n] (category 1) + complete therapeutic lymph node dissection[y]	Locoregional option: • Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[z,aa] (category 2B) Systemic options: • Observation • Nivolumab (category 1) (preferred adjuvant immunotherapy regimen)[u] • Dabrafenib/trametinib for patients with *BRAF* V600 activating mutation (category 1) • High-dose ipilimumab[v] (category 1) • Interferon alfa[x] • Biochemotherapy (category 2B)[bb] → See Follow-up (ME-10)

[e]Mutational analysis for BRAF or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma who are otherwise NED in status, unless required to guide systemic therapy or consideration of clinical trials.

[j]See Principles of Imaging--Workup (ME-C).

[n]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-D).

[u]Nivolumab has shown a clinically significant improvement in relapse free survival (RFS) compared to high-dose ipilimumab, but its impact on overall survial (OS) has not yet been reported. Most panel members prefer adjuvant nivolumab over high-dose ipilimumab based on improved efficacy and less toxicity, even in the absence of reported OS data.

[v]While adjuvant high-dose ipilimumab (10 mg/kg) is associated with improved recurrence-free and overall survival, this regimen was associated with a high incidence of adverse events, which led to the discontinuation of treatment in 53% of patients. There was a 1% drug-related mortality rate. Due to toxicity, careful selection of patients is warranted. In this study, subgroup analyses demonstrated that some groups are unlikely to benefit from adjuvant ipilimumab. For patients who have the lowest risk of developing metastatic disease (AJCC 7th edition stage IIIA), given the hazard ratio (HR) of 0.98 combined with the toxicity, there is disagreement among the panel regarding advisability of the use of adjuvant ipilimumab in this setting. For patients with stage IIIB or stage IIIC with 1–3 positive nodes, adjuvant ipilimumab could be considered despite HRs that are not statistically significant. The benefit for adjuvant ipilimumab is likely to be highest in patients with ≥4 positive nodes.

[x]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1), but there is no impact on overall survival.

[y]In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.

[z]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.

[aa]See Principles of Radiation Therapy for Melanoma (ME-G).

[bb]For biochemotherapy, see Other Systemic Therapies (ME-H 2 of 6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Cutaneous Melanoma

NCCN Guidelines Index
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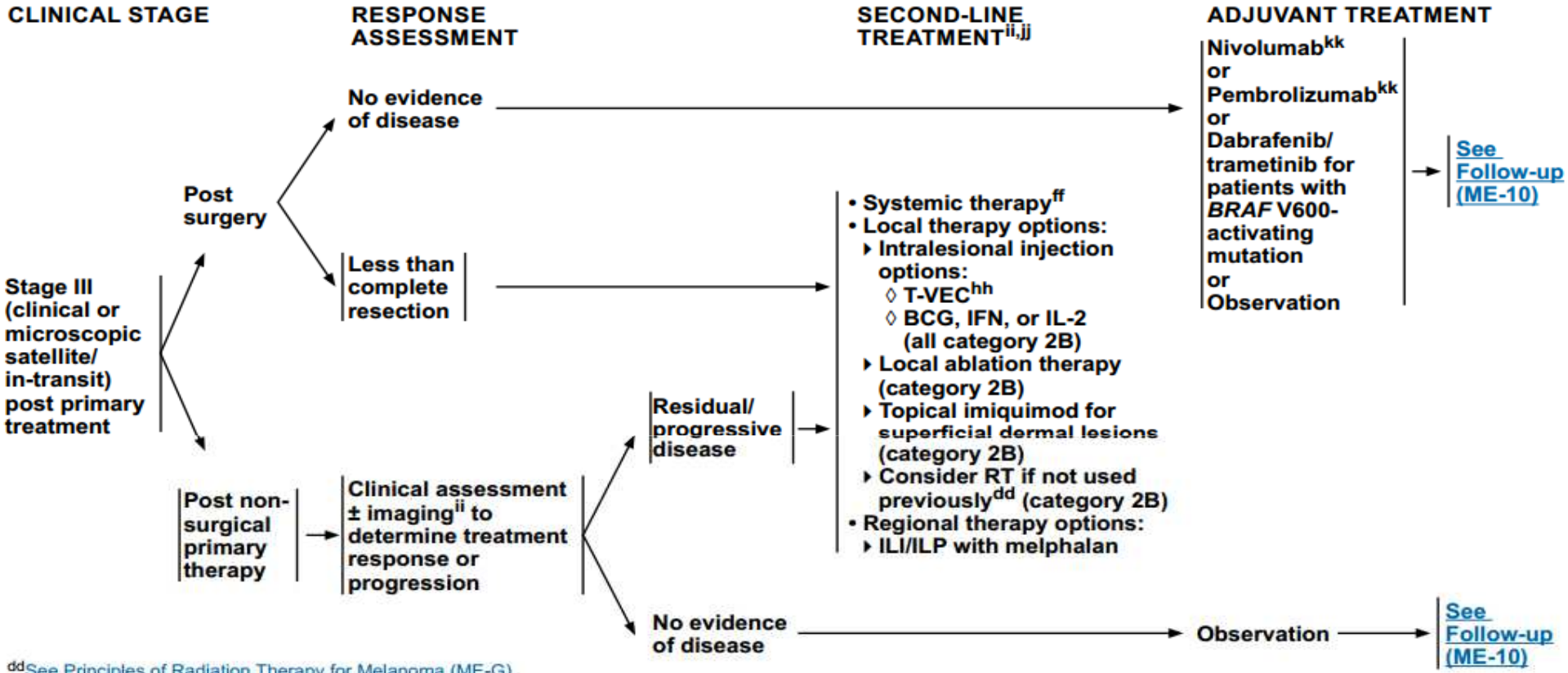
Discussion



[dd] See Principles of Radiation Therapy for Melanoma (ME-G).

[ff] See Systemic Therapy for Metastatic or Unresectable Disease (ME-H 1 of 5).

[hh] T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in AJCC 7th Edition stage IIIB and IIIC disease, and was more likely to be seen in patients who were treatment naive.

[ii] See Principles of Imaging–Treatment Response Assessment (ME-C).

[jj] For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

[kk] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported. Although both trials focused primarily on patients with stage III nodal disease, the NCCN panel agrees that it is appropriate to extend the indication for adjuvant anti-PD-1 therapy to patients with clinical or macroscopic satellite/intransit disease and who are at significant risk of recurrence.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

COMPLEXITY OF SITUATION IN ADJUVANT THERAPY OF MELANOMA

New classification in stage III AJCC 8th ed

MSLT II: completion lymph node dissection CLND is not further standard of therapy due to lack of benefits for MSS

Clinical trials in adjuvant therapy differ in terms of eligibility criteria (stage of disease), comparators, drug dosing

AJCC Eighth Edition
Melanoma Stage III Subgroups

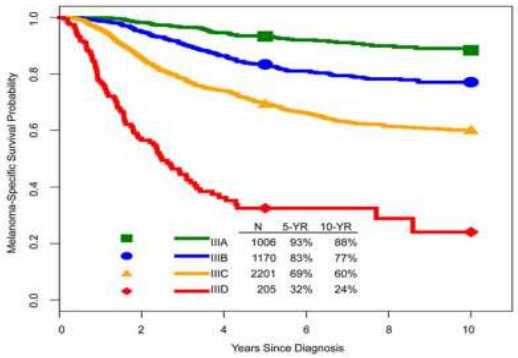
N Category	T Category							
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

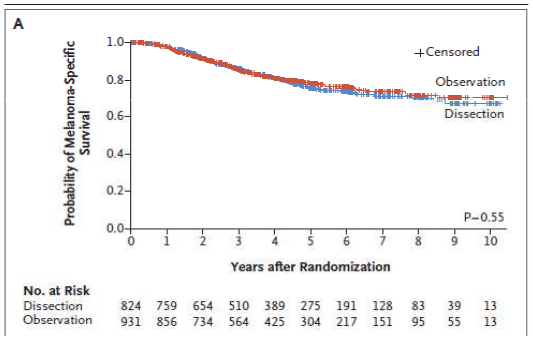
Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.

Legend
A Stage IIIA
B Stage IIIB
C Stage IIIC
D Stage IIID

FIGURE 8. American Joint Committee on Cancer (AJCC) Eighth Edition Stage III Subgroups Based on T and N Categories.

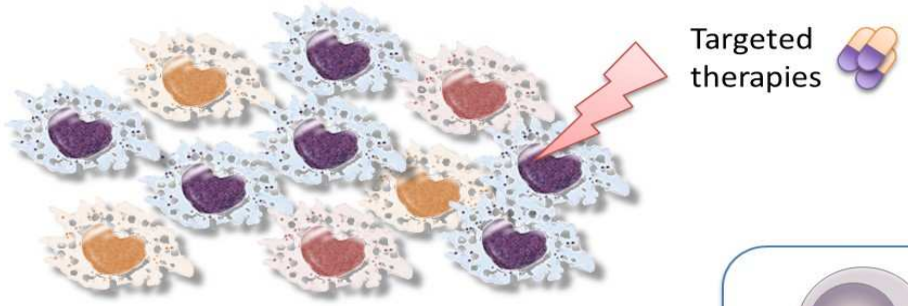




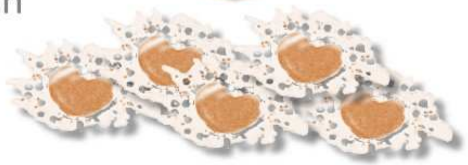
WWW.COI.PL

Targeted therapies: metastatic vs adjuvant setting

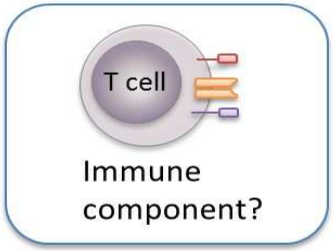
1 Macroscopic disease - metastatic setting



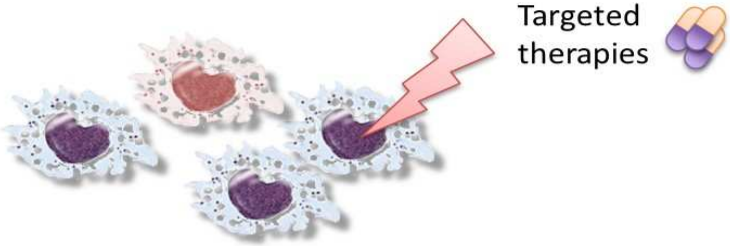
Clonal selection



- ✓ Large clonal heterogeneity
- ✓ Increased capacity towards adaptive resistance (tumor burden associated with PFS and OS[1])



2 Microscopic disease - adjuvant setting



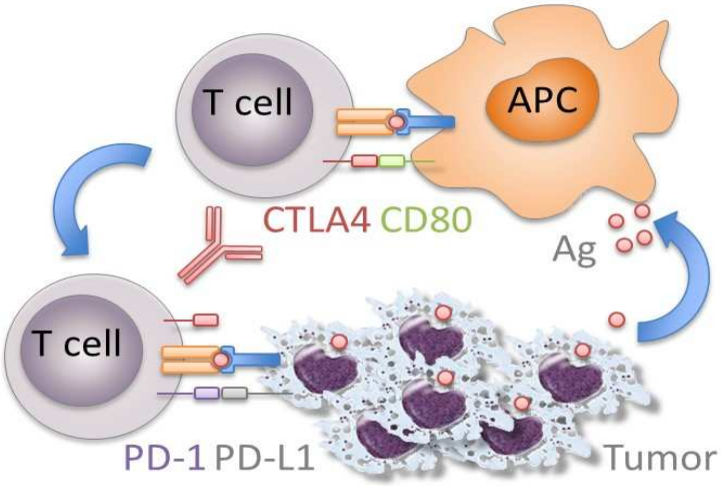
Eradication of clones

- ? Restricted clonal heterogeneity?
- ? Is stage IIIA vs B, C influencing clonal heterogeneity?
- ? Less risk of relapse?

[1] Flaherty, ASCO 2016

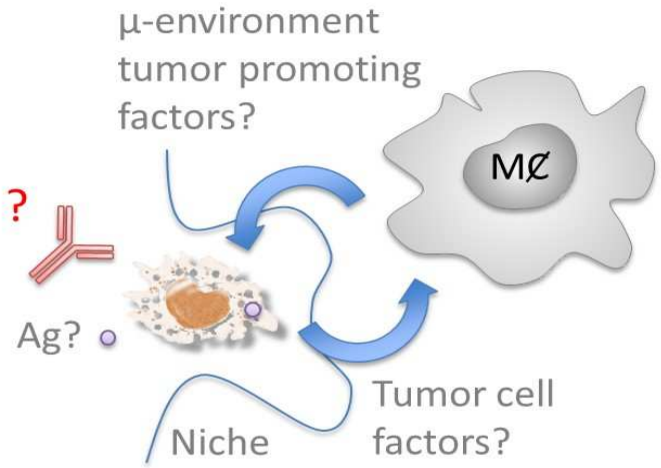
Immunotherapies: metastatic vs adjuvant setting

1 Macroscopic disease - metastatic setting



- ✓ Continuous antigen release
- ✓ T cell infiltrate, INF-γ, PD-L1
- ✓ Clear activity of CTLA-4 and PD-1 blockade

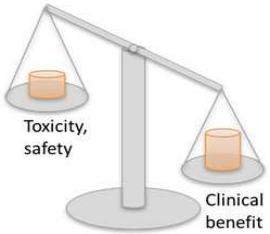
2 Microscopic disease - adjuvant setting

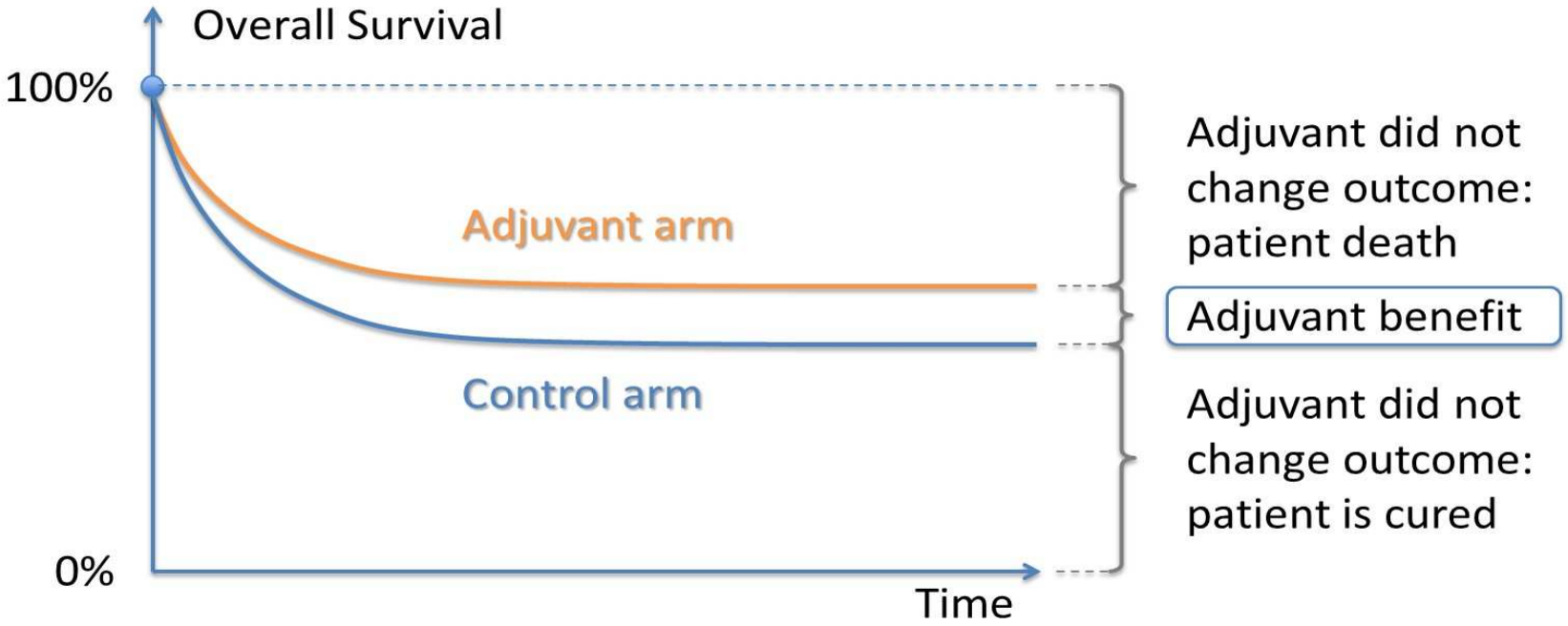


- ? Nature of residual disease, antigens (Ag)?
- ? Composition of (pre-)metastatic niche?
- ? Role of PD-1 / PD-L1[1] and CTLA-4 axis?

[1] Tarhini, *JTM* 2015: SLN are PD-L1 +

Risk / benefit ratio in the adjuvant setting





Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial

Lancet Oncol 2015; 16: 1049–60

Michael A Henderson, Bryan H Burmeister*, Jill Ainslie, Richard Fisher, Juliana Di Iulio, B Mark Smithers, Angela Hong, Kerwin Shannon, Richard A Scolyer, Scott Carruthers, Brendon J Coventry, Scott Babington, Joao Duprat, Harald J Hoekstra, John F Thompson*

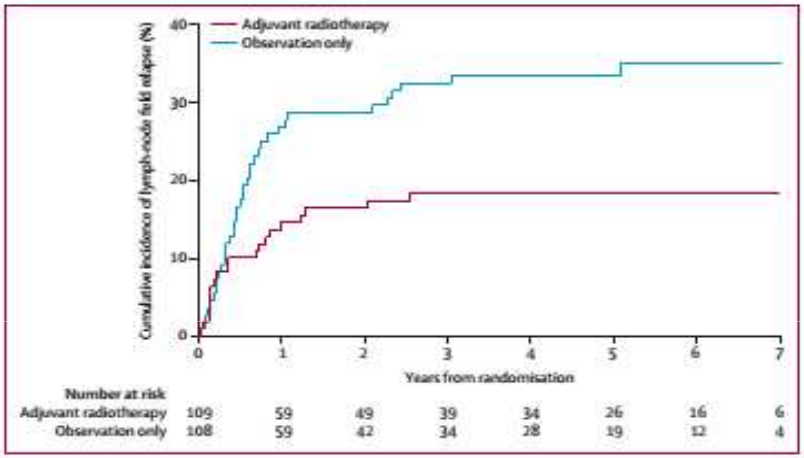


Figure 2: Cumulative incidence curves of lymph-node field relapse as a site of first relapse (competing risks: other relapse and death)

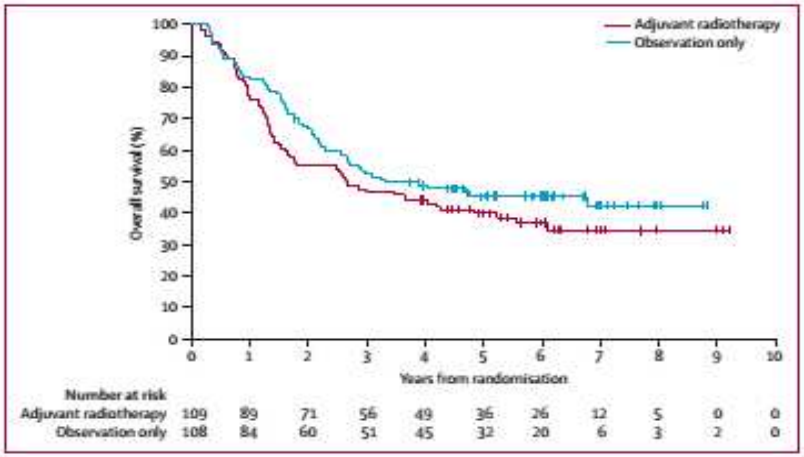


Figure 3: Overall survival of eligible patients

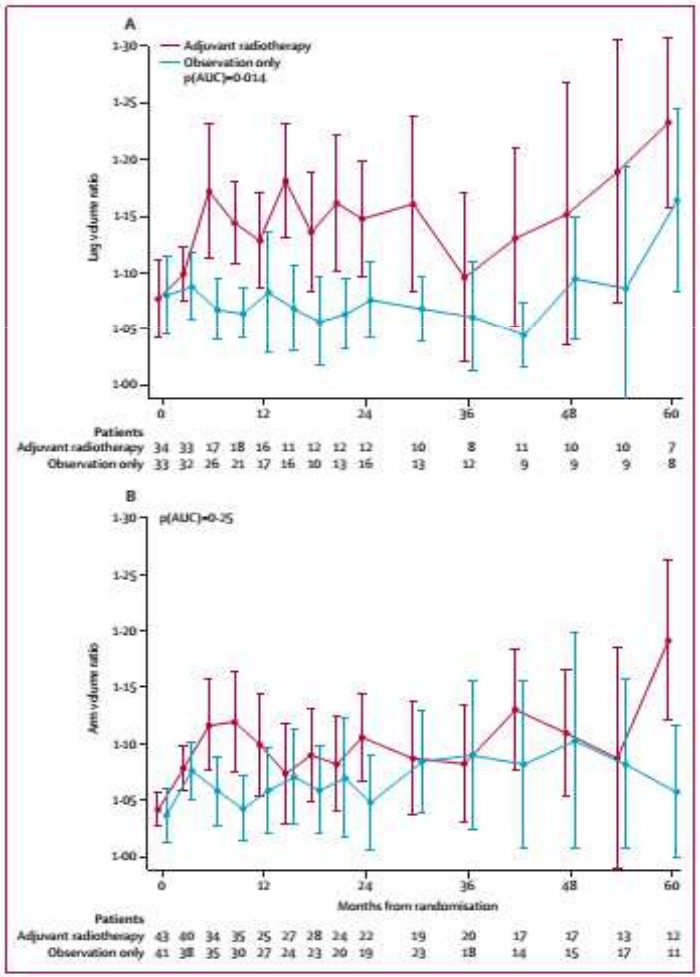


Figure 4: Lymphoedema limb volume ratios
Volume ratios shown for (A) lower limb and (B) upper limb. Bars represent SE of the mean.

Summary of adjuvant therapy trials

		zaawansowanie	BRAF	punkty końcowe I.rz	wyniki	punkty końcowe II.rz	wyniki	me	RFS	OS
BRIM8	vemurafenib	IIC,IIIA,IIIB	+	DFS	HR=0.54 ss	**DMFS**, OS, bezp, jakość	HR 0.91 nss	NR	72% 2yrs	
		vs IIIC			**HR=0.80 nss**					
COMBI AD	dobrafenib plus trametynib	III	+	RFS	HR=0.47 ss	**OS- 3yrs**, DMFS, FFR, BEZP	HR=0.57 ss	NR	58% 3yrs	86% 3yrs
EORTC 18071	ipilimumab	III		RFS	HR=0.76 ss	DMFS, **OS**, bezp, jakość	HR=0.72 ss	27 m-cy	41% 5 yrs	65% 5yrs
E 1609	Ipi 10/3 vs IFN α2b	III		non inferiority	HR=1.0	RFS, OS	not yet			
CheckMate238	nivo vs ipi10	IIIB/C vs IVM1a/b vs IVM1c	PD-L1 5%	RFS	HR=0.65 ss	OS, RFS by PDL1, bezp, jakość	not yet	NR	66% 18 mo	

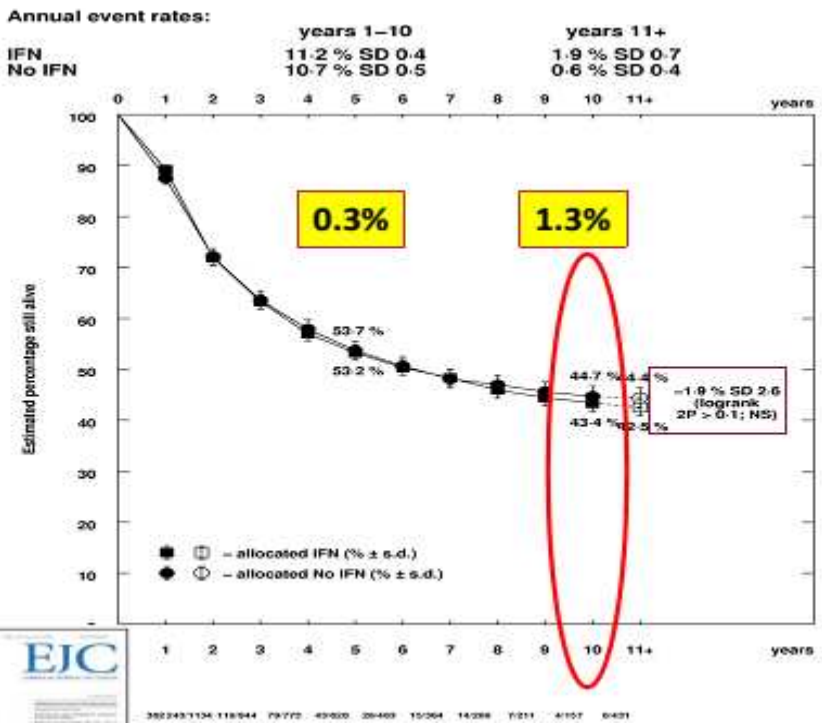
Adjuvant interferon-α for the treatment of high-risk melanoma: An individual patient data meta-analysis

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)

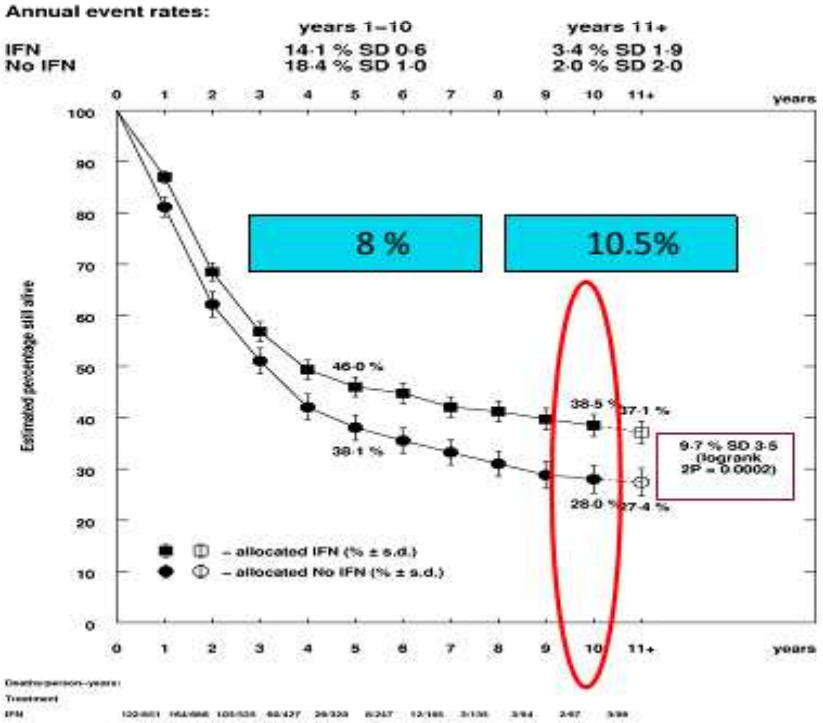
European Journal of Cancer 82 (2017) 171–183

ULCERATION AND IFN-SENSITIVITY OVERALL SURVIVAL

Non-ulcerated primary (67%)



Ulcerated primary (33%)

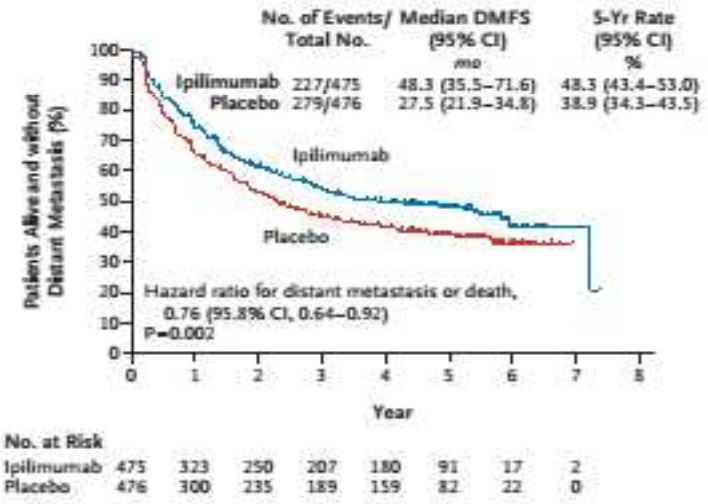


ORIGINAL ARTICLE

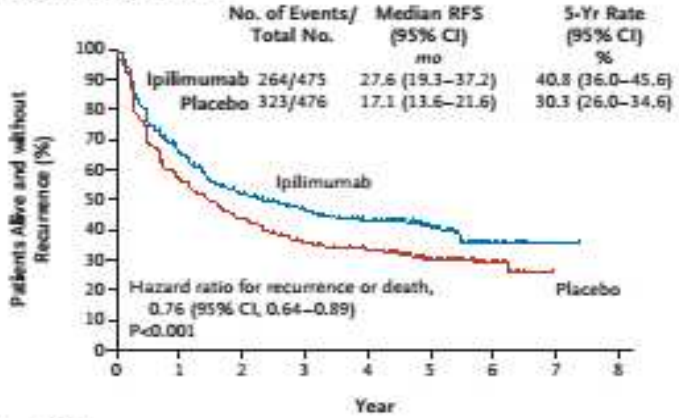
Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

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 Schaetzen, S. Suciu, and A. Testori

C Distant Metastasis–free Survival



A Recurrence-free Survival



B Overall Survival

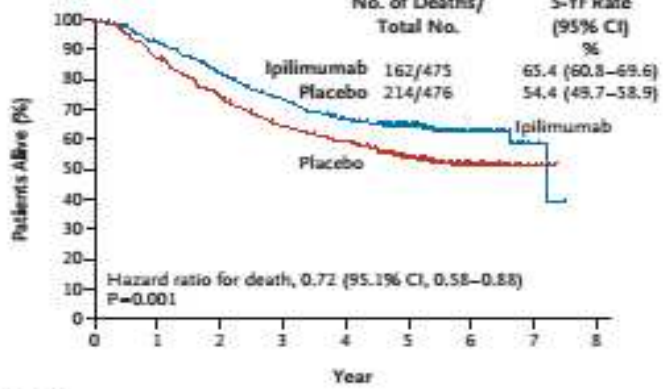


Table 3: Immune-Related Adverse Events.*

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

#9500 adjuwantowy ipilimumab 3 mg/kg vs 10 mg/kg – podobne wyniki RFS, większa toksyczność dla wyższej dawki

Intergroup E1609: Study Design and Accrual

N = 1673

Arm	Activation	Termination	Final
Ipi10	May 2011	April 2014	511
HD-IFN	May 2011	August 2014	636
Ipi3	Feb 2012	August 2014	523

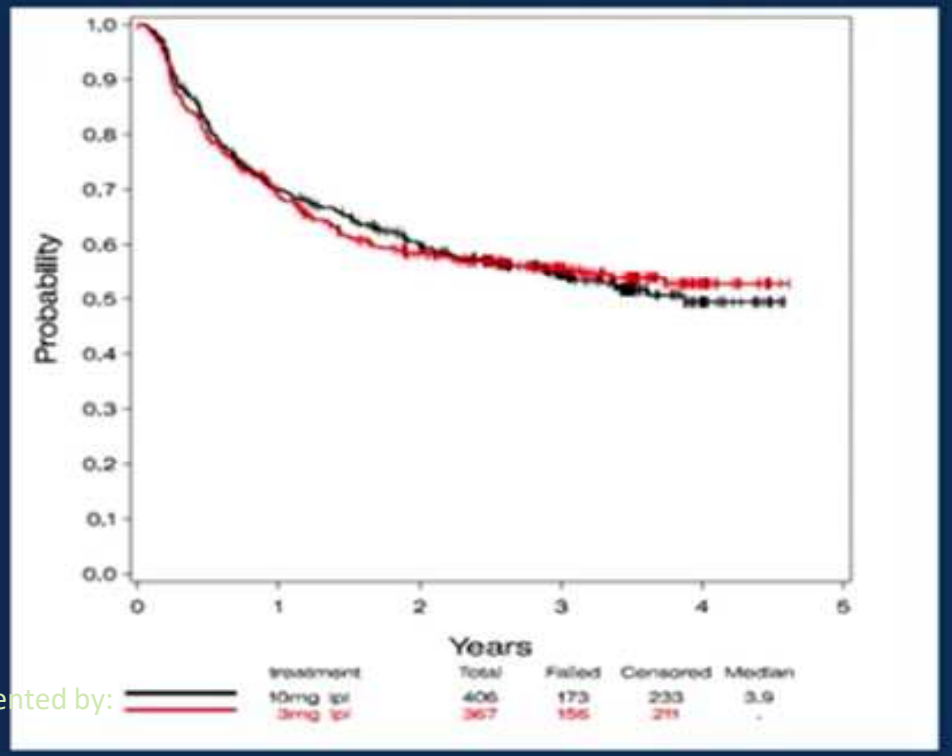
Safety Summary

(Based on all toxicity data as of 3/2/17)

	Ipi3 (n = 516)		Ipi10 (n = 503)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.4	53.3	100	65.4
Treatment-related AE, %	96.0	36.6	98.8	56.5
Treatment-related AE leading to discontinuation, %	34.9	25.0	53.7	42.9
Any immune-related AE, %	73.6	18.8	86.9	34.0

RFS: Ipi10 vs. Ipi3

(Concurrently randomized patients)



Summary: adjuvant therapy trials

	EORTC 18071 Ipilimumab vs placebo	**BRIM-8 Wemurafenib vs placebo**	**COMBI-AD**	**Checkmate 238 IPI vs NIVO**	**EORTC 1325/Keynote 054 Pembrolizumab vs placebo**
	Eggermont 2015 Eggermont 2016	Lewis 2017	Long 2017	Weber 2017	Eggermont 2018?
Population	IIIA (>1mm), IIIB, IIIC	IIC, IIIA, IIIB, IIIC	IIIA (>1mm), IIIB, IIIC	IIIB, IIIC, IV	IIIA (>1mm), IIIB, IIIC
***BRAF*m**	?	100%	100%	41%/43%	
RFS	**41% vs 30% (5l)**	**82% vs 63% (12 m); 62% vs 53% (24 m)** 79% vs 58% (12m) 46% vs 47% (24m)IIIC **84% vs 66% (12m) 72% vs 56% (24 m) IIC-IIIB**	**67% vs 44% (2l) 58% vs 39% (3l)**	**66% vs 53% (18m)**	**HR 0,57**
OS	**65% vs 54% (5l)**	BD	**91% vs 83% (2l) 86% vs 77% (3l)**	**BD**	

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Introduction

Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

New Era (2015–2018)

• ***Ipilimumab (US)**[2]	HR_{RFS}(Ipilimumab vs. Placebo)=0.75	(2015)
• **Nivolumab**[3]	HR_{RFS}(Nivolumab vs. Ipilimumab)=0.65	(2017)
• ***Dabrafenib plus Trametinib**[4]	HR_{RFS}(Dab+Tra vs. Placebo)=0.47	(2018)
• ***Pembrolizumab**[5]	HR_{RFS}(**Pembrolizumab** vs. **Placebo**)=0.57	(EXP/2018)

* Trials performed in identical patient populations at high risk of relapse: IIIA >1mm; IIIB/C

5-year relapse rates: stage IIIA, 37%; stage IIIB, 68%; stage IIIC, 89%[6]

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27; [2]Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30; [3]Weber J, et al. *N Engl J Med* 2017;377:1824-35; [4]Long GV, et al. *N Engl J Med* 2017;377:1813-23; [5]Eggermont AM, et al. *N Engl J Med* 2018;375:1845-55: 15 March; [6]Romano E, et al. *J Clin Oncol* 2010;28:3042-7.

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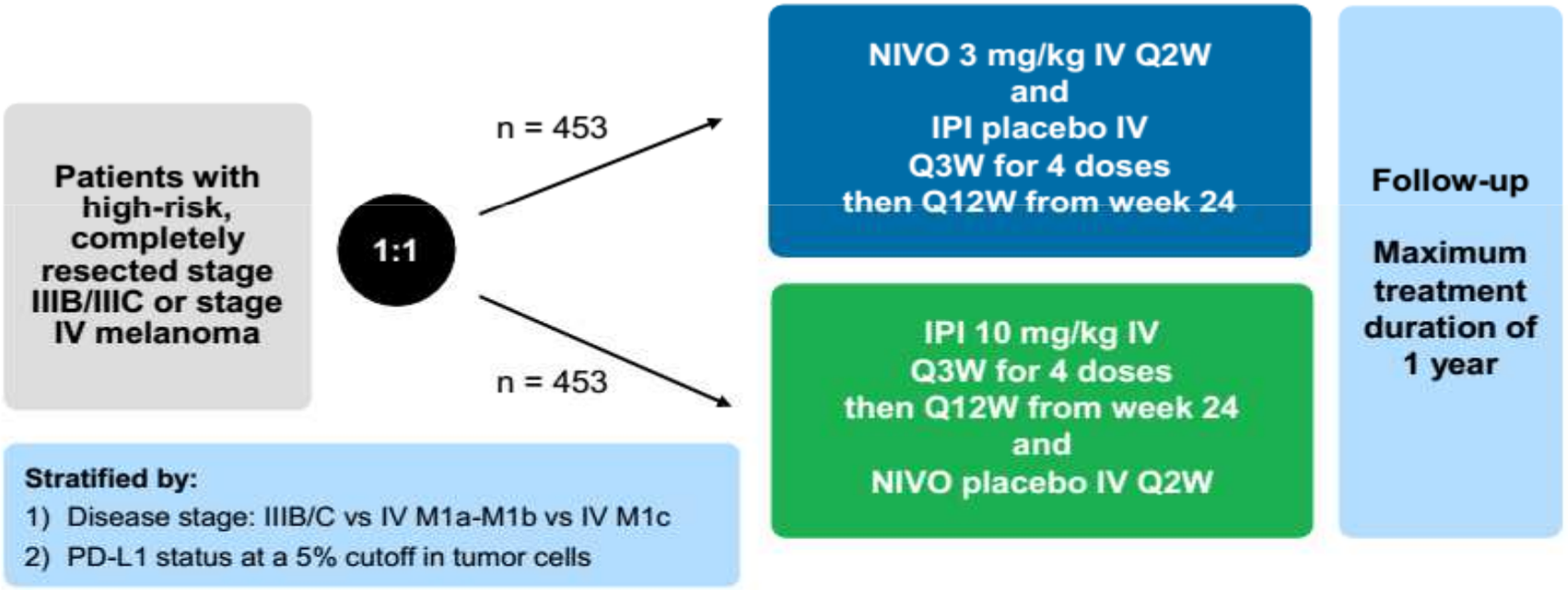
IPI VS NIVO ADJUWANT (RFS)

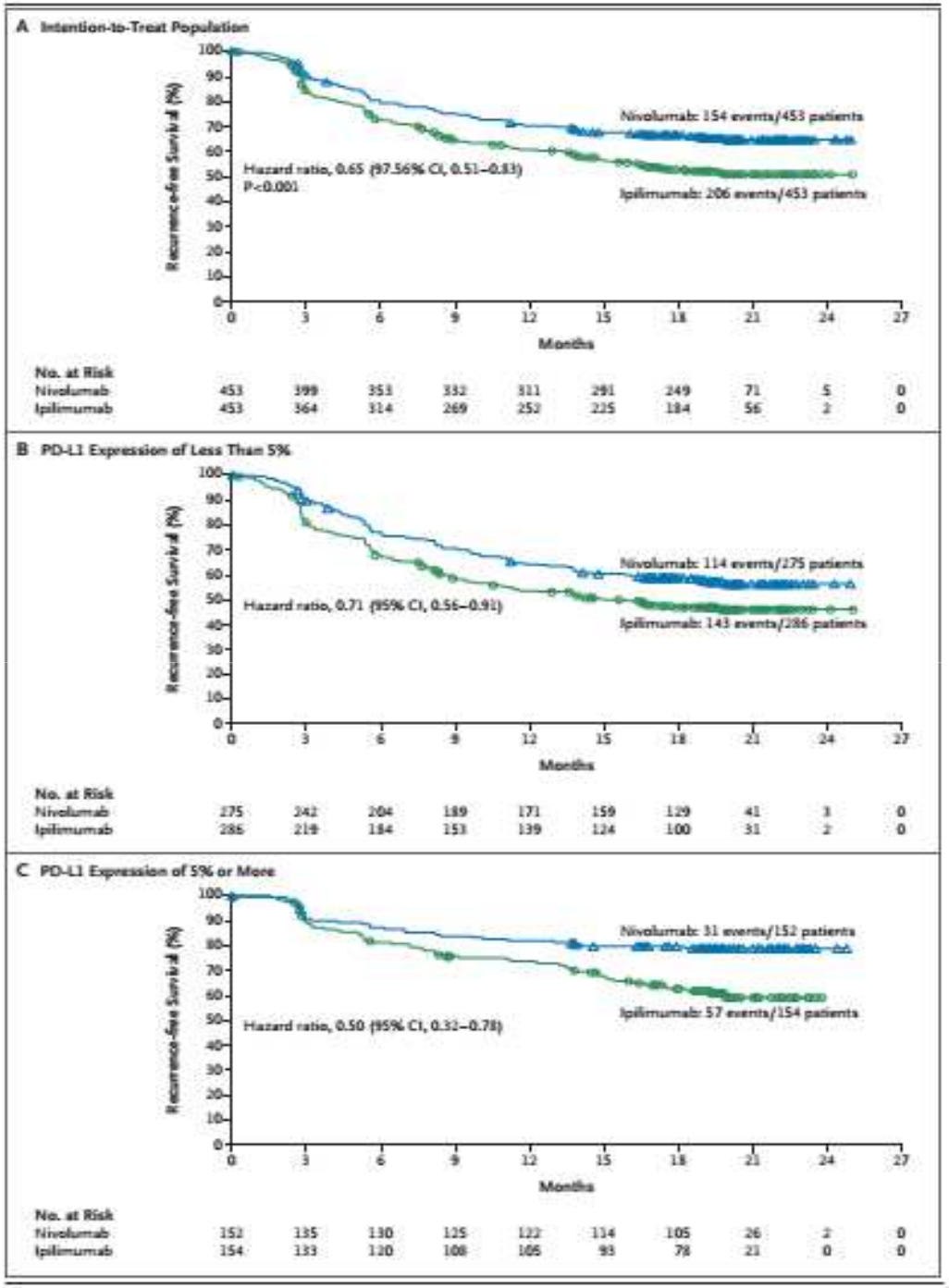
Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

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*

CA209-238: Study Design



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



IPI VS NIVO ADJUWANT (RFS)

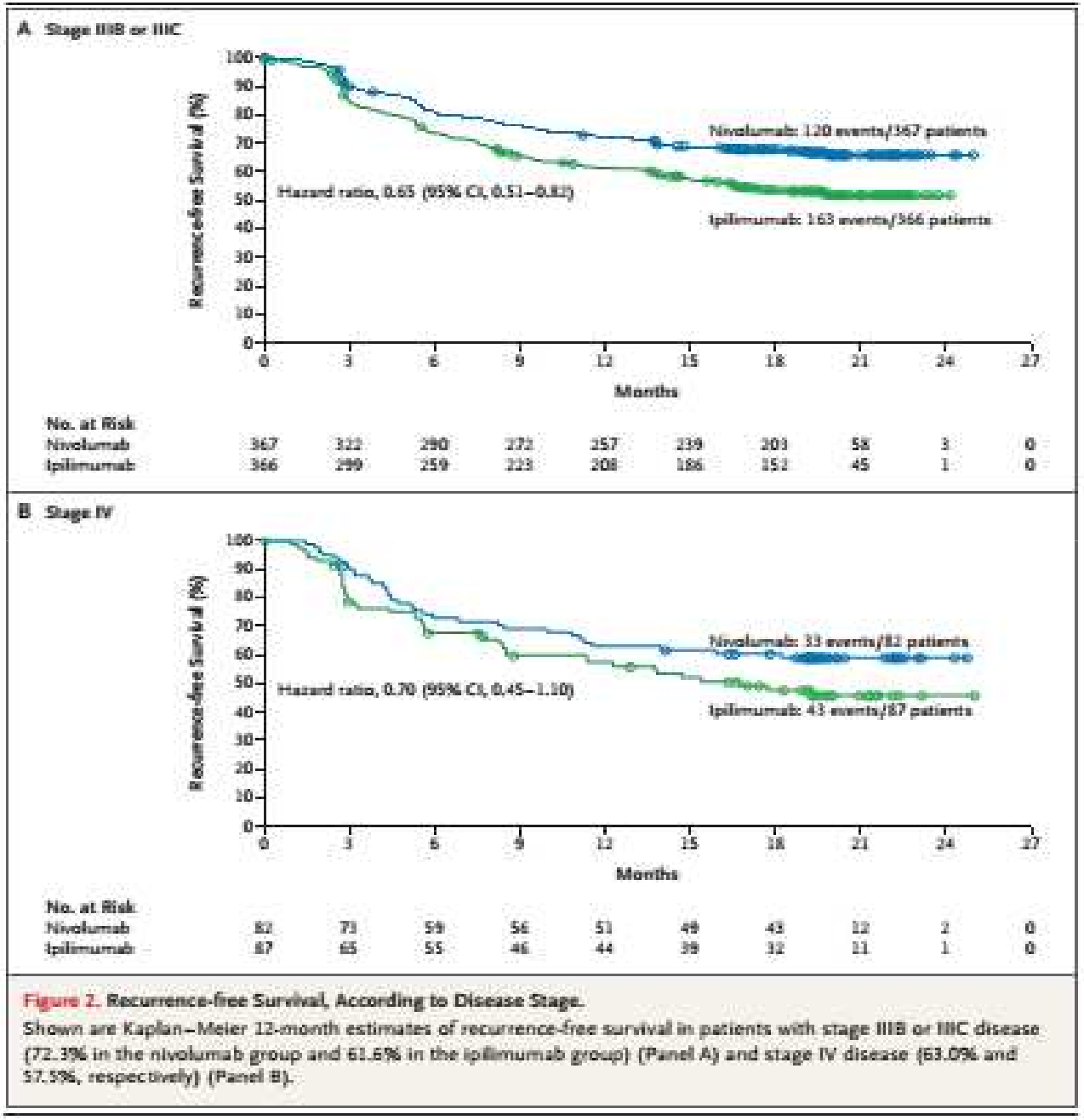


Figure 2. Recurrence-free Survival, According to Disease Stage.

Shown are Kaplan–Meier 12-month estimates of recurrence-free survival in patients with stage IIIB or IIIC disease (72.3% in the nivolumab group and 61.6% in the ipilimumab group) (Panel A) and stage IV disease (63.0% and 57.5%, respectively) (Panel B).

Safety Summary

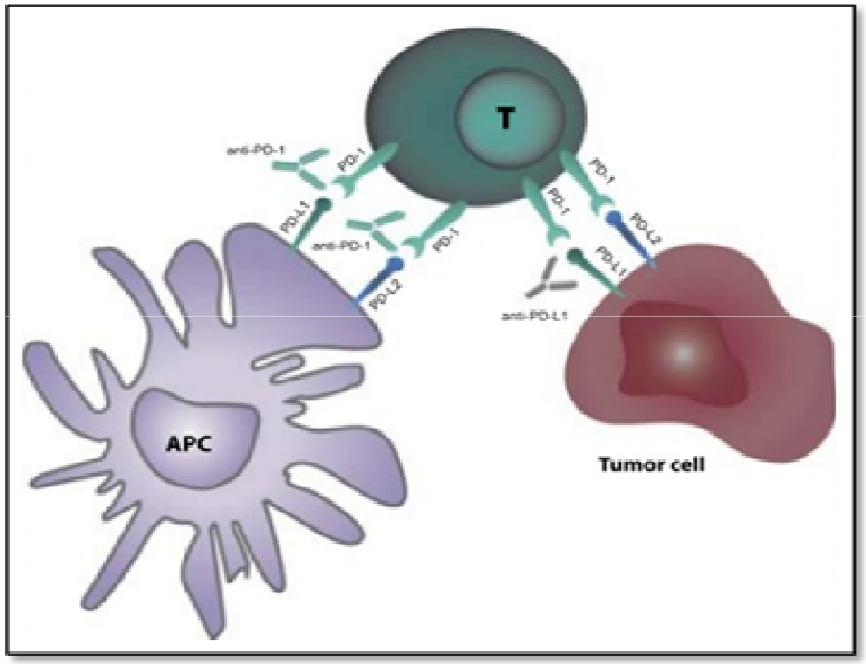
AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

Treatment-Related Select Adverse Events

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin	201 (44.5)	5 (1.1)	271 (59.8)	27 (6.0)
Gastrointestinal	114 (25.2)	9 (2.0)	219 (48.3)	76 (16.8)
Hepatic	41 (9.1)	8 (1.8)	96 (21.2)	49 (10.8)
Pulmonary	6 (1.3)	0	11 (2.4)	4 (0.9)
Renal	6 (1.3)	0	7 (1.5)	0
Hypersensitivity/infusion reaction	11 (2.4)	1 (0.2)	9 (2.0)	0
Endocrine				
Adrenal disorder	6 (1.3)	2 (0.4)	13 (2.9)	4 (0.9)
Diabetes	2 (0.4)	1 (0.2)	1 (0.2)	0
Pituitary disorder	8 (1.8)	2 (0.4)	56 (12.4)	13 (2.9)
Thyroid disorder	92 (20.4)	3 (0.7)	57 (12.6)	4 (0.9)

- 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)

Pembrolizumab (anti-PD-1) Avoids PD1-PDL1/2 Binding, Which Suppresses CTL Activity at Tumor Site



Many cancers suppress cytotoxic T cell activity by expressing PD-L1/PD-L2 on cell surfaces.

Langer CJ. *Am J Clin Oncol* 2015;38:422-30.

Introduction

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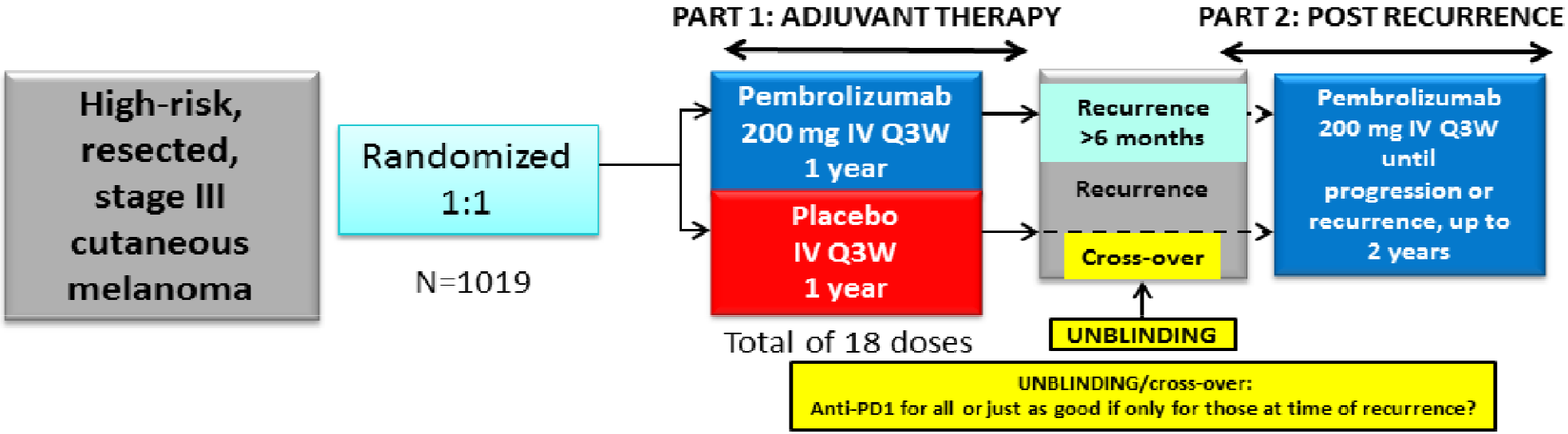
EORTC 1325/KEYNOTE-54: Study Design



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**

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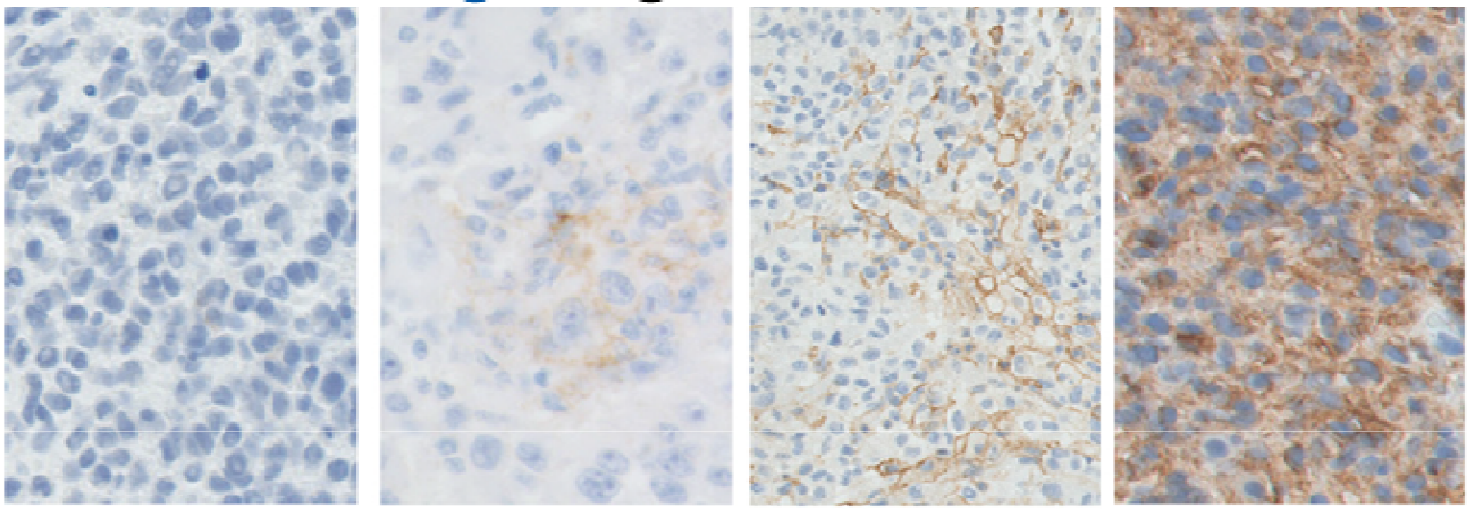
PD-L1 Staining: Negative <1%; Positive ≥1%



PD-L1 Negative	PD-L1 Positive	PD-L1 Positive	PD-L1 Positive
0% staining	1%-9% staining	10%-32% staining	66%-100% staining
MEL score, 0	MEL score, 2	MEL score, 3	MEL score, 5

No membrane staining		0
Membrane staining in tumor and tumor-associated immune cells, range	**PD-L1–**	
>0% – <1%		1
≥1% – <10%		2
≥ 10% – <33%	**PD-L1+**	3
≥ 33% – <66%		4
≥ 66%		5

Daud A, et al. *J Clin Oncol* 2016;34(34):4102-9.

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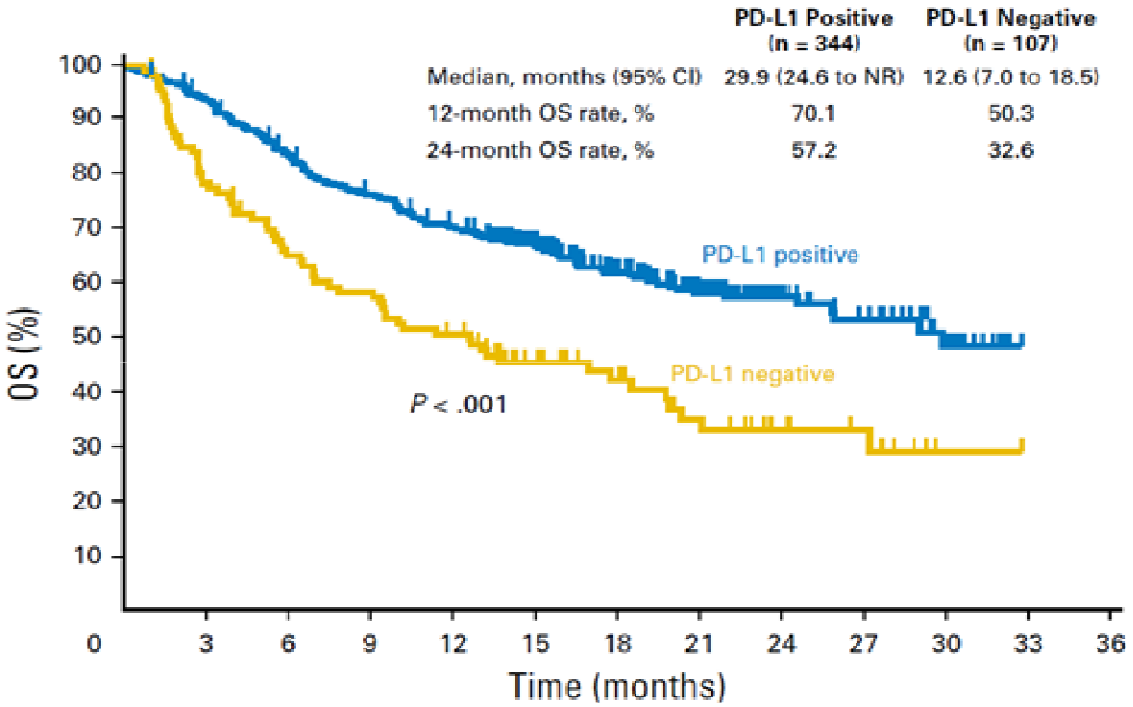
Pembrolizumab in Advanced Melanoma: KEYNOTE-001

PD-L1 Expression and Overall Survival



No. at risk													
PD-L1 positive	344	320	283	254	231	175	125	93	46	34	17	0	0
PD-L1 negative	107	83	67	60	51	35	23	18	11	8	1	0	0

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Daud A, et al. *J Clin Oncol* 2016;34(34):4102-9.

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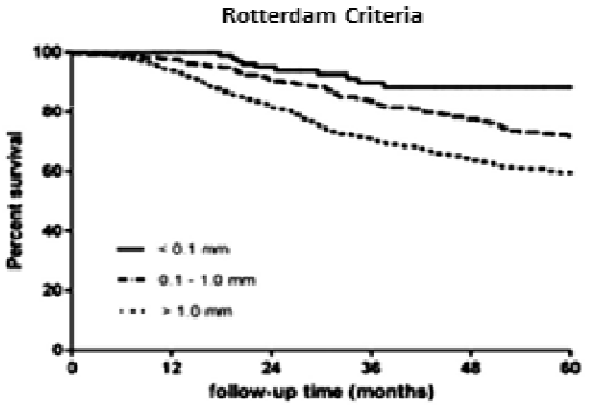
Key Eligibility Criteria

- At least 18 years of age
- Complete and adequate resection of stage III melanoma
- Histologically confirmed melanoma metastatic to lymph node
- Stage **IIIA (if N1a, at least 1 metastasis >1 mm);** stage **IIIB** or **IIIC** (no in transit meta)
- No prior systemic therapy for melanoma
- No autoimmune disease
- Documented NED following surgery
- Randomization within 13 weeks of surgery



Van der Ploeg, et al. *Eur J Cancer* 2014;50:111-20.

Study Overview

Primary endpoint

- **Recurrence-free survival (RFS)** by local investigator: time to loco-regional recurrence, distant metastasis, or death
  - Log-rank test and Cox model stratified by stage; 2-sided α=0.05
  - 409 events required to provide 92% power (target HR=0.70)
  - Interim analysis based on 351 events: 2-sided α=0.016 for the overall ITT population; if positive results, subgroup analysis in PD-L1+ subgroup (α=0.05)

Secondary endpoints

- Distant metastases-free survival (DMFS), overall survival (OS)
- Adverse event profile, health-related quality of life

Enrollment period: Aug-2015 – Nov-2016

Current analysis

- **Primary efficacy endpoint (RFS) in the ITT and PD-L1+ population, and Safety**
  - ***Cut-off date*** (2-Oct-2017); duration of follow-up: median 1.25 years; 351 RFS events
  - ***IDMC recommendation***: Reveal RFS results; study ongoing for DMFS & OS

Baseline Patient Characteristics

	Pembrolizumab (N=514)	Placebo (N=505)
Median age (years)	54	54
Male (%)	63	60
Stage (%)		
IIIA	15	15
IIIB	47	46
IIIC with 1-3 positive LN	17	19
IIIC with ≥4 positive LN	21	20
Ulceration of primary (%)	41	39
1 vs. 2-3 vs. ≥4 positive LN (%)	44 vs. 34 vs. 21	47 vs. 33 vs. 20
Lymph-node involvement (%)		
Microscopic	36	32
Macroscopic	64	68

Baseline Patient Characteristics

	Pembrolizumab (N=514)	Placebo (N=505)
PD-L1 status (%)		
Positive (MEL 2, 3, 4 or 5)	83	84
Negative (MEL 0 or 1)	11	11
Inevaluable	5	5
BRAF-mutation status (%)		
Wild type	45	42
V600E/K mutated	41	46
Other mutation	7	6
Not assessable	7	6

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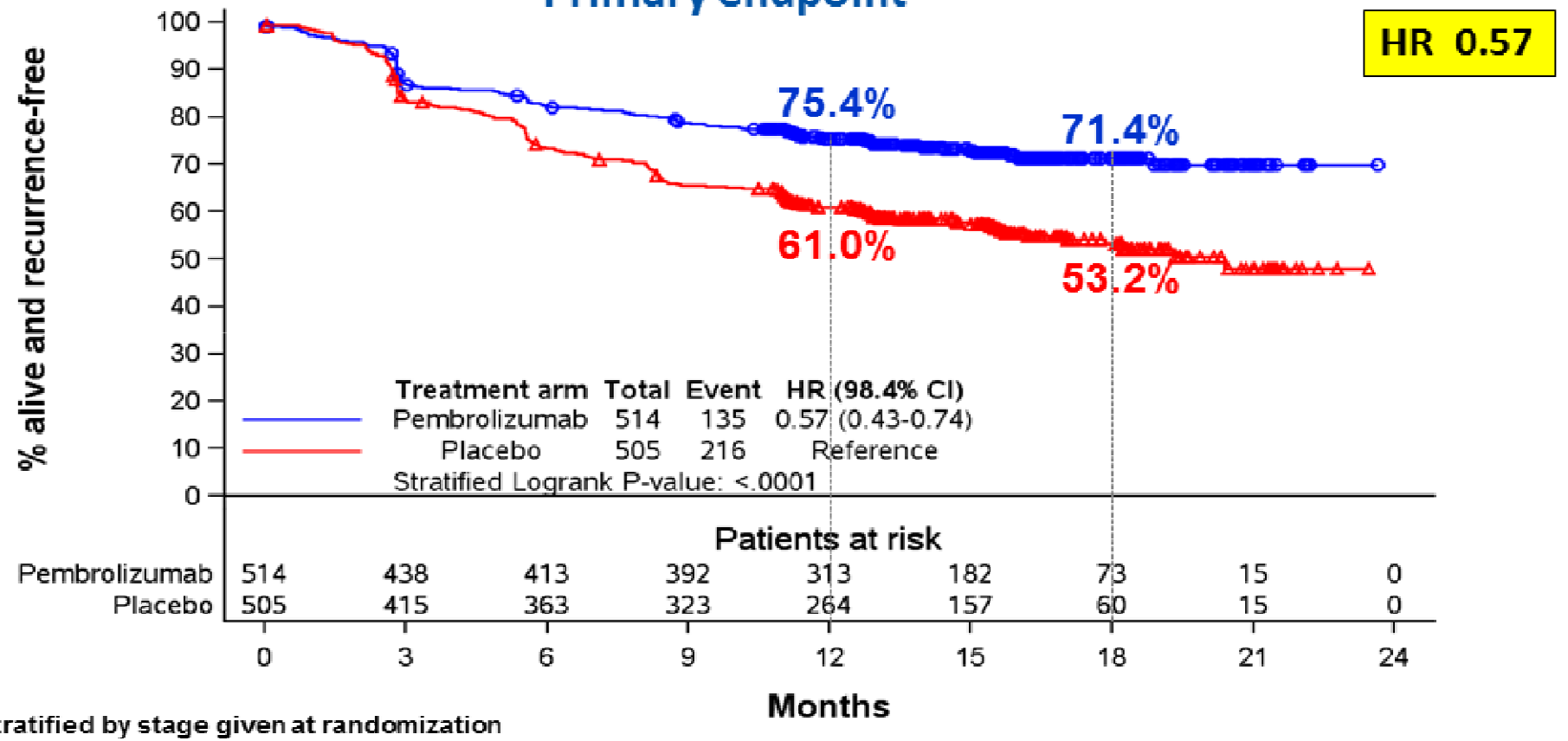
Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

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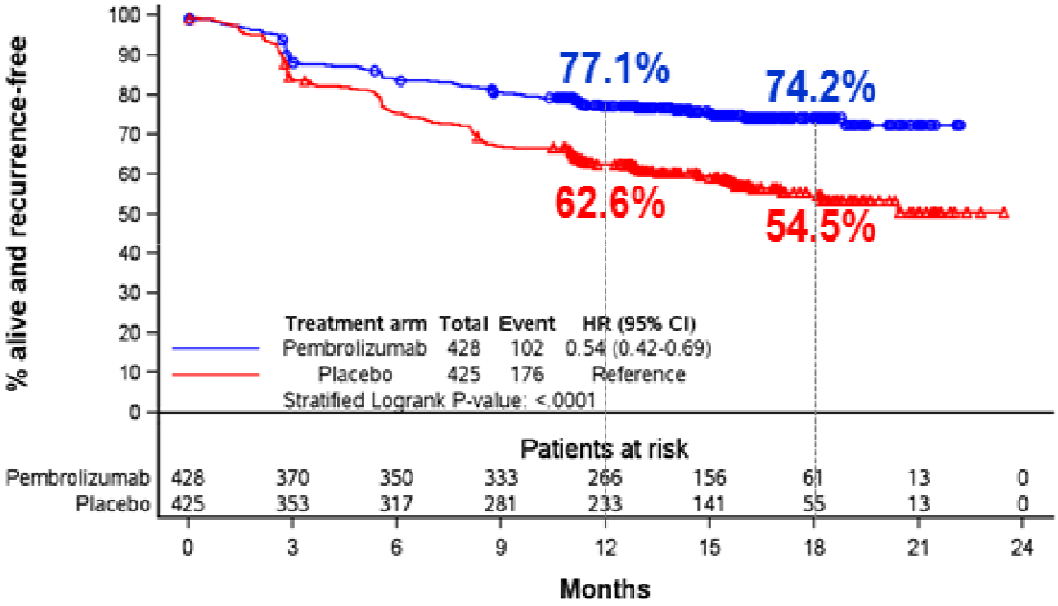
Recurrence-Free Survival

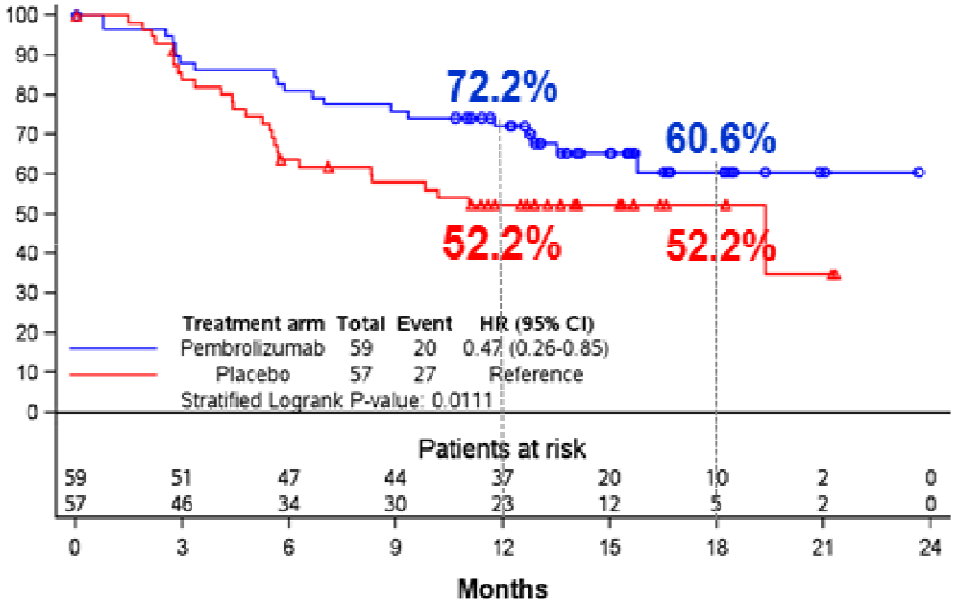
PD-L1+

HR 0.54



PD-L1–

HR 0.47



*Stratified by stage given at randomization

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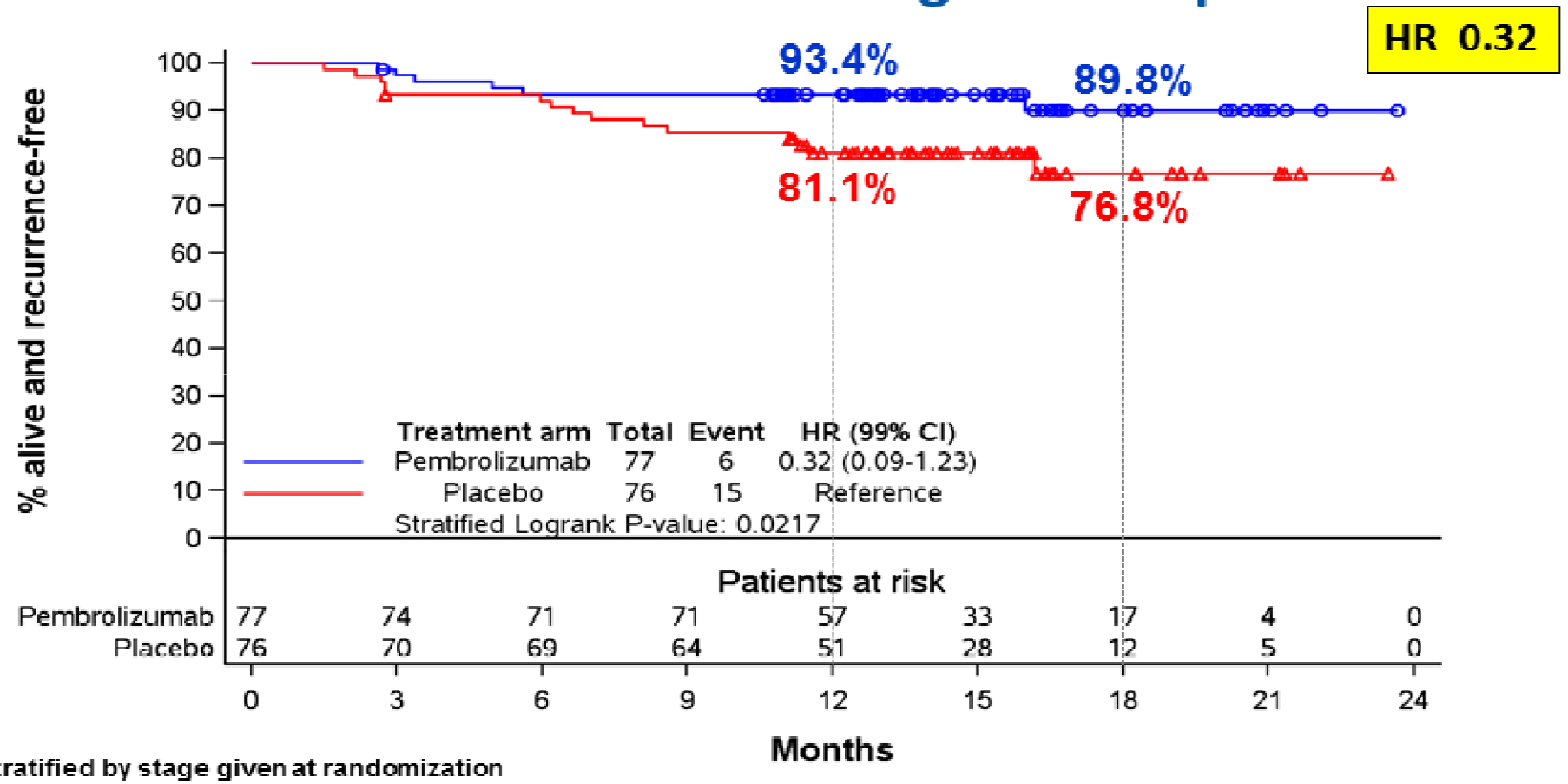
Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

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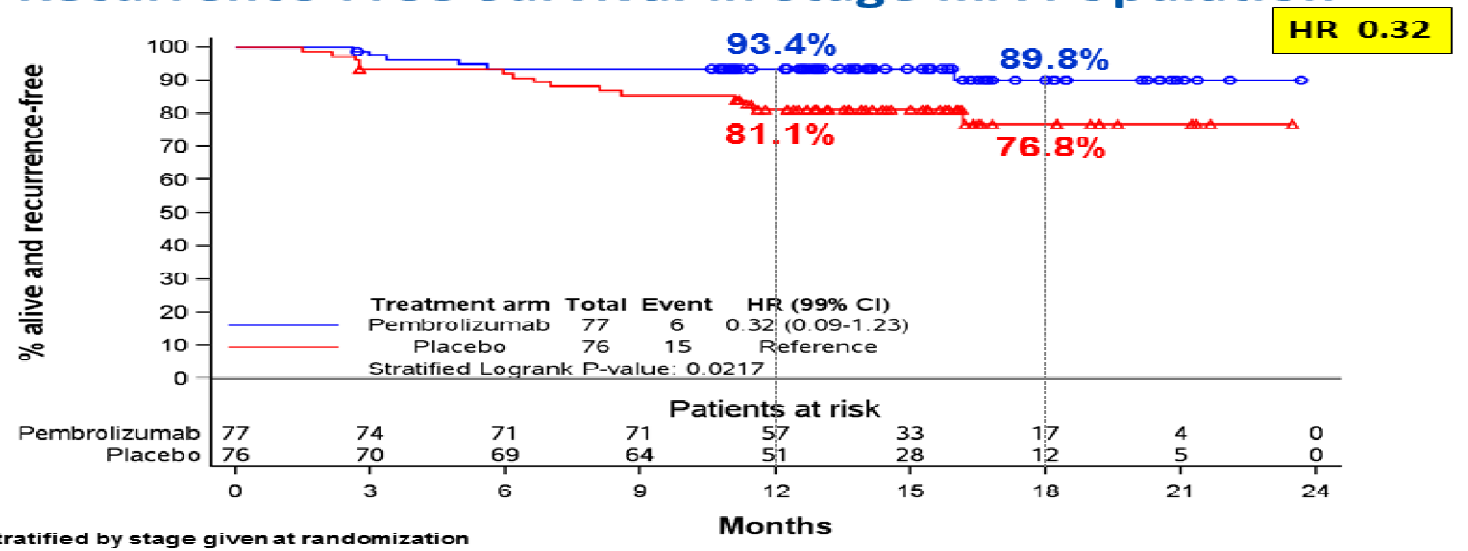
Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

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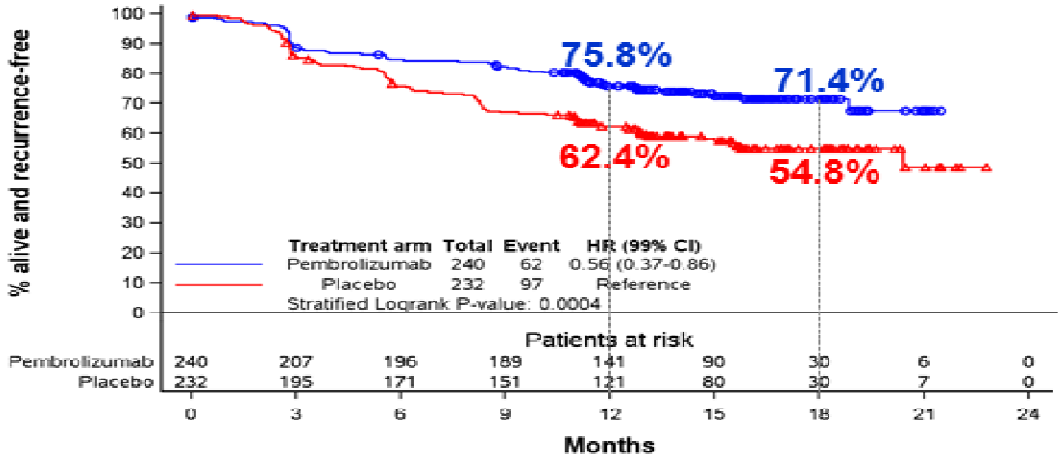
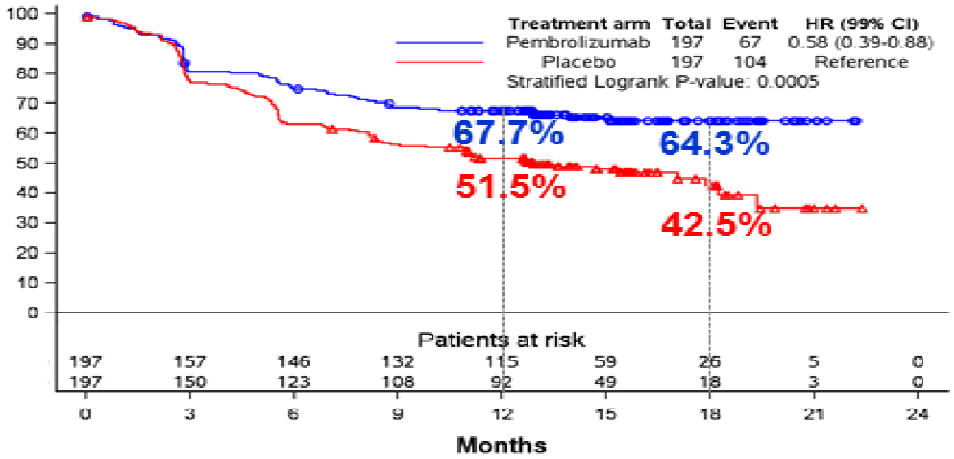
Recurrence-Free Survival

Stage IIIB



Stage IIIC



*Stratified by stage given at randomization

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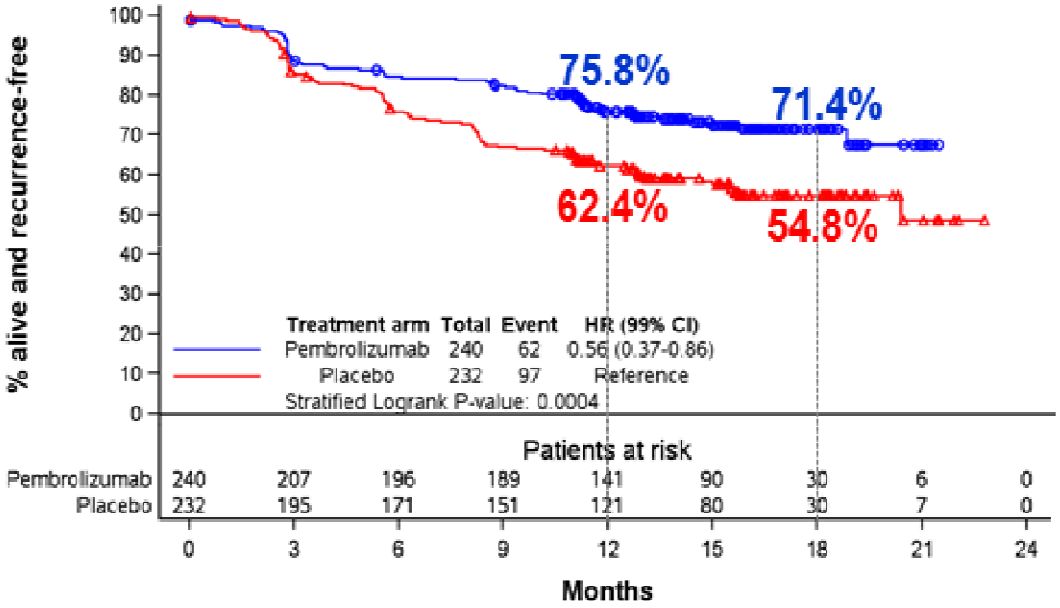
Recurrence-Free Survival

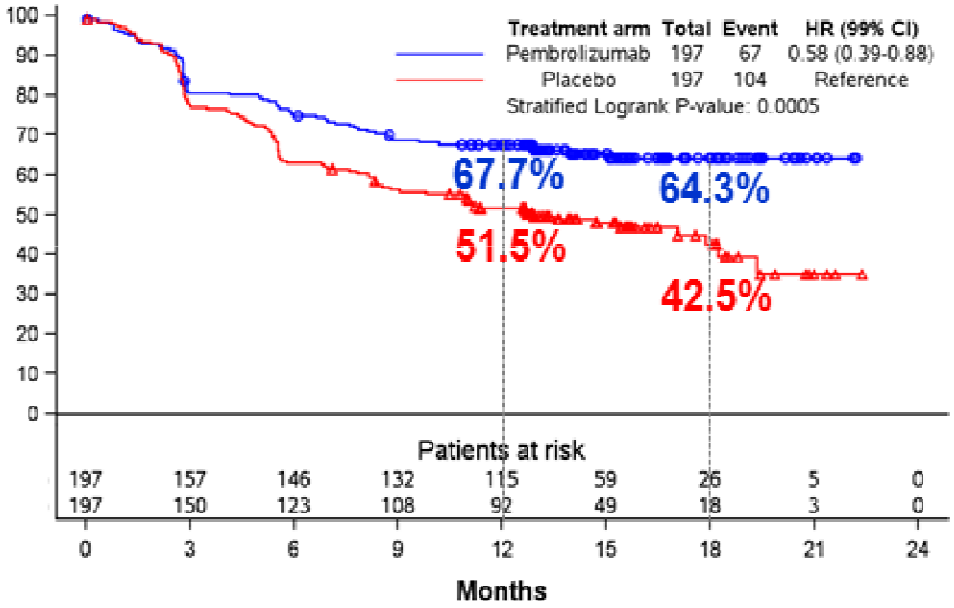
Stage IIIB

HR 0.56



Stage IIIC

HR 0.58



*Stratified by stage given at randomization

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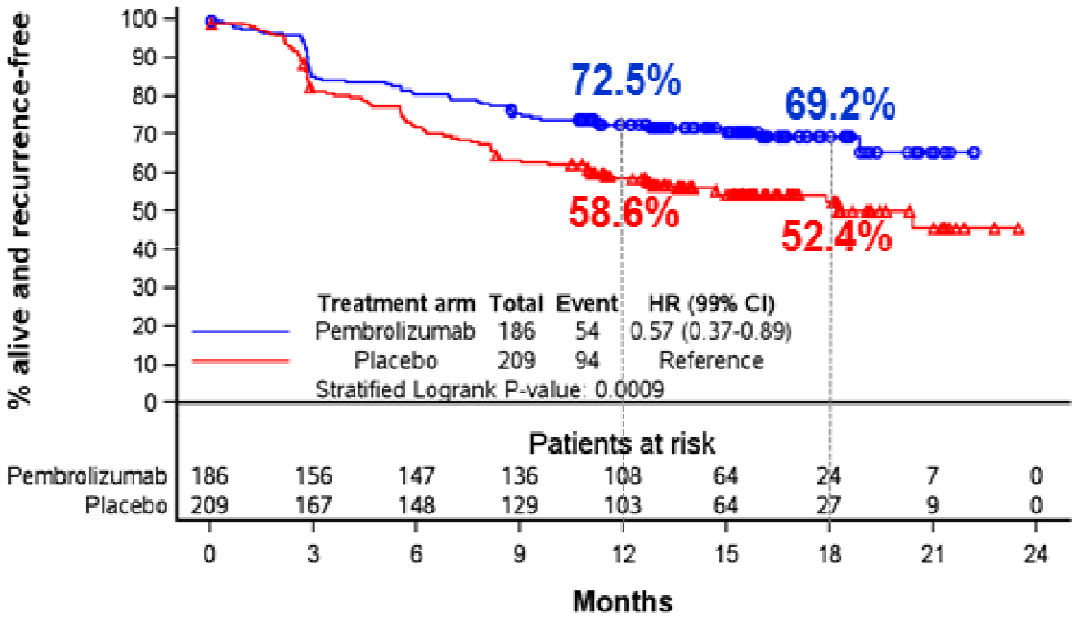
Recurrence-Free Survival

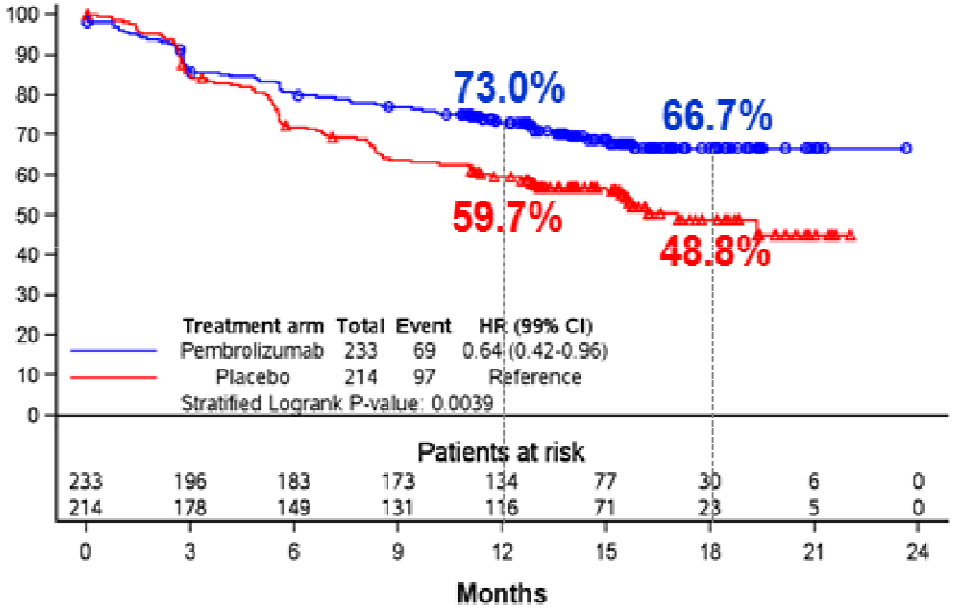
BRAF V600E/K

HR 0.57



BRAF WT

HR 0.64



*Stratified by stage given at randomization

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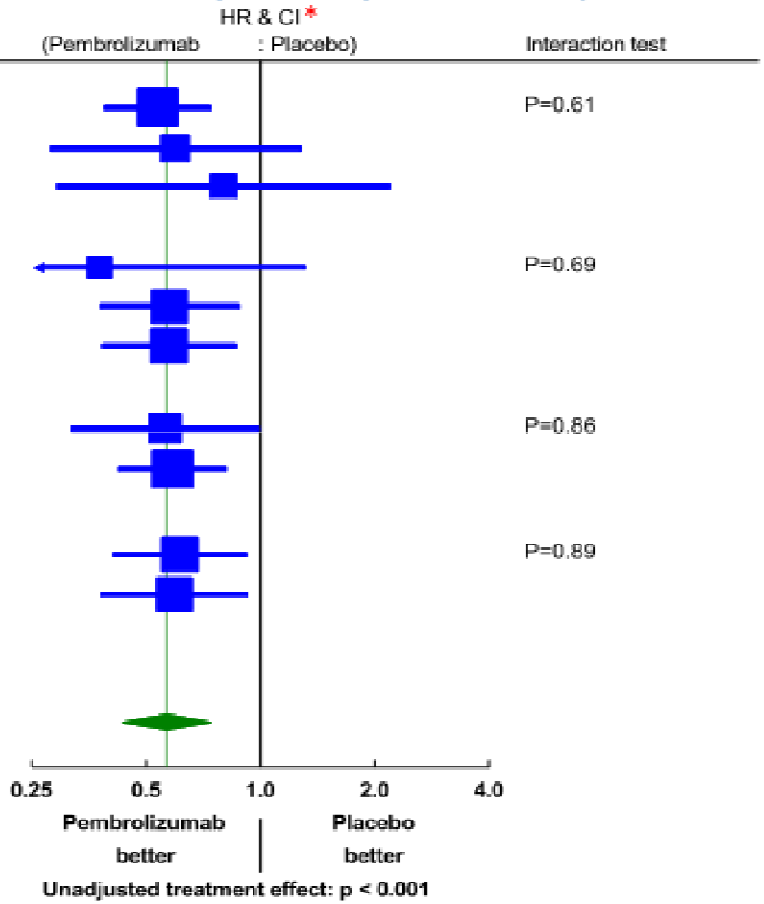
Recurrence-Free Survival: Subgroup Analysis

	Events / Patients Pembrolizumab	Placebo	HR (CI)		HR & CI* (Pembrolizumab : Placebo)	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** (26.3 %)	**216 / 505** (42.8 %)	**0.57**	**(0.43 ; 0.74)**		



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

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CENTRUM ONKOLOGII – INSTYTUT IM. MARII SKŁODOWSKIEJ-CURIE

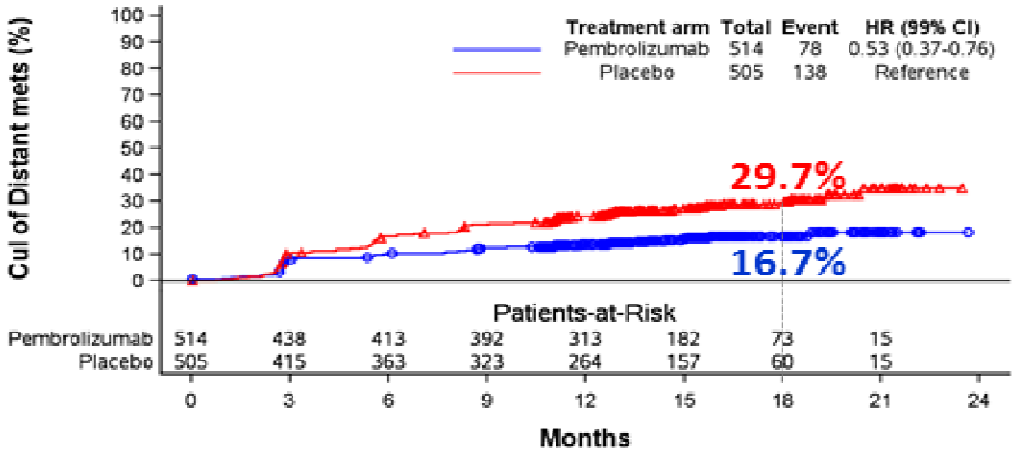
L. Eggermont AACR 2018

Type of First RFS Event

	Pembrolizumab (N=514)	Placebo (N=505)
No RFS event	379 (73.7)	289 (57.2)
Loco-regional recurrence, only	55 (10.7)	77 (15.2)
Distant metastasis, only	69 (13.4)	114 (22.6)
Both, diagnosed within 30 days from each other	9 (1.8)	24 (4.8)
Death without an RFS event	2 (0.4)	1 (0.2)

15.2% vs. **27.4%**

Cumulative Incidence of Distant Metastases As First RFS Event



HR 0.53

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The future of cancer therapy

CENTRUM ONKOLOGII – INSTYTUT
IM. MARII SKŁODOWSKIEJ-CURIE

Patient Disposition and Treatment

	Pembrolizumab (N=514)	Placebo (N=505)
Started allocated treatment	N=509	N=502
Reasons for discontinuation, %	96.3%	98.8%
Normal completion	55.4	58.6
Disease recurrence	21.4	35.7
Adverse event	13.8	2.2
Patient/investigator decision	3.5	1.2
Other malignancy	0.8	1.0
Non-compliance/Other reason	1.3	0.2
Still on treatment, %	3.7	1.2
Median (IQR) doses received per patient	18 (9-18)	18 (8-18)

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

Immune-Related Adverse Events
Any grade – grade 3-4 (%) (0.2% = 1 patient)

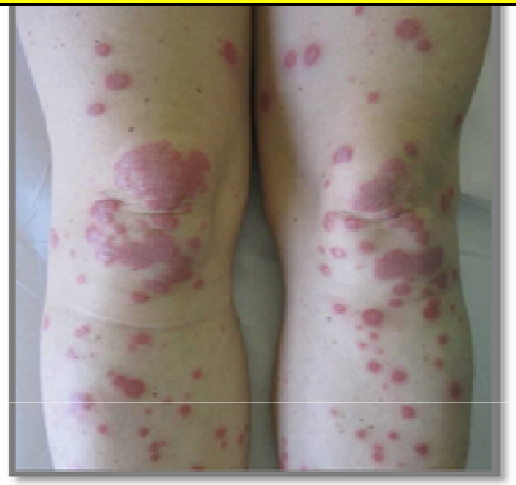
(0.2% = 1 patient)

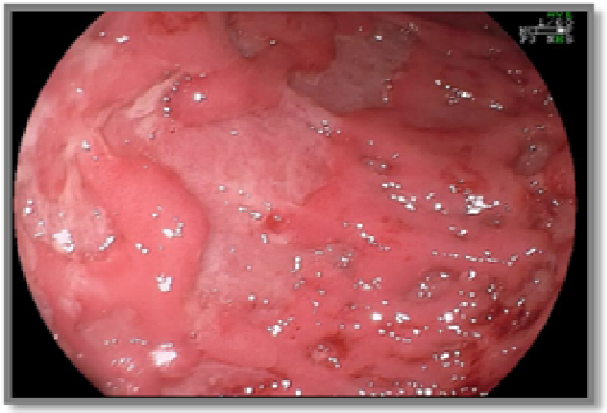
Skin
5.3 – 0.6

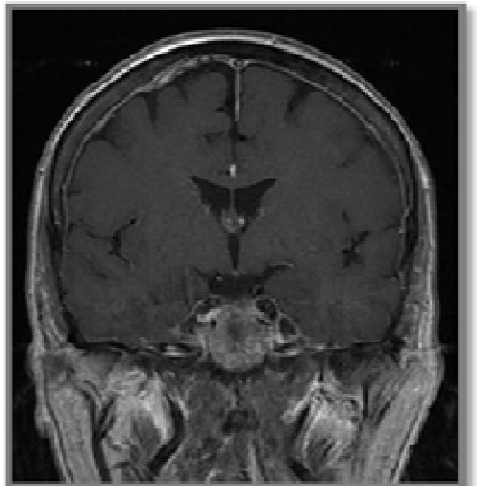
Myositis*
(grade 5)
0.2 – 0.2

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

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CENTRUM ONKOLOGII – INSTYTUT
IM. MARII SKŁODOWSKIEJ-CURIE

L. Eggermont AACR 2018

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

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Immune-Related Adverse Events

Regardless of investigator attribution

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Respiratory, thoracic and mediastinal disorders	4.7	0.8	0.6	0
Pneumonitis/interst. lung disease	3.3	0.8	0.6	0
Sarcoidosis	1.4	0	0	0
Vitiligo or severe skin	5.3	0.6	1.6	0
Vitiligo	4.7	0	1.6	0
Severe skin reactions	0.6	0.6	0	0

L. Eggermont AACR 2018

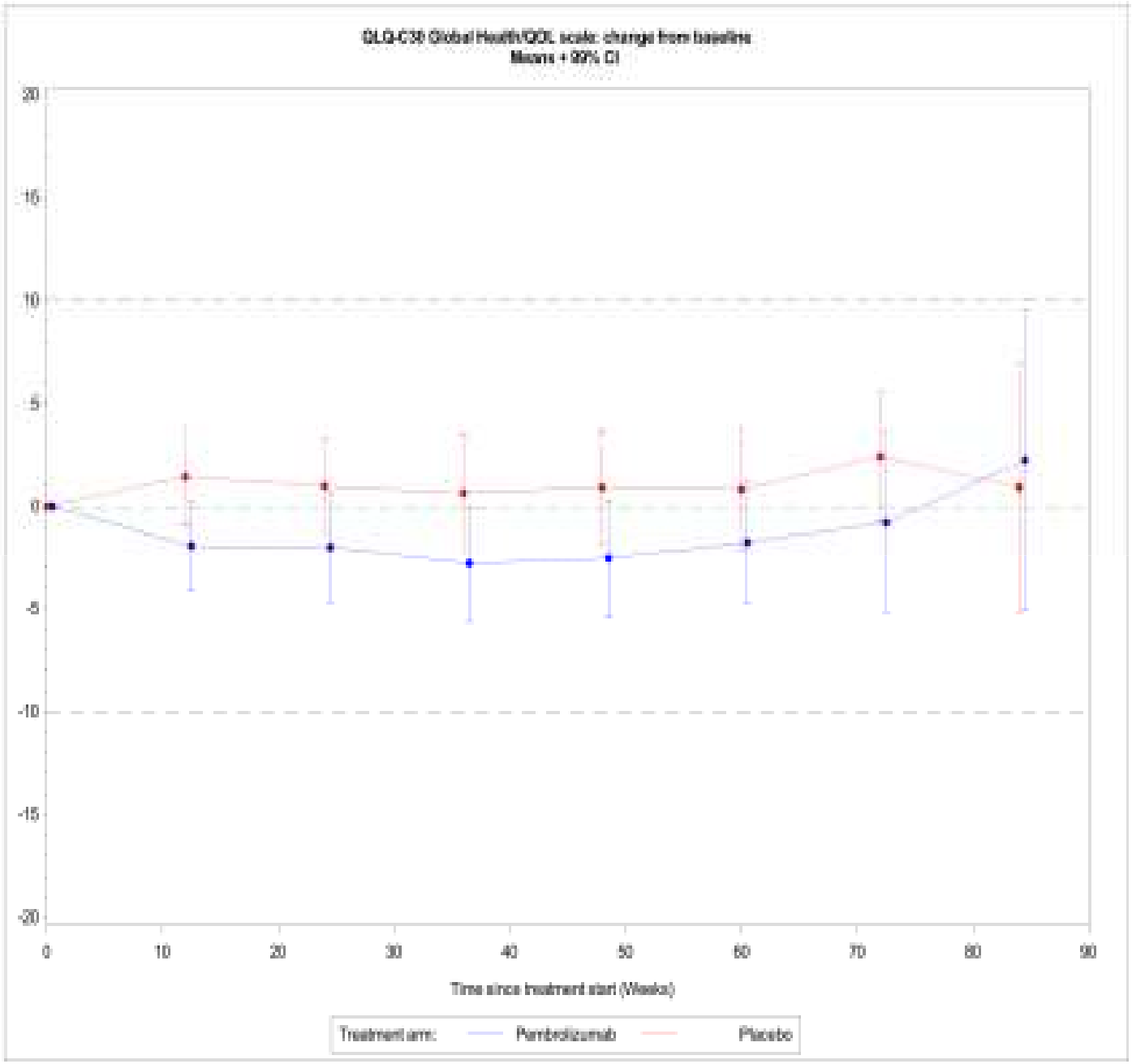
Immune-Related Adverse Events

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any grade	Grade 3–5*	Any grade	Grade 3–5
Gastrointestinal	3.9	2.0	0.8	0.4
Colitis	3.7	2.0	0.6	0.2
Pancreatitis	0.4	0.2	0.2	0.2
Hepatitis	1.8	1.4	0.2	0.2
Other irAE	2.9	1.0	1.0	0
Nephritis	0.4	0.4	0.2	0
Uveitis	0.4	0	0	0
Myositis*	0.2	0.2	0.2	0
Myocarditis	0.2	0.2	0	0

Baseline GHQ scores were similar between both treatment arms at 77 points (IQR: 67 - 92) and remained stable over time (see figure).

Global health/QoL	Pembrolizumab	Placebo	Difference	P-value
	mean (95% confidence interval)			
Overall	75.1 (73.6 - 76.6)	77.3 (76.0 - 78.7)	-2.2 (-4.3 - -0.2)	0.042
During treatment	76.9 (75.4 - 78.4)	78.0 (76.6 - 79.5)	-1.1 (-3.2 - 0.9)	0.263
After treatment	75.0 (73.1 - 77.0)	77.2 (75.4 - 78.9)	-2.2 (-4.8 - 0.4)	0.160

Treatment differences in the average QLQ-C30 GHQ score during treatment, after treatment and overall were not significant and < 5 points, well below the clinical relevance threshold.


QLQ-C30 Global Health/QOL scale: change from baseline
Means + 99% CI
20
15
10
5
0
-5
-10
-15
-20
0
10
20
30
40
50
60
70
80
90
Time since treatment start (Weeks)
Treatment arm:
Pembrolizumab
Placebo

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

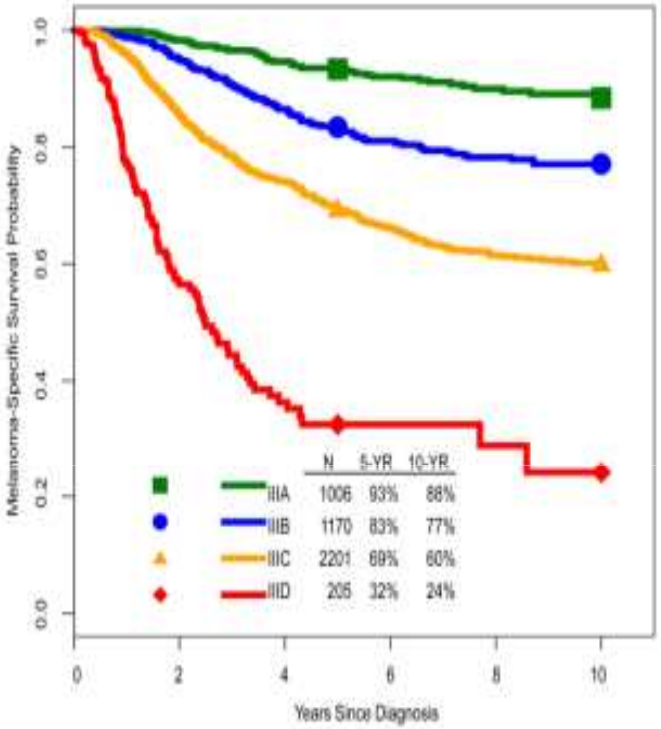
Instructions

(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[1]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID



Gershenwald et al. CA: A Cancer Journal for Clinicians; 2017; 67 6, 472-492,

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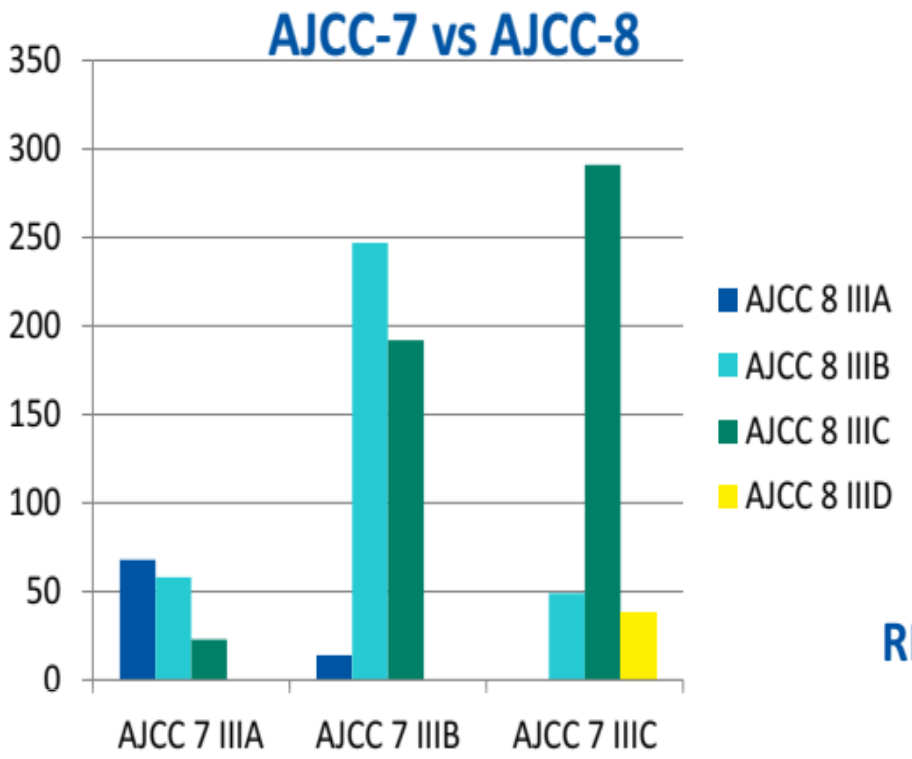
Baseline Patient Characteristics

	Pembrolizumab (N=514)	Placebo (N=505)
AJCC-7 Stage, n (%)		
IIIA	77 (15.0)	76 (15.0)
IIIB	240 (46.7)	232 (45.9)
IIIC	197 (38.3)	197 (39.0)
AJCC-8 Stage, n (%)		
IIIA	42 (8.2)	40 (7.9)
IIIB	163 (31.7)	191 (37.8)
IIIC	267 (51.9)	239 (47.3)
IIID	20 (3.9)	18 (3.6)
Inevaluable	22 (4.3)	17 (3.4)

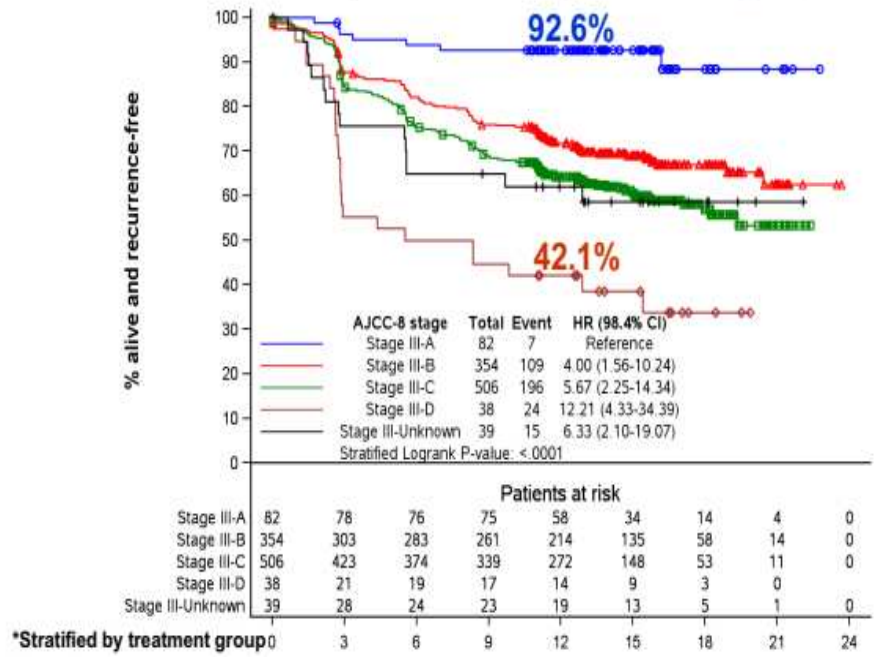
AJCC-7 vs AJCC-8

	AJCC-8 Stage					
AJCC-7 Stage	IIIA	IIIB	IIIC	IIID	Unknown	Total
IIIA	68	58	23	0	4	153 (15.0%)
IIIB	14	247	192	0	19	472 (46.3%)
IIIC	0	49	291	38	16	394 (38.6%)
Total (100%)	82 (8%)	354 (34.7%)	506 (49.6%)	38 (3.7%)	39 (3.8%)	1019 (100%)

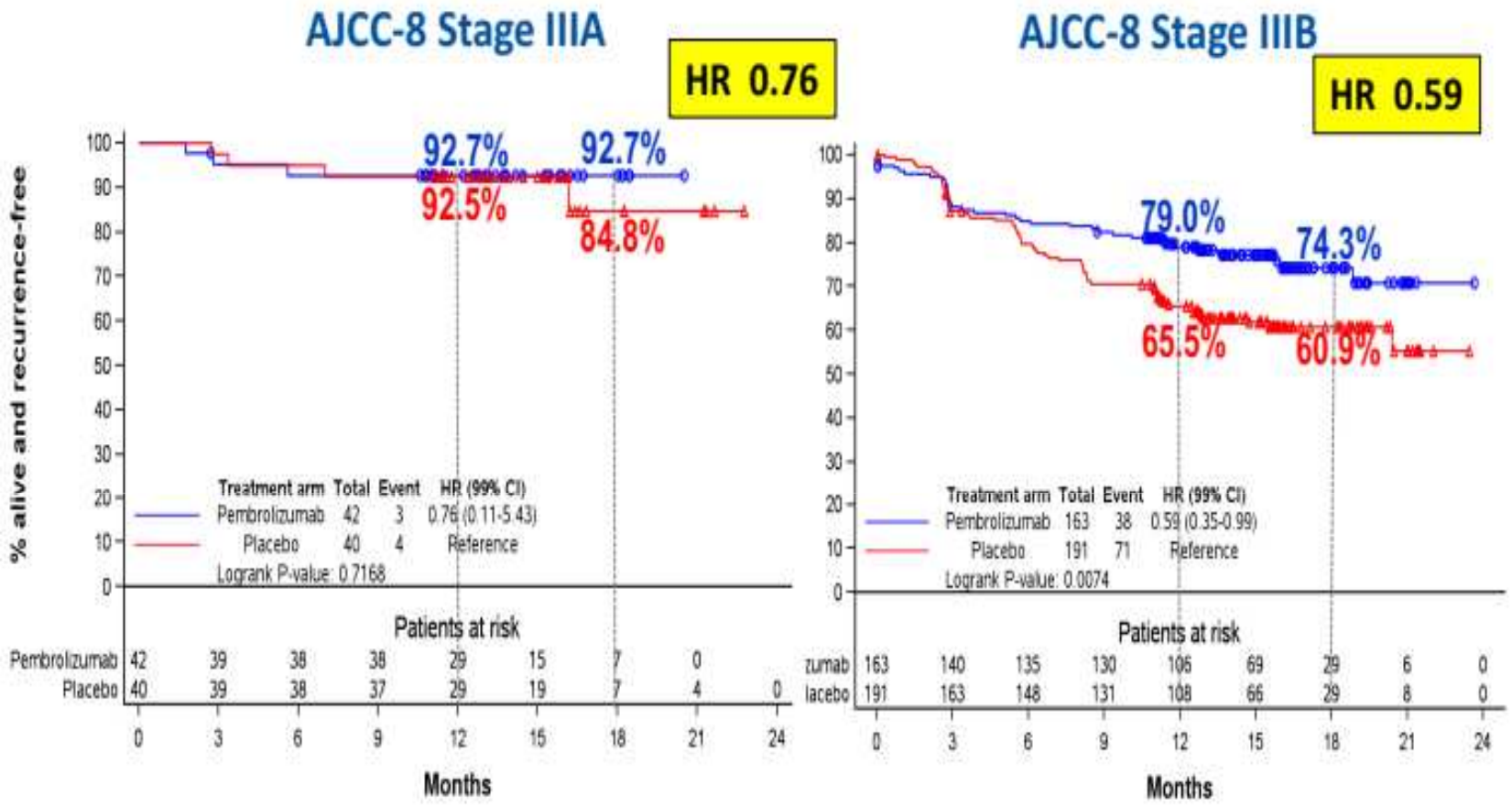


RFS: Prognostic importance of AJCC-8 classification

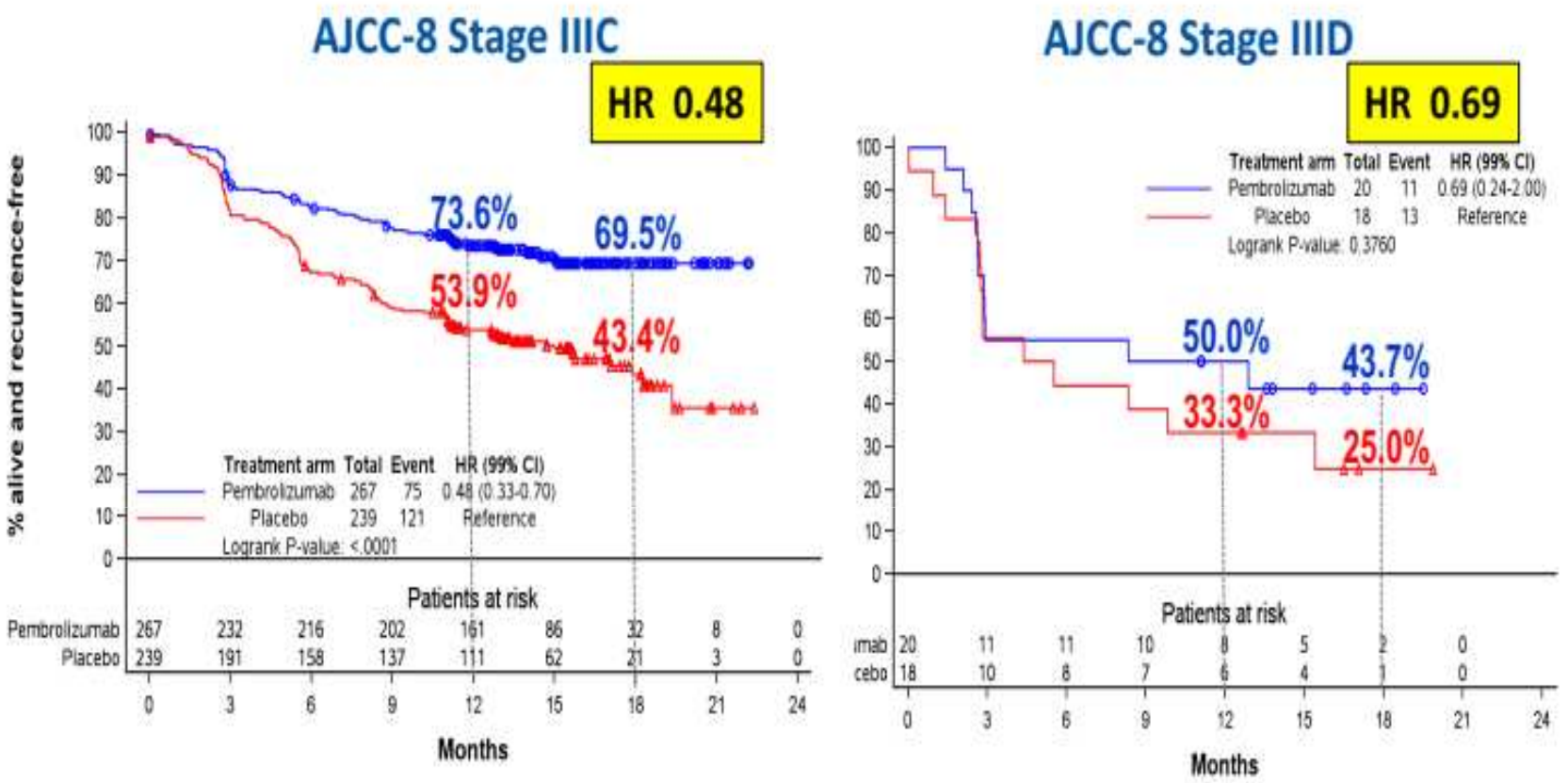
ITT analysis stratified by treatment group



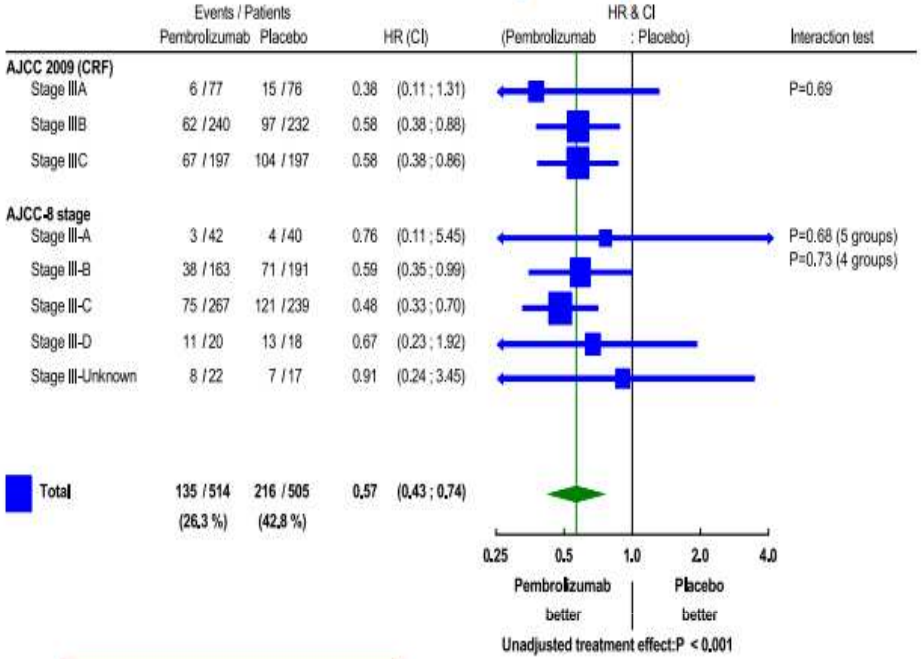
Recurrence-Free Survival: subgroup analysis by AJCC-8



Recurrence-Free Survival: subgroup analysis by AJCC-8 (cont)



Recurrence-Free Survival: Forest plot by AJCC-7 and AJCC-8



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

EORTC

- Study EORTC 1325/KEYNOTE-054 met its primary endpoint of a significant improvement in RFS with 200 mg I.V. Q3W **pembrolizumab** vs. **placebo**
  - **ITT overall population**: **HR = 0.57**, *P*<0.0001, **18 mos RFS difference: 18.2%**
  - **PD-L1+ population**: **HR = 0.54**, *P*<0.0001, **18 mos RFS difference: 19.7%**
- AJCC-8 classification identified more selected subgroups: stage IIIA (8%) and IIID (4%); these have different 1-yr RFS rates (~90% vs ~40%) ➡ AJCC-8 **strong prognostic factor**
- The RFS benefit of **pembrolizumab** was observed across AJCC-8 subgroups in resected high-risk stage III melanoma patients ➡ AJCC-8 **has no predictive importance**
  - Longer follow-up is required to confirm these results, especially in stage IIIA

Summary/Conclusions

- Study EORTC 1325/KEYNOTE-054 met its primary endpoint of a significant improvement in RFS with 200 mg I.V. Q3W **pembrolizumab** vs. **placebo**
  - **ITT overall population: HR = 0.57**, *P*<0.0001, **18 mos RFS difference: 18.2%**
  - **PD-L1+ population: HR = 0.54**, *P*<0.0001, **18 mos RFS difference: 19.7%**
- **Consistent results** across prespecified subgroups with HRs favoring **pembrolizumab** relative to **placebo**
- **Favorable safety profile**, where severe irAEs are rare, is generally consistent with that observed in advanced melanoma. There were many grade 1-2 thyroid events in about 1/5 pts, but severe endocrine events only in 9 pts (hypophysitis, diabetes, adrenal)
  - Most irAEs were managed and resolved with established treatment algorithms
- Data remain blinded for DMFS and OS (will be reported at future meetings)

Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

New Era (2015–2018)

• *Ipilimumab (US)[2]	HR_{RFS}(Ipilimumab vs. Placebo)=0.75	(2015)
• Nivolumab[3]	HR_{RFS}(Nivolumab vs. Ipilimumab)=0.65	(2017)
• *Dabrafenib plus Trametinib[4]	HR_{RFS}(Dab+Tra vs. Placebo)=0.47	(2018)
• *Pembrolizumab[5]	HR_{RFS}(Pembrolizumab vs. Placebo)=0.57	(2018)

*** Trials performed in identical patient populations at high risk of relapse: IIIA >1mm; IIIB/C**

5-year relapse rates: AJCC-7 stage IIIA, 37%; stage IIIB, 68%; stage IIIC, 89%[6]

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27; [2]Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30; [3]Weber J, et al. *N Engl J Med* 2017;377:1824-35; [4]Long GV, et al. *N Engl J Med* 2017;377:1813-23; [5]Eggermont AM, et al. *N Engl J Med* 2018;375;1845-55; [6]Romano E, et al. *J Clin Oncol* 2010;28:3042-7.

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. L

This article was published on September 10, 2017, at NEJM.org.

ADJUWANTOWY DABRAFENIB + TRAMETYNIB

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.

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

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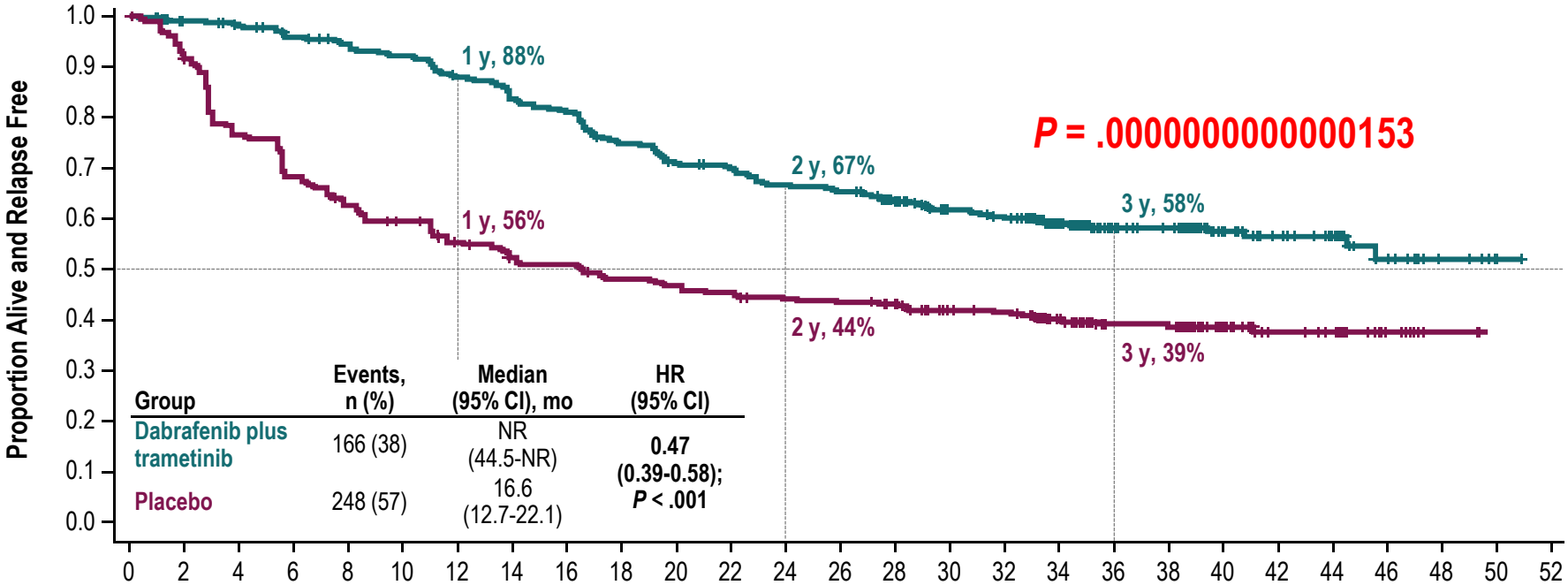
PRESENTED AT ESMO 2017.

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.

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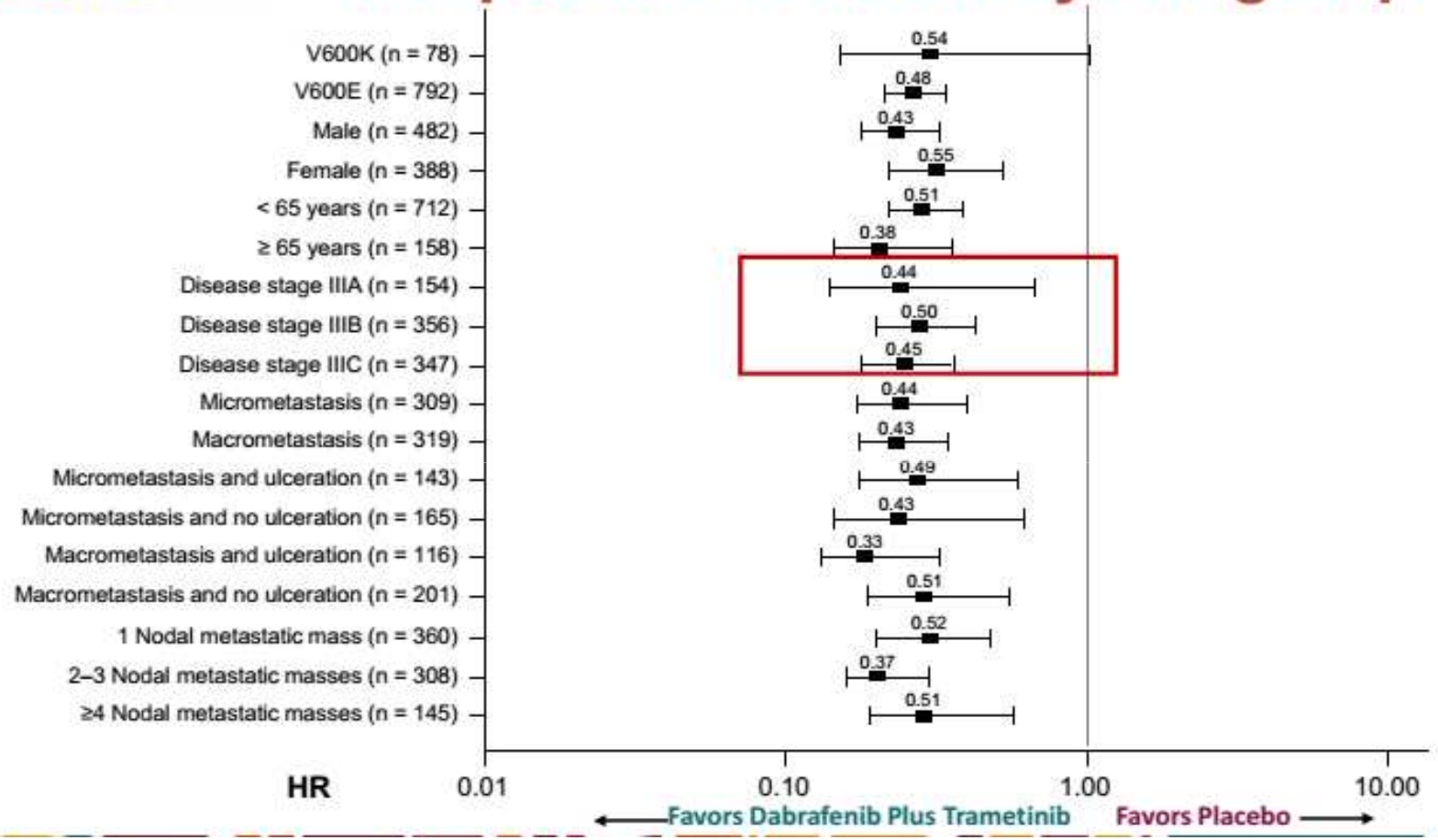
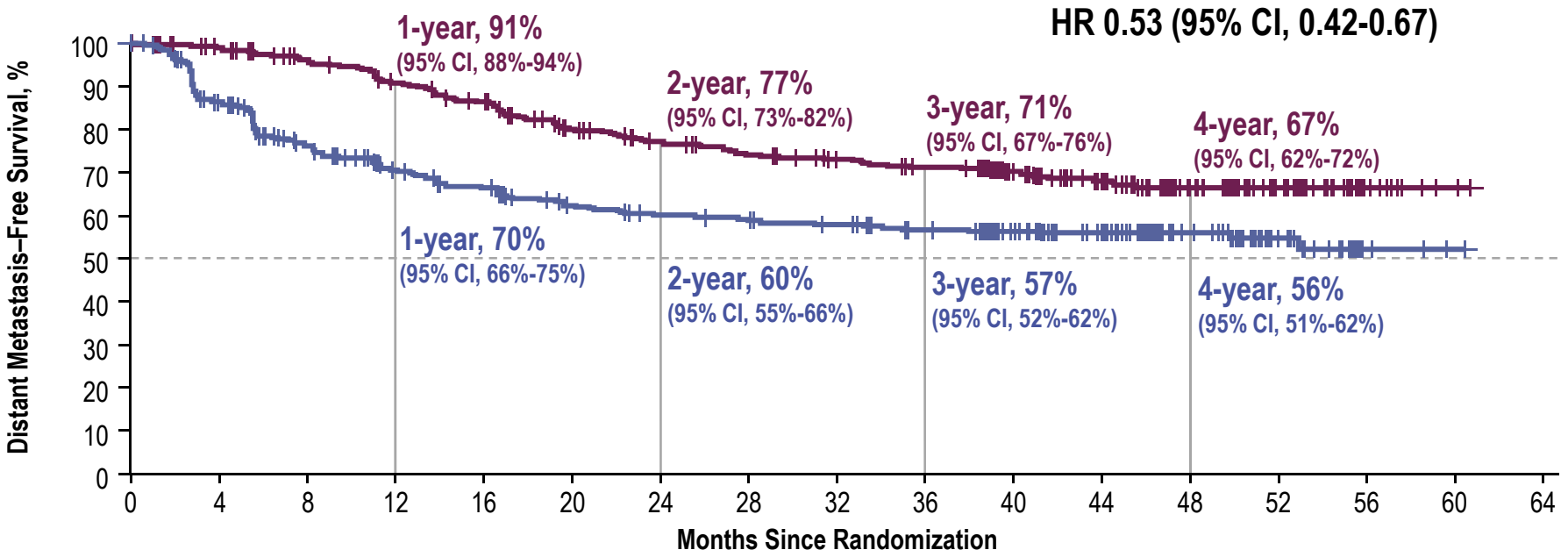
Relapse-free survival by Subgroup



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

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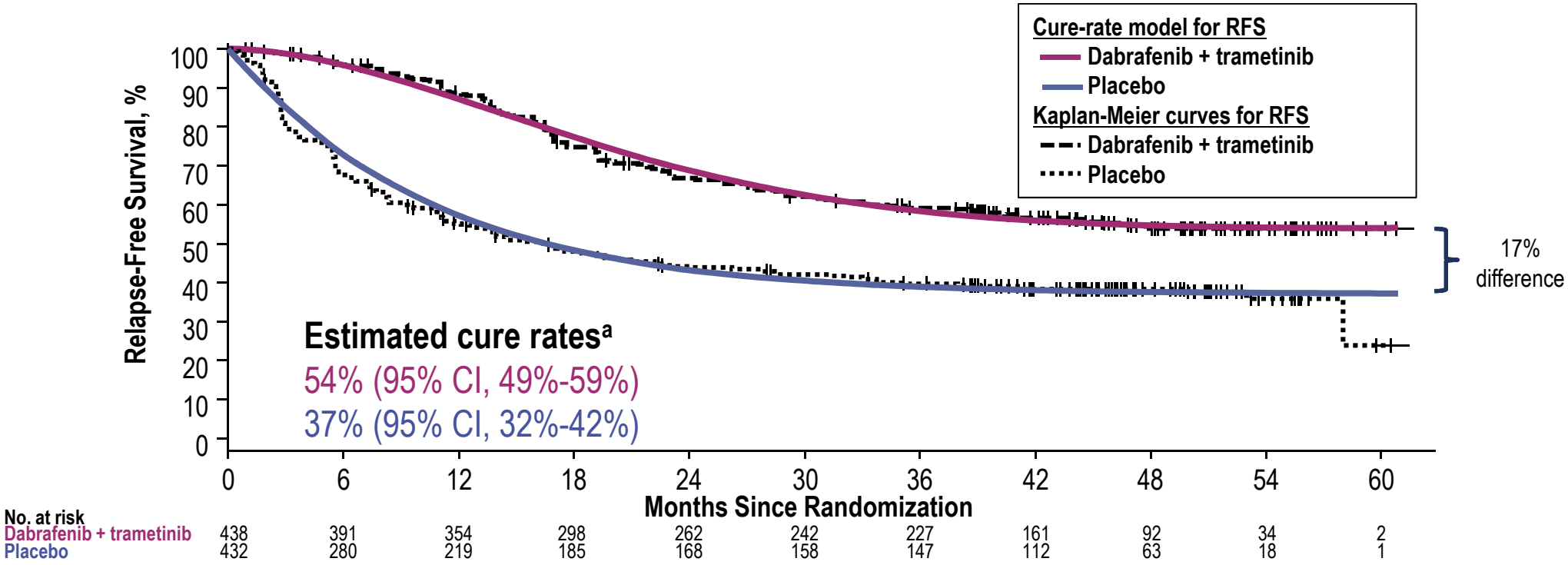
CURE-RATE MODEL RESULTS

A higher proportion of patients are estimated to be relapse-free long term with D + T vs placebo



[a] Proportion of patients expected to remain relapse-free long term.

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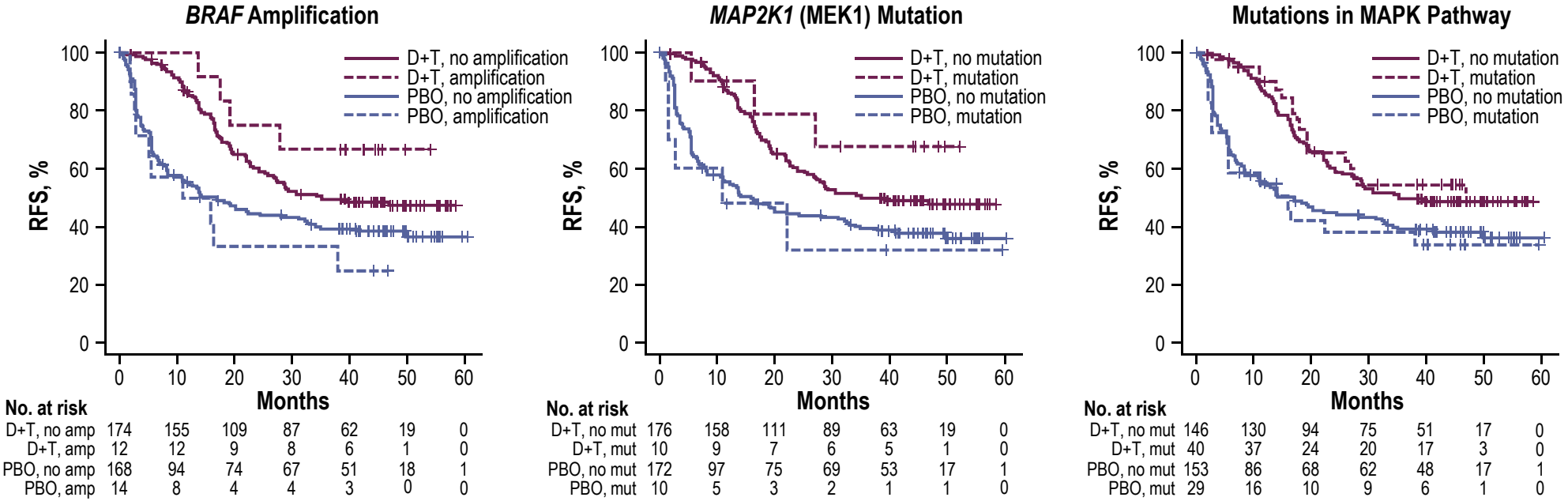
GENETIC ALTERATIONS IN THE MAPK PATHWAY WERE NOT ASSOCIATED WITH CLINICAL OUTCOME/RESPONSE TO THERAPY



amp, amplification; BRAFi, BRAF inhibitor; MEKi, MEK inhibitor; mut, mutation.

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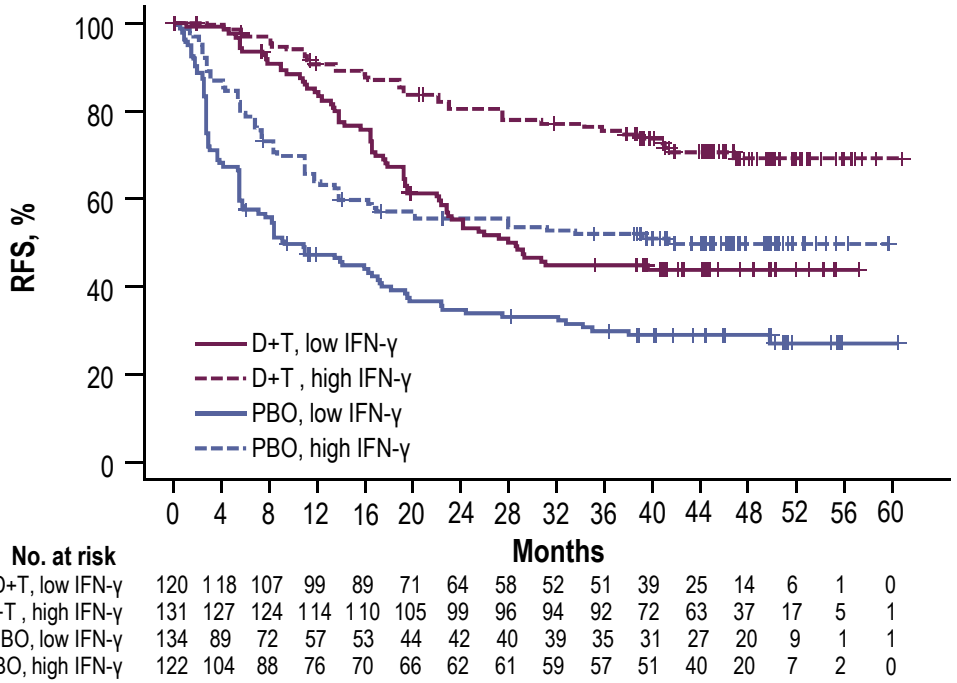
IMMUNE GENE EXPRESSION SIGNATURES WERE STRONGLY PROGNOSTIC FOR RFS



Placebo

Factor	HR	Lower	Upper	*P* Value
(Baseline)[a]	(1)	–	–	–
IIIB	1.63	0.94	2.84	0.076
IIIC	1.89	1.07	3.36	
Ulceration	1.13	0.80	1.59	0.488
IFN-γ	0.76	0.67	0.86	< 0.001

Dabrafenib + Trametinib

Factor	HR	Lower	Upper	*P* Value
(Baseline)[a]	(1)	–	–	–
IIIB	1.31	0.67	2.55	0.045
IIIC	2.04	1.05	3.96	
Ulceration	0.99	0.64	1.53	0.952
IFN-γ	0.61	0.52	0.73	< 0.001

Multivariate Cox analysis.

[a] Stage IIIA, no ulceration, INF-γ = 0.

IFN, interferon; PBO, placebo.

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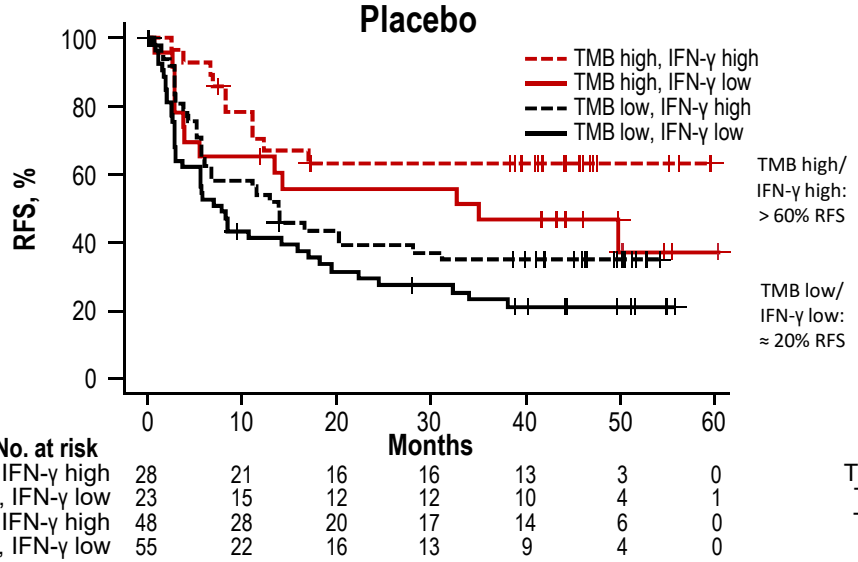
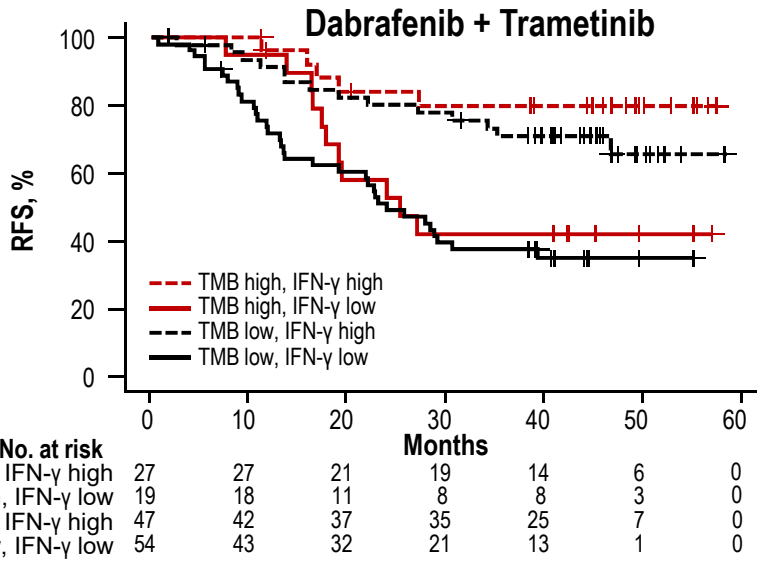
TUMOR MUTATIONAL BURDEN (TMB) AND IMMUNE GENE EXPRESSION SIGNATURES (PAIRED DNA/RNA DATA SET, n = 301)



No. at risk							
TMB high, IFN-γ high	28	21	16	16	13	3	0
TMB high, IFN-γ low	23	15	12	12	10	4	1
TMB low, IFN-γ high	48	28	20	17	14	6	0
TMB low, IFN-γ low	55	22	16	13	9	4	0



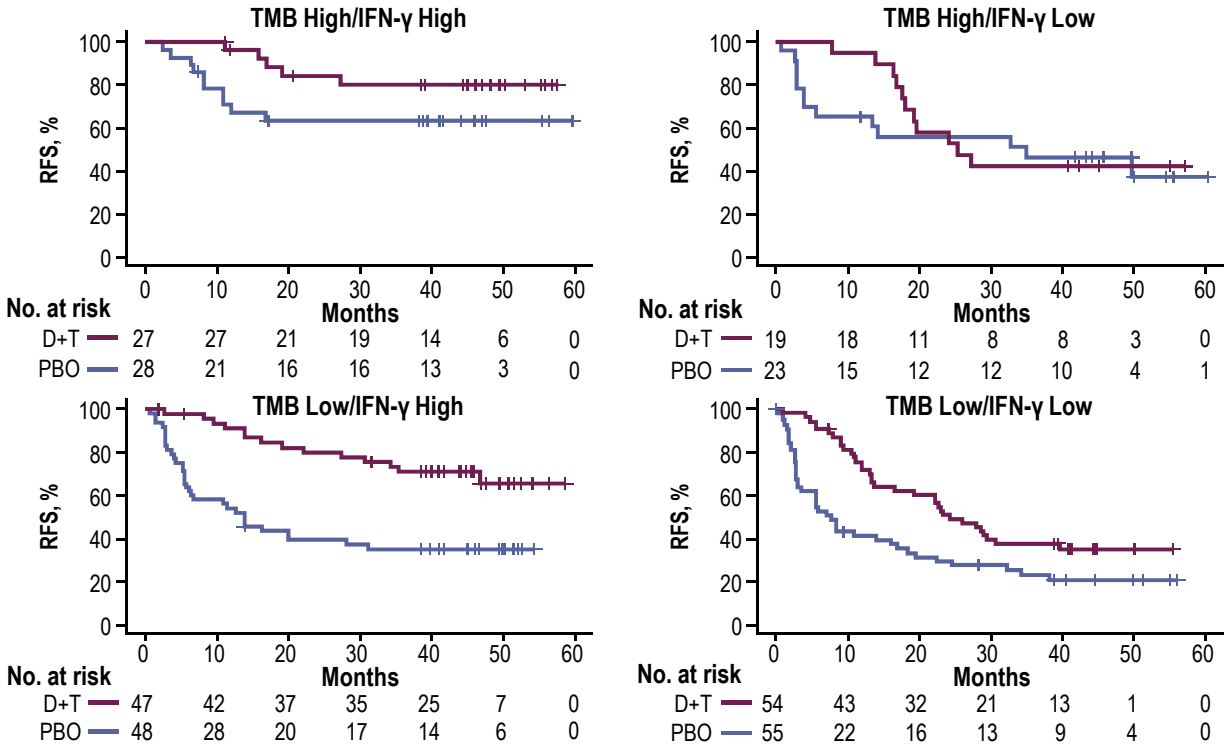
No. at risk							
TMB high, IFN-γ high	27	27	21	19	14	6	0
TMB high, IFN-γ low	19	18	11	8	8	3	0
TMB low, IFN-γ high	47	42	37	35	25	7	0
TMB low, IFN-γ low	54	43	32	21	13	1	0

- High tumor mutational burden (using the top third as a threshold) added positive prognostic value to immune gene signatures in the placebo arm (high IFN-γ and high TMB associated with longer RFS)
- In the dabrafenib + trametinib arm, IFN-γ gene signature identified patients with longer RFS independently of TMB status

PRESENTED BY GV LONG AT ESMO 2018

MUNICH 2018 ESMO congress

EXPLORATORY ANALYSIS OF THE PREDICTIVE VALUE OF TMB/IFN-γ



The analysis was not powered to assess treatment interactions, but results suggest that low TMB or high TMB/high IFN-γ may be associated with greater RFS benefit than high TMB/low IFN-γ

PRESENTED BY GV LONG AT ESMO 2018

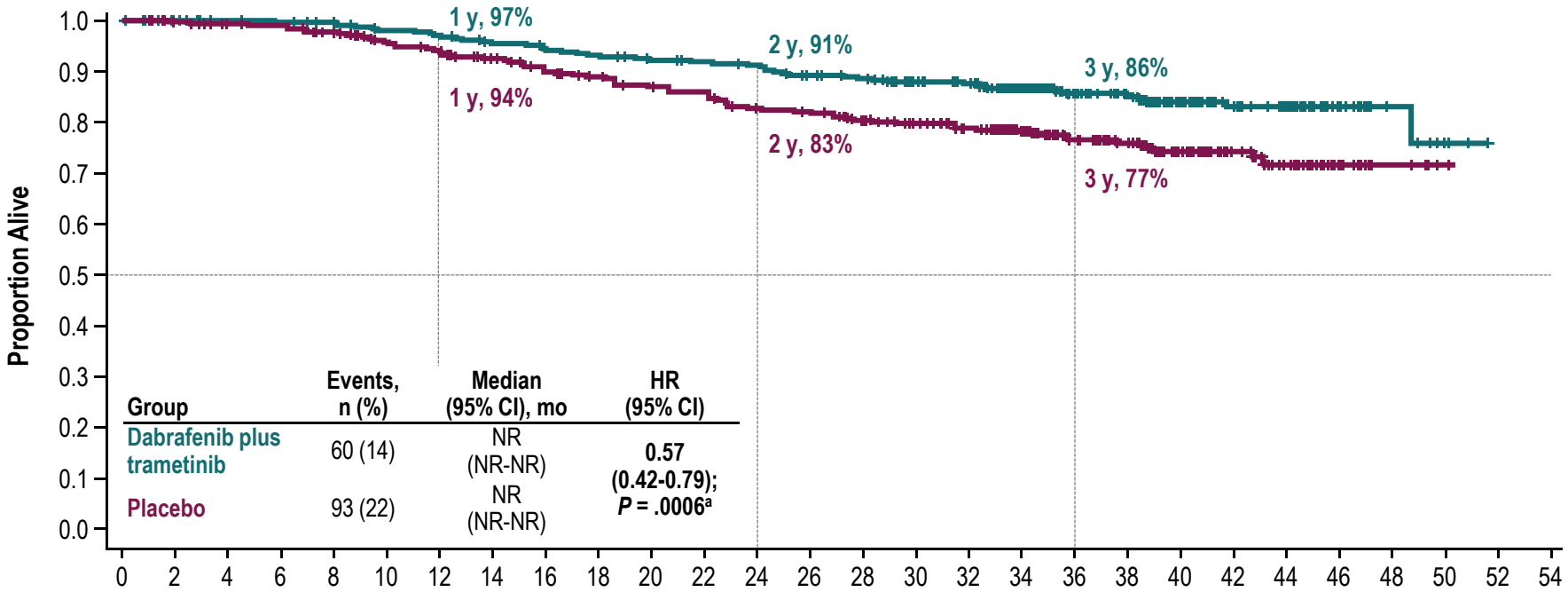
MUNICH 2018 ESMO congress

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

PRESENTED AT ESMO 2017.

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).

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%).

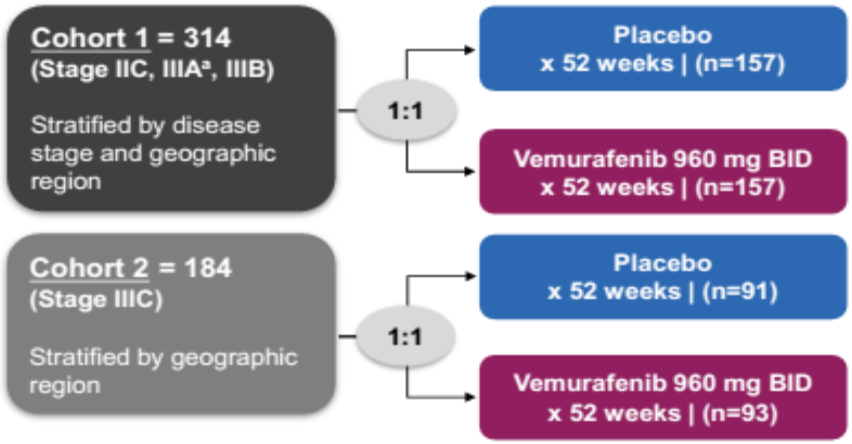
Table 3. Adverse Events (Safety Population).*

Adverse Event	Dabrafenib plus Trametinib (N=435)		Placebo (N=432)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	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)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Elevated alanine aminotransferase	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza-like illness	67 (15)	2 (<1)	29 (7)	0
Elevated aspartate aminotransferase	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in limb	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)
Peripheral edema	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0
Adverse event leading to dose interruption	289 (66)	NA	65 (15)	NA
Adverse event leading to dose reduction	167 (38)	NA	11 (3)	NA
Adverse event leading to discontinuation of study regimen	114 (26)	NA	12 (3)	NA

ADJUWANTOWY WEMURAFENIB

BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients with completely resected *BRAF*$^{V600+}$ melanoma at high risk for recurrence

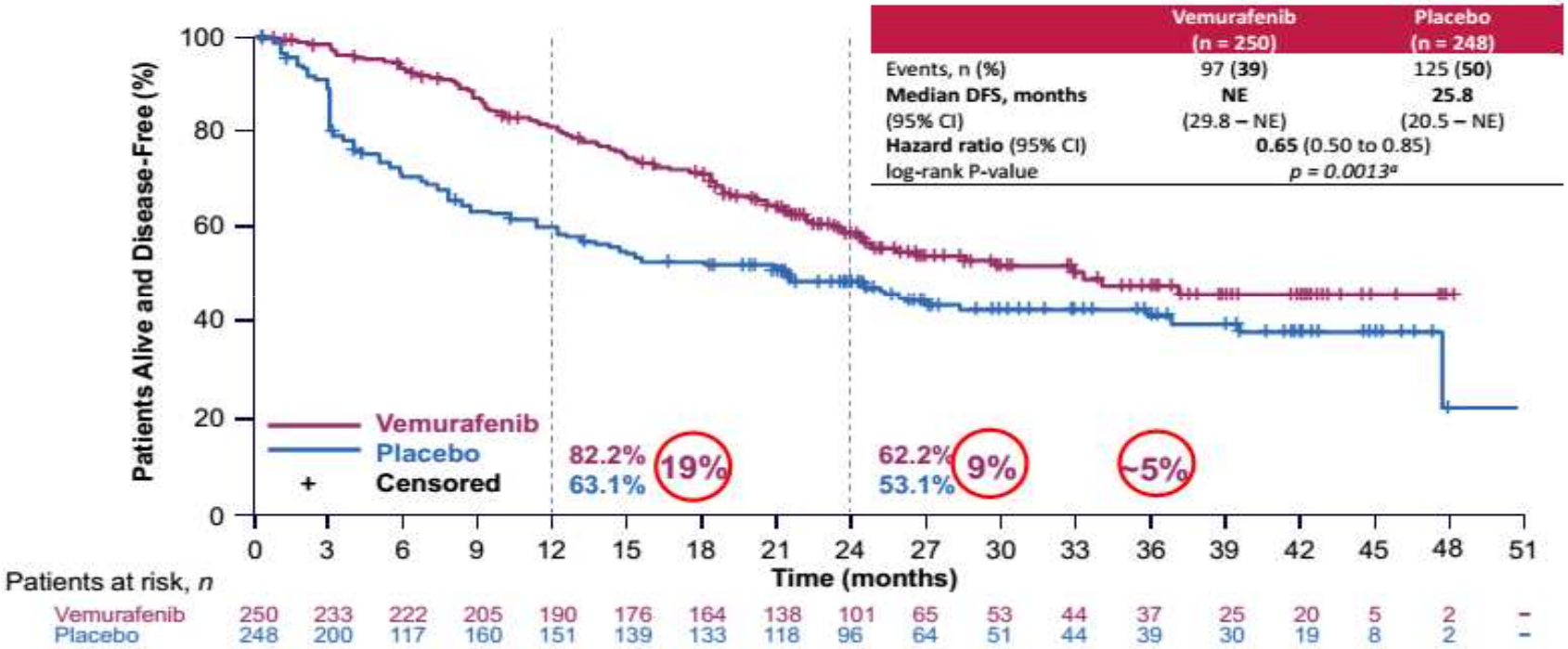
Karl Lewis,[1] Michele Maio,[2] Lev Demidov,[3] Mario Mandalà,[4] Paolo A. Ascierto,[5] Christopher Herbert,[6] Andrzej Mackiewicz,[7] Piotr Rutkowski,[8] Alexander Guminski,[9] Grant Goodman,[10] Brian Simmons,[10] Chenglin Ye,[10] Yibing Yan,[10] Dirk Schadendorf[11]



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

BRIM8: Pre-specified exploratory DFS analysis in pooled ITT population

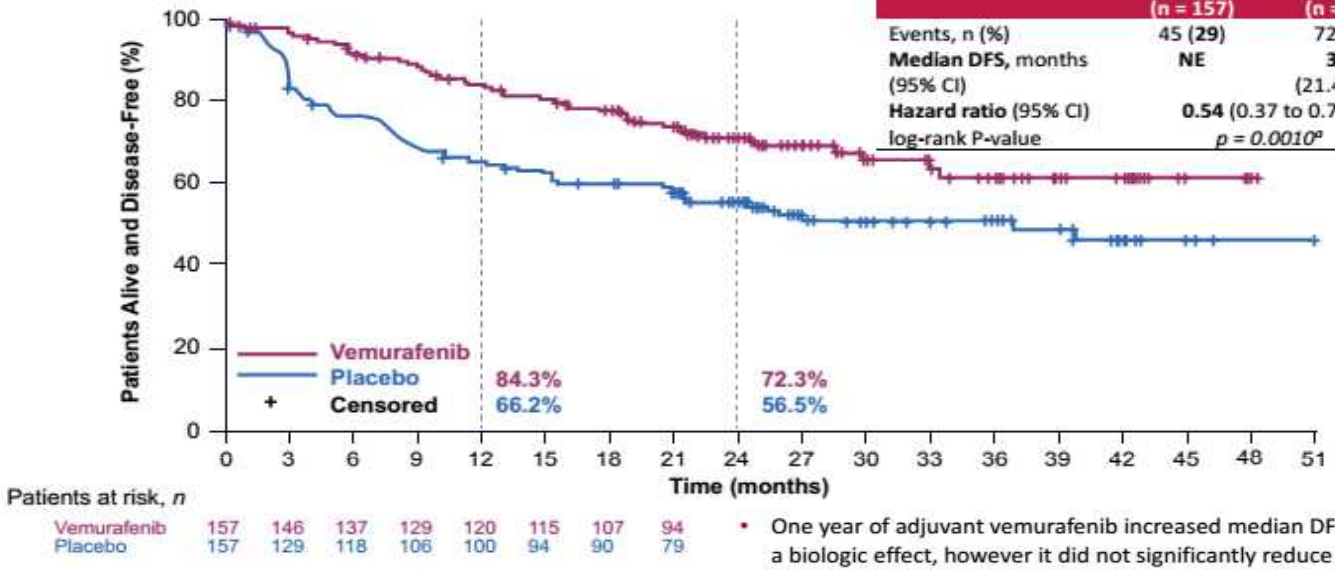
- The pre-specified exploratory pooled analysis of the 2 cohorts demonstrates an overall clinical benefit



	Vemurafenib (n = 250)	Placebo (n = 248)
Events, n (%)	97 (39)	125 (50)
Median DFS, months	**NE**	**25.8**
(95% CI)	(29.8 – NE)	(20.5 – NE)
Hazard ratio (95% CI)	**0.65** (0.50 to 0.85)	
log-rank P-value	*p = 0.0013*[a]	

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

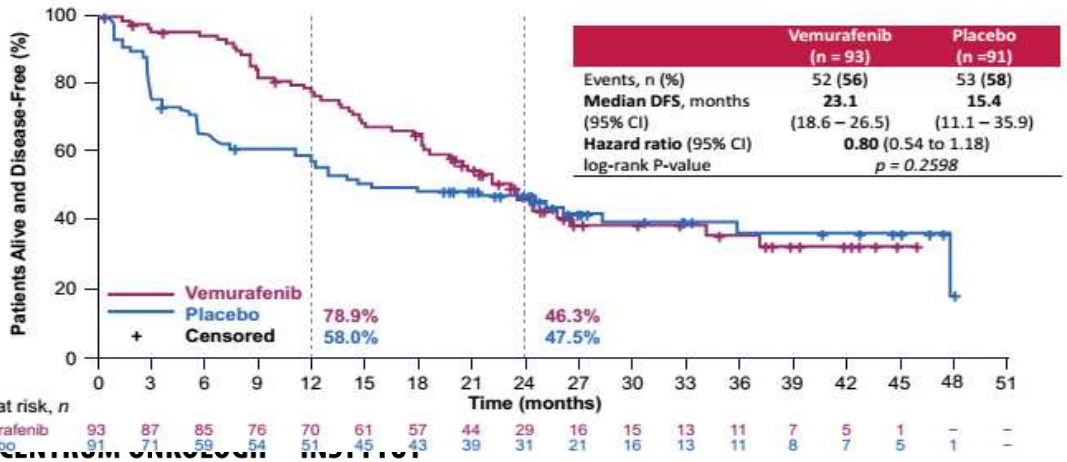


	Vemurafenib (n = 157)	Placebo (n = 157)
Events, n (%)	45 (29)	72 (46)
Median DFS, months (95% CI)	**NE**	**36.9** (21.4 – NE)
Hazard ratio (95% CI)	**0.54** (0.37 to 0.78)	
log-rank P-value	*p = 0.0010*[a]	

Patients at risk, *n*

Vemurafenib	157	146	137	129	120	115	107	94
Placebo	157	129	118	106	100	94	90	79

- 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 (95% CI)	**23.1** (18.6 – 26.5)	**15.4** (11.1 – 35.9)
Hazard ratio (95% CI)	**0.80** (0.54 to 1.18)	
log-rank P-value	*p = 0.2598*	

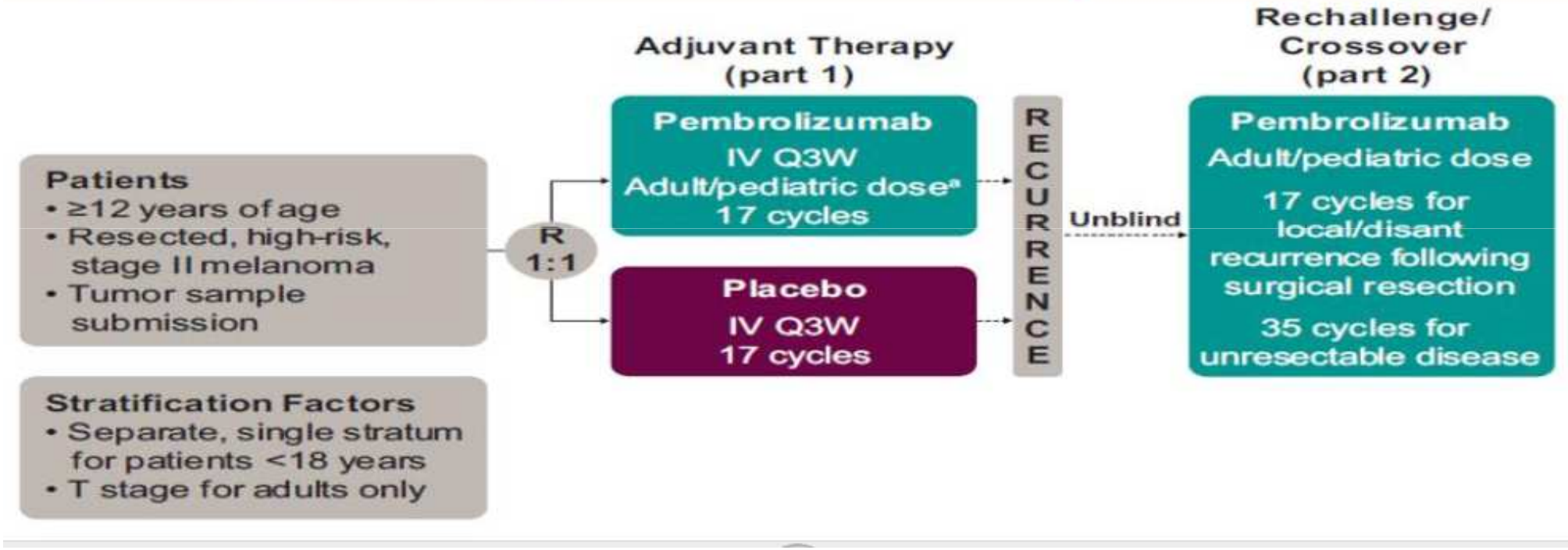
Patients at risk, *n*

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	–

Adjuvant Therapy With Pembrolizumab Versus Placebo in Resected High-Risk Stage II Melanoma: The Phase 3 KEYNOTE-716 Study

J. J. Luke[1], P. A. Ascierto[2], M. S. Carlino[3-5], A. M. Eggermont[6,7], J.-J. Grob[8], A. Hauschild[9], J. M. Kirkwood[10], G. V. Long[5,11,12], P. Mohr[13], C. Robert[7,14], J. E. Gershenwald[15], A. Poklepovic[16], R. A. Scolyer[5,17,18], J. R. Anderson[19], S. Ahsan[19], N. Ibrahim[19], V. K. Sondak[20]

[1]University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; [2]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale," Naples, Italy; [3]Westmead Hospital, Sydney, NSW, Australia; [4]Blacktown Hospital, Blacktown, NSW, Australia; [5]Melanoma Institute Australia, Sydney, NSW, Australia; [6]The University of Sydney, Sydney, NSW, Australia; [7]Gustave Roussy Cancer Centre, Villejuif, France; [8]University of Paris-Saclay, Paris, France; [9]Aix-Marseille Université, Marseille, France; [10]University Hospital Schleswig-Holstein, Kiel, Germany; [11]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [12]Mater Hospital, Sydney, NSW, Australia; [13]Royal North Shore Hospital, Sydney, NSW, Australia; [14]Elbe Kliniken Stadehude, Buxtehude, Germany; [15]University of Paris Sud, Paris, France; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [17]VCU Massey Cancer Center, Richmond, VA, USA; [18]Royal Prince Alfred Hospital, Sydney, NSW, Australia; [19]Merck & Co., Inc., Kenilworth, NJ, USA; [20]Moffitt Cancer Center, Tampa, FL, USA



Overview of PFS outcome per stage subgroup

			Stage - AJCC 7th Edition (All patients NED)				
	Study	**Design**	**IIC**	**IIIA**	**IIIB**	**IIIC**	**IV**
FDA 11.15	EORTC 18071	Ipi 10 mg vs. placebo		SN > 1mm, HR 0.98	HR 0.75	HR 1.00, 1-3 n HR 0.48, ≥4 n	
	EORTC 1325	Pembro vs. placebo		SN > 1mm, HR 0.38	HR 0.58	HR 0.58	
FDA 12.17	Checkmate 238	Ipi 10 vs. nivo			HR 0.67	HR 0.65	HR 0.63 M1a/b, *HR 1.0 M1c*[2]
	ECOG 1609	Ipi 10 vs ipi 3 vs. HD INF-α2b			HR NA	HR NA	M1a-b, HR NA
FDA 04.18	BRIM-8	Vem vs. placebo	HR 0.0-NE	SN > 1mm, HR 0.52	HR 0.63	HR 0.8	
	COMBI-AD	Dabra + trame vs. placebo		SN > 1mm, HR 0.44	HR 0.50	HR 0.45	

Data not randomized head to head, should not be compared directly; NA, Not Available; NE, Not Estimated; [1]AJCC 8th Edition staging; [2]CI 0.37-2.66!

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Melanoma

NCCN Guidelines Index
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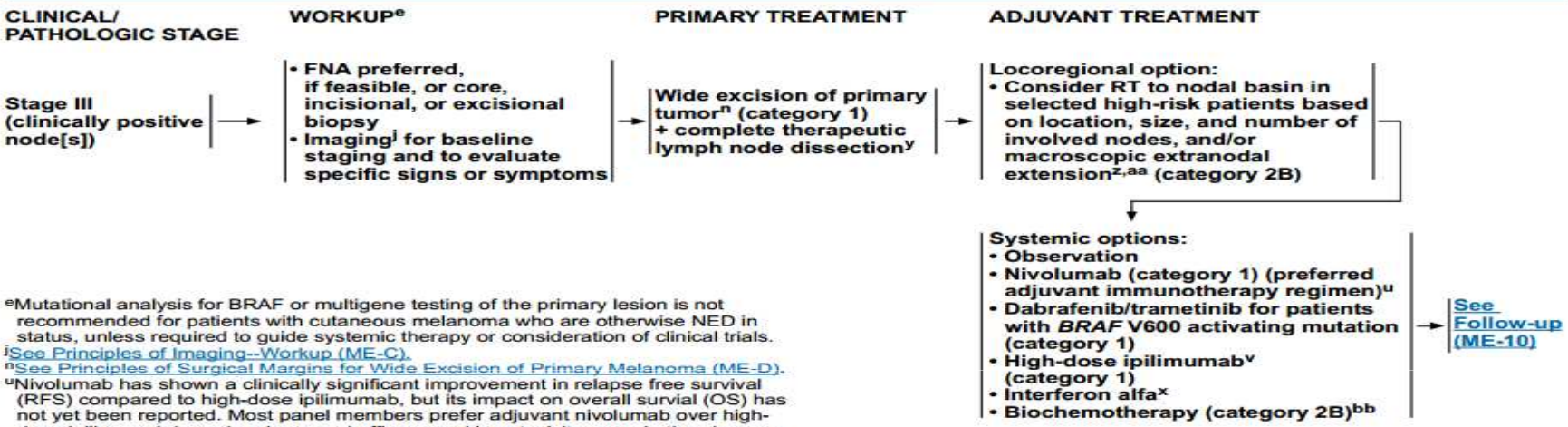
Discussion



[e]Mutational analysis for BRAF or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma who are otherwise NED in status, unless required to guide systemic therapy or consideration of clinical trials.

[j]See Principles of Imaging--Workup (ME-C).

[n]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-D).

[u]Nivolumab has shown a clinically significant improvement in relapse free survival (RFS) compared to high-dose ipilimumab, but its impact on overall survial (OS) has not yet been reported. Most panel members prefer adjuvant nivolumab over high-dose ipilimumab based on improved efficacy and less toxicity, even in the absence of reported OS data.

[v]While adjuvant high-dose ipilimumab (10 mg/kg) is associated with improved recurrence-free and overall survival, this regimen was associated with a high incidence of adverse events, which led to the discontinuation of treatment in 53% of patients. There was a 1% drug-related mortality rate. Due to toxicity, careful selection of patients is warranted. In this study, subgroup analyses demonstrated that some groups are unlikely to benefit from adjuvant ipilimumab. For patients who have the lowest risk of developing metastatic disease (AJCC 7th edition stage IIIA), given the hazard ratio (HR) of 0.98 combined with the toxicity, there is disagreement among the panel regarding advisability of the use of adjuvant ipilimumab in this setting. For patients with stage IIIB or stage IIIC with 1–3 positive nodes, adjuvant ipilimumab could be considered despite HRs that are not statistically significant. The benefit for adjuvant ipilimumab is likely to be highest in patients with ≥4 positive nodes.

[x]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1), but there is no impact on overall survival.

[y]In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.

[z]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.

[aa]See Principles of Radiation Therapy for Melanoma (ME-G).

[bb]For biochemotherapy, see Other Systemic Therapies (ME-H 2 of 6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Adjuvant in melanoma: important data are still missing!

		Efficacy data		
Study	**Design**	**HR RFS**	**HR DMFS**	**HR OS**
EORTC 18071[1]	Ipi 10 mg vs. placebo	0.76	0.76	0.72
EORTC 1325[2]	Pembro vs. placebo	0.57	*0.53*[6]	NA
Checkmate 238[2]	Ipi 10 vs. nivo	0.65	*0.73*[7]	NA
ECOG 1609	Ipi 10 vs ipi 3 vs. HD INF-α2b	1.0	NA	NA
BRIM-8[4]	Vem vs. placebo	0.54 (IIC-IIIB) 0.8 (IIIC)	NA	NA
COMBI-AD[5]	Dabra + trame vs. placebo	0.47	0.51	0.57

Stage III patients from these trials were required to have complete lymph node dissection!

How do we integrate those results in a post MSLT-2/ DeCOG[8,9] trial era?

[1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM* 2017; [4]Maio, Lancet Oncol 2018; [5]Long, *NEJM* 2017; [6]Preliminary, Eggermont, AACR 2018; [7]Exploratory; [8]Faries, NEJM 2017; [9]Leiter, Lancet 2016; Time in months; NA: Not Available;

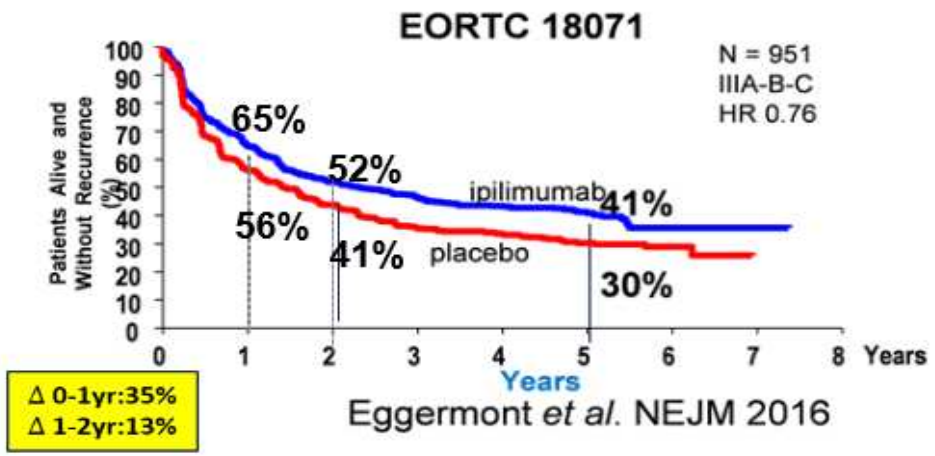
Data not randomized head to head, should not be compared directly; NA, Not Available; NE, Not Estimated; [1] AJCC 8th Edition staging

AEs comparison: EORTC 18071, Checkmate 067 & CA 184-169

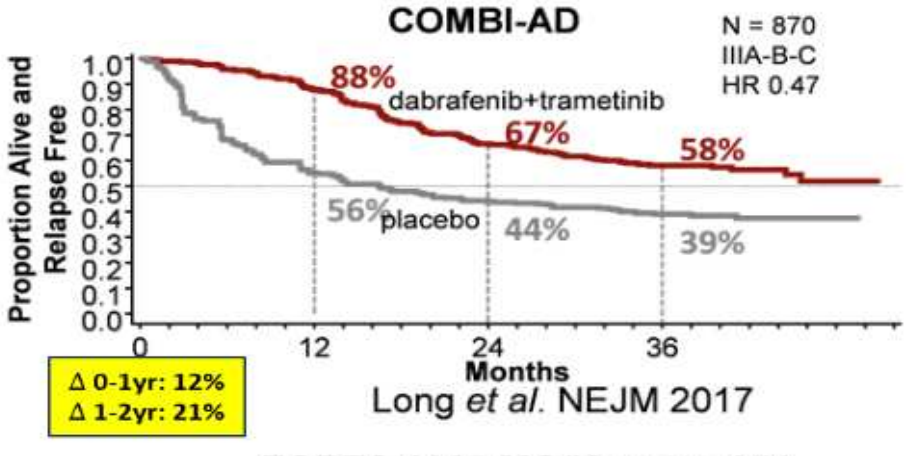
Toxicity	Ipilimumab 10 mg/kg[1,2], data[2]		Nivolumab 3 mg/kg[2]		Pembrolizumab 200 mg[3,4]		Dabrafenib + trametinib[5,6]	
All values in %	All	G 3-4	All	G 3-4	All	G 3-4	All	G 3-4
Any AE	99	55	97	25	93	32	97	41
Any drug related AE	96	46	85	14	78	15	91[6]	31[6]
Fatigue	33	1	35	<1	37	1	47	4
Rash	29	3	20	1	16	<1	24	0
Diarrhea / colitis	46/10	10/8	24/2	2/1	19/4	1/2	33/NR	1/NR
Increased AST/ALT	13/15	4/6	6/6	<1/1	NR/NR	NR/NR	14/15	4/4
Pneumonitis	2	1	1	0	3	1	-	-
Hypophysitis	11	3	2	<1	2	1	-	-
Adrenal disorder	3	1	1	<1	1	<1	-	-
Thyroid disorder	13	1	20	1	21	<1	-	-
Type I diabetes	<1	<1	<1	0	1	1	-	-

[1] Eggermont, *NEJM* 2016; [2] Weber, *NEJM* 2017; [3] Eggermont, *NEJM* 2018; [4] Eggermont, AACR 2018; [5] Long, *NEJM* 2017; [6] Long, SMR 2017; NR – Not Reported

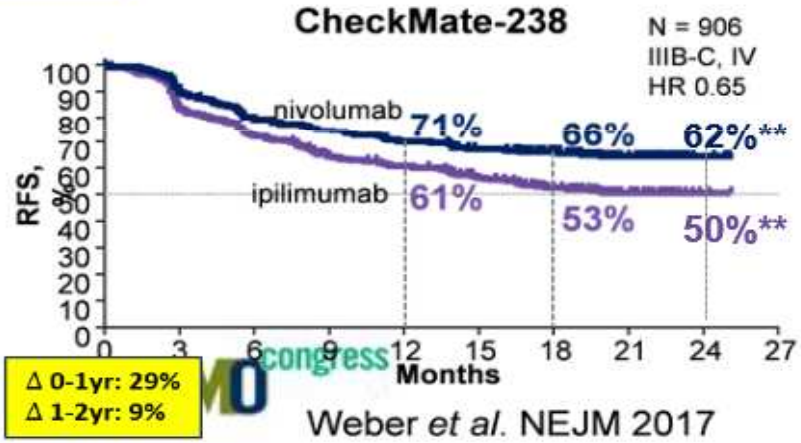
Improvement in RFS in high risk melanoma



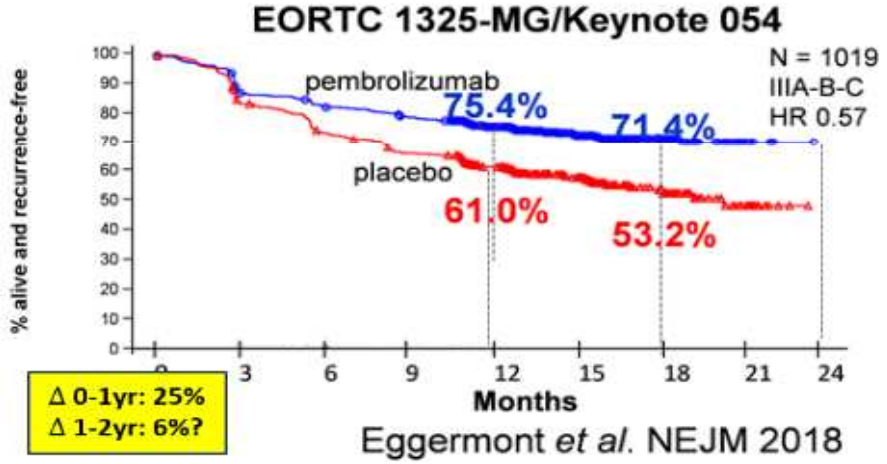
Eggermont *et al*. NEJM 2016



Long *et al*. NEJM 2017



Weber *et al*. NEJM 2017



Eggermont *et al*. NEJM 2018

Summary of available data for targeted and immunotherapies

Immunotherapies

- 3 independent prospective randomized trials[1,2,3]
  - 2 trials placebo controlled[1,3]
  - All positive for RFS primary endpoint
  - 1 trial positive for secondary OS endpoint[1]

No head to head comparison!

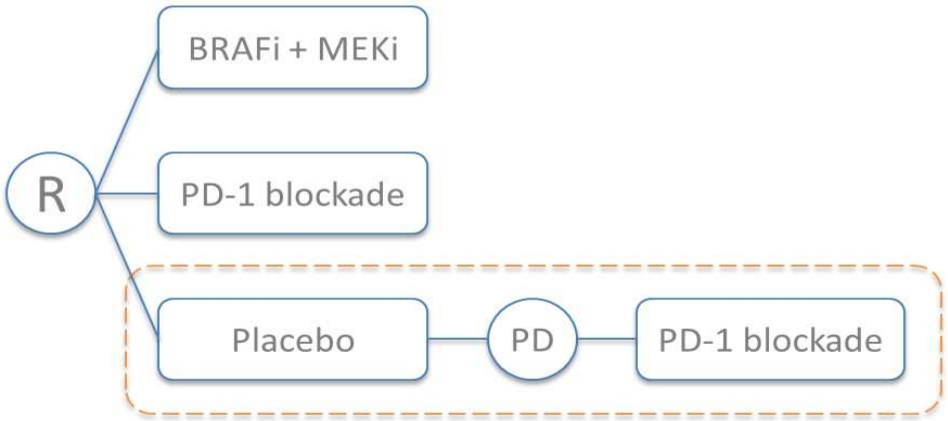
Targeted therapies

- 1 prospective, placebo controlled, randomized trial[4]
  - positive for RFS primary endpoint and for secondary OS endpoint
  - 3-year OS estimates available
- 1 prospective, placebo controlled randomized trial[5] with single BRAF inhibition
  - negative for stage IIIC regarding RFS primary endpoint
  - But with numerically improved RFS for stage IIC-IIIB

[1] Eggermont, *NEJM* 2016; [2] Weber, *NEJM* 2017; [3] Eggermont, *NEJM* 2018;
[4] Long, *NEJM* 2017; [5] Maio, *Lancet Oncol.* 2018

What would we need to provide a definitive answer?

- We currently do not have the prospective data to answer definitively the question of targeted vs. immunotherapies in the adjuvant setting
- This would formally require a head to head trial
- Such data will not be available anywhere soon

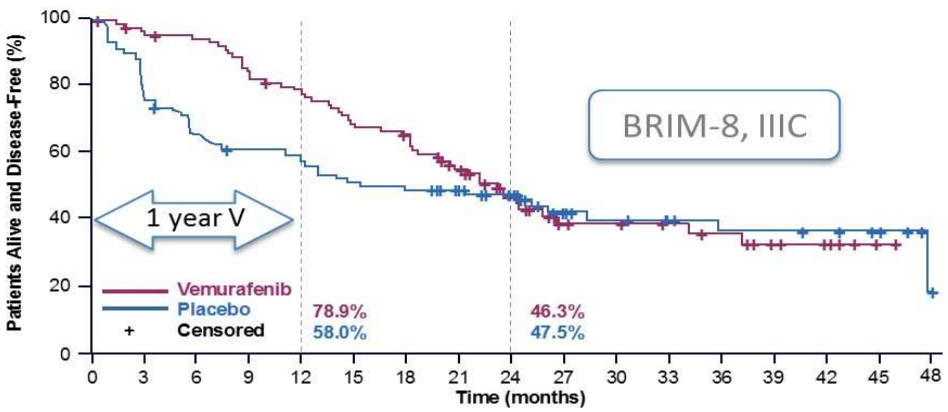


- Including short and long term OS and toxicity data comparison!

- In the ideal scenario, we would need to also test for immunotherapies in the adjuvant setting vs. at relapse, as pioneered in the EORTC 1325 trial (cross over from the placebo arm at relapse)[1]

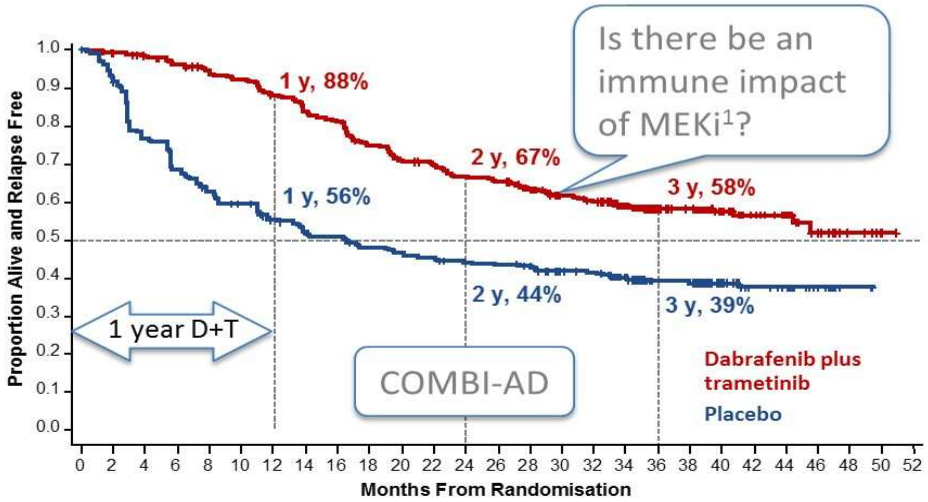
[1] Eggermont, *NEJM* 2018 & AACR 2018

3-year OS data available from COMBI-AD: do we need more?



- In Cohort 2 of BRIM-8 (stage IIIC), benefit is lost rapidly after the end of the 1 year adjuvant
- Is such an effect still possible in COMBI-AD?

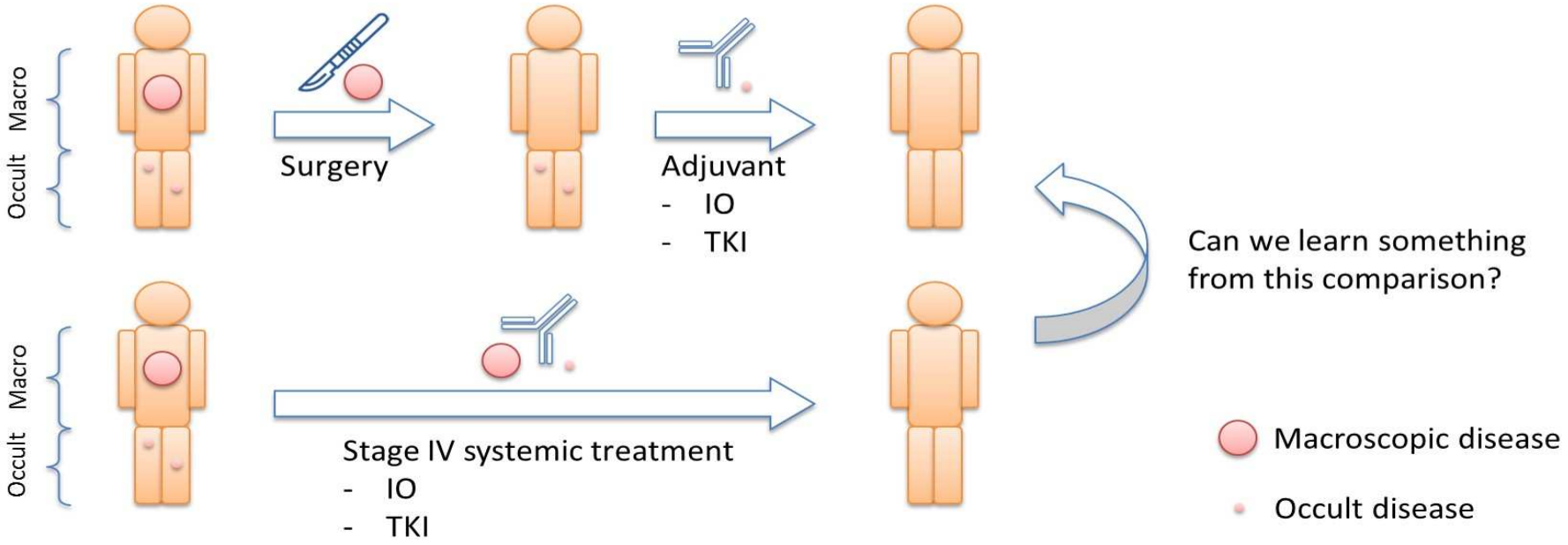
- COMBI-AD OS data is mature up to 3 years
- Is longer time FU required?
- Could targeted therapies delay relapse but not cure patients?
- Definitive answer will come with longer FU



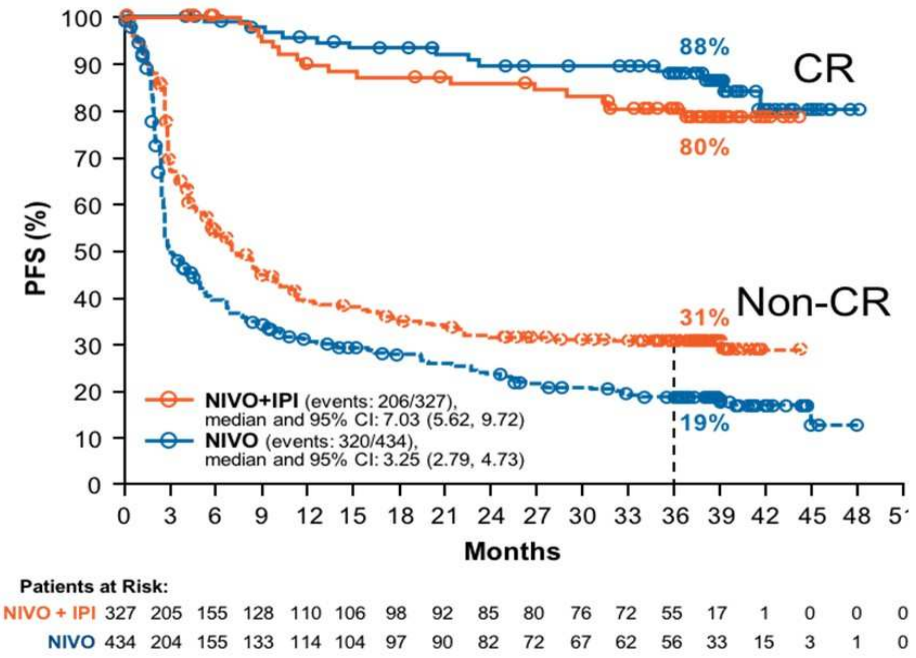
[1]Ebert, *Immunity* 2016

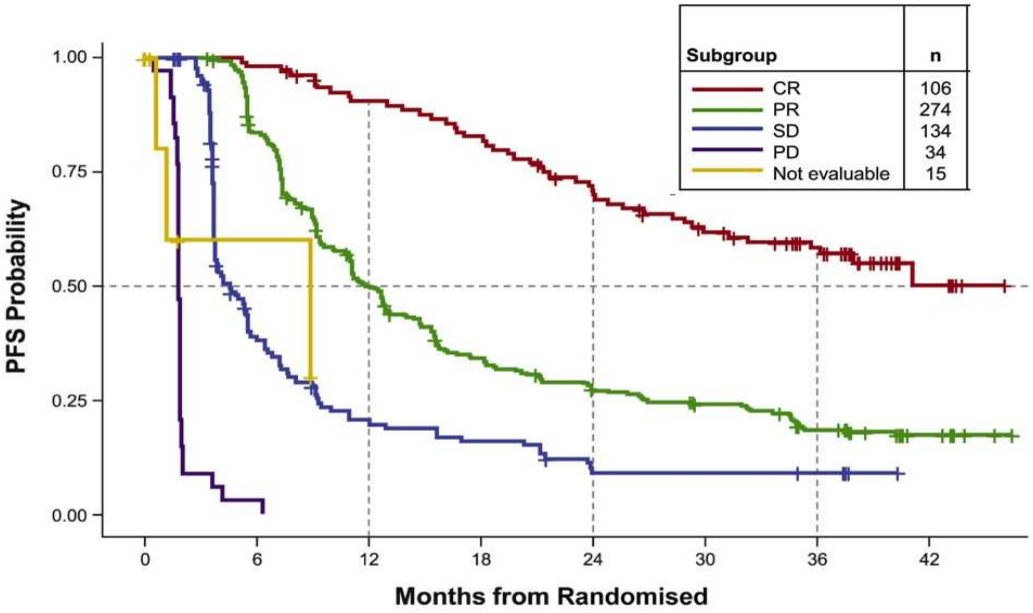
Immuno vs. targeted therapies: can we learn more from stage IV?

- We currently do not have the prospective data to answer the question of TKI vs. I-O in the adjuvant setting. Such an answer would require a head to head trial (ongoing?).



PFS by response for NIVO[1], IPI+NIVO[1], and MAPKi[2]

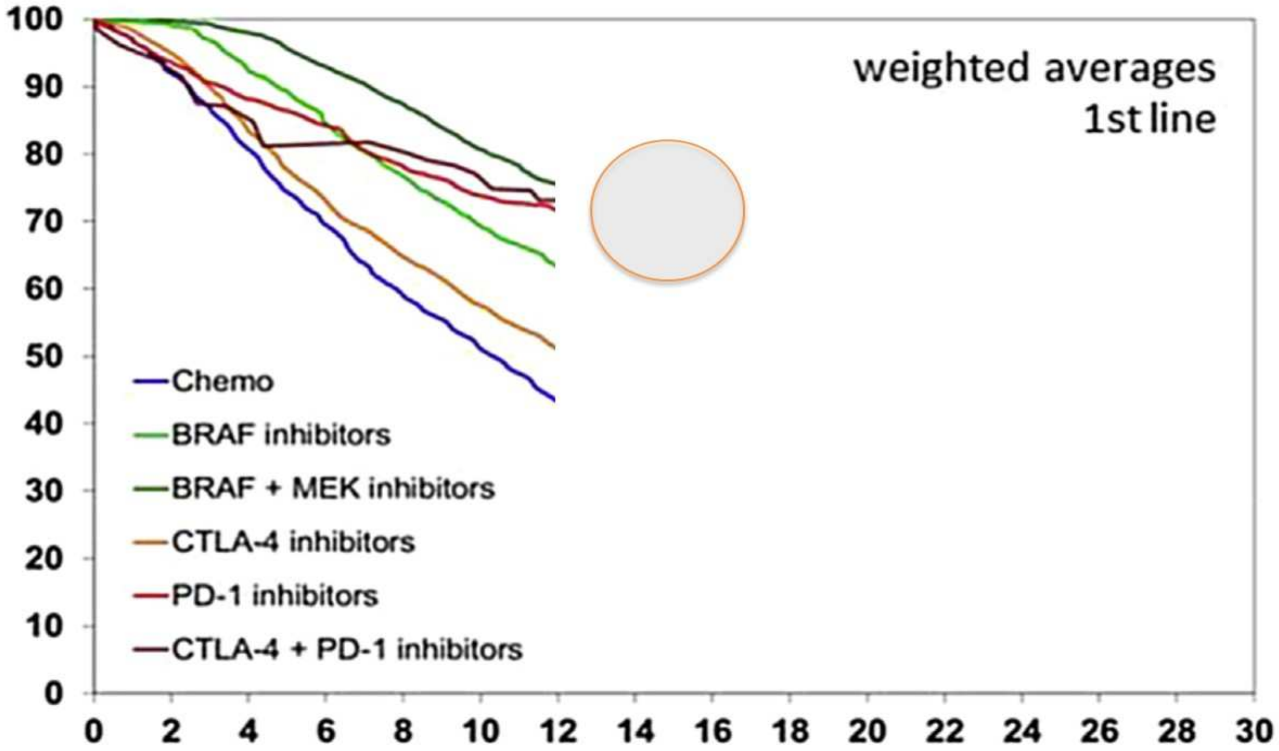




Pooled analysis from COMBI-d, COMBI-v:
PFS by RECIST response [2]

[1] Robert ESMO 2017; [2] Schadendorf, *EJC* 2017

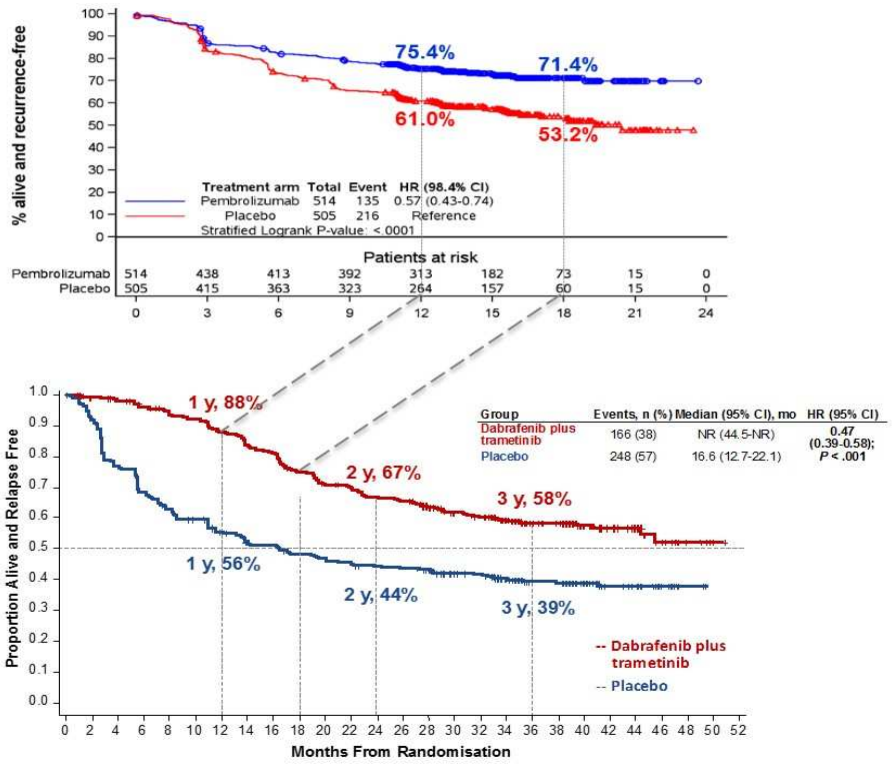
Meta-analysis comparing targeted and immunotherapies: stage IV



- Targeted therapies provide better early outcome…
- … but both PD-1 based immunotherapy curves are crossing at around 14-18 months [1]

[1] Ugurel, *EJC* 2017

Could a similar pattern be observed *in the adjuvant*?



- Comparison between EORTC 1325 and COMBI-AD is indirect and quantitative conclusions cannot be drawn
- Indeed:
  - Only BRAF patients treated in COMBI-AD and in transit metastases allowed
- However:
  - Subgroup inclusion criteria are similar
    - IIIA (SN < 1mm), B and C
  - Placebo arms are within confidence intervals
- Landmark analysis reveals RFS of 88 vs. 75.4% at 12 months, but the slope of EORTC 1325 is flatter than that of COMBI-AD
- Is a crossing to be expected in the adjuvant setting similar to stage IV?

CONCLUSIONS

- The end of interferon (maybe except thick, ulcerated melanomas N0?)
- The end of adjuvant ipilimumab (maybe in the future in low doses in combination)
- Monotherapy BRAFi – NO
- BRAFi + MEKi: **benefits for RFS+DMFS+OS in stage III** > 1mm mikromet, orally, convinient
- Anti-PD-1: convinient (flat dose), **improvement of outcomes also in M1**, lack of final data for OS
- Lack of direct comparison of BRAFi+MEKi vs a-PD-1 in *BRAF*m stage III

CONCLUSION PART 2

- Abandon CLND requirement in SN+ patients? (MSLT-2)
  - BUT: Loss of risk calculation information !!! Necessary for adjuvant therapy decision !!!
- ANTI-PD1 FOR ALL?
  - Convenience q2wk (nivo) vs q3wk/flat dose (pembro)
- BRAFi+MEKi for BRAFmut
  - Convenience: ORAL, no irAEs
- Still role IFN? (for part of world where no other options)
  - ONLY in ulcerated melanoma
  - Availibility/price
- Still role ipilimumab in near future?
  - 4 doses at 3mg/kg vs alternatives?
  - After nivo approval and D+T approval probably no more role
- NEXT GENERATION? NEOADJUVANT + ADJUVANT
  - IMPROVE LOCOREGIONAL CONTROL
  - Reduce # TLNDs in WHICH % OF PATIENTS with palpable nodes, in which SN+ pts?

Rada Przejrzystości
działająca przy
Prezesie Agencji Oceny Technologii Medycznych i Taryfikacji

Opinia Rady Przejrzystości
nr 56/2019 z dnia 5 marca 2019 roku
w sprawie oceny zasadności finansowania ze środków publicznych, w ramach ratunkowego dostępu do technologii lekowych, leków Tafinlar (dabrafenib) i Mekinist (trametynib) we wskazaniu: czerniak skóry z obecnością mutacji BRAF V600 w stopniu zaawansowania III po radykalnej resekcji (ICD-10: C43)

Rada Przejrzystości uznaje za zasadne finansowanie ze środków publicznych, w ramach ratunkowego dostępu do technologii lekowych, leków Tafinlar (dabrafenib) i Mekinist (trametynib) we wskazaniu: czerniak skóry z obecnością mutacji BRAF V600 w stopniu zaawansowania III po radykalnej resekcji (ICD-10: C43).

Agencja Oceny Technologii Medycznych i Taryfikacji
www.aotmit.gov.pl

Opinia nr 17/2019
z dnia 7 marca 2019 r.
Agencji Oceny Technologii Medycznych i Taryfikacji
w sprawie zasadności finansowania ze środków publicznych leku Opdivo (niwolumab) we wskazaniu: czerniak skóry w III stopniu zaawansowania (ICD10: C43) po radykalnej resekcji, leczenie uzupełniające, w ramach ratunkowego dostępu do technologii lekowych

Agencja Oceny Technologii Medycznych i Taryfikacji, biorąc pod uwagę kryteria, o których mowa w art. 12 pkt 3-6 oraz pkt 8-10 ustawy z dnia 12 maja 2011 roku o refundacji leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych (Dz. U. z 2017 poz. 1844 z późn. zm.) **opiniuje pozytywnie** zasadność finansowania ze środków publicznych leku Opdivo (niwolumab) we wskazaniu: czerniak skóry w III stopniu zaawansowania (ICD10: C43) po radykalnej resekcji, leczenie uzupełniające, w ramach ratunkowego dostępu do technologii lekowych.

Rada Przejrzystości
działająca przy
Prezesie Agencji Oceny Technologii Medycznych i Taryfikacji

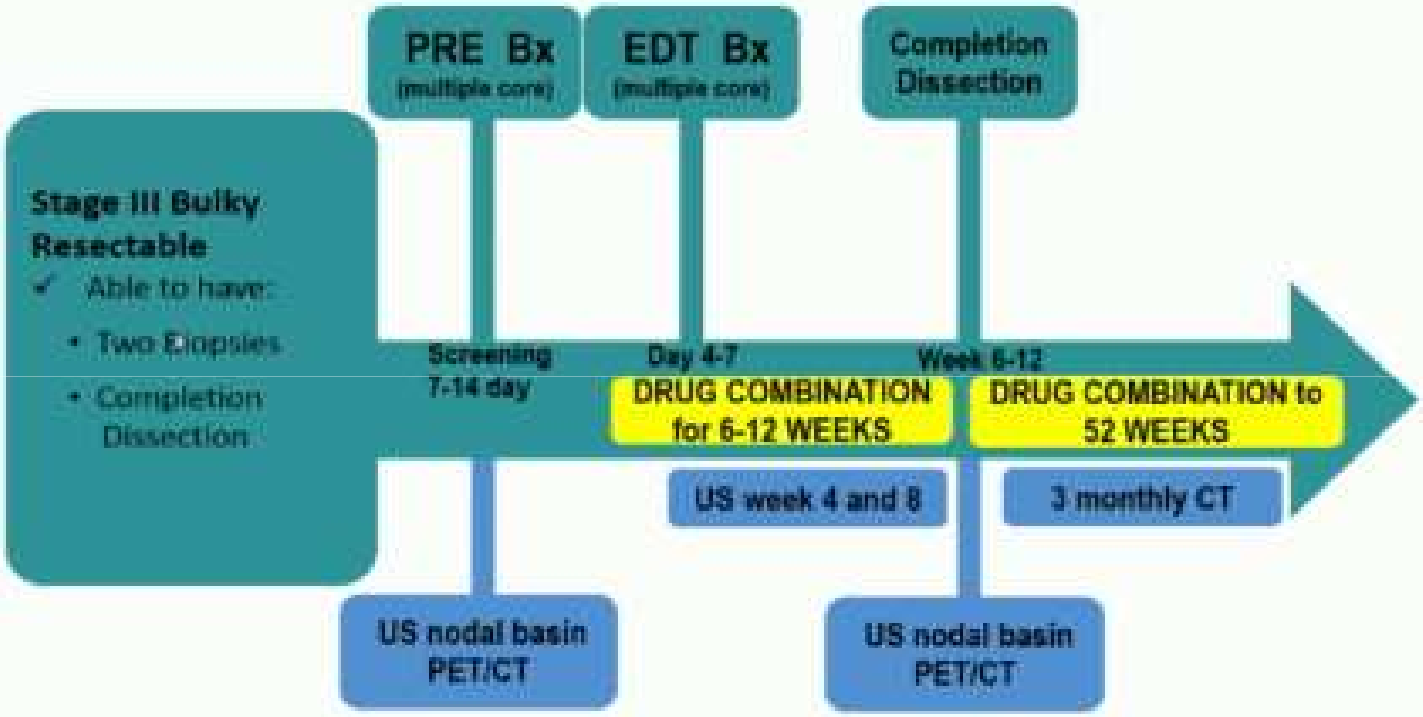
Opinia Rady Przejrzystości
nr 58/2019 z dnia 5 marca 2019 roku
w sprawie oceny zasadności finansowania ze środków publicznych, w ramach ratunkowego dostępu do technologii lekowych, leku Opdivo (niwolumab) we wskazaniu: czerniak w III stadium zaawansowania po całkowitej resekcji (ICD-10 C43), leczenie uzupełniające

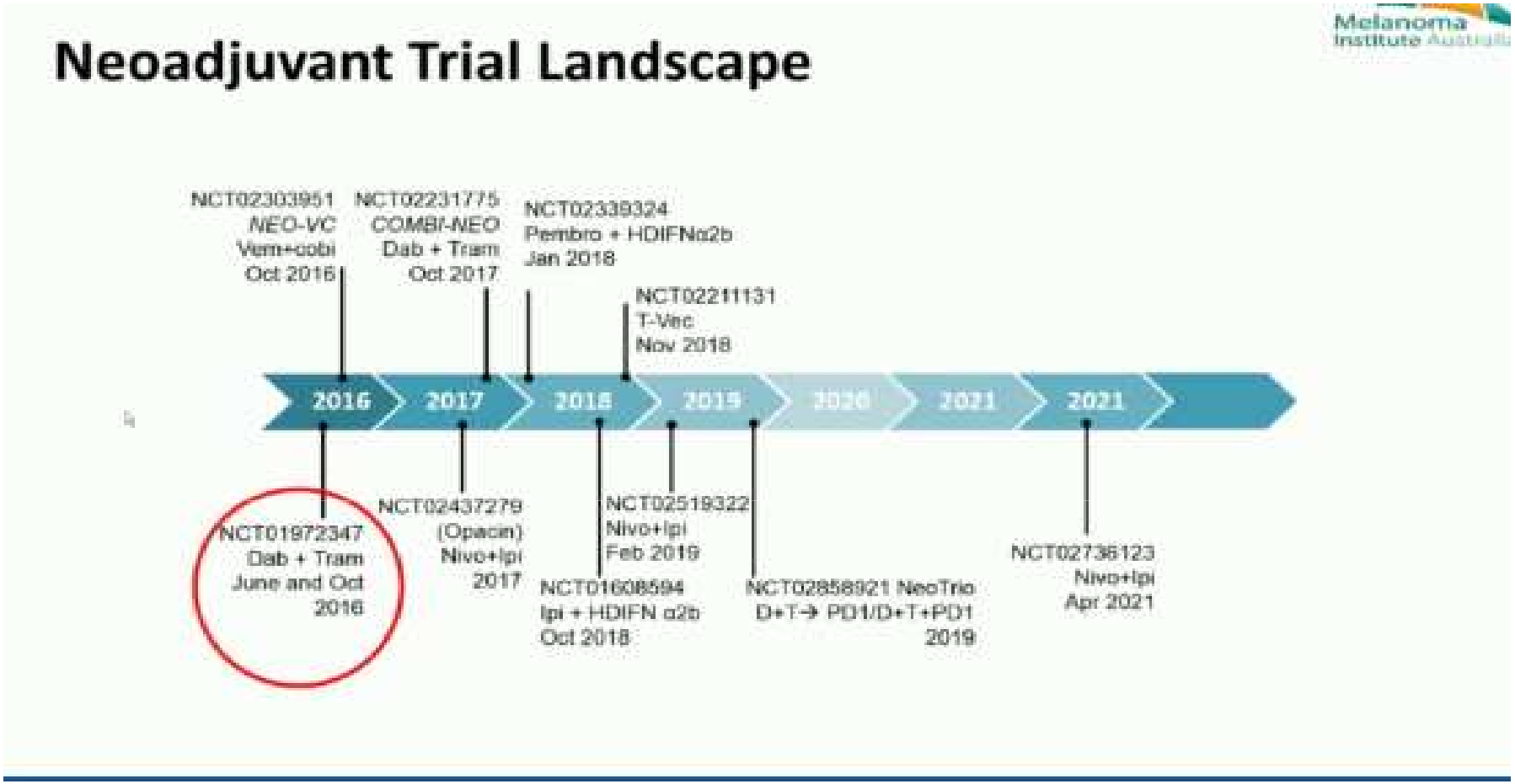
Rada Przejrzystości uznaje za zasadne finansowanie ze środków publicznych, w ramach ratunkowego dostępu do technologii lekowych, leku Opdivo (niwolumab) we wskazaniu: czerniak w III stadium zaawansowania po całkowitej resekcji (ICD-10 C43), leczenie uzupełniające.

Neoadjuvant therapy

Neoadjuvant Model

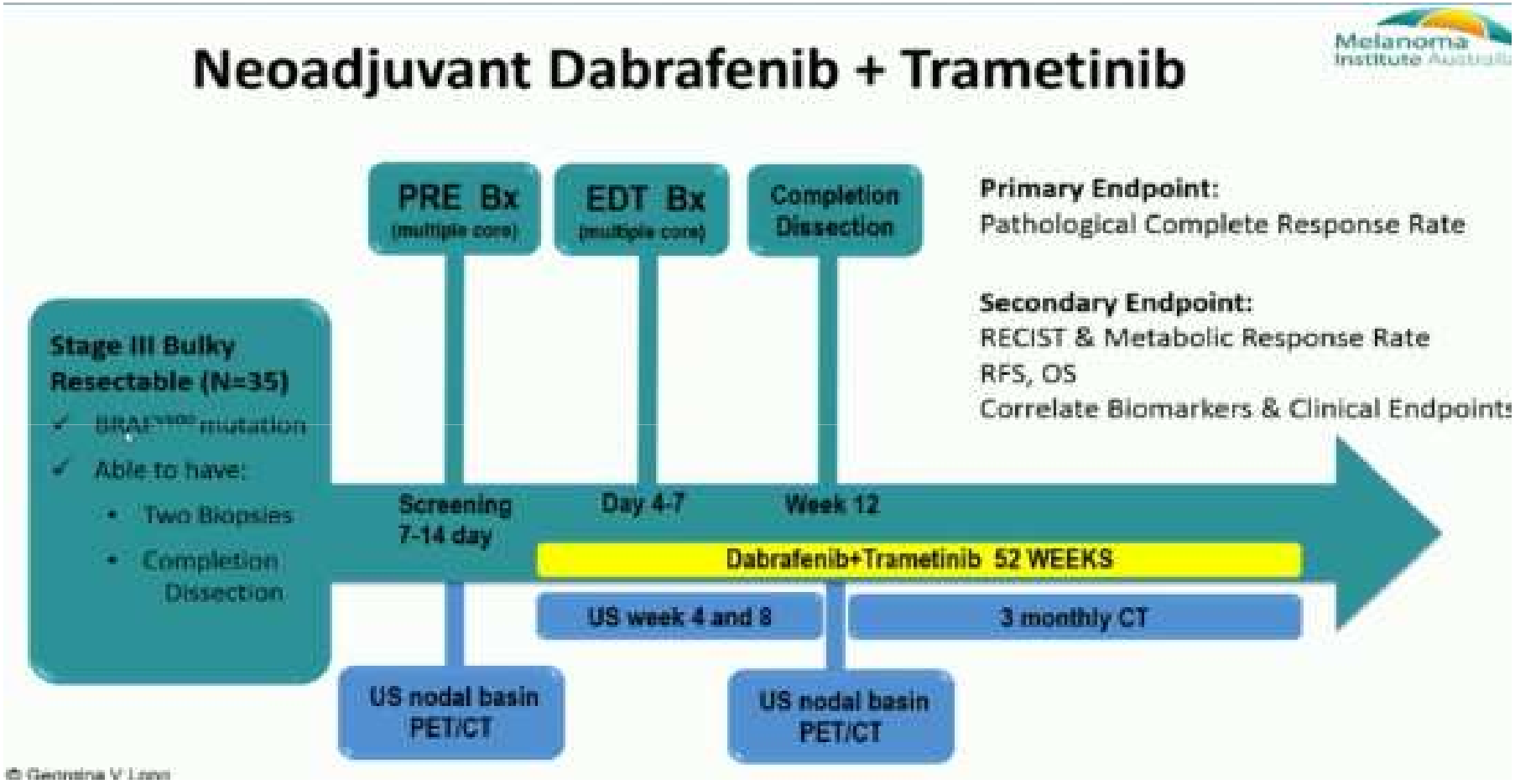
Melanoma Institute Australia





Reductos trial

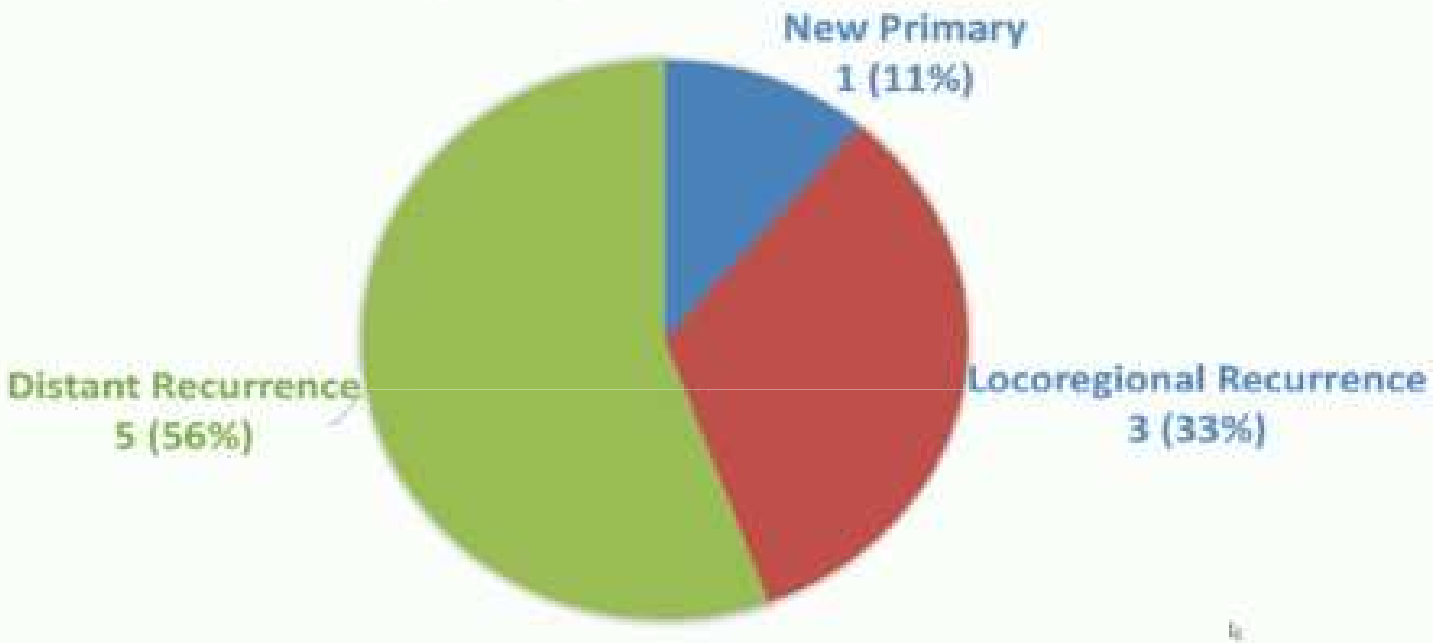
Neoadjuvant Dabrafenib + Trametinib



Neoadjuvant Dabrafenib + Trametinib
Week 12 Response (n=30) median follow up 53 weeks

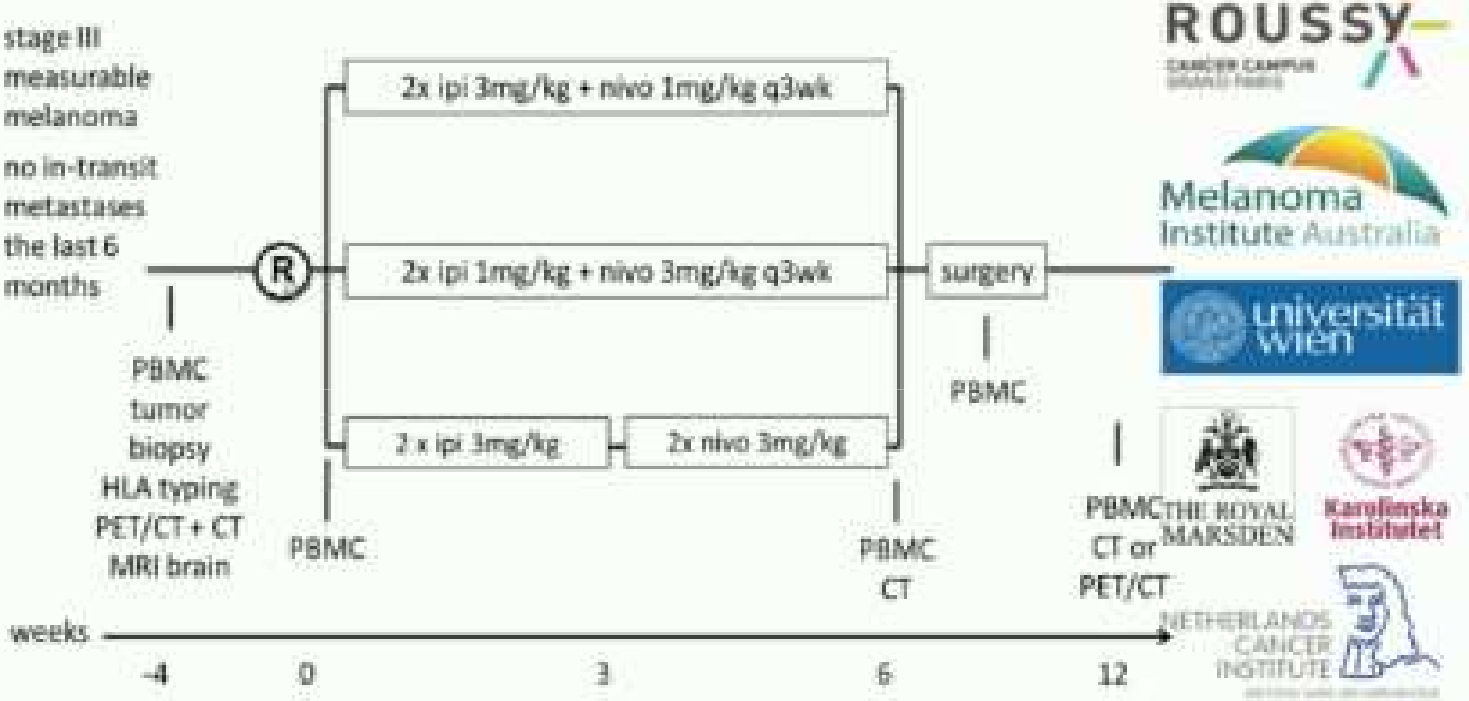
Median follow up time 53 weeks

Recurrence in 9/30 (30%) Patients



For the 9 patients, median time to recurrence = 51 (25-112) weeks
No patient recurred during 12 weeks neoadjuvant therapy
1 death (due to melanoma) at 66 weeks

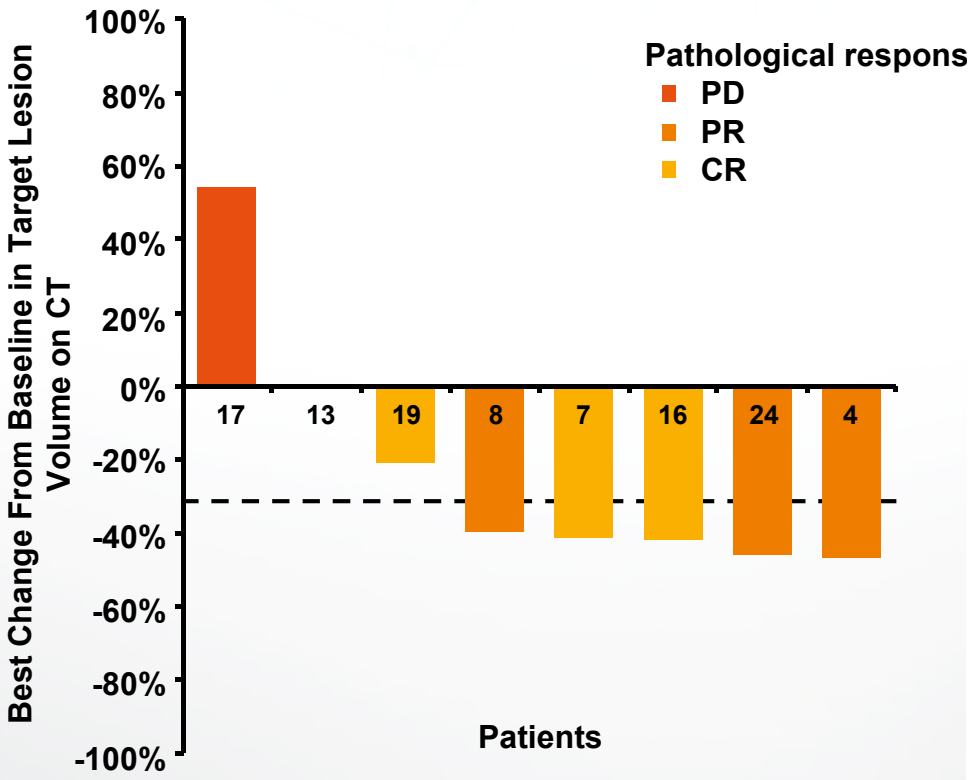
OpACIN-NEO


stage III
measurable
melanoma
no in-transit
metastases
the last 6
months
PBMC
tumor
biopsy
HLA typing
PET/CT + CT
MRI brain
R
2x ipi 3mg/kg + nivo 1mg/kg q3wk
2x ipi 1mg/kg + nivo 3mg/kg q3wk
2 x ipi 3mg/kg
2x nivo 3mg/kg
surgery
PBMC
PBMC
PBMC
CT
PBMC
CT or
PET/CT
weeks
-4
0
3
6
12
GUSTAVE ROUSSY
Melanoma Institute Australia
universität wien
THE ROYAL MARSDEN
Karolinska Institutet
NETHERLANDS CANCER INSTITUTE

OpACIN (Ipilimumab + Nivolumab; phase 1b): Preliminary Clinical Activity

Pt ID	Courses, n	Radiological Response (CT scans, mm)	Pathological Response
7	2	31 × 50 → 18 × 31	pCR
16	2	23 × 36 → 17 × 23 & 22 × 24 → 9 × 12	pCR
19	2	24 × 40 → 19 × 24	pCR
4	3	21 × 47 → 11 × 34	Micrometastases (< 1 mm)
5	2	9 × 10 → ND	Micrometastasis (0.5 mm)
8	2	10 × 12 → 6 × 9	Micrometastasis (sporadic tumor cells)
14	4	18 × 19 & 25 × 37 → ND	Micrometastasis (sporadic tumor cells)
24	2	28 × 40 → 15 × 21	Macrometastasis (75% necrosis)
13	2	22 × 40 → 22 × 40	LNs 35 mm, 2 mm, 1 mm, 0.5 mm, 0.1 mm
17	1	11 × 18 → 17 × 25	LNs 30 mm, 13 mm, 6.0 mm, 3.5 mm

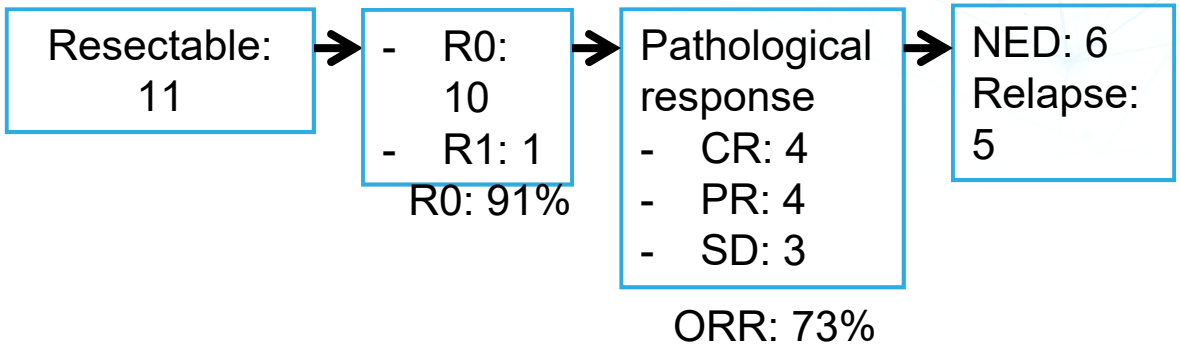
Pathological Response to Treatment Was Not Represented by CT Response

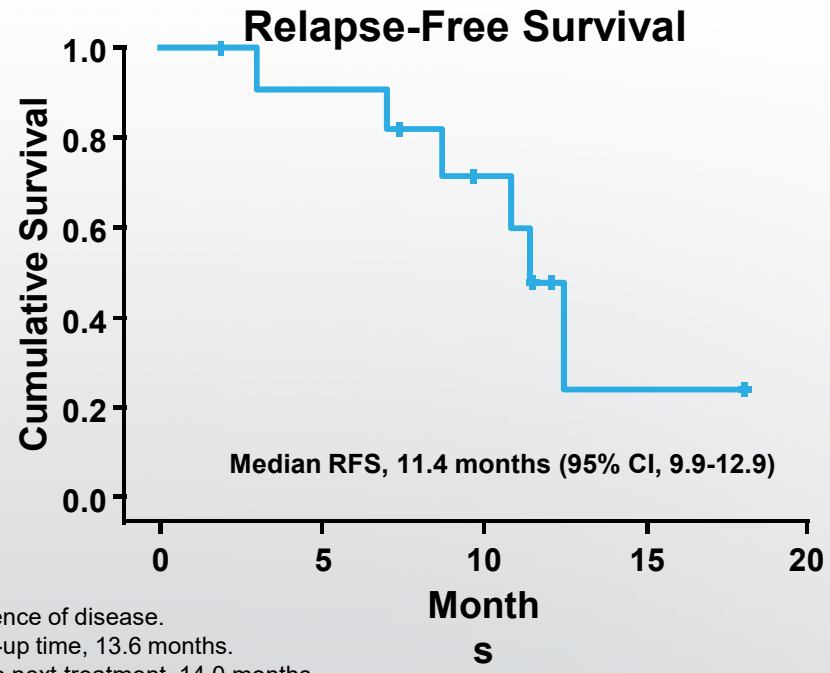


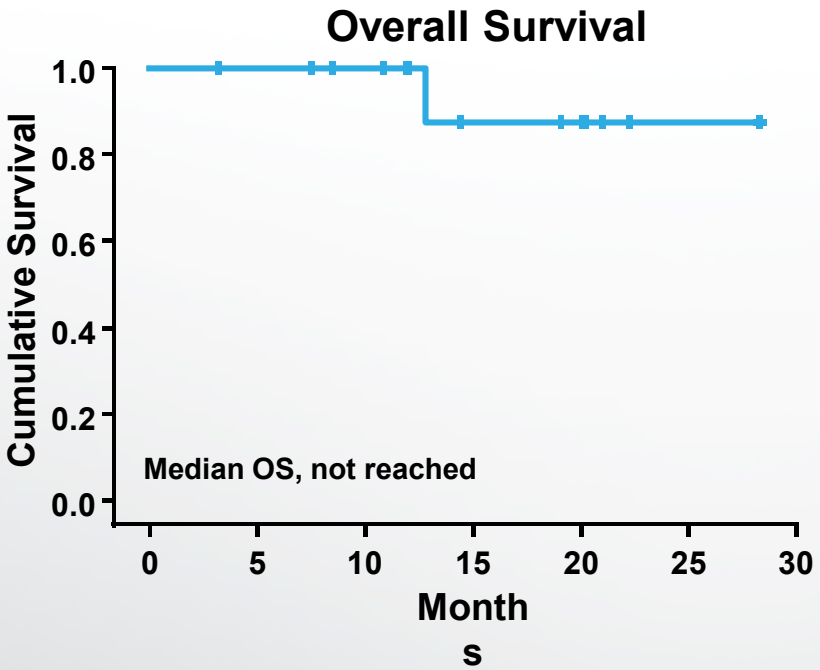
8/10 patients receiving neoadjuvant ipilimumab + nivolumab had a response after 6 weeks

LN, lymph node; ND, not determined; pCR, pathological complete response.
Blank CU, et al. Oral presentation at SMR 2016.

REDUCTOR (Dabrafenib + Trametinib; phase 2): Clinical Activity







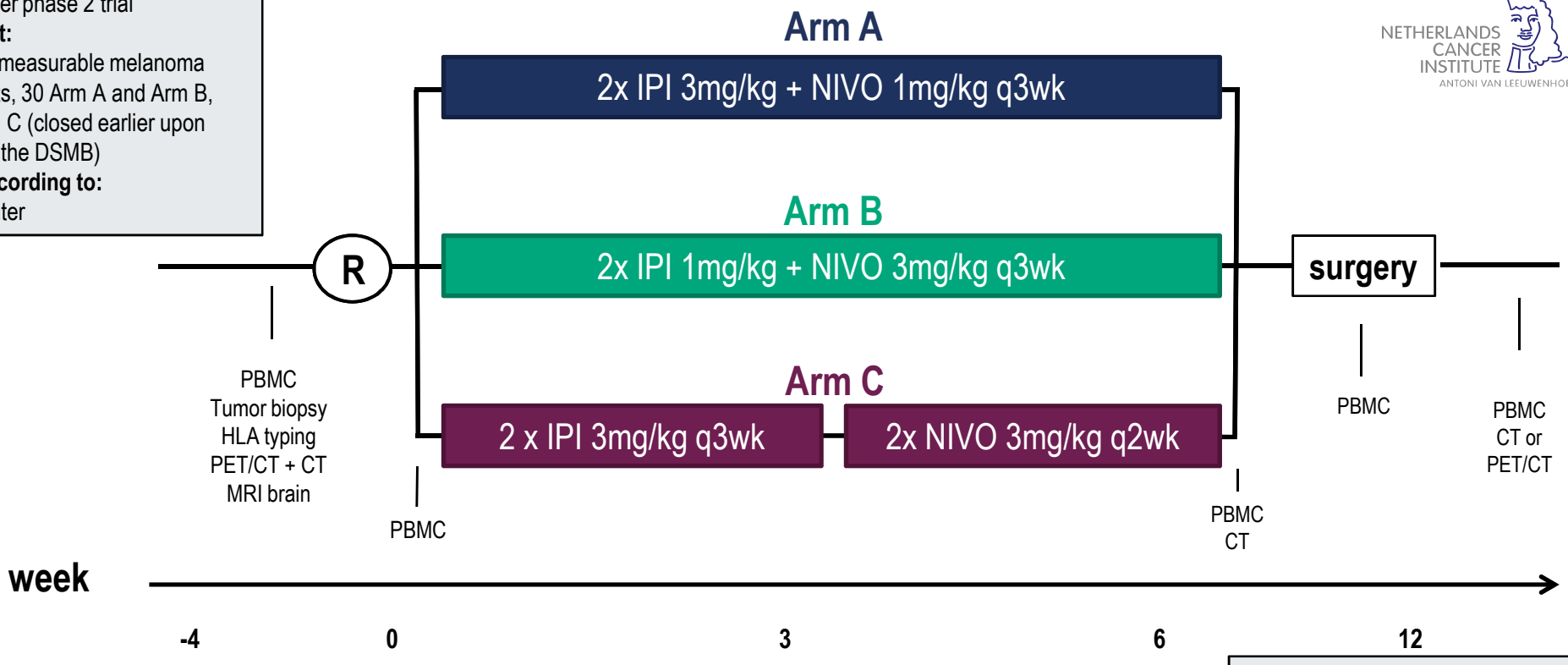
NED, no evidence of disease.
Median follow-up time, 13.6 months.
Median time to next treatment, 14.0 months.
Haanen JBAG, et al. Oral presentation at ECCO 2017 [abstract 1146].

OPACIN-NEO: STUDY DESIGN

Study design:
- Multi-center phase 2 trial

Study cohort:
- Stage IIII measurable melanoma
- 86 patients, 30 Arm A and Arm B, 26 in Arm C (closed earlier upon advice of the DSMB)

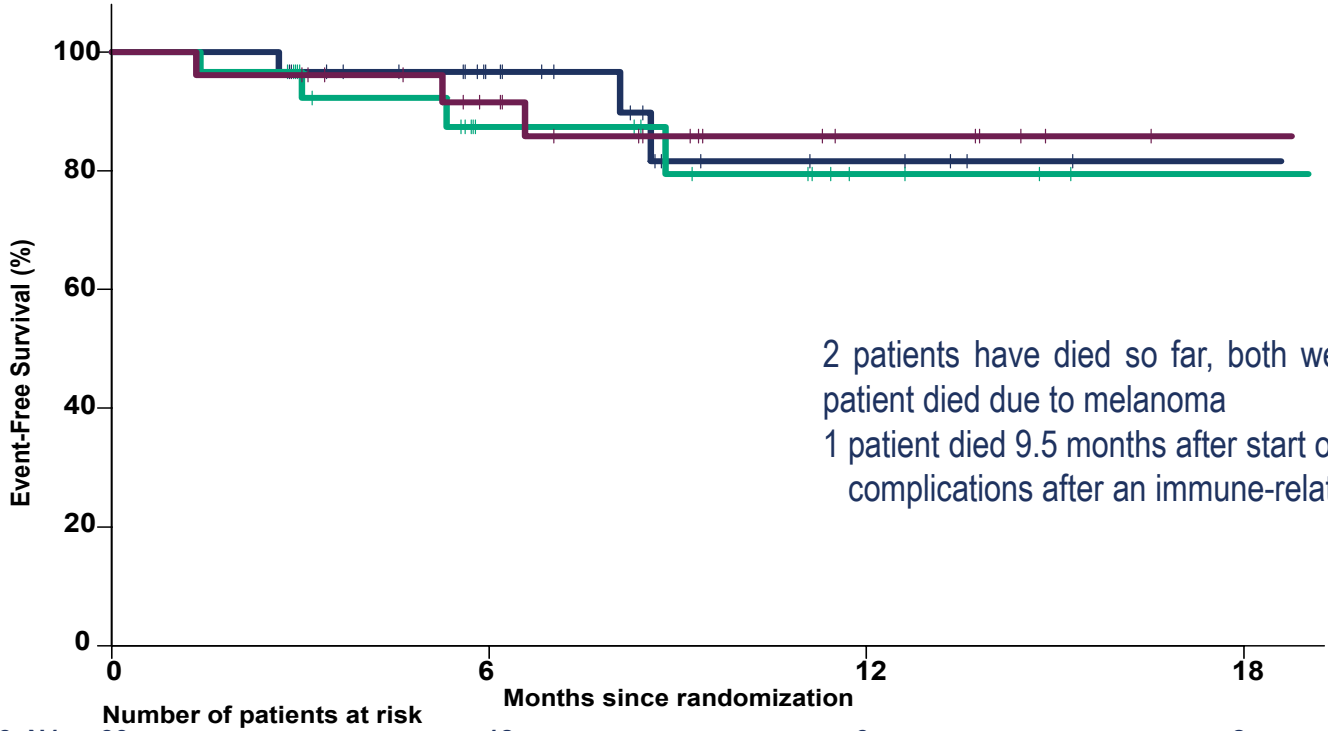
Stratified according to:
- Study center



Dosing in Arm A, B, and C based on data from Blank, Rozeman, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink, Rozeman, et al. Ann Oncol 2017

Data lock: 28 Sep 2018
Median follow-up 8.3 months

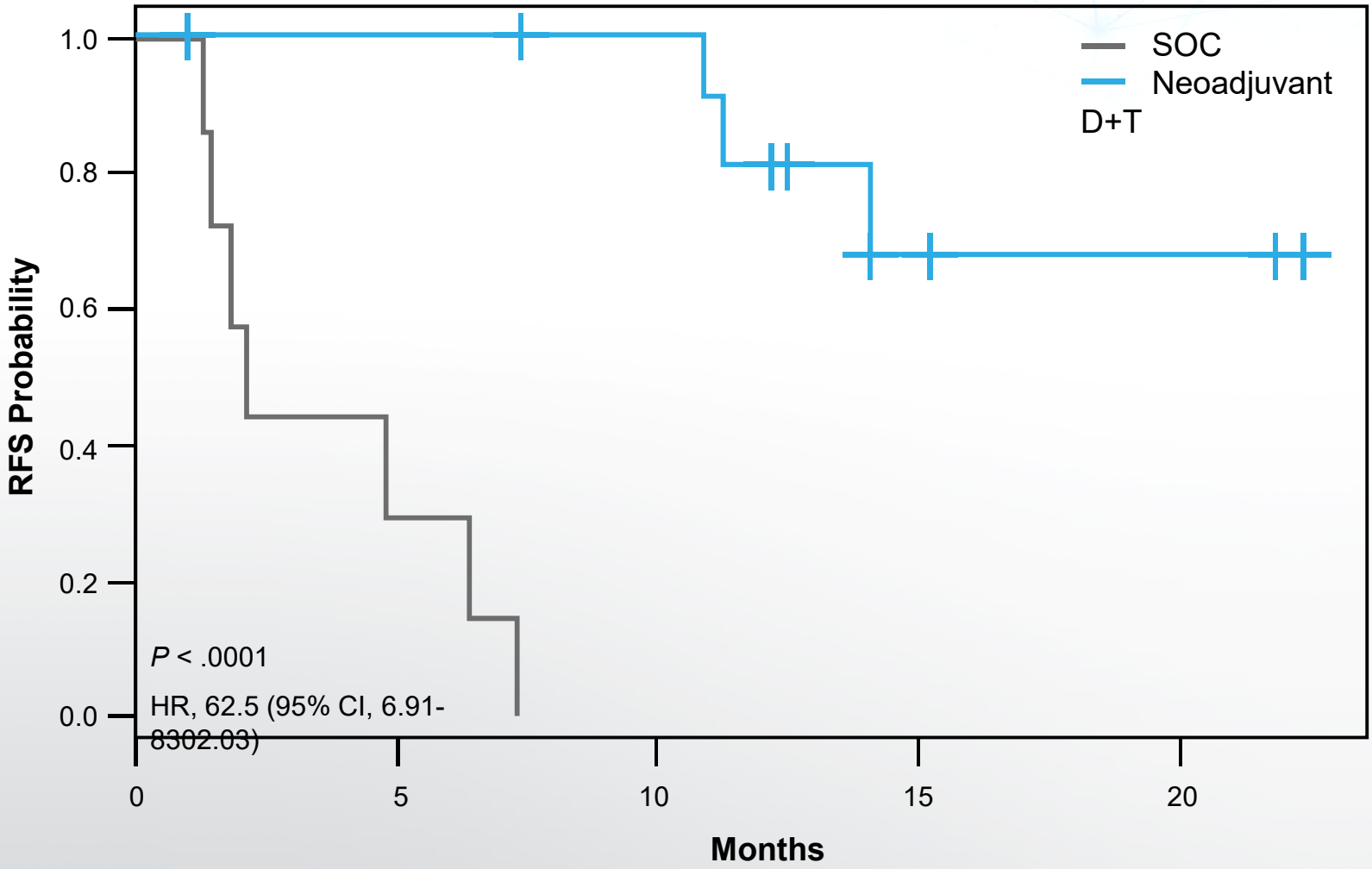
EVENT-FREE SURVIVAL PER TREATMENT ARM



Arm A: 2xI3+N1
Arm B: 2xI1+N3
Arm C: 2xI3-2xN3

2 patients have died so far, both were treated in **Arm A** 1 patient died due to melanoma
1 patient died 9.5 months after start of therapy due to complications after an immune-related encephalitis.

Neoadjuvant/Adjuvant Dabrafenib + Trametinib vs SOC: RFS



Amaria RN, et al. Oral presentation at ECCO 2017.

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Cutaneous Melanoma

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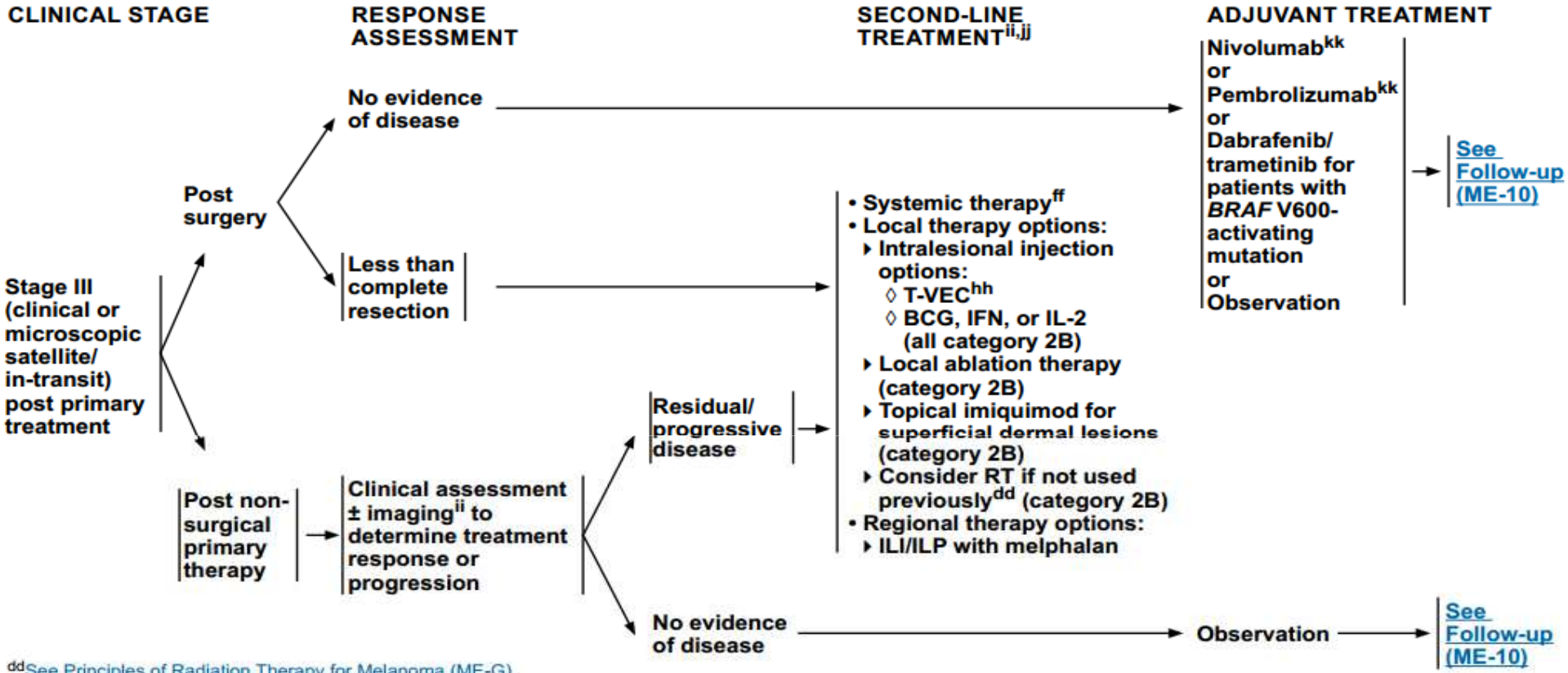
Discussion



[dd] See Principles of Radiation Therapy for Melanoma (ME-G).

[ff] See Systemic Therapy for Metastatic or Unresectable Disease (ME-H 1 of 5).

[hh] T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in AJCC 7th Edition stage IIIB and IIIC disease, and was more likely to be seen in patients who were treatment naive.

[ii] See Principles of Imaging–Treatment Response Assessment (ME-C).

[jj] For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

[kk] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported. Although both trials focused primarily on patients with stage III nodal disease, the NCCN panel agrees that it is appropriate to extend the indication for adjuvant anti-PD-1 therapy to patients with clinical or macroscopic satellite/intransit disease and who are at significant risk of recurrence.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

WHAT NEXT?

- Combos?
  - Anti-PD1 + BRAFi+MEKi (A Ribas) 1+1 = 1.2/1.3 ???
  - Anti-PD1 + Low dose anti-CTLA4 (Georgina Long)
  - New immuno combos

- NEOADJUVANT + ADJUVANT: CHANGE PARAGDIM

  - MIA Sydney: D+T 50% pCR, 100% ORR in palpable stage III

  - NKI-Amsterdam: nivo+ipi 40% pCR , 80% RR, TCR++ DIVERSITY !!

    - Facilitate Surgery and IMPROVE LOCOREGIONAL CONTROL?
    - Avoid TLND in WHICH % OF PATIENTS with palpable nodes?
    - Long term perspective: CHANGES SURGERY FIRST PARADIGM

Przewodniczący Komitetu Organizacyjnego:
prof. dr hab. n. med. Piotr Rutkowski

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