Adjuvant Immunotherapy for Cutaneous Melanoma

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Conflict of Interest

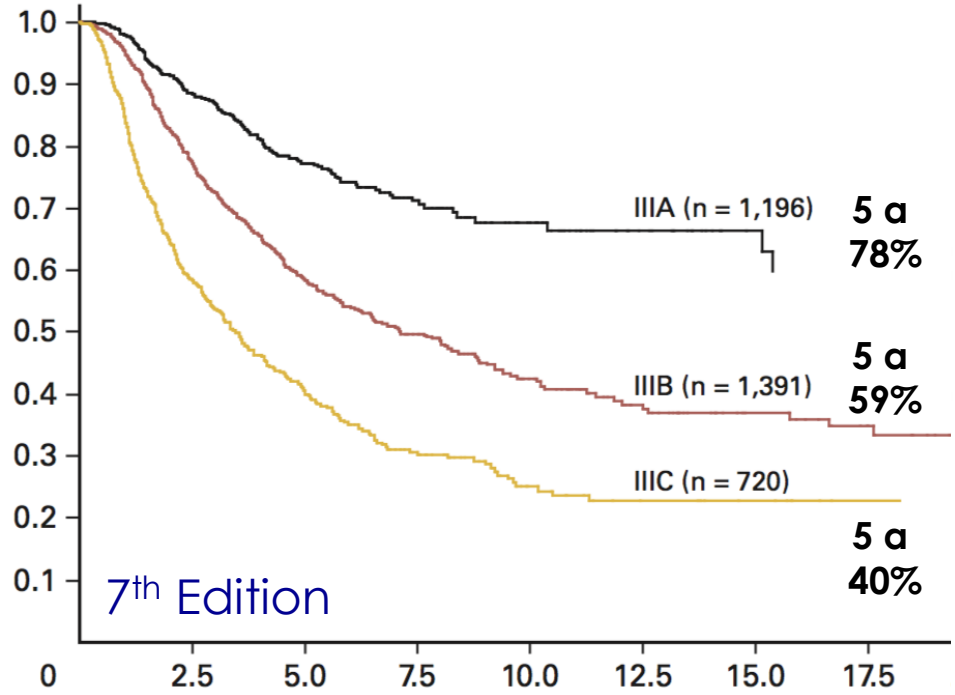
Clinical Research: **Roche, MSD, BMS, Novartis, Pfizer**

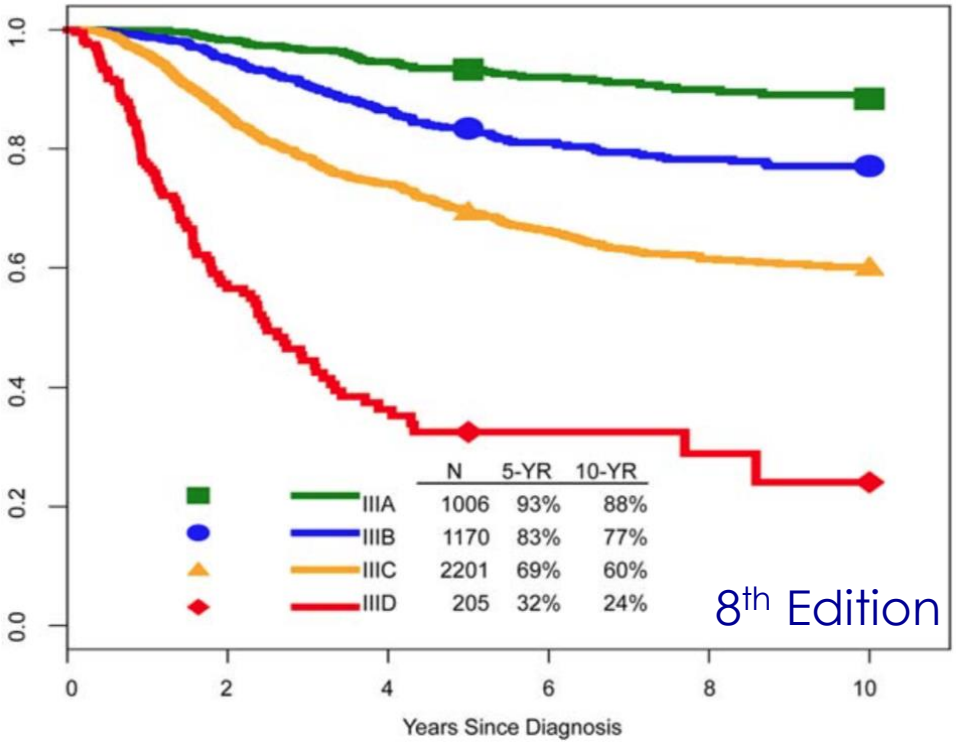
Speaker: **Roche, MSD, BMS, Novartis, Pfizer, Eisai, AstraZeneca**

Advisory Board: **Roche, MSD, BMS, Novartis, Pfizer, Eisai, AstraZeneca, Blau**

AJCC, 7ª vs 8ª edição

Survival Stage III





Balch et al. J Clin Oncol, 2009; Gershenwald et al. CA Journal, 2017

IFN
Rest in Peace

Journal of Clinical Oncology

The Official Journal of the American Society of Clinical Oncology

Vol 14, No 1 **January 1996**

EDITORIAL

Finally, a Successful Adjuvant Therapy for High-Risk Melanoma

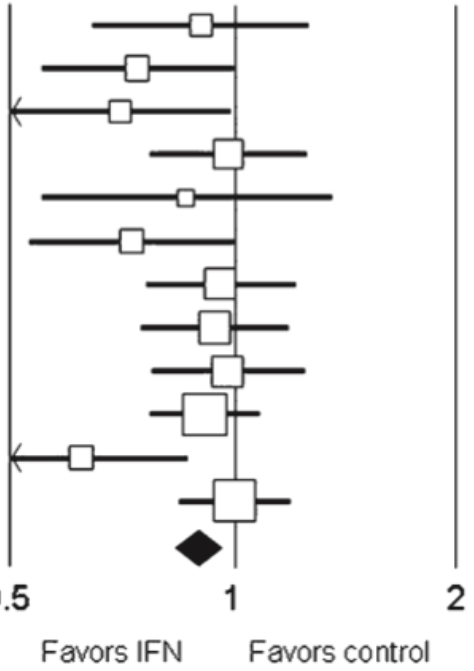
Charles M. Balch
Antonio C. Buzaid
The University of Texas M.D. Anderson Cancer Center
Houston, TX

Adjuvant IFN Adjuvant Studies

Sobrevida Global

HR 0,89 IC95% 0,83-0,96; p=0.02

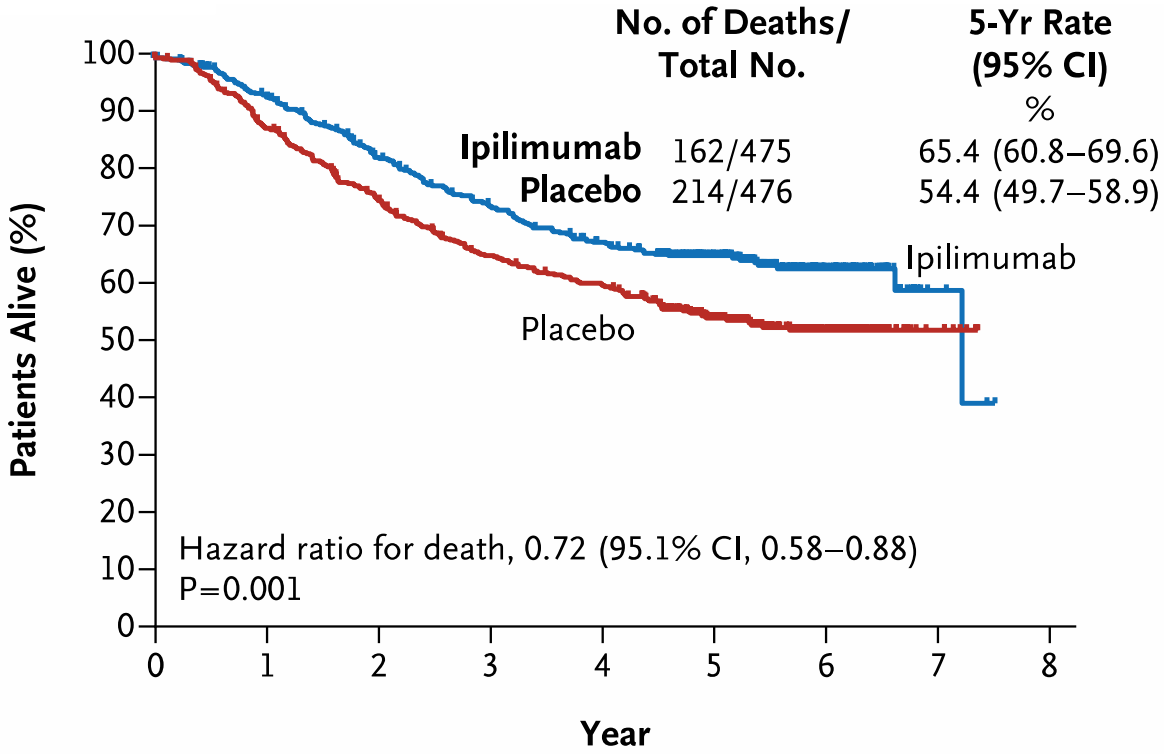
	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



Mocellin et al. J Natl Cancer Inst 102: 493-501, 2010

Ipilimumab

Ipilimumabe – Overall Survival



No. at Risk

Ipilimumab	475	431	369	325	290	199	62	4
Placebo	476	413	348	297	273	178	58	8

Eggermon et al. N Engl J Med, 2016

Ipilimumabe 10mg/kg - Toxicity

Event	Ipilimumab (N=471)				Placebo (N=474)			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Any immune-related adverse event								
Any dermatologic event								
Rash								
Any gastrointestinal event†								
Diarrhea								
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

Grade 3	Grade 4	Grade 5
169 (35.9)	27 (5.7)	5 (1.1)

Eggermon et al. N Engl J Med, 2016

Nivolumab vs Ipilimumab

Nivolumab vs Ipilimumab

R

Ipilimumab 10mg/kg Q3w x 4 →Q12w up to 3 years

Nivolumab 3mg/kg q2w X 1 year

	Nivolumab (N = 43)	Ipilimumab (N = 453)
Disease stage - no. (%)		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or not reported	4 (1.0)	0

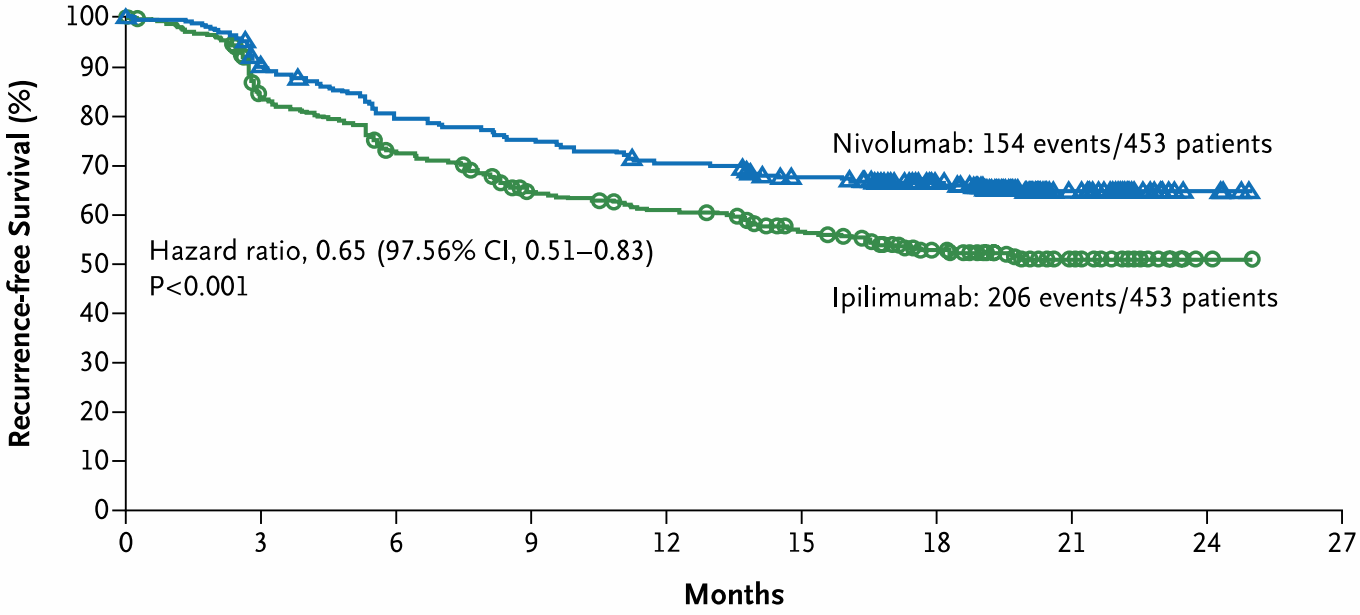
	Nivolumab		Ipilimumab	
	Any grade	G3 / G4	Any grade	G3 / G4
Any grade*		14%		46%
Fatigue	35%	0,5%	33%	1%
Diarrhea	24%	2%	46%	10%
Pruritus	23%	0	34%	1%
Rash	20%	1%	29%	3%
Hipothyroidism	11%	0,2%	17%	2%
Hipophysitis	2%	0,4%	11%	2%
Event that led to discontinuation	8%	4%	42%	30%

Weber et al. N Engl J Med, 2017

* Treatment related

Nivolumab vs Ipilimumab

Relapse Free Survival



No. at Risk										
Nivolumab	453	399	353	332	311	291	249	71	5	0
Ipilimumab	453	364	314	269	252	225	184	56	2	0

Weber et al. N Engl J Med, 2017

BARCELONA 2019 ESMO congress

Adjuvant Nivolumab Versus Ipilimumab in Resected Stage III/IV Melanoma: 3-Year Efficacy and Biomarker Results From the Phase 3 CheckMate 238 Trial

Jeffrey Weber,[1] Michele Del Vecchio,[2] Mario Mandala,[3] Helen Gogas,[4] Ana M. Arance,[5] Stéphane Dalle,[6] C. Lance Cowey,[7] Michael Schenker,[8] Jean-Jacques Grob,[9] Vanna Chiarion-Sileni,[10] Iván Márquez-Rodas,[11] Marcus Butler,[12] Michele Maio,[13] Hao Tang,[14] Abdel Saci,[14] Veerle de Pril,[14] Maurice Lobo,[14] James Larkin,[15]* Paolo A. Ascierto[16]*

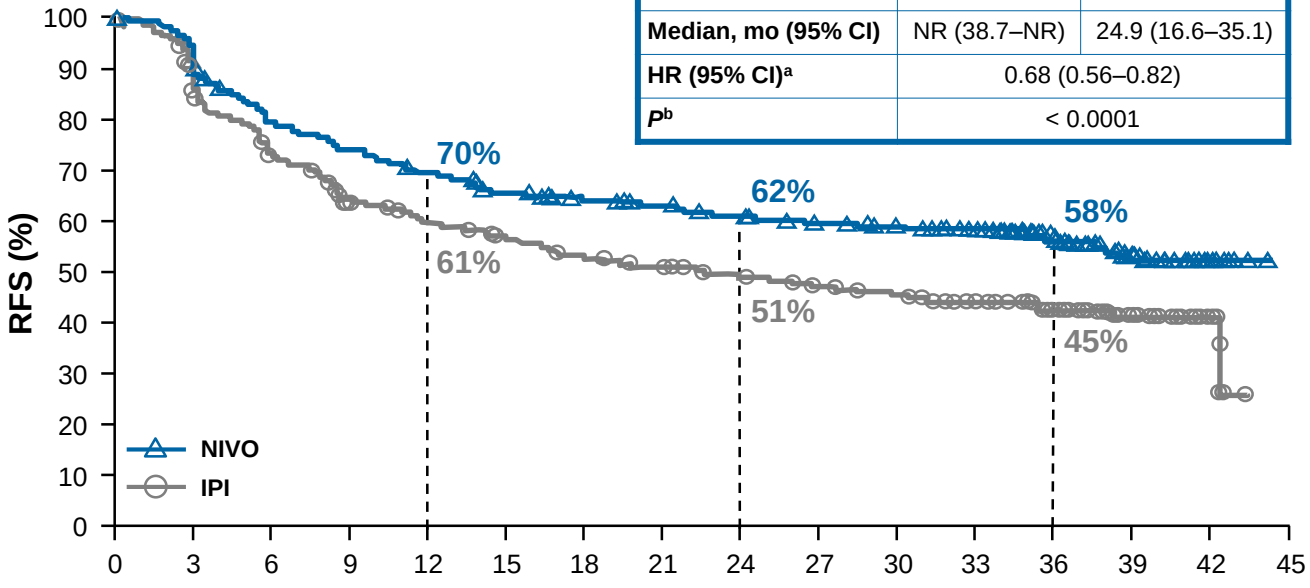
[1]NYU Perlmutter Cancer Center, New York, NY, USA; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Papa Giovanni XIII Hospital, Bergamo, Italy; [4]National and Kapodistrian University of Athens, Athens, Greece; [5]Hospital Clínic de Barcelona, Barcelona, Spain; [6]Hospices Civils de Lyon, Pierre Bénite, France; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [8]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [9]Hôpital de la Timone, Marseille, France; [10]Veneto Institute of Oncology IOV – IRCCS, Padua, Italy; [11]General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [14]Bristol-Myers Squibb, Princeton, NJ, USA; [15]The Royal Marsden NHS Foundation Trust, London, UK; [16]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

*Contributed equally.

Abstract Number 2801

Primary Endpoint: RFS in All Patients

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



No. at risk

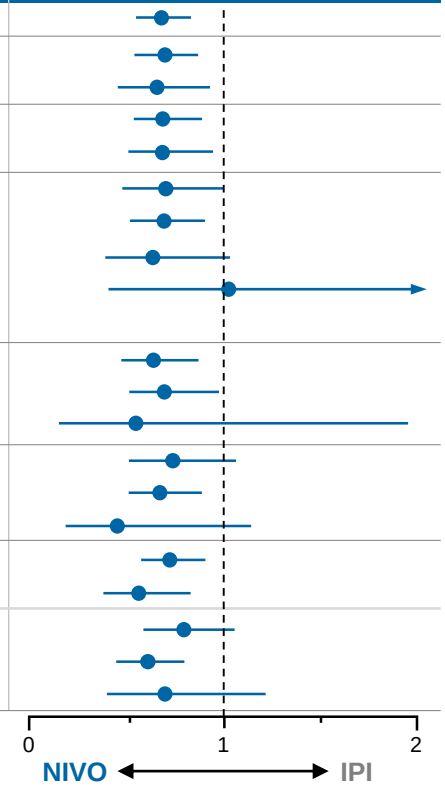
NIVO	453	394	353	331	311	290	280	270	261	249	243	234	178	50	13	0
IPI	453	365	316	272	254	235	221	209	203	193	185	170	122	37	12	0

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

RFS: Prespecified Subgroup Analysis

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	188/453	239/453	0.68 (0.56–0.83)
Age	< 65 years	131/333	170/339	0.69 (0.55–0.87)
	≥ 65 years	57/120	69/114	0.65 (0.46–0.93)
Sex	Male	116/258	151/269	0.69 (0.54–0.88)
	Female	72/195	88/184	0.69 (0.50–0.94)
Stage	Stage IIIB	53/163	65/147	0.70 (0.48–1.00)
	Stage IIIC	96/205	125/219	0.68 (0.52–0.89)
	Stage IV M1a–M1b	29/62	40/66	0.63 (0.39–1.02)
	Stage IV M1c	9/20	9/21	1.02 (0.40–2.57)
	Not reported	1/1	0/0	–
Stage III: ulceration	Absent	73/201	107/216	0.64 (0.48–0.87)
	Present	72/154	77/135	0.70 (0.51–0.97)
	Not reported	4/15	6/15	0.54 (0.15–1.94)
Stage III: lymph node involvement	Microscopic	50/127	64/133	0.73 (0.51–1.06)
	Macroscopic	91/219	115/215	0.68 (0.51–0.89)
	Not reported	8/24	11/18	0.45 (0.18–1.13)
Tumor PD-L1 status[a]	< 5%/indeterminate	144/300	171/299	0.73 (0.58–0.91)
	≥ 5%	44/153	68/154	0.57 (0.39–0.83)
***BRAF* mutation status**	Mutant	82/187	98/194	0.79 (0.59–1.06)
	Wild-type	79/197	117/212	0.60 (0.45–0.80)
	Not reported	27/69	24/47	0.70 (0.40–1.21)

Unstratified HR (95% CI)

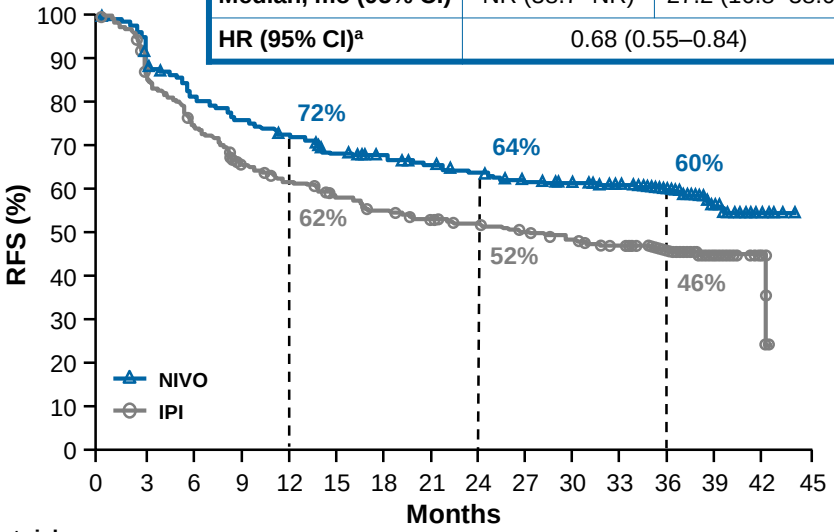


[a]PD-L1 IHC 28-8 pharmDx assay.

Subgroup Analysis of RFS: Disease Stage III and IV

Stage III

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

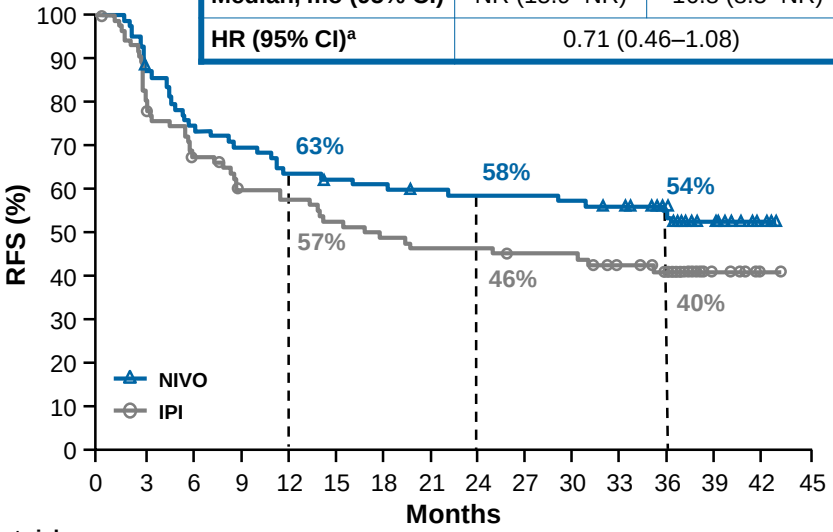


No. at risk

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

Stage IV

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



No. at risk

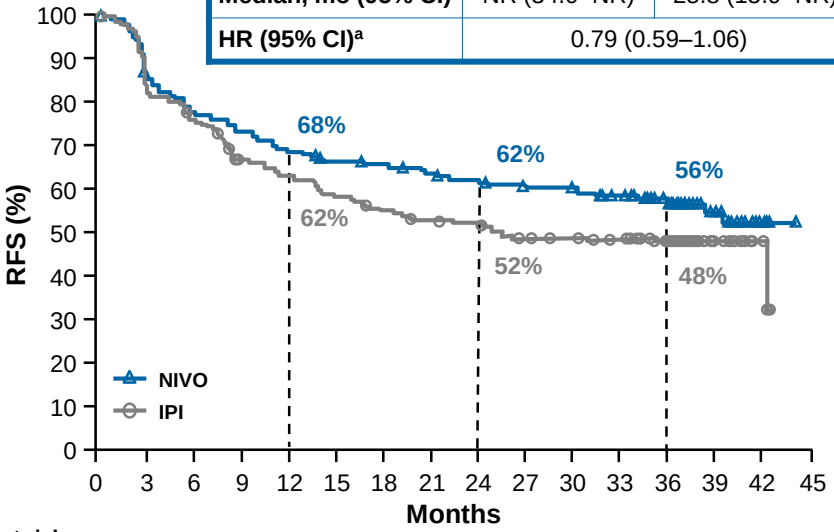
NIVO	82	71	59	56	51	49	48	46	45	45	44	42	31	11	3	0
IPI	87	65	55	47	45	41	38	36	36	34	34	29	22	6	1	0

[a]Unstratified.

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

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

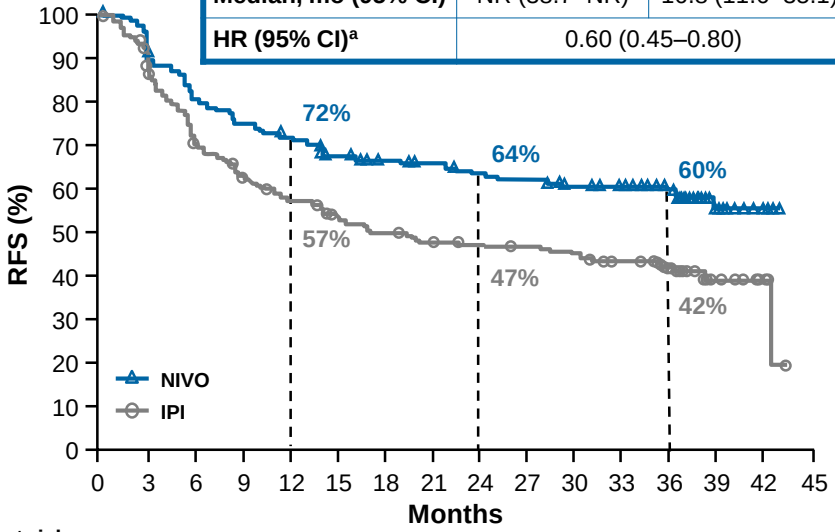


No. at risk

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

BRAF Wild-type

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



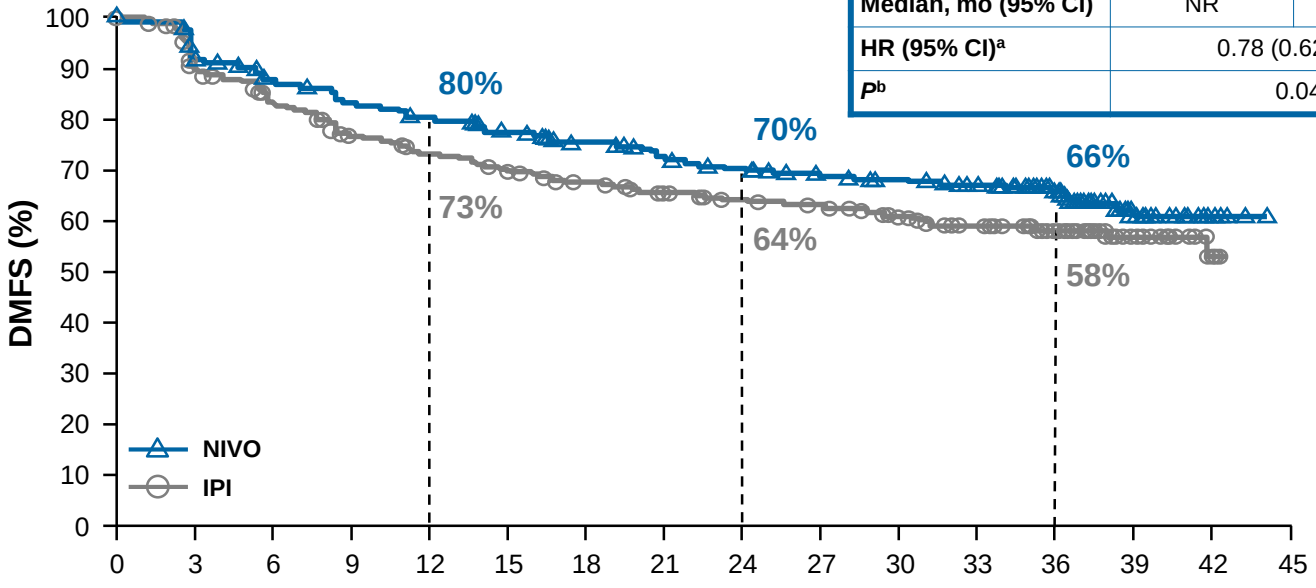
No. at risk

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

[a]Unstratified.

Exploratory Endpoint: DMFS in Stage III Disease

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



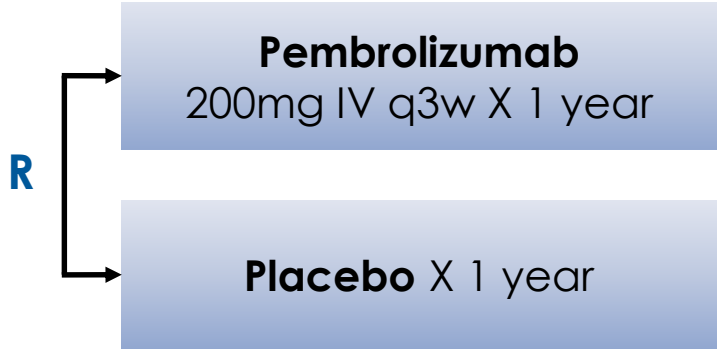
No. at risk															
NIVO	370	334	312	295	284	270	253	240	231	221	215	208	157	41	11	0
IPI	366	314	287	258	244	232	220	208	200	195	181	168	118	40	12	0

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

Pembrolizumab vs Placebo (Pembro now vs later)

Pembrolizumbe vs. Placebo

	Pembro	Placebo
Disease stage - no. (%)		
At randomization		
Stage IIIA	80 (15.6)	80 (15.8)
Stage IIIB	237 (46.1)	230)45.5)
Stage IIIC with 1-3 positive lymph nodes	95 (18.5)	93 (18.4)
Stage IIIC ≥ 4 positive lymph nodes	102 (19.8)	102 (20.2)



	Pembrolizumab	
	Any grade	G3 / G4
Any event*	78%	15%
Fatigue	37%	1%
Diarrhea	19%	1%
Pruritus	18%	0
Rash	16%	0.2%
Hipothyroidism	14%	
Pneumonitis	3%	1%
Event which led to discontinuation	13%	

* Treatment related

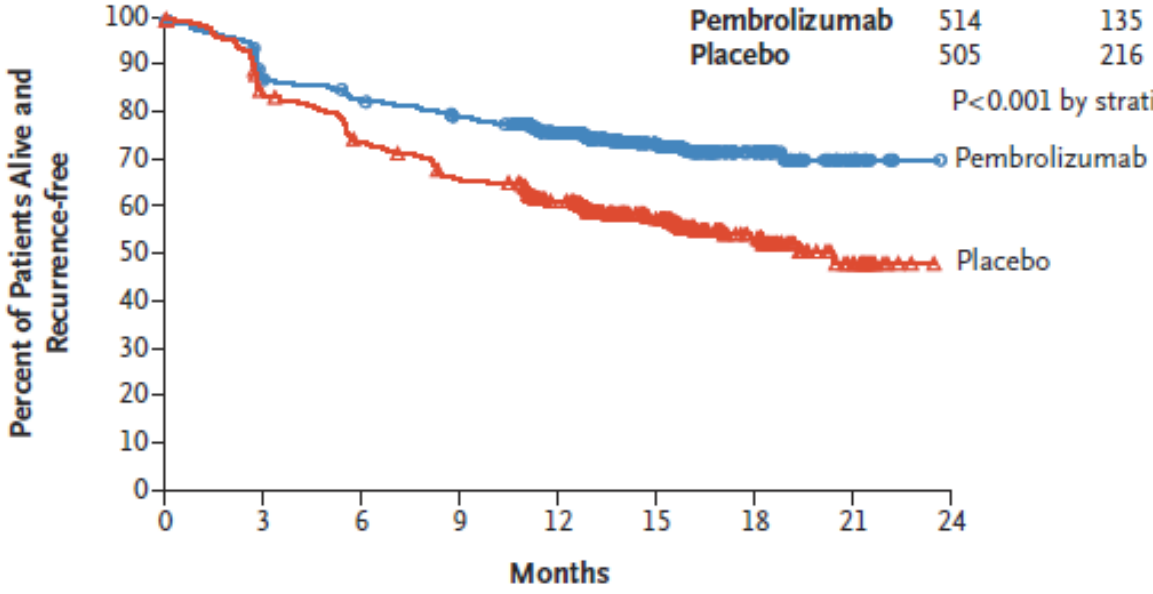
Eggermont et al, N Engl J Med 2018

Pembrolizumb vs. Placebo

Overall Intention-to-Treat Population

	Total No.	No. with Event	Hazard Ratio (98.4% CI)
Pembrolizumab	514	135	0.57 (0.43–0.74)
Placebo	505	216	1.00

P<0.001 by stratified log-rank test



No. at Risk

Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

Eggermont et al, N Engl J Med 2018

The IMMUNED Study

Adjuvant **IMMU**notherapy with nivolumab (NIVO) alone or in combination with ipilimumab (IPI) vs. placebo in stage IV melanoma patients with no evidence of disease (**NED**): A randomized, double-blind, phase II trial (**IMMUNED**) on behalf of DeCOG

Dirk Schadendorf[1], Jessica C. Hassel[2], Michael Fluck[3], Thomas Eigentler[4], Carmen Loquai[5], Mark Berneburg[6], Ralf Gutzmer[7], Friedegund Meier[8], Peter Mohr[9], Axel Hauschild[10], Jürgen Becker[11,12], Christian Menzer[2], Felix Kiecker[13], Edgar Dippel[14], Jan-Christoph Simon[15], Beate Conrad[3], Claus Garbe[4], Silvia Körner[2], Elisabeth Livingstone[1*], Lisa Zimmer[1*]

[1]Department of Dermatology, University Hospital Essen, Essen; [2]Department of Dermatology, University Hospital Heidelberg, Heidelberg; [3]Department of Dermatology Hornheide, Münster; [4]Department of Dermatology, University Hospital Tübingen, Tübingen; [5]Department of Dermatology, University Hospital Mainz, Mainz; [6]Department of Dermatology, University Hospital Regensburg, Regensburg; [7]Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover; [8]Department of Dermatology, University Hospital Dresden, Dresden; [9]Department of Dermatology, Buxtehude; [10]Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel; [11]Translational Skin Cancer Research (TSCR), German Cancer Consortium (DKTK), Partner Site Essen, Medical Faculty, University of Duisburg-Essen, Essen; [12]German Cancer Research Center (DKFZ), Heidelberg; [13]Department of Dermatology, Charité Campus Mitte, Berlin; [14]Department of Dermatology, Ludwigshafen; [15]Department of Dermatology, University Hospital Leipzig, Leipzig; all facilities are from Germany; *contributed equally to

this study

THE IMMUNED STUDY
Study design

Enrollment period: Sept. 2015 to Nov. 2018

Patients with:
- High-risk stage IV (AJCC 7th edition) melanoma with NED after complete resection or radiotherapy conducted within 8 weeks prior to enrollment
- Known *BRAF* status
- ECOG 0-1

R 1:1:1

n = 59 → **NIVO 3 mg/kg iv Q2W**

n = 56 → **NIVO 1 mg/kg iv Q3W and IPI 3 mg/kg iv Q3W for 4 doses**

n = 52 → **placebo**

Stratified by:
1) PD-L1 status in tumor cells at a 5% cut-off
2) Site of metastasis
3) Trial site

→ **Follow up* Minimum of 6 months after end of treatment**

*will be amended to a minimum of 2 years after end of treatment

Maintenance therapy:
NIVO (A/B, 3 mg/kg) or placebo (C) iv Q2W up to 1 y after initial dosing or until PD

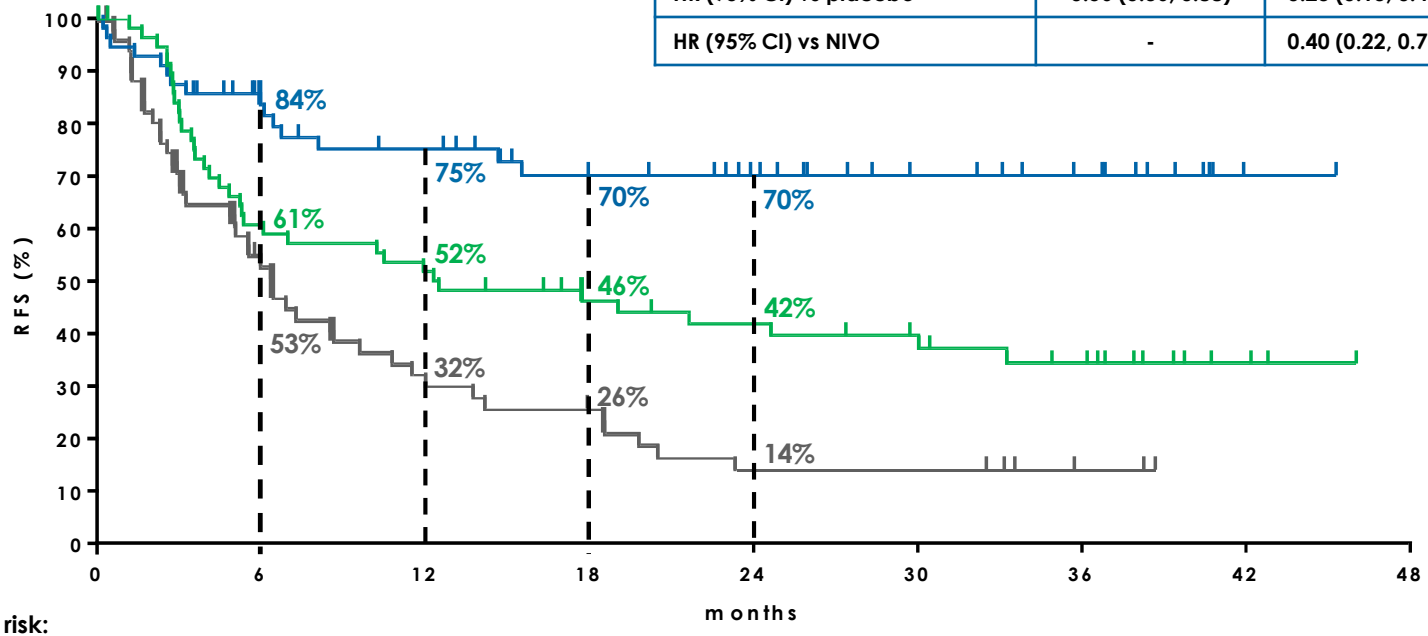
ECOG: Eastern Cooperative Oncology Group PD: Progressive disease

THE IMMUNED STUDY
RFS in all patients

Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

	NIVO (n=59)	NIVO+IPI (n=56)	Placebo (n=52)
Median RFS, mo (95% CI)	12.4 (5.30, 33.26)	NR[1]	6.4 (3.26, 9.61)
HR (95% CI) vs placebo	0.56 (0.36, 0.88)	0.23 (0.13, 0.41)	-
HR (95% CI) vs NIVO	-	0.40 (0.22, 0.73)	-

[1]NR: not reached



Patients at risk:

NIVO	59	34	29	22	19	16	11	3	-
NIVO + IPI	56	40	34	26	21	14	10	1	-
Placebo	52	26	15	11	6	6	2	-	-

THE IMMUNED STUDY

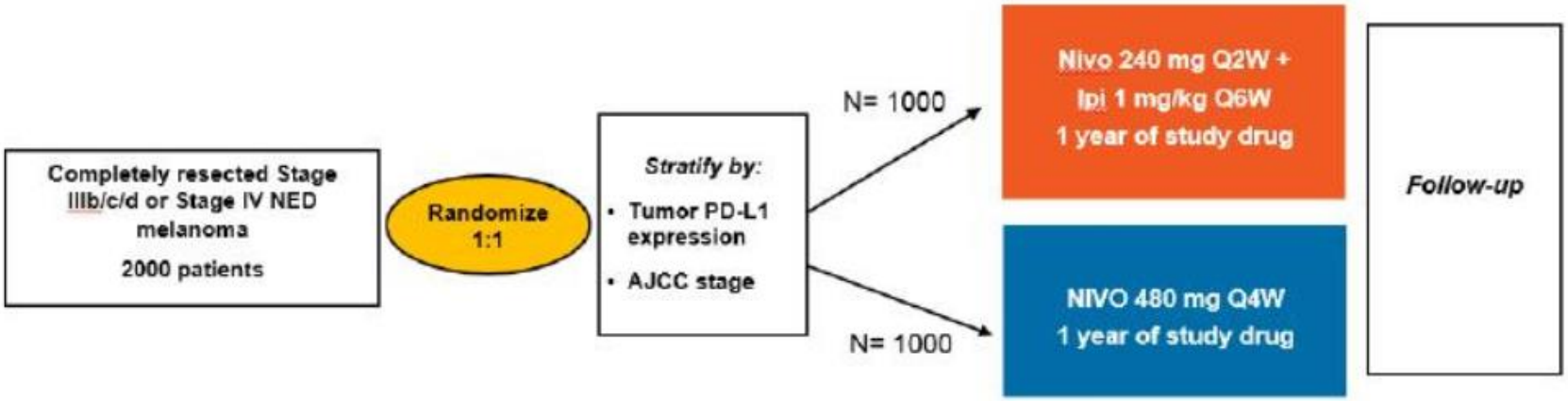
Safety overview

	NIVO (n=56)				NIVO + IPI (n=55)				Placebo (n=51)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
	n	%	n	%	n	%	n	%	n	%	n	%
Any treatment-related AE	47	83.9	15	26.8	53	96.4	39	70.9	28	54.9	3	5.9
Skin	19	33.9	1	1.8	33	60.0	3	5.5	7	13.7	0	0
Gastrointestinal	19	33.9	1	1.8	25	45.5	8	14.5	8	15.7	0	0
Hepatic	9	16.1	5	8.9	33	60.0	26	47.3	1	2.0	0	0
Endocrine	14	25.0	2	3.6	33	60.0	7	12.7	1	2.0	0	0
Neurological	10	17.9	2	3.6	11	20.0	1	1.8	9	17.6	0	0
Musculoskeletal	14	25.0	3	5.4	14	25.5	1	1.8	5	9.8	0	0
Any immune-related AE	40	71.4	14	25.0	51	92.7	38	69.1	17	33.3	3	5.9
Treatment-related AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	1	2.0	-	-
Any AE leading to discontinuation	7	12.5	5	8.9	34	61.8	29	52.7	2	3.9	1	2.0

- No treatment-related deaths have occured!

Data cut-off date July 2nd, 2019
Median follow-up time: 28.4 months (n=167)

CheckMate 915



Bristol-Myers Squibb

Bristol-Myers Squibb Announces Update on CheckMate -915 for Opdivo (nivolumab) Plus Yervoy (ipilimumab) Versus Opdivo Alone in Patients with Resected High-Risk Melanoma and PD-L1 <1%

CATEGORY:

CORPORATE/FINANCIAL NEWS

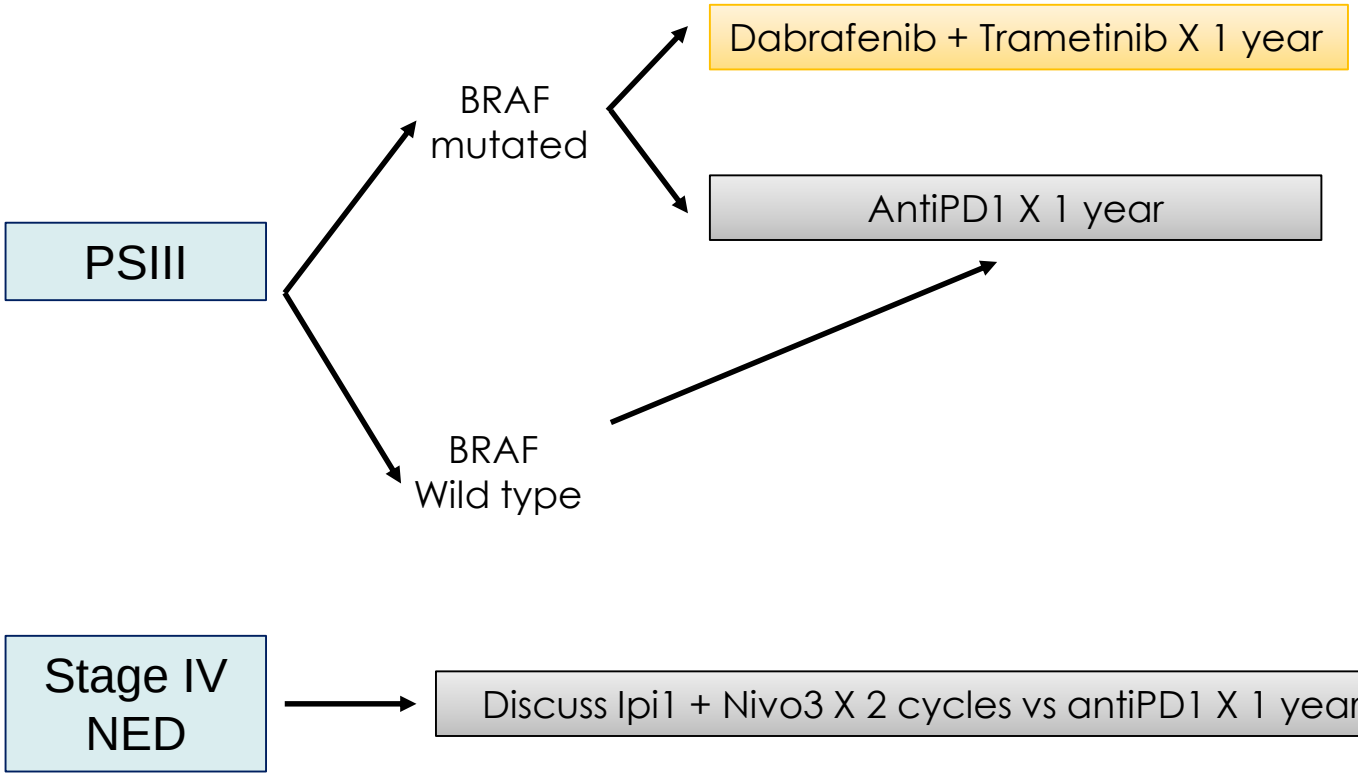
WEDNESDAY, NOVEMBER 20, 2019 6:58 AM EST

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced results for one of the co-primary endpoints from CheckMate -915, a randomized Phase 3 study evaluating *Opdivo* (nivolumab) plus *Yervoy* (ipilimumab) versus *Opdivo* alone for the adjuvant treatment of patients who have had a complete surgical removal of stage IIIb/c/d or stage IV (no evidence of disease) melanoma. A statistically significant benefit was not reached for the co-primary endpoint of recurrence-free survival (RFS) in patients whose tumors expressed PD-L1 <1%. The Data Monitoring Committee recommended that the study continue unchanged. The study remains double-blinded and will continue to assess the other co-primary endpoint of RFS in the all-comer (intent-to-treat) population.

In summary…

Study	Eligibility	HR for DFS
Nivo vs Ipi	IIIB, IIIC, IV NED	0.68 (0,54 se vs placebo)
Pembro vs Placebo	IIIA, IIIB e IIIC	0.57
Ipi3+Nivo1 (phase II)	IV NED	0.23
Dabra + Trame vs Placebo	IIIA, IIIB, e IIIC	0.49
Vemu vs Placebo	IIC, IIIA, IIIB e IIIC	NS

Adjuvant Therapy for Stage IIIA (node ≥ 1 mm), IIIB, C, D or IV NED



Thank you