Advances in the Adjuvant Setting: Systemic Therapy

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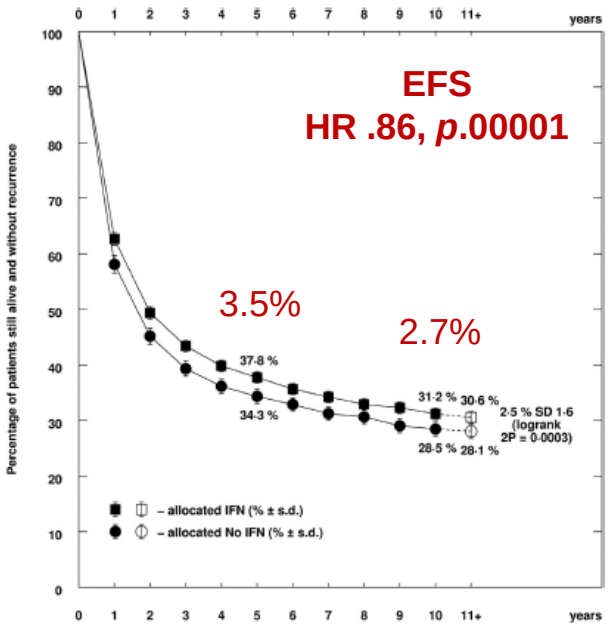
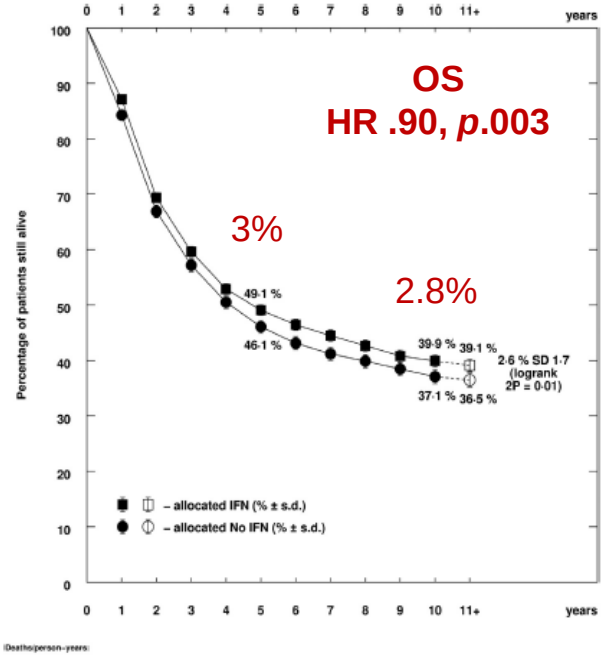
Interferon





Ulceration:					
Yes	624/898	421/545	–52·6	222·4	0.79 (0.66, 0.94)
No	856/1429	556/893	–17·1	310·8	0.95 (0.82, 1.10)
Unknown/Missing	733/1112	654/949	–42·6	322·6	0.88 (0.76, 1.01)

Ives Eur J Cancer 2017

Use of Adjuvant Therapy in Patients With Stage IIIB/IIIC Melanoma

Real-World Data From the 2016 MELABIS Observational Study (France, Germany, UK)

Adjuvant Systemic Therapy Received, n (%)	France (n = 199)	Germany (n = 164)	UK (n = 195)	Overall (n = 558)
None	185 (93.0)	109 (66.5)	190 (97.4)	484 (86.7)
Interferon				
High dose	3 (1.5)	18 (11.0)	0	21 (3.8)
Intermediate dose	1 (0.5)	8 (4.9)	0	9 (1.6)
Low dose	0	25 (15.2)	0	25 (4.5)
Pegylated	0	3 (1.8)	0	3 (0.5)
Unknown[b]	1 (0.5)	0	0	1 (0.2)
Other[c]	9 (4.5)	1 (0.6)	5 (2.6)	15 (2.7)
Disease progression, n (%)				
Deceased	66 (33.2)	59 (36.0)	71 (36.4)	196 (35.1)
Any recurrence	131 (65.8)	100 (61.0)	120 (61.5)	351 (62.9)
Type of first occurrence				
Locoregional	57 (43.5)	39 (39.0)	48 (40.0)	144 (41.0)
Further progression to distant metastases	32 (57.1)[d]	17 (43.6)	26 (54.2)	75 (52.4)
Distant metastasis	74 (56.5)	61 (61.0)	72 (60.0)	207 (59.0)

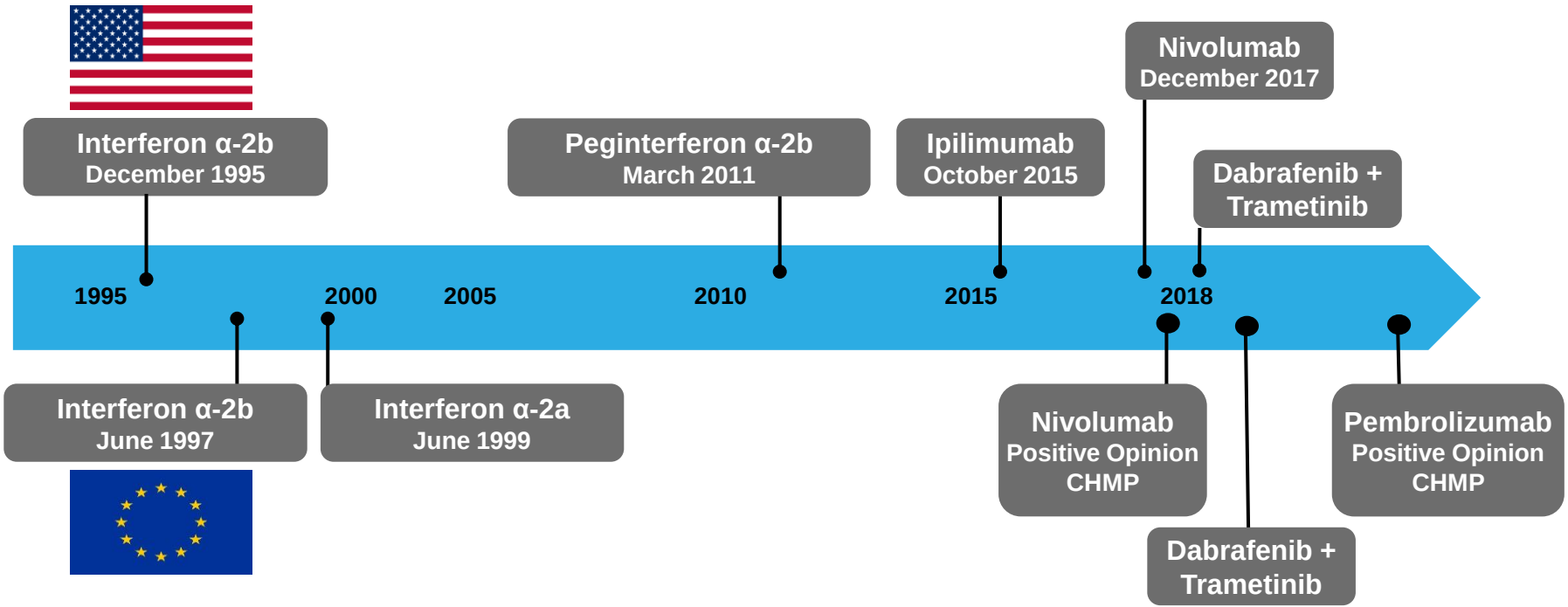
Considerable variation in use of adjuvant therapy (mostly interferon) between patients with stage IIIB/IIIC melanoma in Germany (≈ 33% use) and France/UK (3-7% use)

UK, United Kingdom.

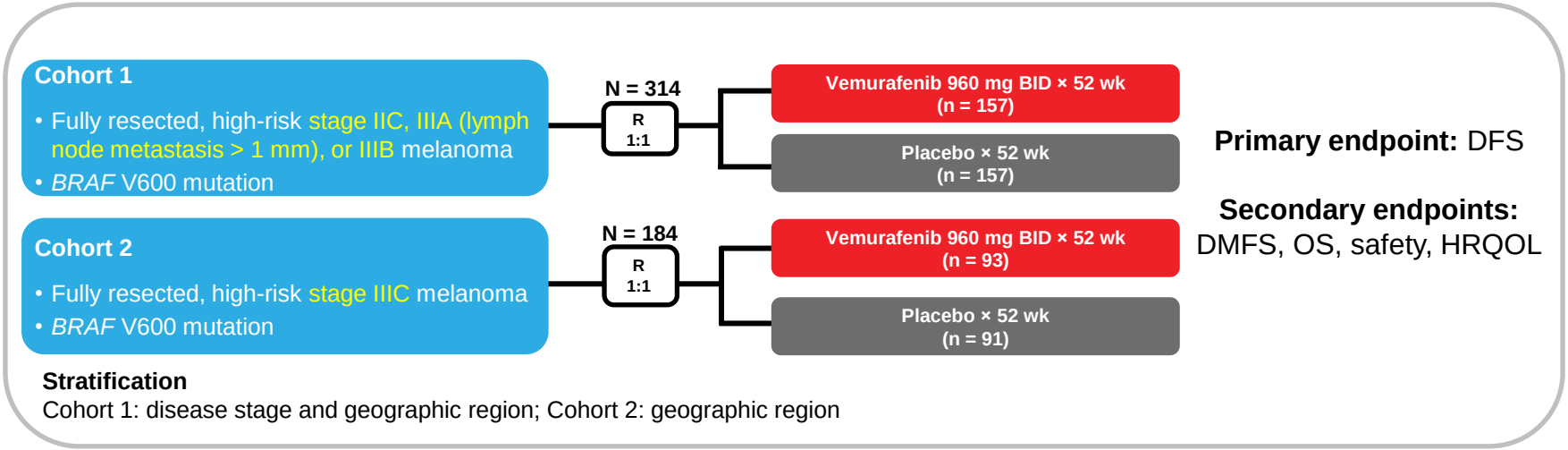
[a] Diagnosis made between 1 January 2009 and 31 December 2011; [b] Unknown therapy given in a blinded clinical trial investigating therapies licensed for stage IIIA/B melanoma; [c] Includes carboplatin/paclitaxel, bacillus Calmette-Guérin, radiotherapy and radiochemotherapy. In France, "other" also included 5 patients treated with interferon regimens at unspecified doses; [d] Data missing for 1 patient. Percentage equals the number of patients with further progression of locoregional recurrence divided by all patients with locoregional recurrence.

Harries M, et al. *Int J Clin Pract*. 2017;71:e12946.

Approved Treatments for Melanoma in the Adjuvant Setting



BRIM8



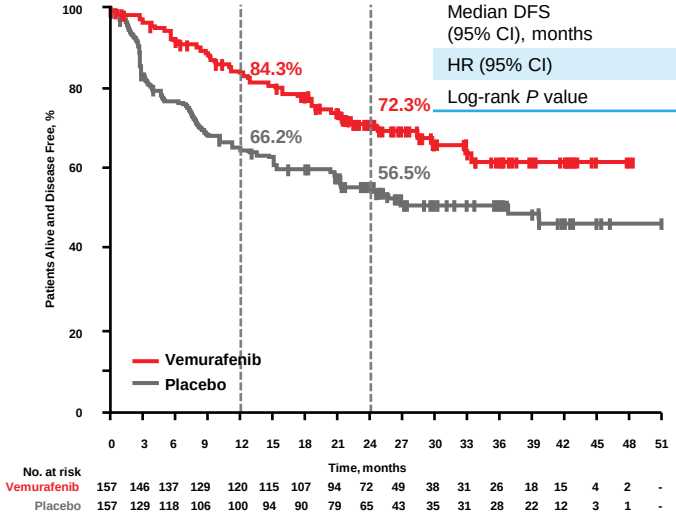
BID, twice daily; DFS, disease-free survival; DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; R, randomisation.

Maio M, et al. *Lancet Oncol*. 2018 18 Feb [ePub ahead of print] doi: 10.1016/S1470-2045(18)30106-2.

BRIM8: Vemurafenib Was Associated With Improved DFS vs Placebo

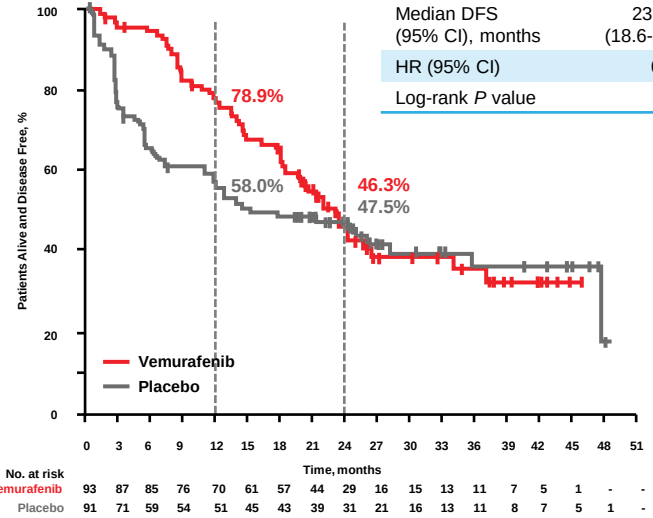
Cohort 1 (stage IIC-IIIB)

	Vemurafenib (n = 157)	Placebo (n = 157)
Events, n (%)	45 (29)	72 (46)
Median DFS (95% CI), months	NE	36.9 (21.4-NE)
HR (95% CI)	0.54 (0.37-0.78)	
Log-rank *P* value	.0010	



Cohort 2 (stage IIIC)

	Vemurafenib (n = 93)	Placebo (n = 91)
Events, n (%)	52 (56)	53 (58)
Median DFS (95% CI), months	23.1 (18.6-26.5)	15.4 (11.1-35.9)
HR (95% CI)	0.80 (0.54-1.18)	
Log-rank *P* value	.2598	



- *P* value for DFS in cohort 1 cannot be considered significant because the primary endpoint was not met in cohort 2

HR, hazard ratio; NE, not estimable.

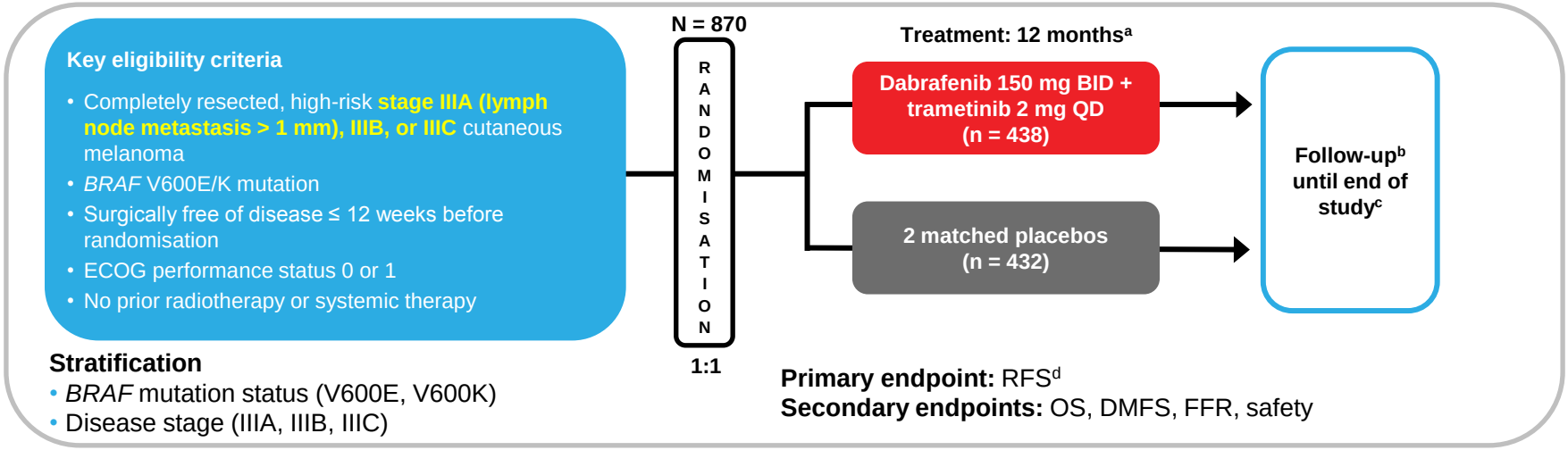
BRIM8: Conclusions

- The primary disease-free survival end-point was not met in patients with resected stage IIIC *BRAF* V600 mutation-positive melanoma

- However, 1 year of adjuvant vemurafenib showed a numerical benefit in disease-free survival for patients with resected stage IIC–IIIA–IIIB disease

Maio M, et al. *Lancet Oncol*. 2018 18 Feb [ePub ahead of print] doi: 10.1016/S1470-2045(18)30106-2.

COMBI-AD

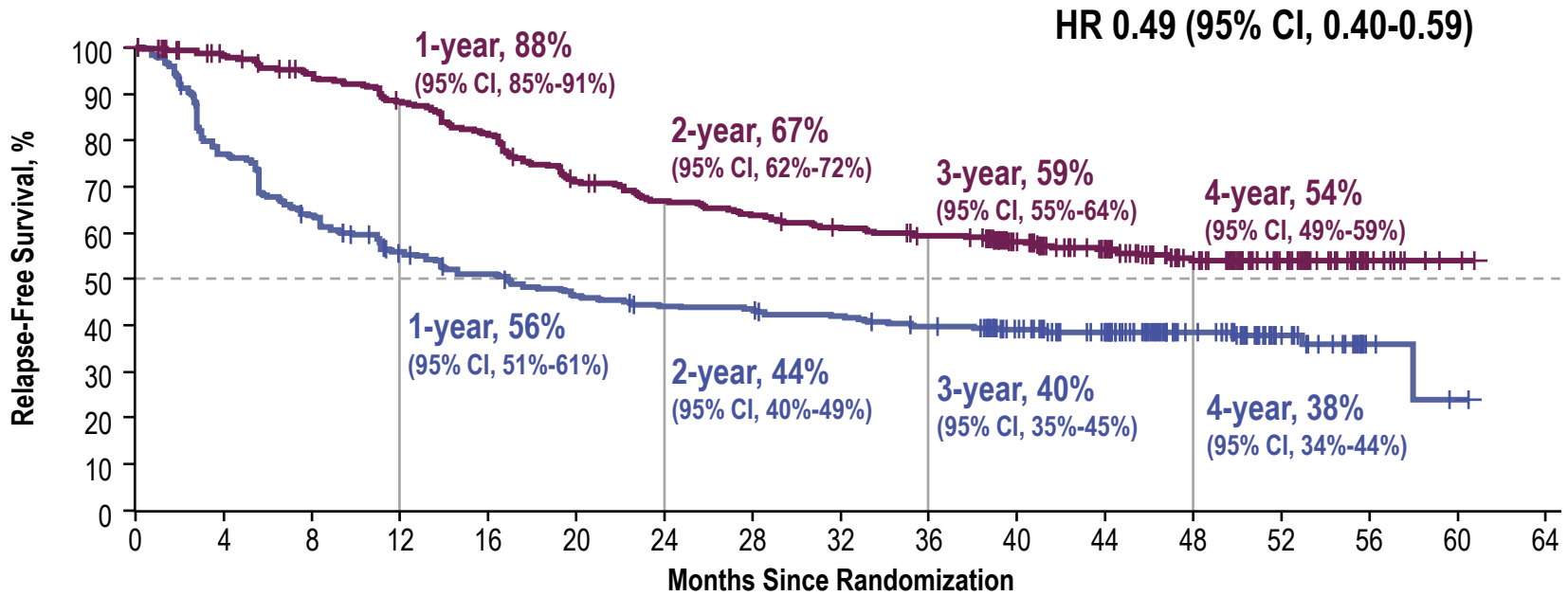


ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; QD, once daily; RFS, relapse-free survival.

[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 randomised patients have died or are lost to follow-up; [d] New primary melanoma was considered an event.

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

COMBI-AD: DABRAFENIB + TRAMETINIB was associated with improved RFS

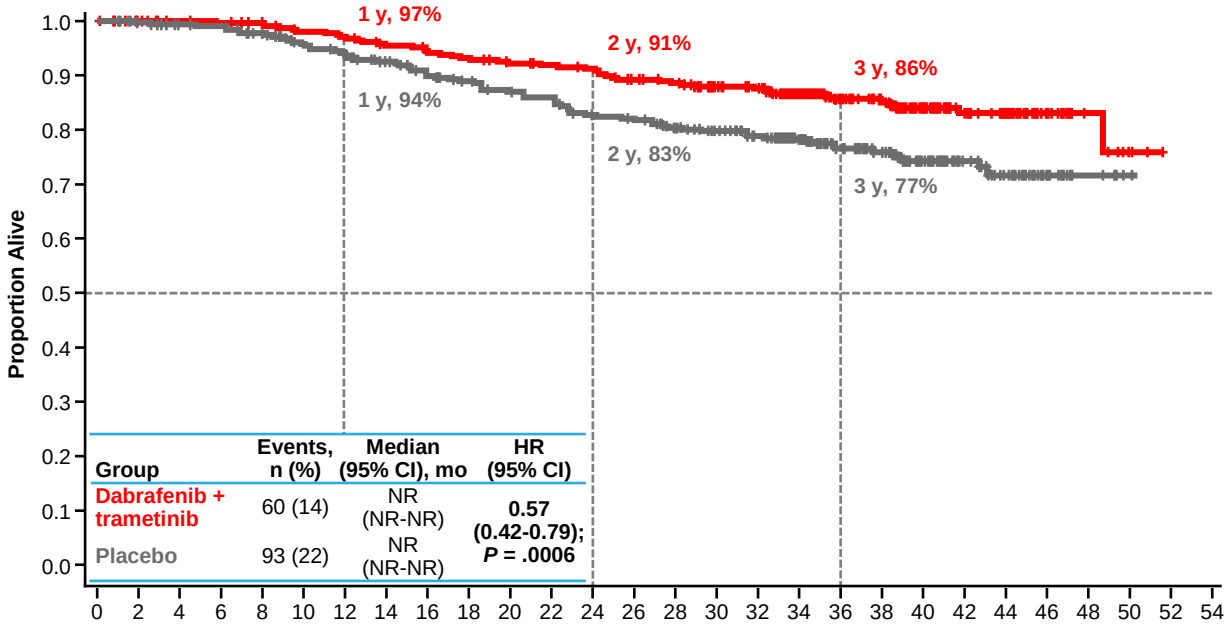


No. at risk																
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; Hauschild et al. J Clin Oncol 2018

COMBI-AD: Dabrafenib + Trametinib Was Associated With Improved OS

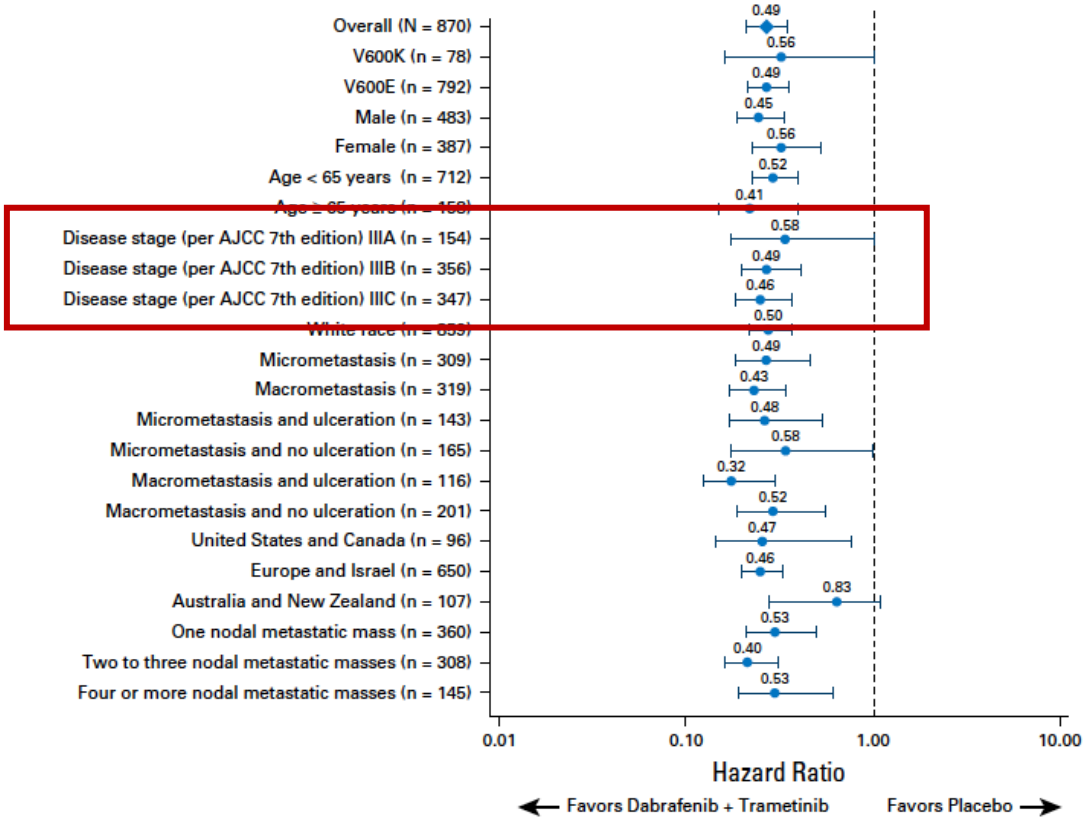
Median follow-up, 33.6 months



No. at risk																											
Dabrafenib + 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

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823

COMBI-AD Primary Analysis: RFS by Subgroup



Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; Hauschild et al. J Clin Oncol 2018

COMBI-AD: Safety Summary

- In the primary analysis, the most common AEs in the dabrafenib + trametinib arm were pyrexia (63%) and fatigue (47%)

AE Category, n (%)	Dabrafenib + Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AE related to study treatment	398 (91)	272 (63)
Grade 3/4 AE related to study treatment	136 (31)	21 (5)
Any SAE	155 (36)	44 (10)
SAE related to study treatment	117 (27)	17 (4)
AE leading to dose interruption	289 (66)	65 (15)
AE leading to dose reduction	167 (38)	11 (3)
AE leading to treatment discontinuation[a]	114 (26)	12 (3)
Fatal AE related to study drug	0	0

14-16%
COMBI-D & -V

Data cutoff: 30 June 2017.

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

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; Hauschild A, et al. ESMO. 2017 .

COMBI-AD: Conclusions

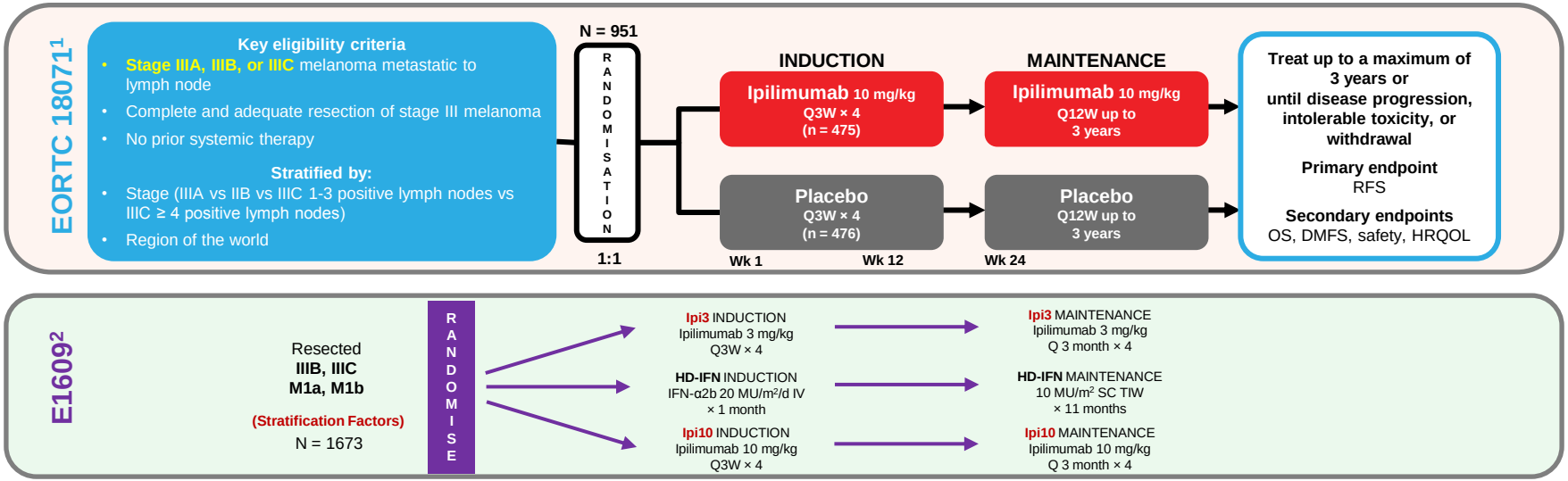
- Combined adjuvant dabrafenib + trametinib for patients with stage III *BRAF*-mutant melanoma was associated with improved RFS compared with placebo

- With a median follow-up of nearly 3 years, OS was also improved in the dabrafenib + trametinib arm vs the placebo arm

- Safety profile for dabrafenib + trametinib in the adjuvant setting was consistent with that in the metastatic setting for *BRAF*-mutant melanoma, and no new safety signals were observed

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

Ipilimumab: EORTC 18071, E1609



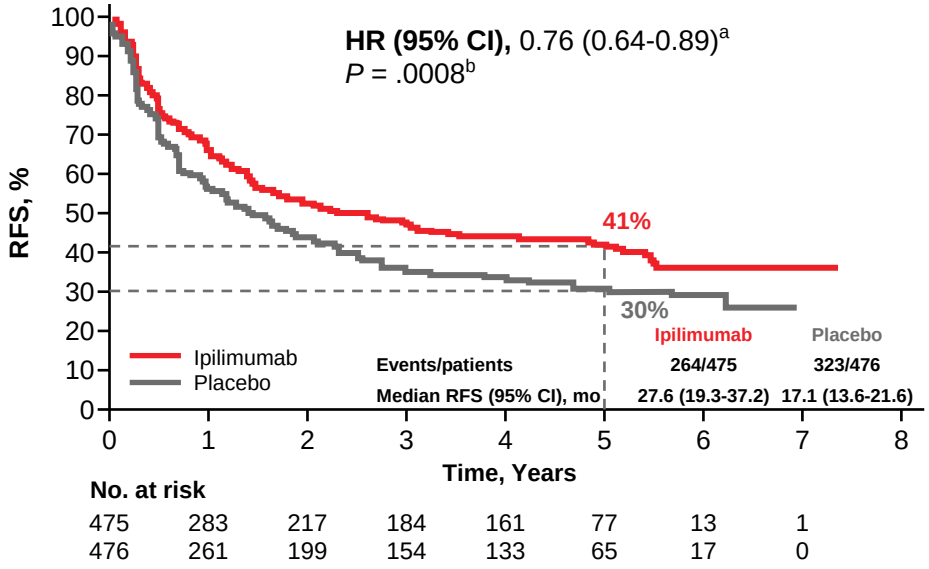
HD, high dose; IFN, interferon; IV, intravenously; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; SC, subcutaneously; TIW, 3 times weekly.

1. Eggermont AM, et al. *N Engl J Med.* 2016;375:1845-1855; 2. Tarhini AA, et al. *J Clin Oncol.* 2017;35 [abstract 9500].

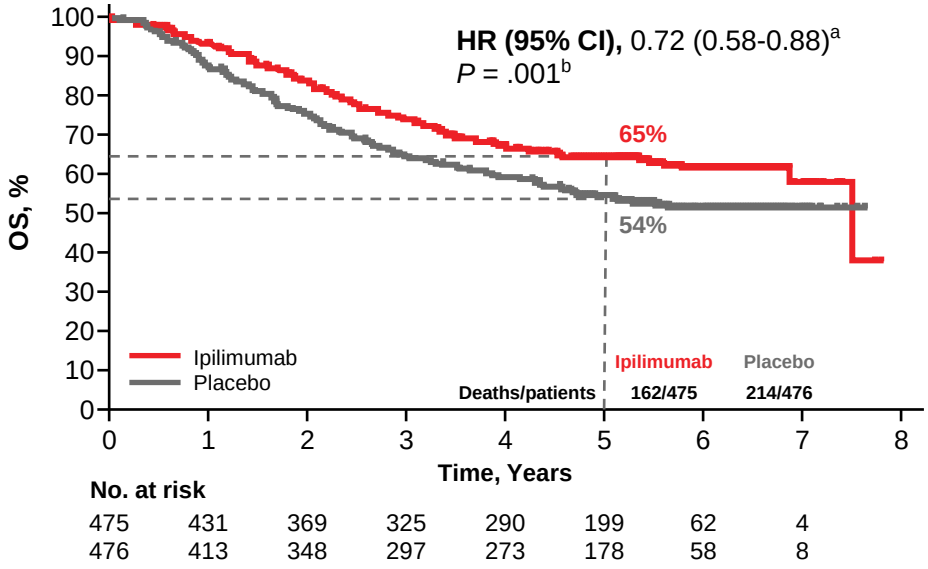
EORTC 18071

Randomised Phase 3 Trial of Adjuvant Ipilimumab 10 mg/kg vs Placebo in Resected Stage III Melanoma

Recurrence-Free Survival



Overall Survival



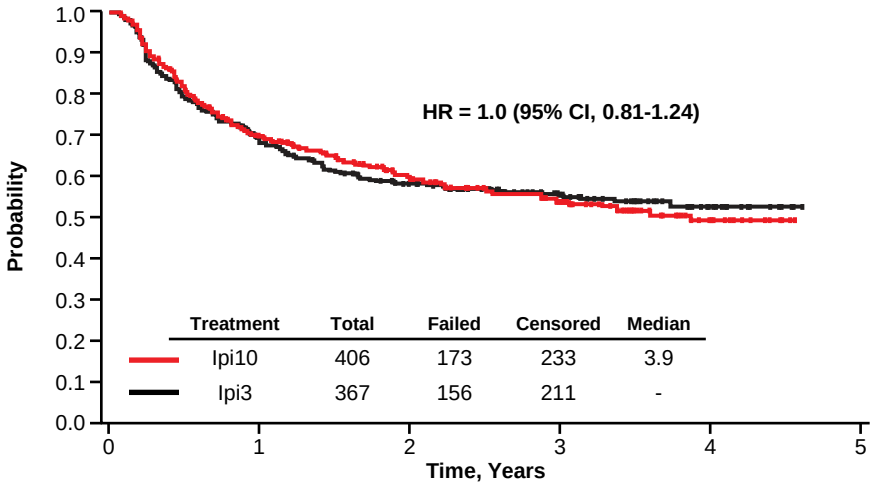
Note: RFS was per independent review committee.

[a] Stratified by stage provided at randomisation; [b] Log-rank *P* value.

E1609

Randomised Phase 3 Trial of Adjuvant Ipilimumab 10 or 3 mg/kg vs High-Dose Interferon α-2b in Resected Stage III Melanoma

Recurrence-Free Survival[a]



AE, %[b]	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

Treatment-related deaths

- **Ipi3: 2 patients (0.4%)—**colitis/bowel perforation; colitis/death not otherwise specified
- **Ipi10: 8 patients (1.6%)—**colitis; colitis/colonic perforation; colitis; colitis/ventricular tachycardia; colitis/nervous system disorder; pneumonitis; thromboembolic event/hypopituitarism; cardiac arrest

[a] Based on an unplanned analysis of a subgroup of patients; RFS data for ipilimumab 10 mg/kg (Ipi10) vs 3 mg/kg (Ipi3) derived from a comparison of concurrently randomised patients only; [b] Based on all toxicity data as of 2 March 2017.

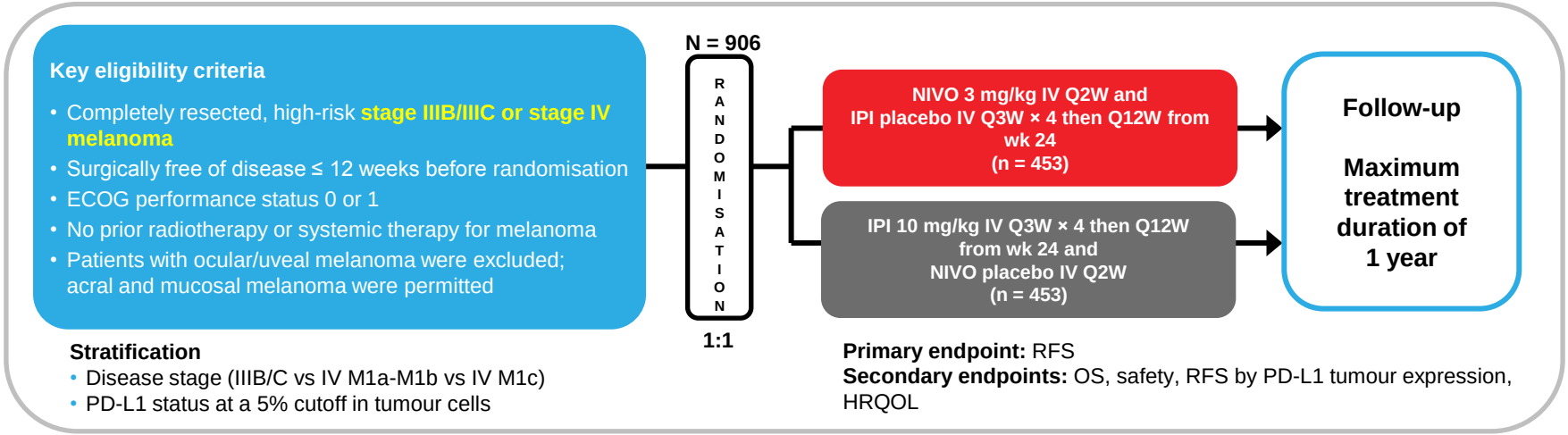
From Tarhini AA, et al. In: Proceedings from the American Society of Clinical Oncology; June 2-6, 2017; Chicago, IL [abstract 9500].

EORTC 18071, E1609: Conclusions

- In the EORTC 18071 trial, ipilimumab 10 mg/kg was associated with a reduced risk of recurrence compared with placebo in patients with resected stage III melanoma
- An unplanned analysis of patients in the E1609 study demonstrated no difference in RFS between adjuvant ipilimumab 10 mg/kg vs 3 mg/kg
  - However, greater toxicity (including higher rates of AEs, treatment-related AEs leading to discontinuation and treatment-related deaths) was observed in the 10-mg/kg arm vs the 3-mg/kg arm
- Updated analyses, including the planned co-primary endpoints of RFS and OS for ipilimumab 3 mg/kg vs high-dose interferon, are expected

1. Eggermont AM, et al. *N Engl J Med.* 2016;375:1845-1855; 2. Tarhini AA, et al. *J Clin Oncol.* 2017;35 [abstract 9500].

CheckMate 238

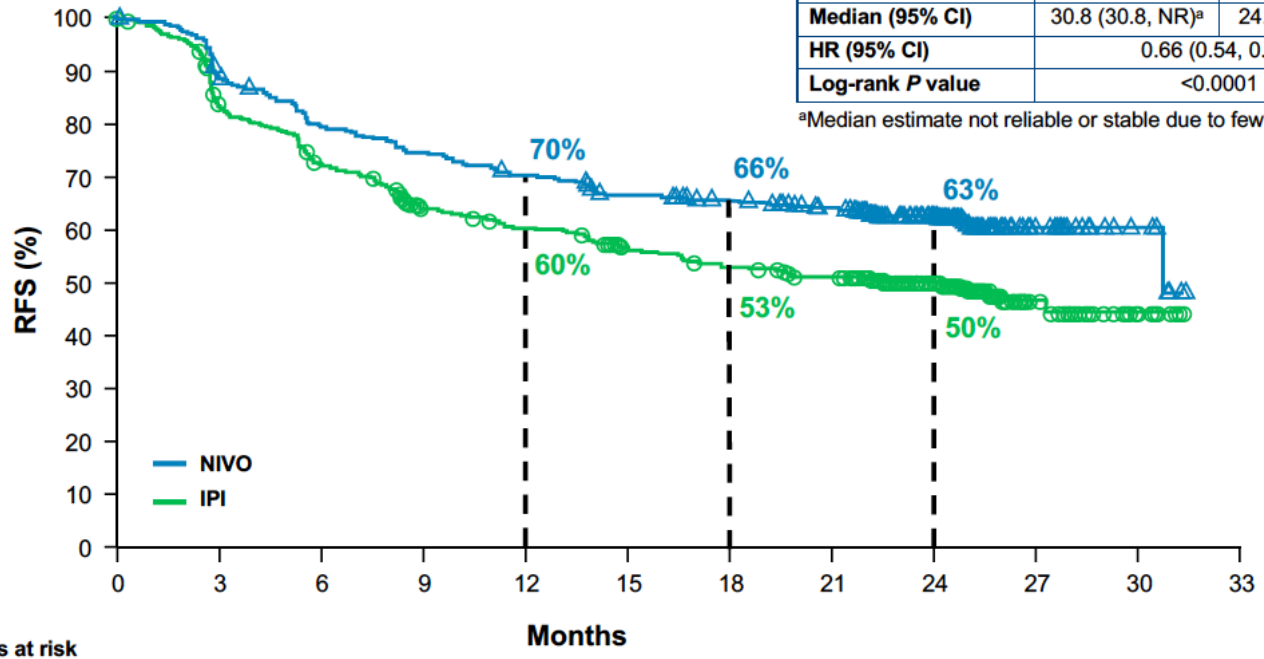


Weber J, et al. *N Engl J Med*. 2017;377:1824-1835.

CheckMate 238: Nivolumab Treatment Was Associated With Improved RFS vs Ipilimumab

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

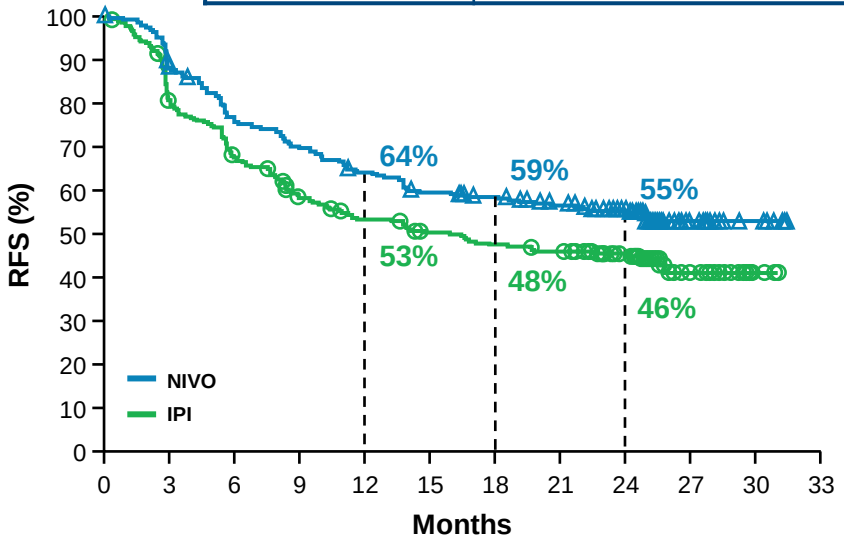
NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

Weber J, et al. ASCO. 2018

Subgroup Analysis of RFS: 5% PD-L1 Expression Level

PD-L1 <5%

	NIVO	IPI
Events/patients	123/275	151/286
Median (95% CI)	NR (21.7, NR)	15.9 (10.3, 25.5)
HR (95% CI)	0.73 (0.57, 0.92)	



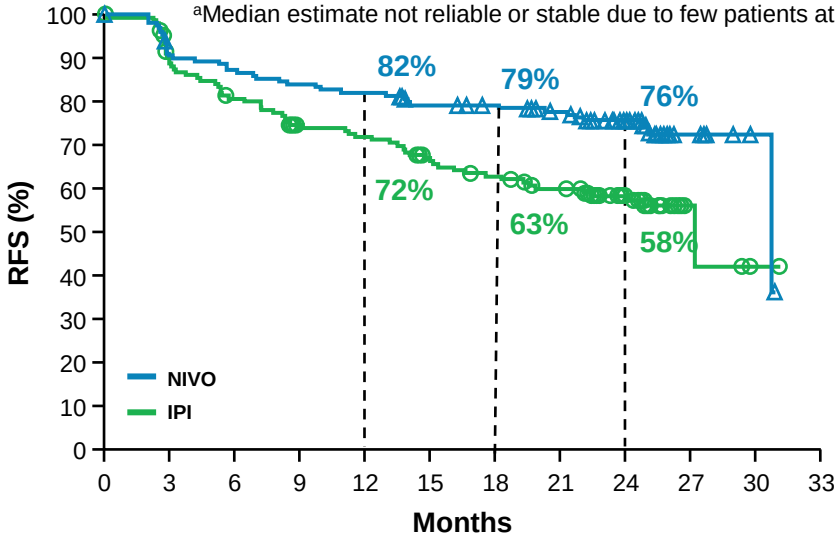
Number of patients at risk

NIVO	275	238	204	188	171	158	151	141	108	17	5	0
IPI	286	218	184	154	139	128	121	116	83	17	3	0

PD-L1 ≥5%

	NIVO	IPI
Events/patients	39/152	64/154
Median (95% CI)	30.8 (30.8, NR)[a]	27.2 (22.4, NR)[a]
HR (95% CI)	0.54 (0.36, 0.81)	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

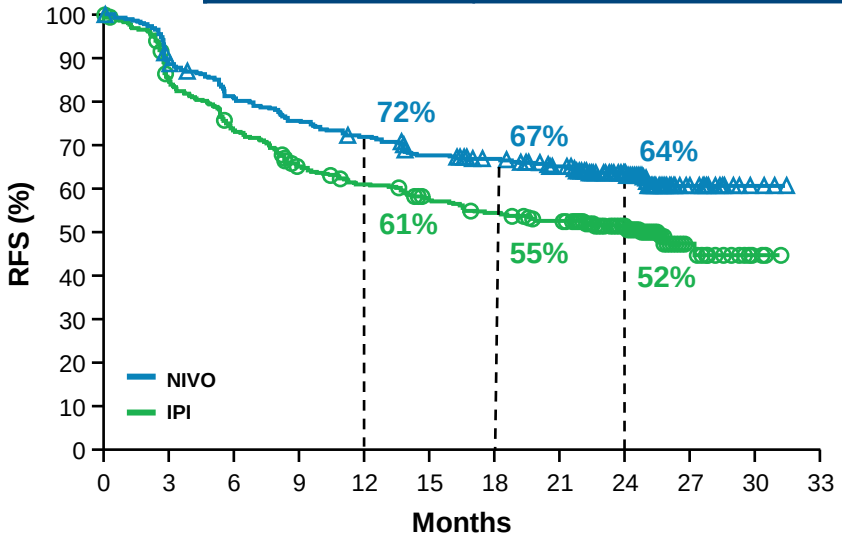
NIVO	152	135	130	125	122	115	112	106	87	10	2	0
IPI	154	133	120	108	104	94	88	81	61	4	1	0

Weber J, et al. ASCO. 2018

Subgroup Analysis of RFS: Disease Stage III and IV

Stage III

	NIVO	IPI
Events/patients	135/368	174/366
Median (95% CI)	NR	25.5 (16.6, NR)
HR (95% CI)	0.68 (0.54, 0.85)	



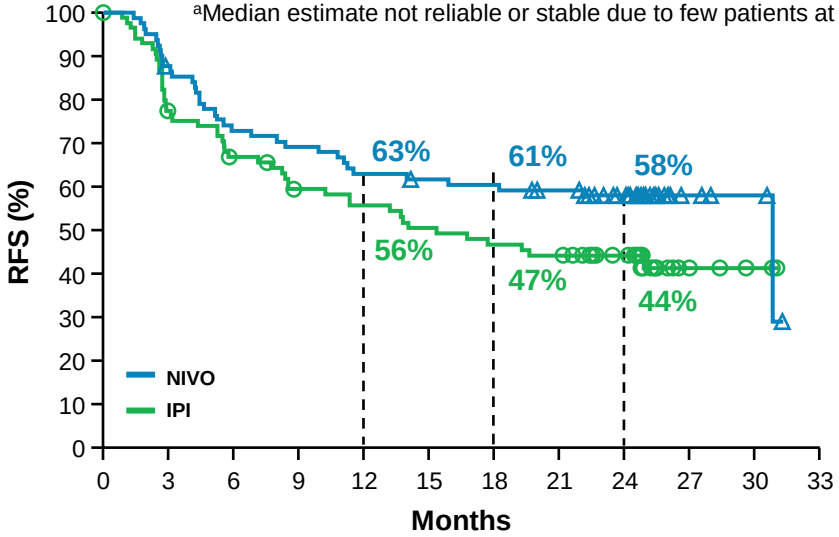
Number of patients at risk

NIVO	368	320	291	272	258	240	230	217	166	22	4	0
IPI	366	298	259	223	207	190	179	169	121	18	3	0

Stage IV

	NIVO	IPI
Events/patients	35/82	47/87
Median (95% CI)	30.8 (15.9, NR)[a]	15.4 (8.5, NR)
HR (95% CI)	0.68 (0.44, 1.06)	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

NIVO	82	71	59	56	51	49	48	45	37	6	3	0
IPI	87	65	55	47	44	40	37	35	28	5	2	0

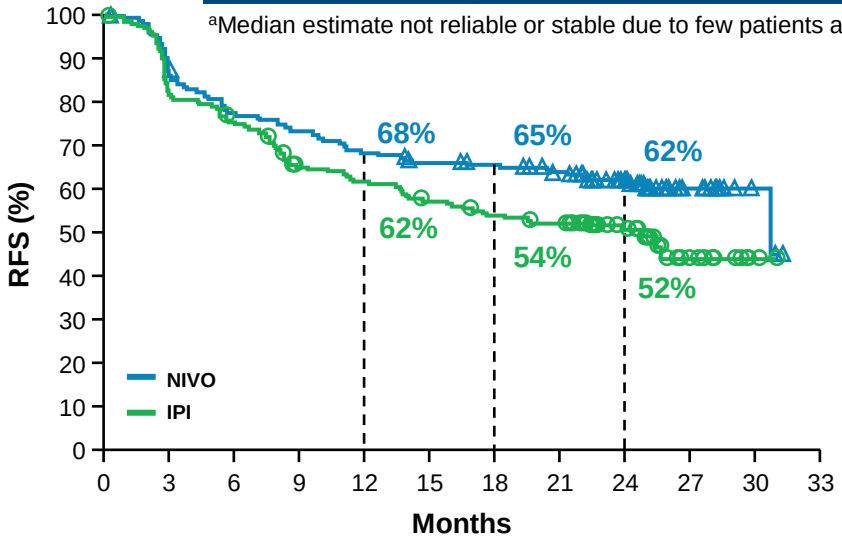
Weber J, et al. ASCO. 2018

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

	NIVO	IPI
Events/patients	73/187	95/194
Median (95% CI)	30.8 (30.8, NR)[a]	24.6 (14.8, NR)
HR (95% CI)	0.73 (0.54, 0.99)	

[a]Median estimate not reliable or stable due to few patients at risk.

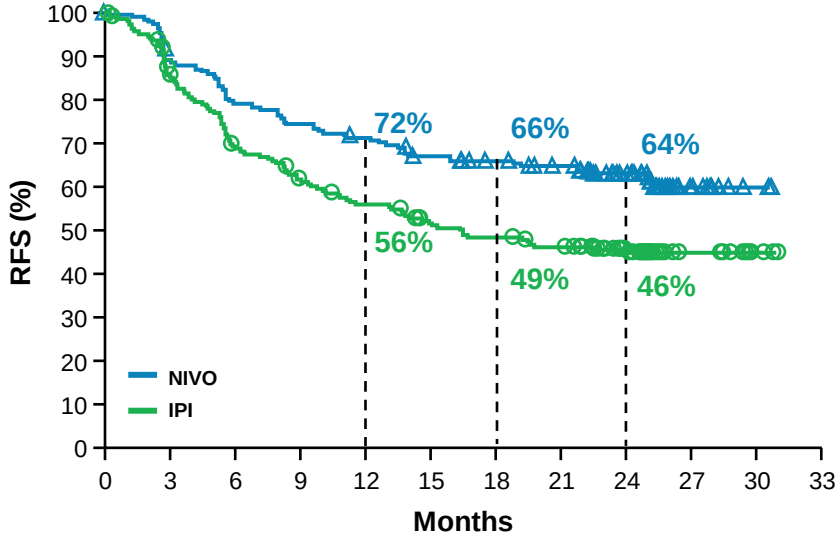


Number of patients at risk

NIVO	187	157	142	135	126	120	117	110	83	16	4	0
IPI	194	155	142	118	112	103	96	91	67	11	2	0

BRAF Wild type

	NIVO	IPI
Events/patients	73/197	107/212
Median (95% CI)	NR	16.6 (11.4, NR)
HR (95% CI)	0.61 (0.45, 0.82)	



Number of patients at risk

NIVO	197	172	154	144	137	127	121	115	91	11	2	0
IPI	212	171	138	121	109	97	91	85	62	9	3	0

Weber J, et al. ASCO. 2018

CheckMate 238: Safety Summary

	NIVO (n = 452)		IPI (n = 453)	
AE, n (%)	**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)

- No treatment-related deaths in the nivolumab arm
- 2 (0.4%) treatment-related deaths in the ipilimumab arm (marrow aplasia and colitis), both > 100 days after the last dose

Weber J, et al. *N Engl J Med*. 2017;377:1824-1835.

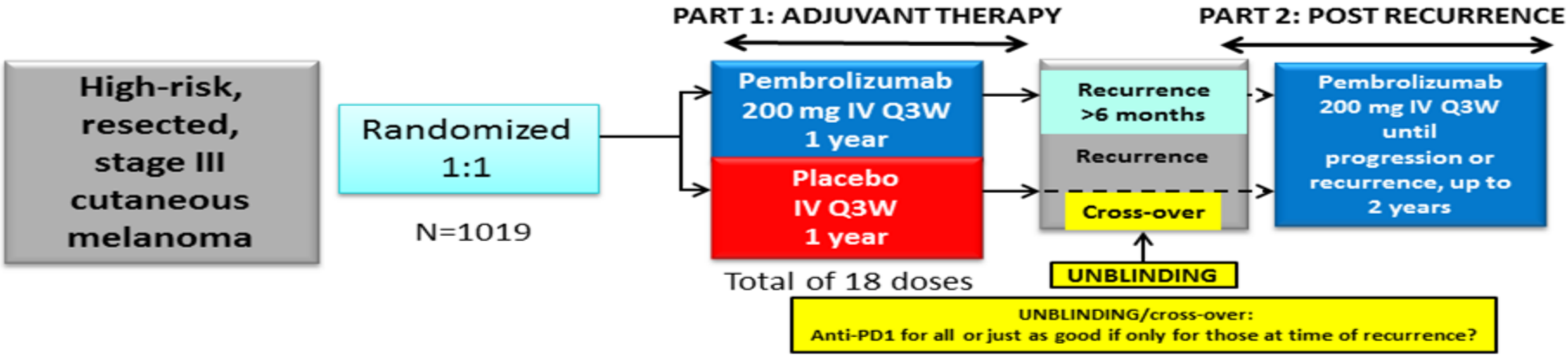
CheckMate 238: Conclusions

- Adjuvant nivolumab was associated with improved RFS compared with ipilimumab in patients with completely resected, high-risk stage IIIB/C or stage IV melanoma irrespective of *BRAF* mutation status

- Patients in the nivolumab arm experienced fewer grade 3/4 treatment-related AEs and fewer treatment-related AEs that led to discontinuation compared with the ipilimumab arm
  - 2 patients in the ipilimumab arm had treatment-related deaths, whereas no treatment-related deaths occurred in the nivolumab arm

Weber J, et al. *N Engl J Med*. 2017;377:1824-1835.

Keynote-54



Stratification factors:

✓ **Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

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

Secondary Endpoints:

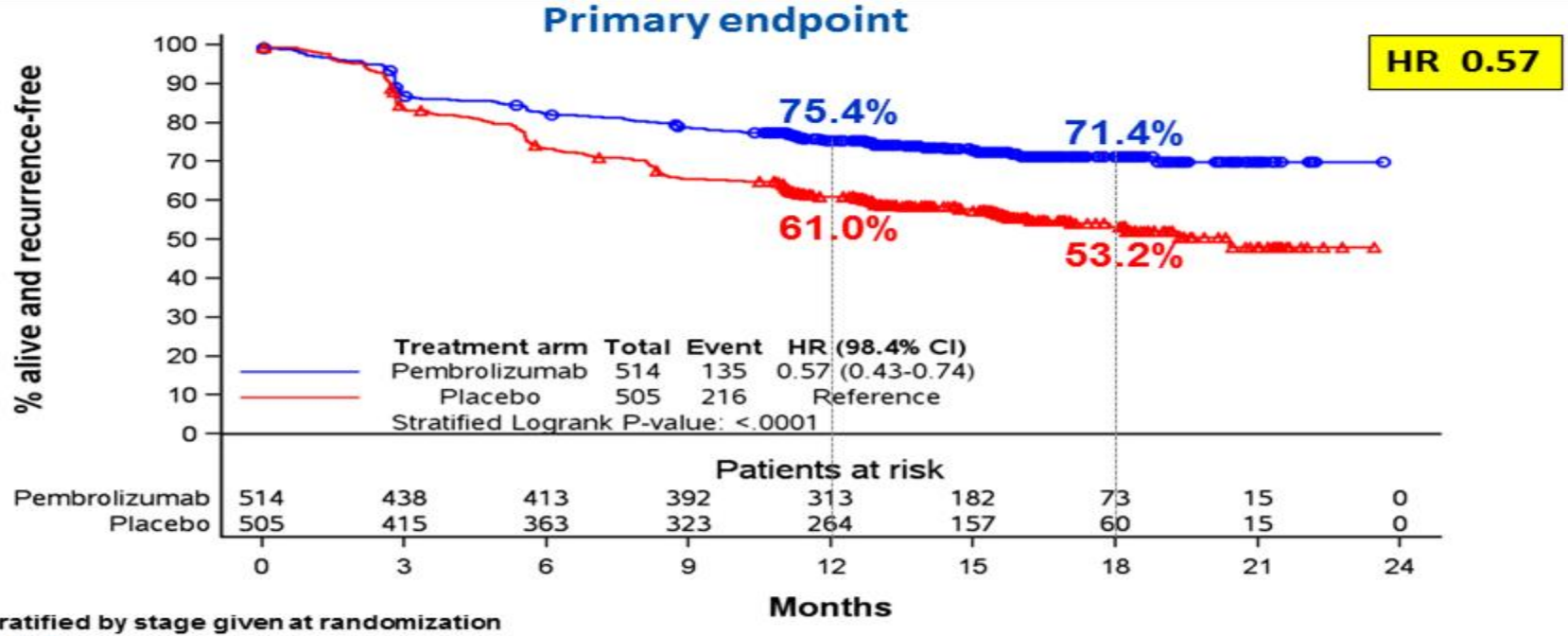
- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

EORTC

The future of cancer therapy

Eggermont et al. AACR 2018

Keynote-54: Pembrolizumab Was Associated With Improved RFS



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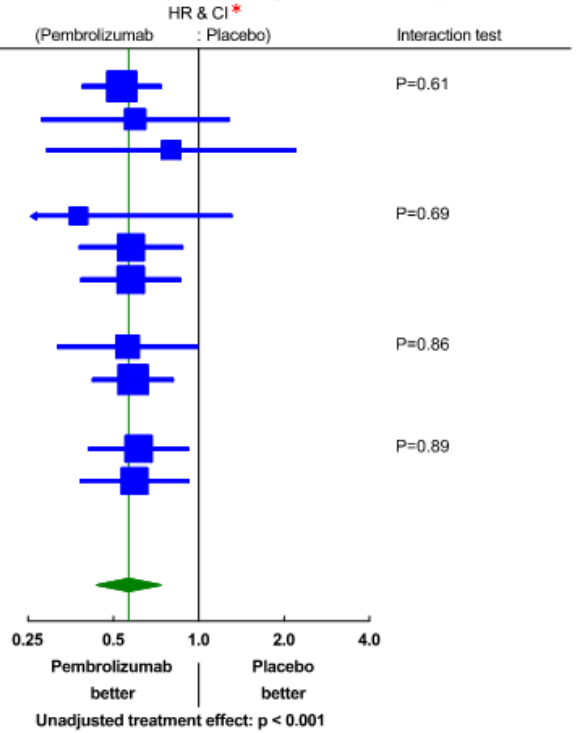
Recurrence-Free Survival: Subgroup Analysis

	Events / Patients Pembrolizumab	Placebo	HR (CI)		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

EORTC

The future of cancer therapy

Eggermont et al, NEJM April 2018

Keynote-54:Safety

	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

1 (0.2%) Treatment-related death in Pembro arm Myositis

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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)

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Keynote-54 : Conclusions

- Adjuvant pembrolizumab was associated with improved RFS compared with placebo in patients with completely resected, high-risk stage IIIA (>1mm), IIIB-C melanoma

- Favorable safety profile consistent with that observed in advanced melanoma.
  - -1 patient in the pembrolizumab arm had a treatment-related death.

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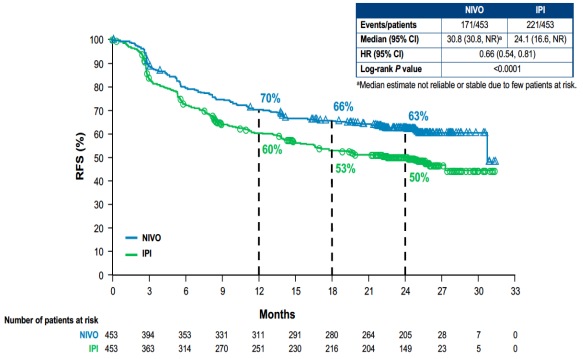
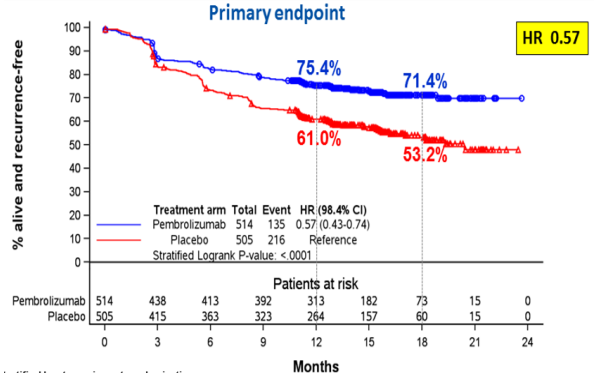
Systemic Adjuvant Therapy: Conclusions

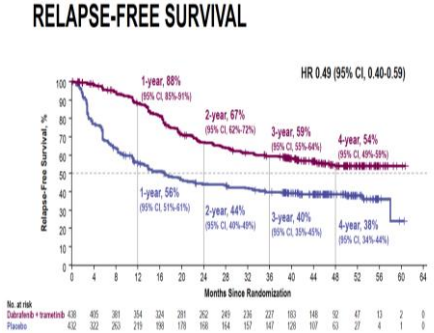
Nivolumab
vs
Ipilimumab

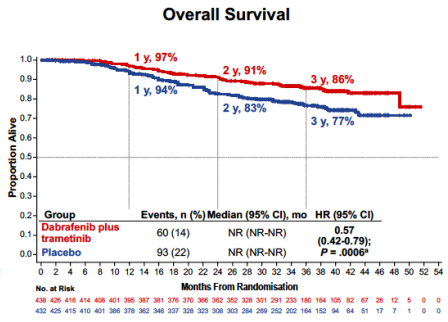


Pembrolizumab
vs
Placebo



Dabrafenib +
Trametinib
vs
Placebo





Adjuvant Anti-PD-1 and Dabra+Trame have demonstrated improved clinical outcomes, including marked reductions in the risk of disease recurrence

ADJUVANT TREATMENT: OPEN QUESTIONS

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

- How do we integrate those results in the post MSLT-2 trial era?

CA209-915: Ipi + Nivo vs Nivo did not require CLND as a criterion for entry. So this trial will provide important information.

ADJUVANT TREATMENT: OPEN QUESTIONS

BRAF MUT melanoma First choice: Adjuvant targeted therapy vs immunotherapy?

- No head to head comparison
- Nature of microscopic disease? Antigen release?
- Less tumoral clonal heterogeneity? Less capacity towards resistance?

  IIIA vs IIIB vs IIIC vs M1?
- Role of T cell infiltrates, PD1/PDL1 axis
- Role of BRAF/MEKi immunomodulation

Systemic Adjuvant Therapy: Conclusions

BRAF WT patients:

- PD-1 blockade is the first choice
- Due to its reduced efficacy and increased toxicity compared to Nivolumab, Ipilimumab is no longer recommended

BRAF MUTANT patients:

- Both PD-1 blockade and Dabrafenib + Trametinib are excellent options
- Toxicity profile and compliance should be decision factors
- Development of predictive biomarkers should be a priority to best select patients for targeted vs immunotherapy

Muchas Gracias

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