Clinical breakthrough with immunotherapy Melanoma

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Past-Present-Future

- In the adjuvant treatment
- In the treatment of metastatic disease

Do we need adjuvant treatment?

Metastatic melanoma 2019

- The majority of patients succumb to their disease

Nivolumab 3mg/kg (067)

- *48 mo OS 46% - Median OS 36.9 mo*

Pembrolizumab (KeyNote 006 and 001)

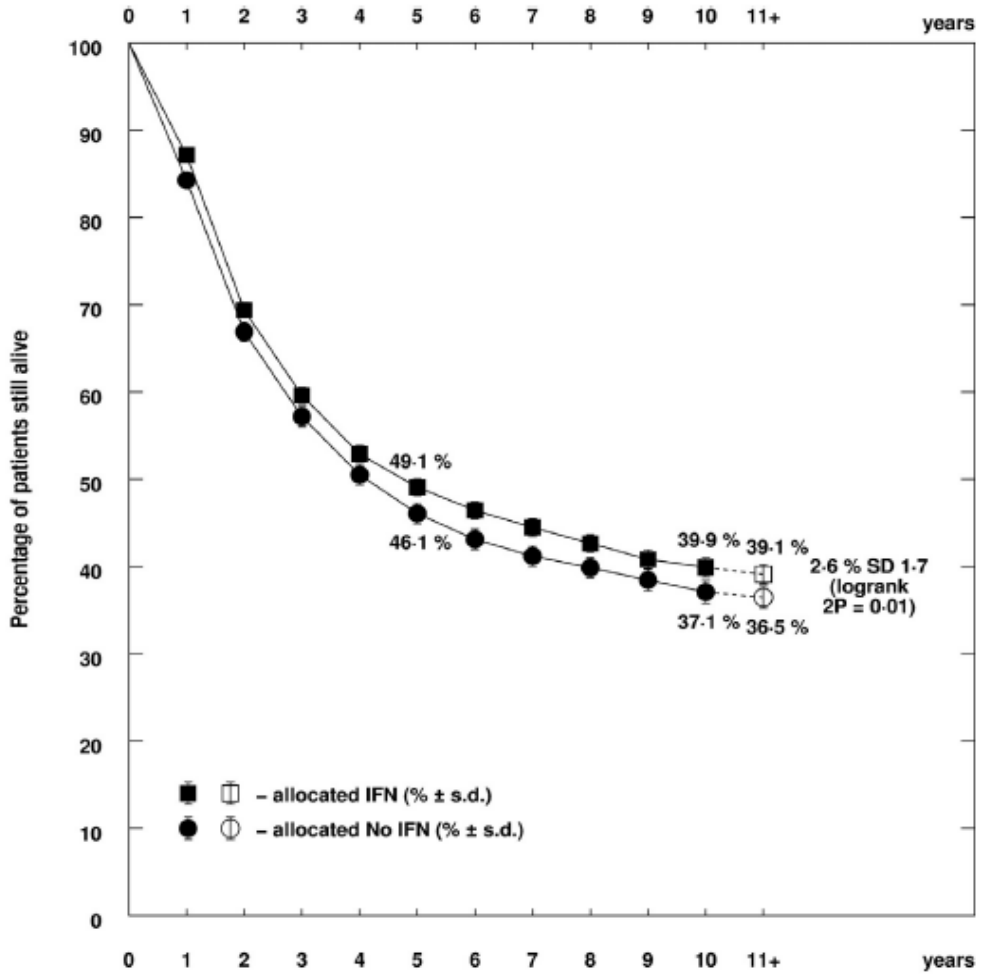
48 mo OS 41% – Median OS 32.3 mo – 38.7 mo

60 mo OS 34% - 60 mo OS 41%Treatment naïve

BRAF and MEK inhibitor

- *Median OS 25 mo – 3 yr OS 44% - 5 yr OS 28%*

Adjuvant immunotherapy with interferon

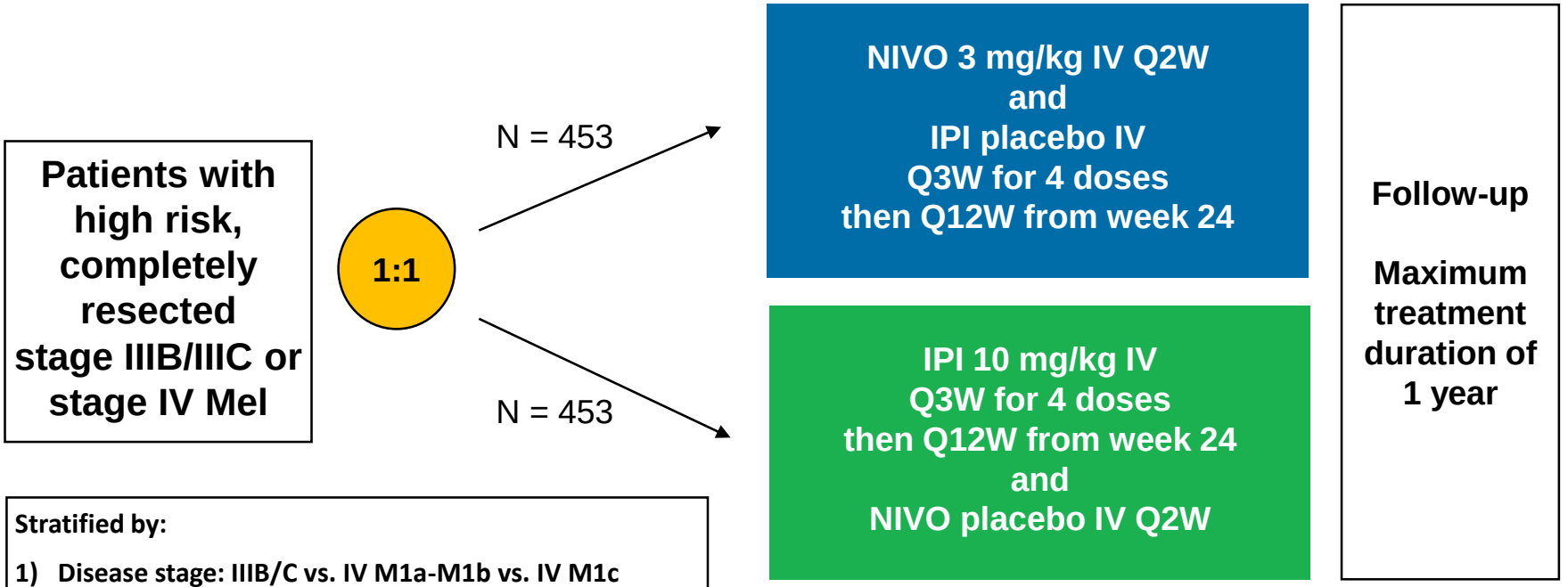


Deaths/person–years:											
Treatment											
IFN	453/3260	602/2639	324/2135	203/1733	106/1376	58/1038	34/790	23/581	17/409	7/299	16/812
No IFN	282/2222	402/1742	223/1410	150/1166	89/963	52/770	28/621	15/412	11/288	9/209	11/667

Fig. 4. Survival curve for overall survival (only includes data from trials providing IPD).

CA209-238: Study Design

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



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

Baseline Patient Characteristics

	NIVO (N = 453)	IPI (N = 453)
Median age (years)	56	54
Male (%)	57	59
Stage (%) — IIIB+IIIC	81	81
Macroscopic LN involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV (%)	18	19
M1c without brain metastases (% of Stage IV)	17	17
PD-L1 expression ≥5% (%)	34	34
BRAF mutation (%)	41	43
LDH ≤ULN (%)	91	91

- All 905 treated patients off treatment; median doses 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group
- 397 patients completed 1 year treatment (61% of the NIVO group and 27% of the IPI group)
- Most of the patients had cutaneous melanoma (85%) while 4% had acral and 3% had mucosal melanoma

Safety Summary

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

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

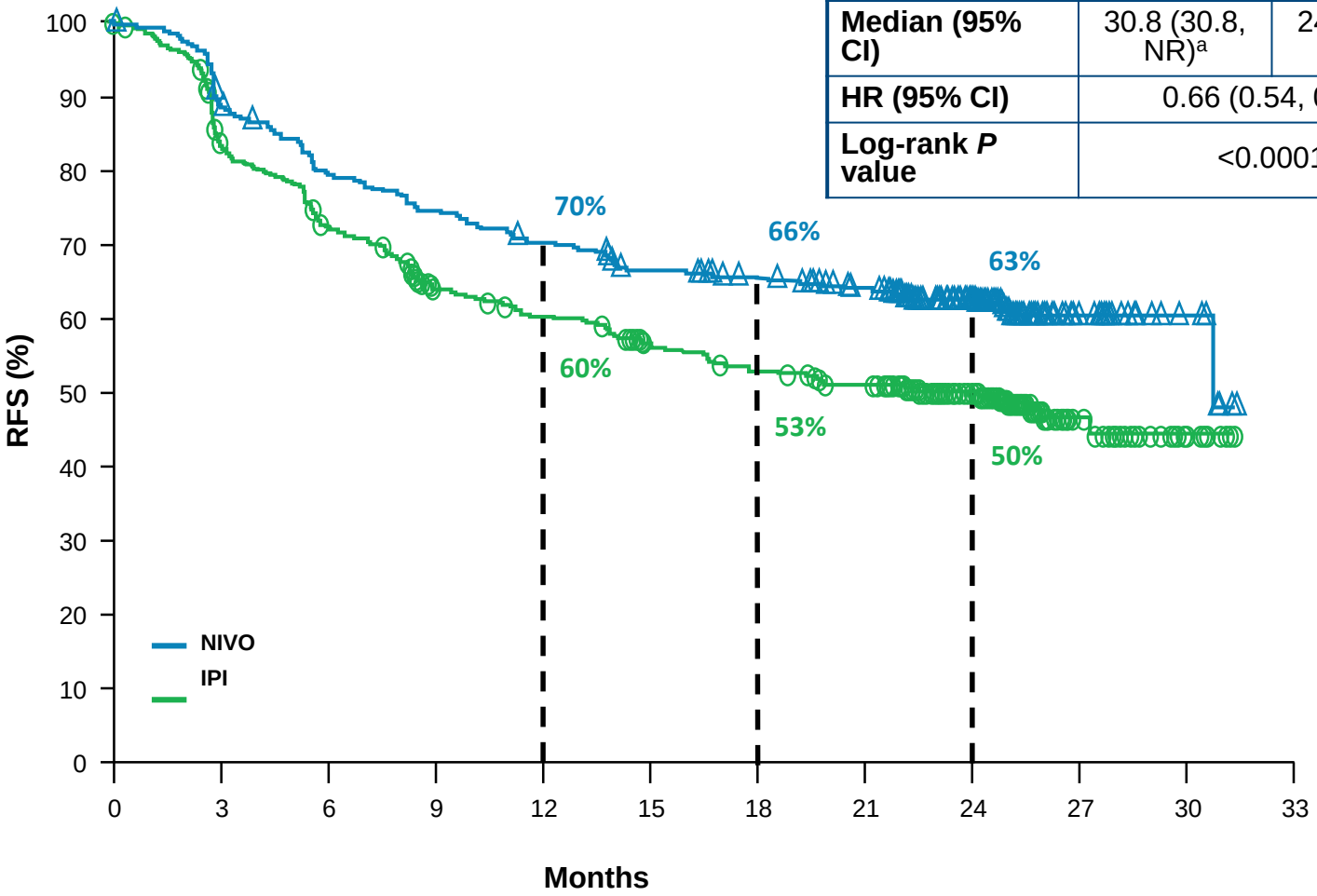
Treatment-related Select Adverse Events

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 NIVO (range 3.3-14.2 weeks)

Primary Endpoint: RFS in All Patients

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



Number of patients at risk

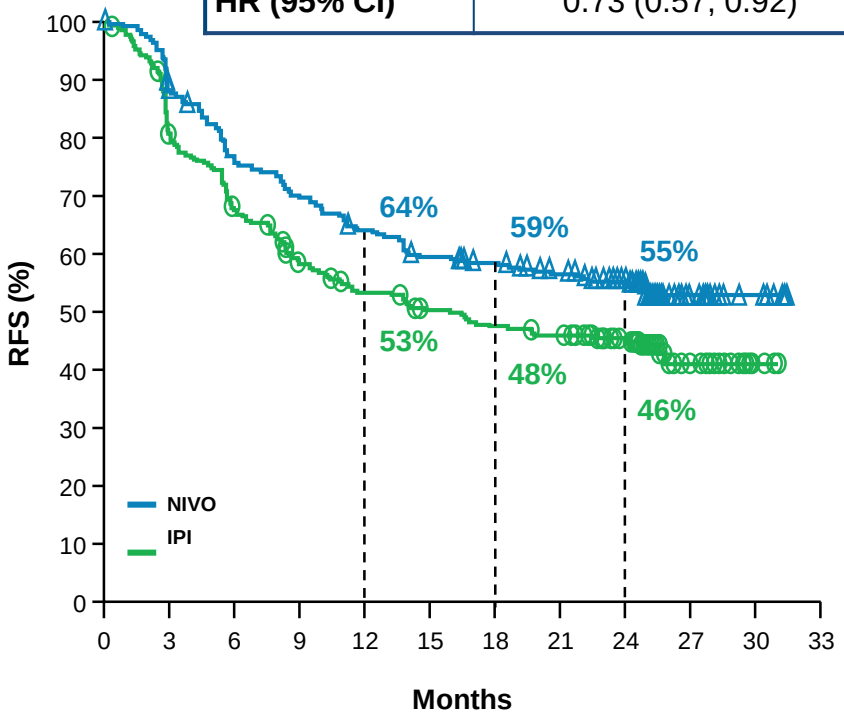
NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

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

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)	



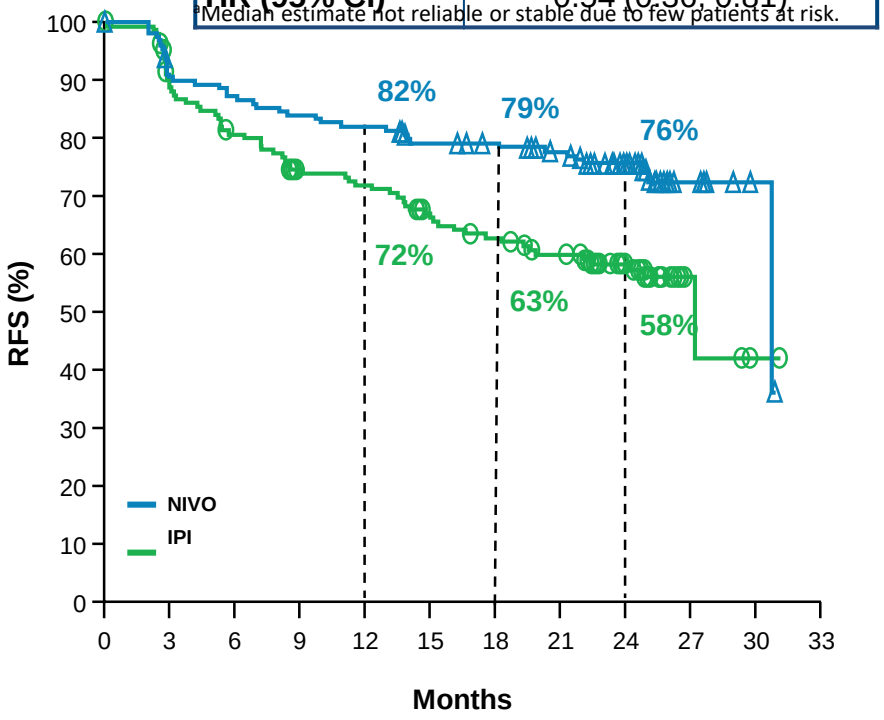
Number of patients at risk

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.



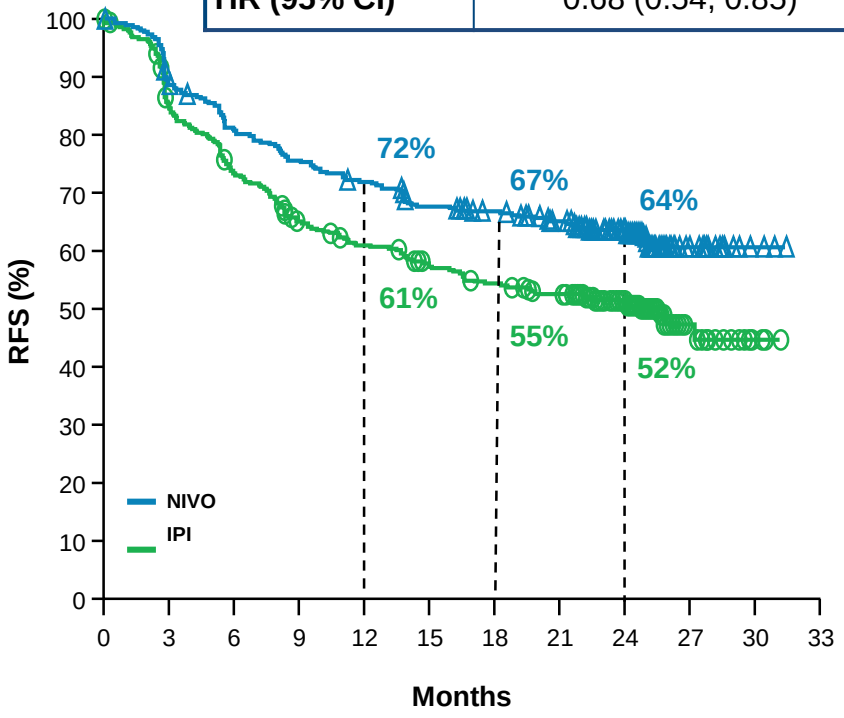
Number of patients at risk

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

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)	



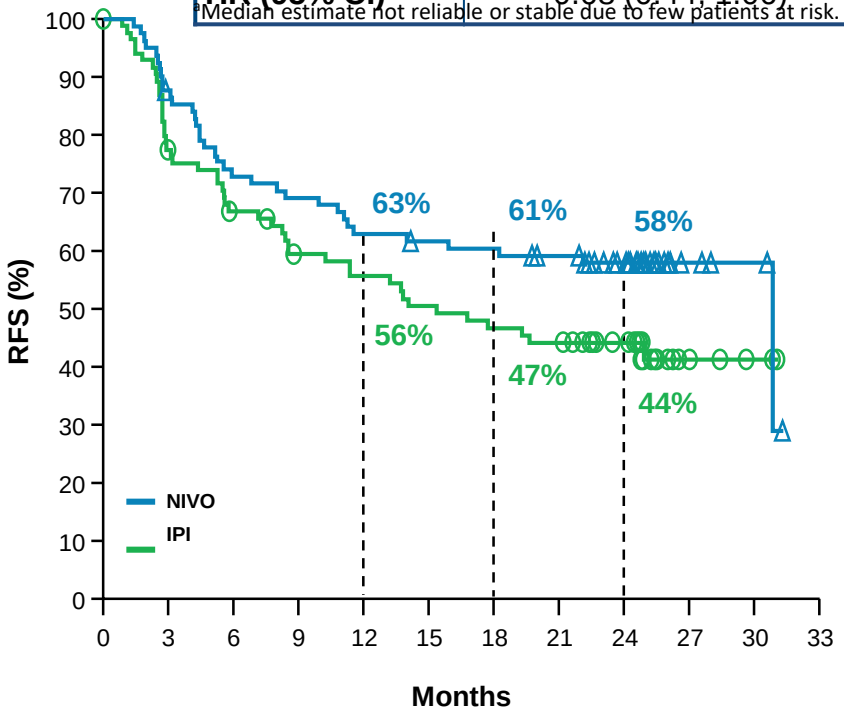
Number of patients at risk

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.



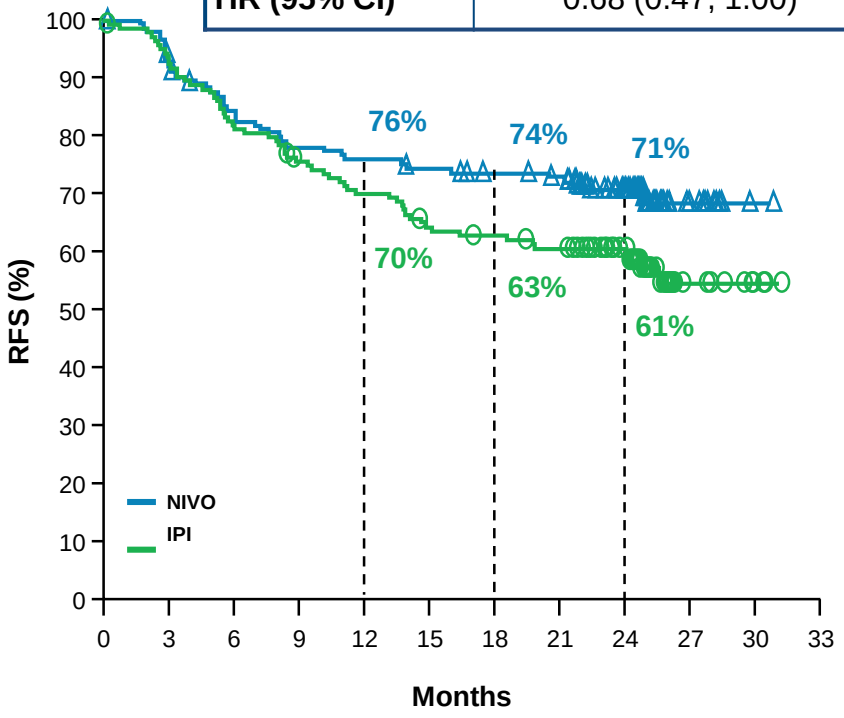
Number of patients at risk

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

Subgroup Analysis of RFS: Disease Stage IIIB and Stage IIIC

Stage IIIB

	NIVO	IPI
Events/patients	48/165	60/148
Median (95% CI)	NR	NR (24.2, NR)
HR (95% CI)	0.68 (0.47, 1.00)	

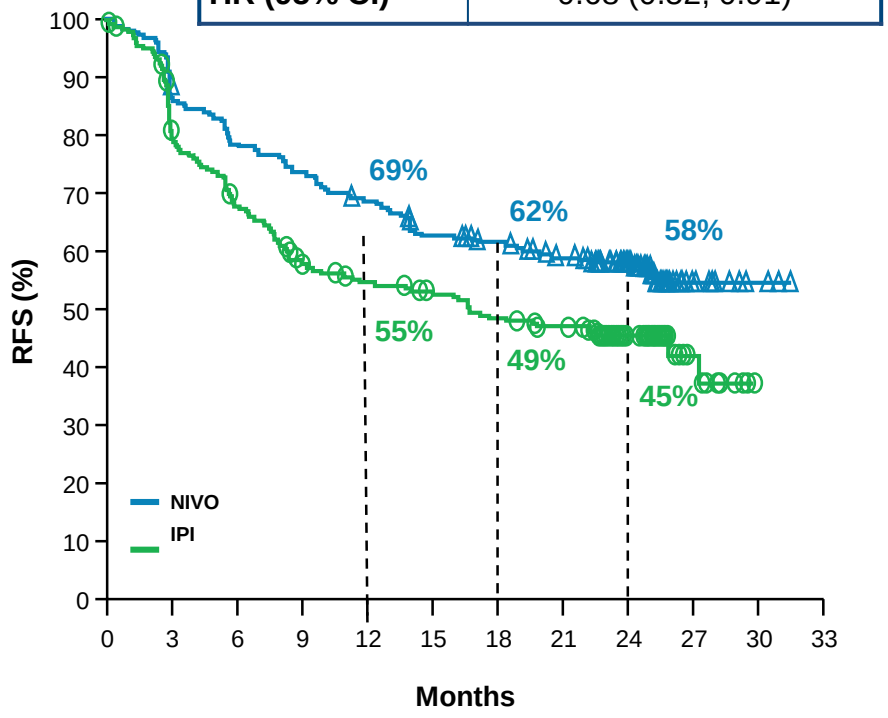


Number of patients at risk

NIVO	165	146	132	123	120	116	112	109	84	13	1	0
IPI	148	133	118	107	99	89	86	82	58	9	3	0

Stage IIIC

	NIVO	IPI
Events/patients	87/203	114/218
Median (95% CI)	NR (24.9, NR)	16.6 (9.4, 27.2)
HR (95% CI)	0.68 (0.52, 0.91)	



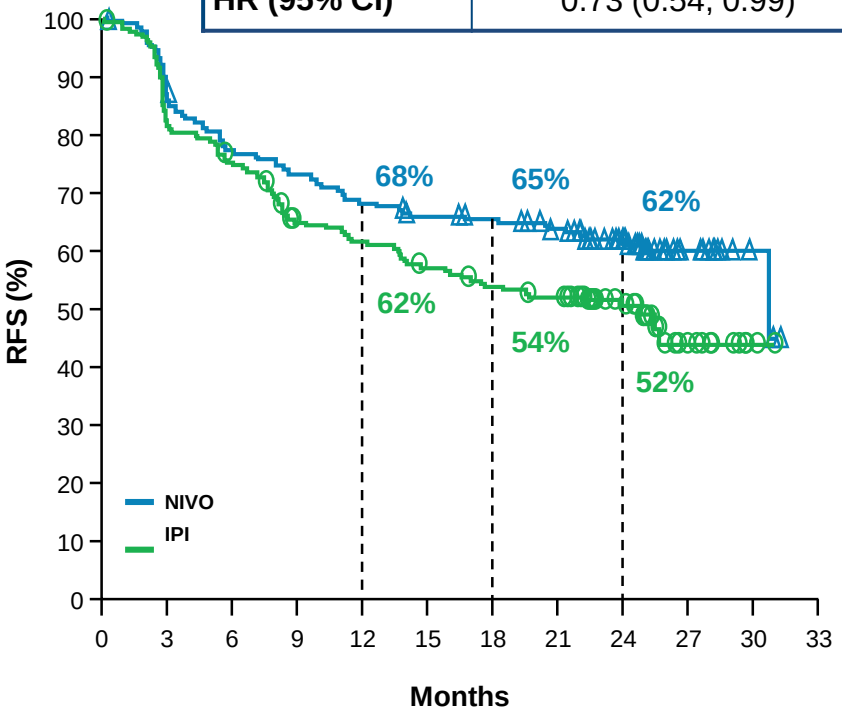
Number of patients at risk

NIVO	203	174	159	149	138	124	118	108	82	9	3	0
IPI	218	165	141	116	108	101	93	87	63	9	0	0

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)	

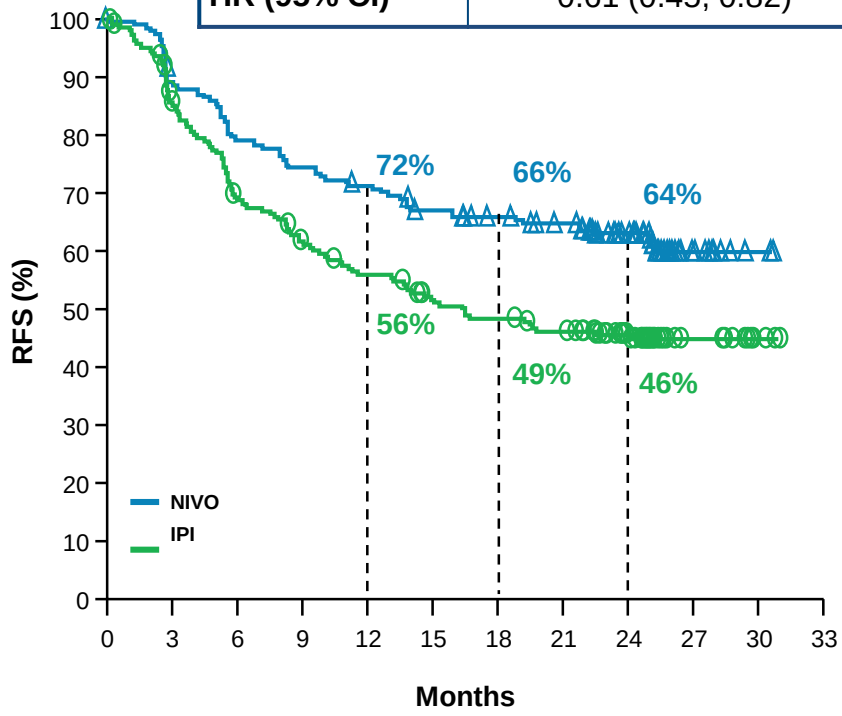


Number of patients at risk

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)	

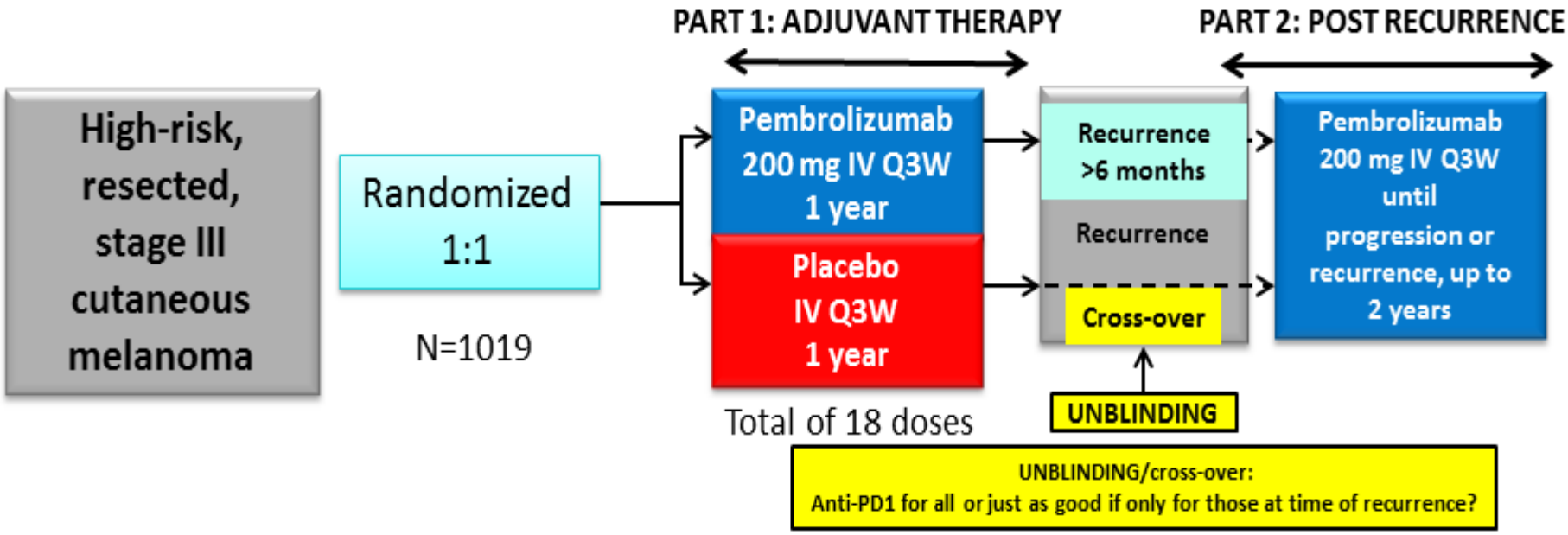


Number of patients at risk

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

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

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:

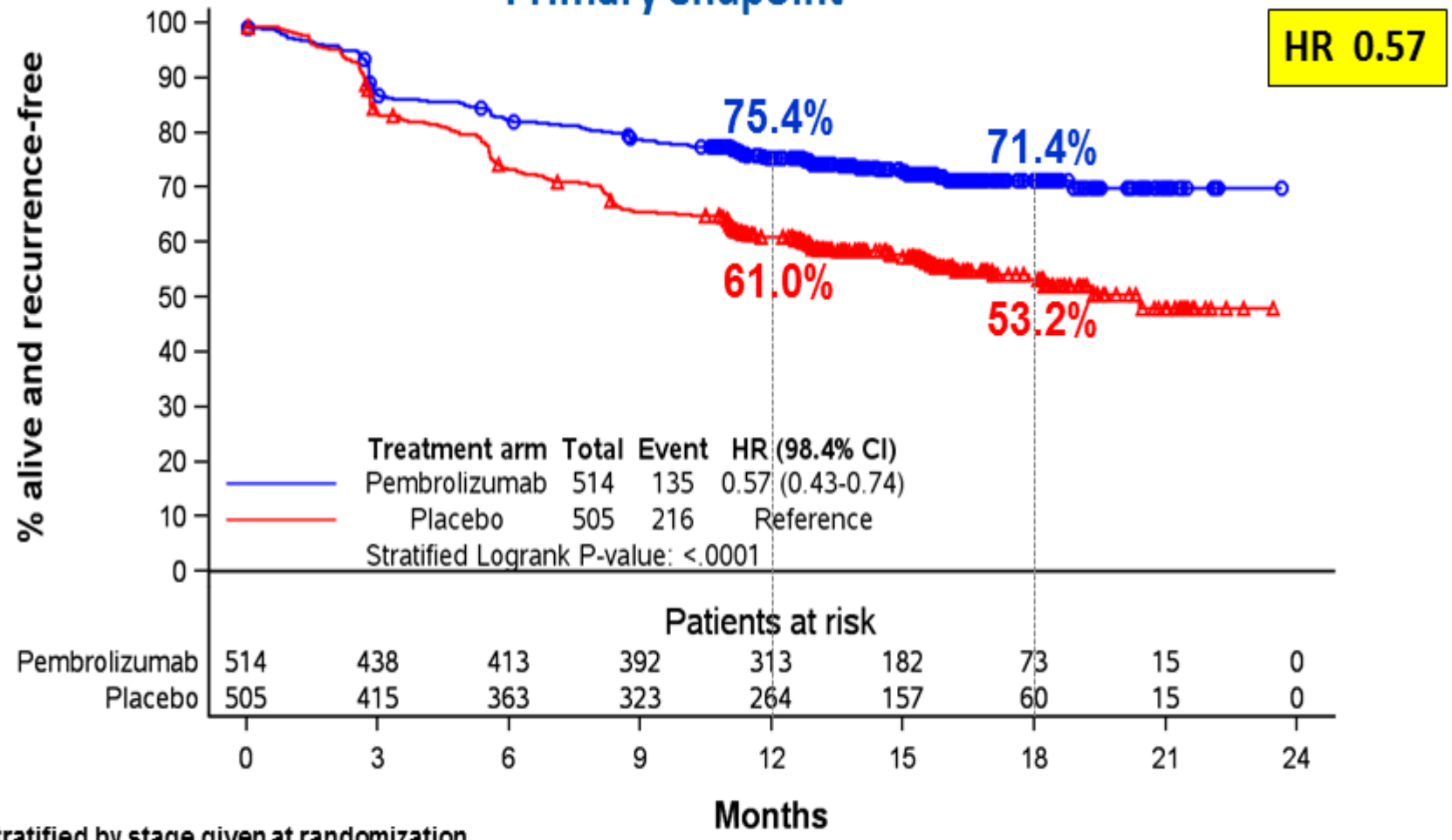
- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:

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

Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

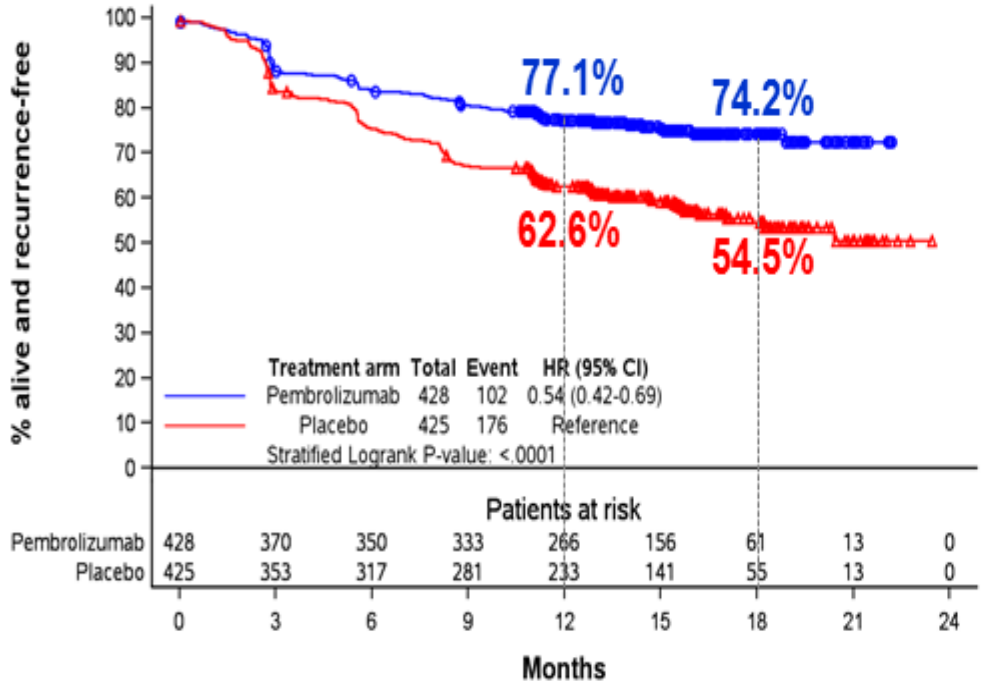
EORTC

The future of cancer therapy

Recurrence-Free Survival

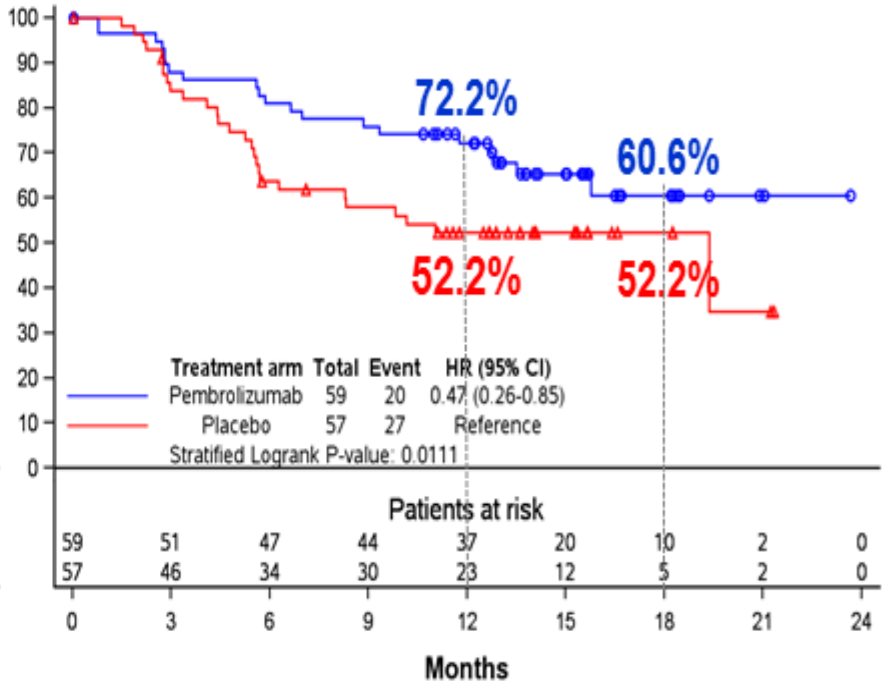
PD-L1+

HR 0.54



PD-L1–

HR 0.47



*Stratified by stage given at randomization

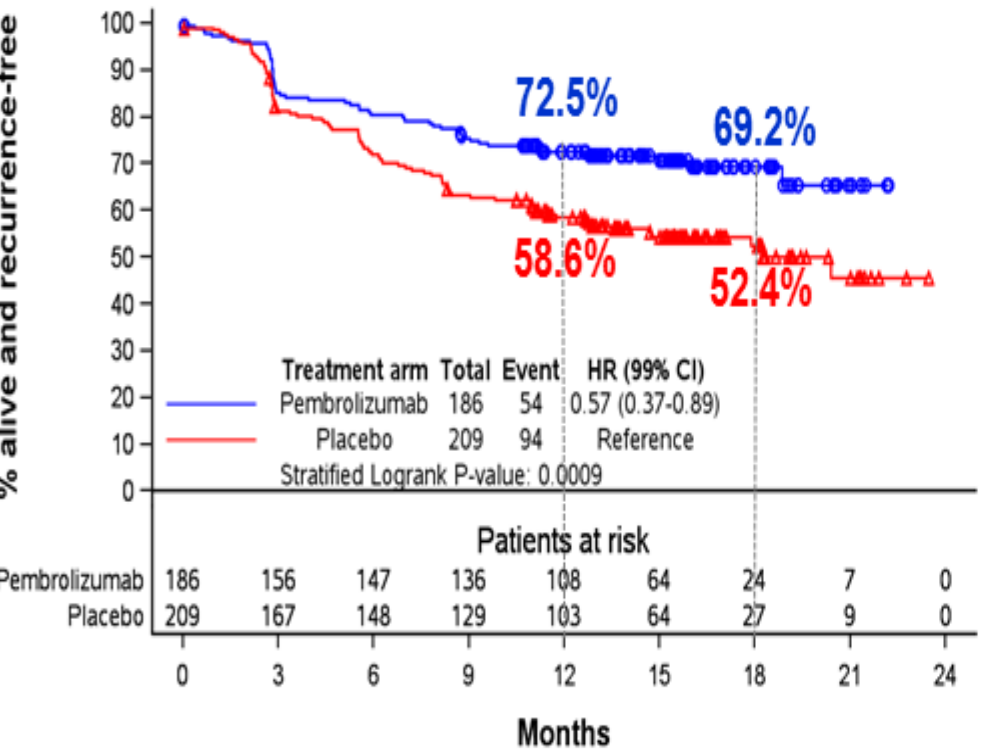
EORTC

The future of cancer therapy

Recurrence-Free Survival

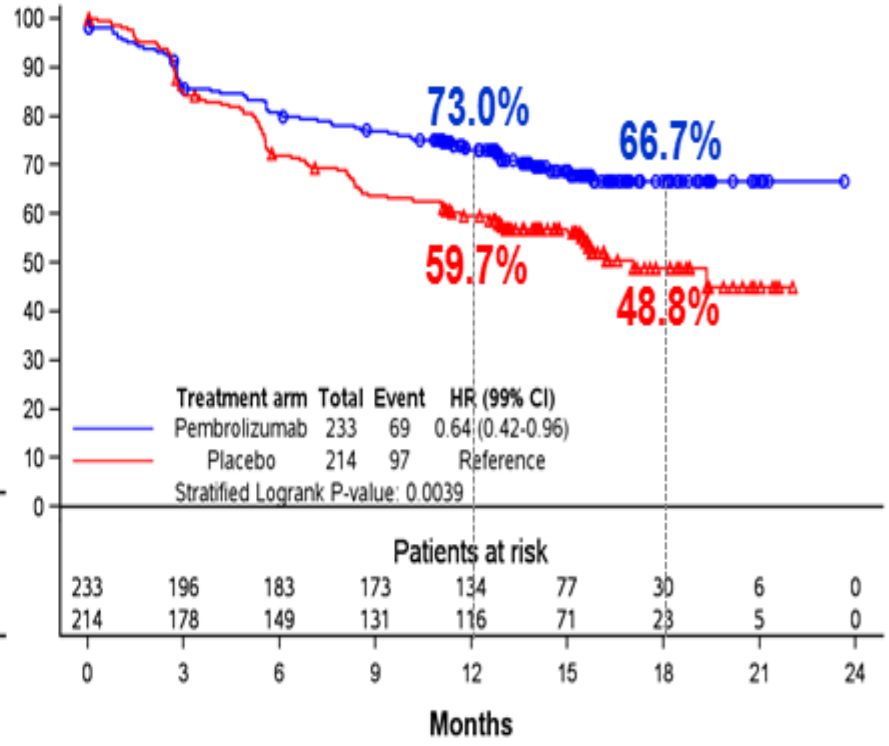
BRAF V600E/K

HR 0.57



BRAF WT

HR 0.64



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

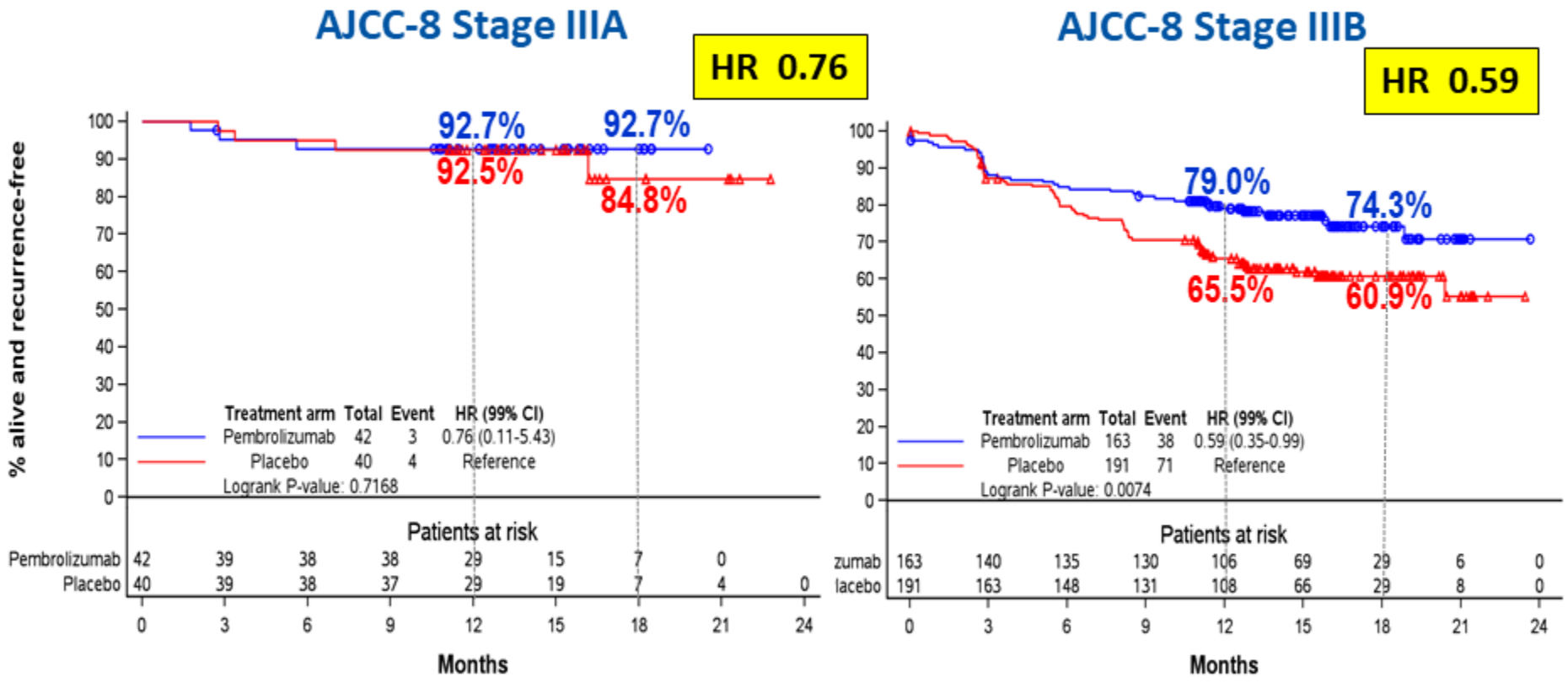
Eggermont KN054 SMR 2018

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%)

Eggermont KN054 SMR 2018

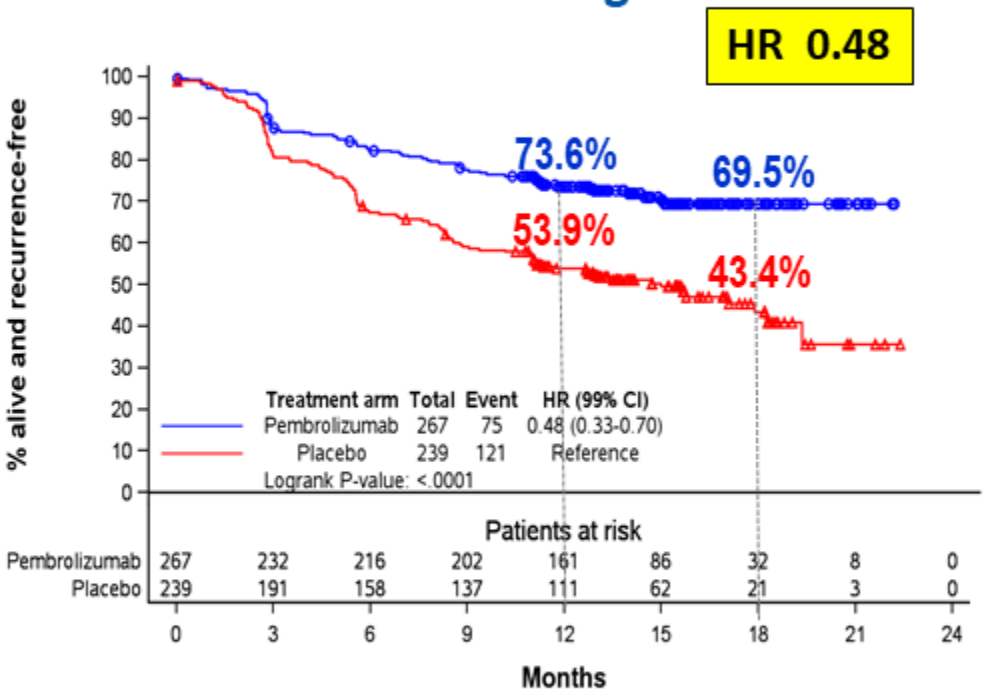
Recurrence-Free Survival: subgroup analysis by AJCC-8



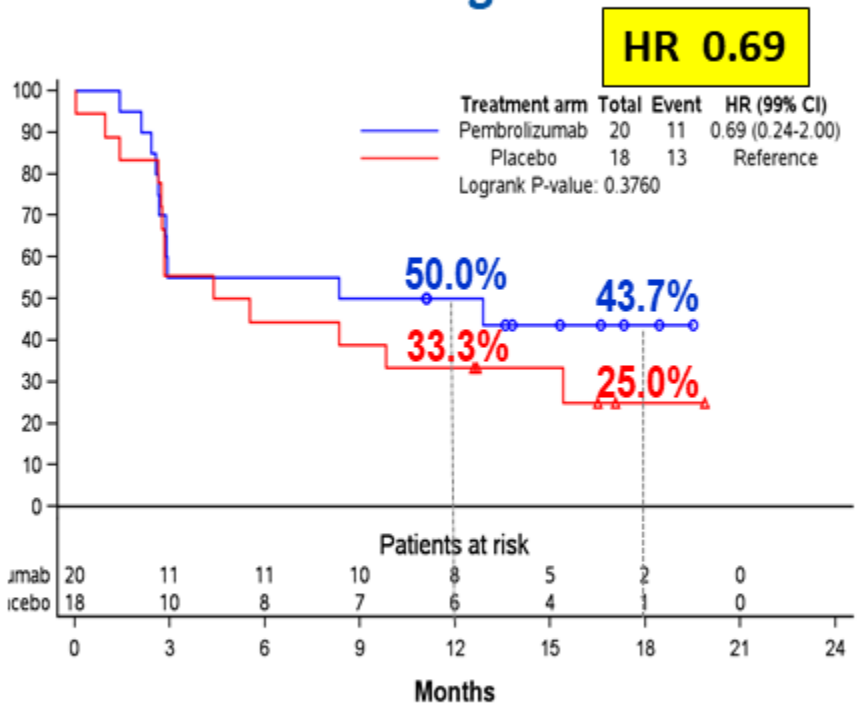
Eggermont KN054 SMR 2018

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

AJCC-8 Stage IIIC



AJCC-8 Stage IIID



Ipilimumab in the adjuvant setting

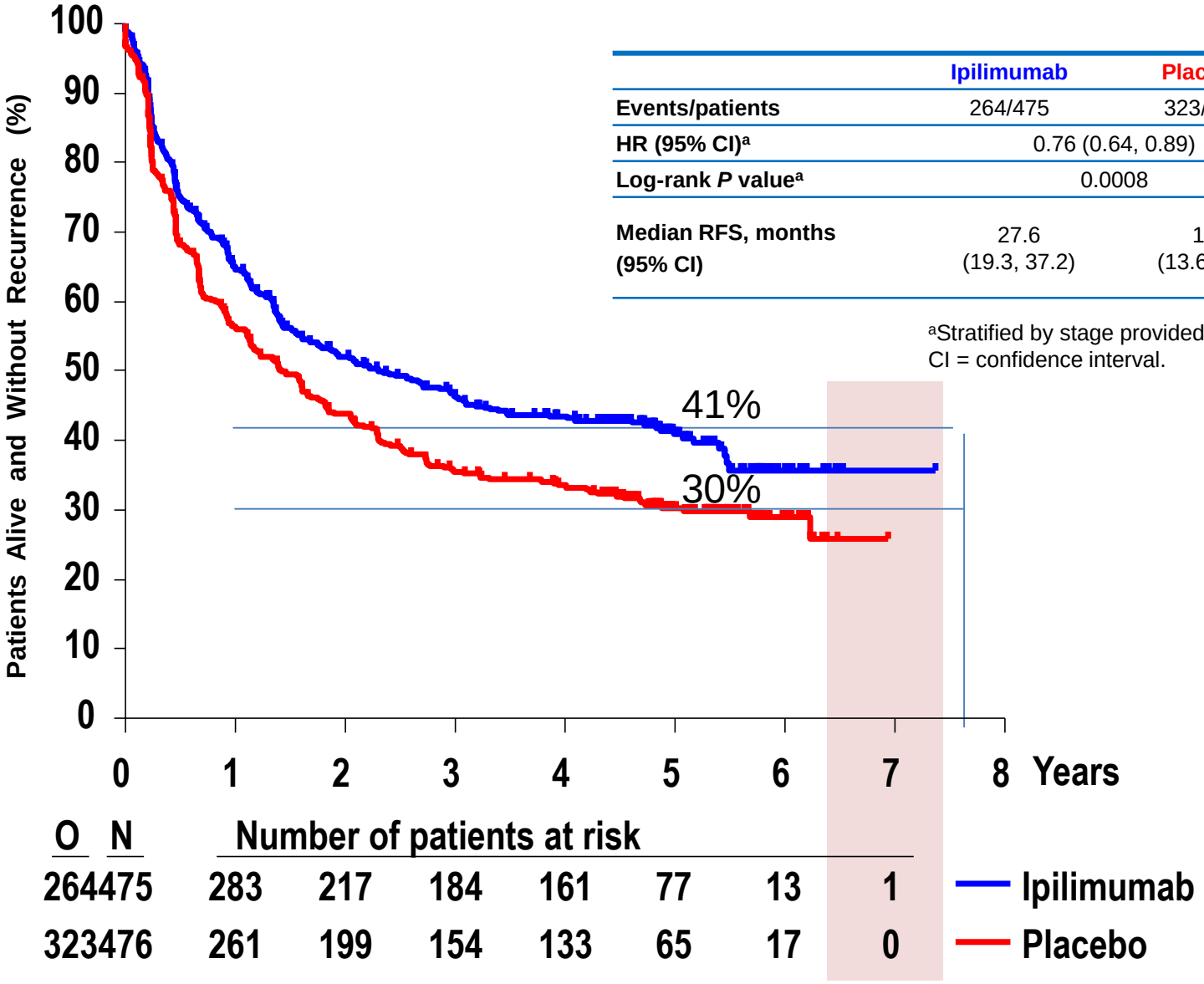
28th of October, 2015: FDA approves YERVOY for stage III melanoma

Ipilimumab had shown survival benefit in stage IV melanoma

RFS (per IRC)

	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95% CI)[a]	0.76 (0.64, 0.89)	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

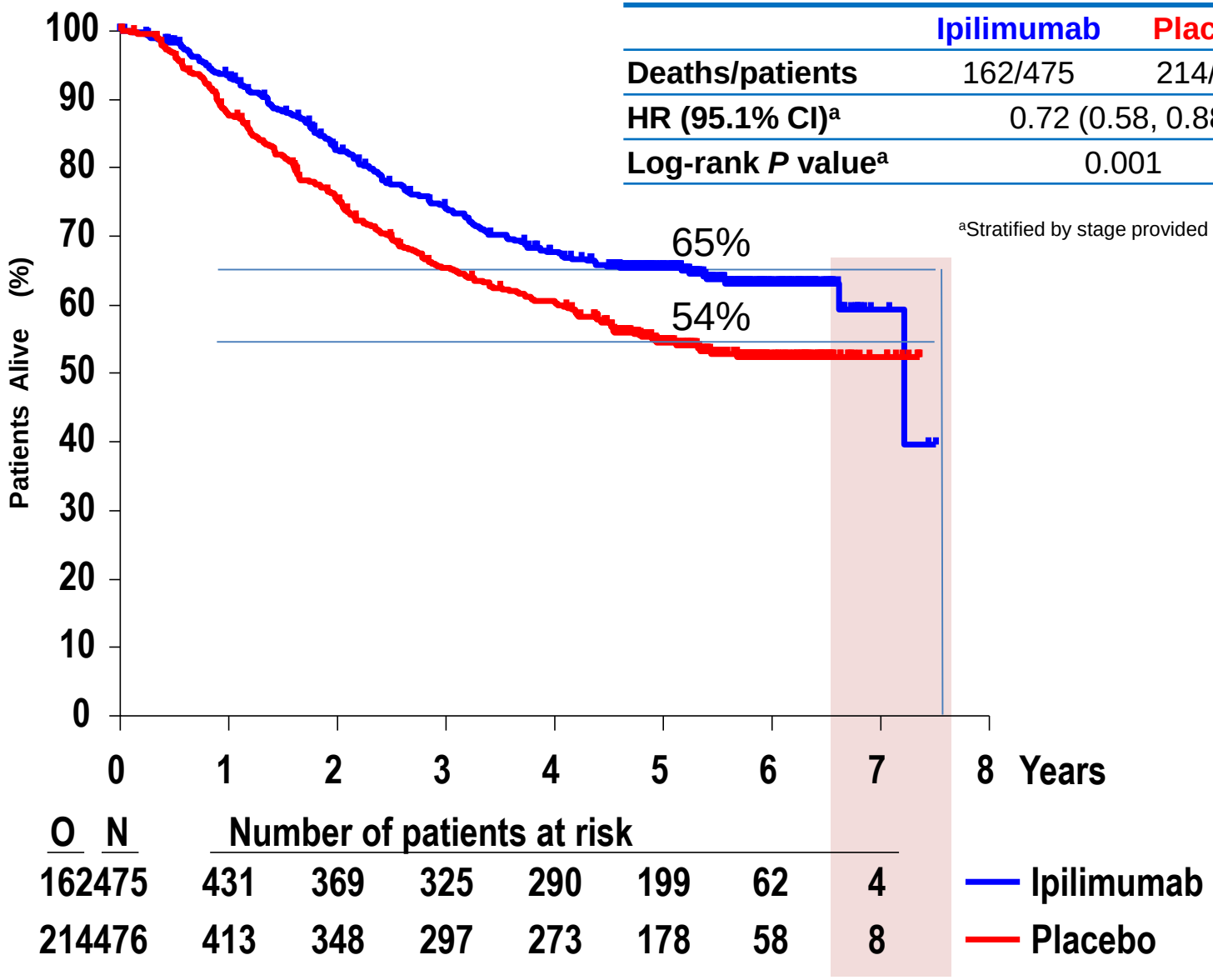
[a]Stratified by stage provided at randomization.
CI = confidence interval.



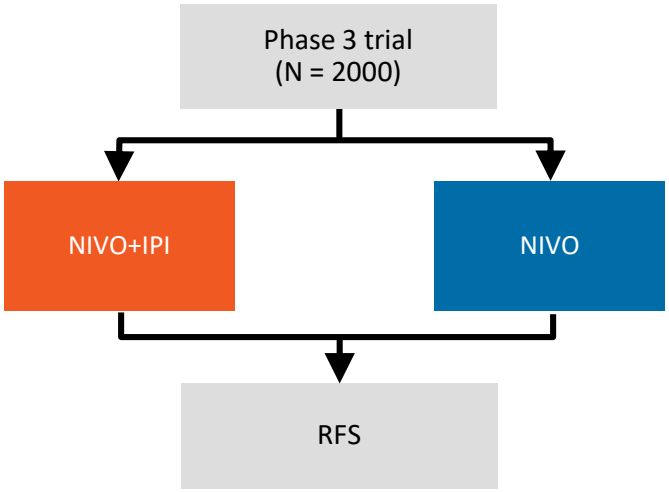
OS

	Ipilimumab	Placebo
Deaths/patients	162/475	214/476
HR (95.1% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

[a]Stratified by stage provided at randomization.



Study of Nivolumab Combined With Ipilimumab Compared With Nivolumab Alone After Complete Surgical Removal of Stage IIIB/C/D or IV Melanoma (CheckMate 915/CA209-915/NCT03068455)



Study Start Date:
April 2017

Estimated Study Completion Date:
February 2023

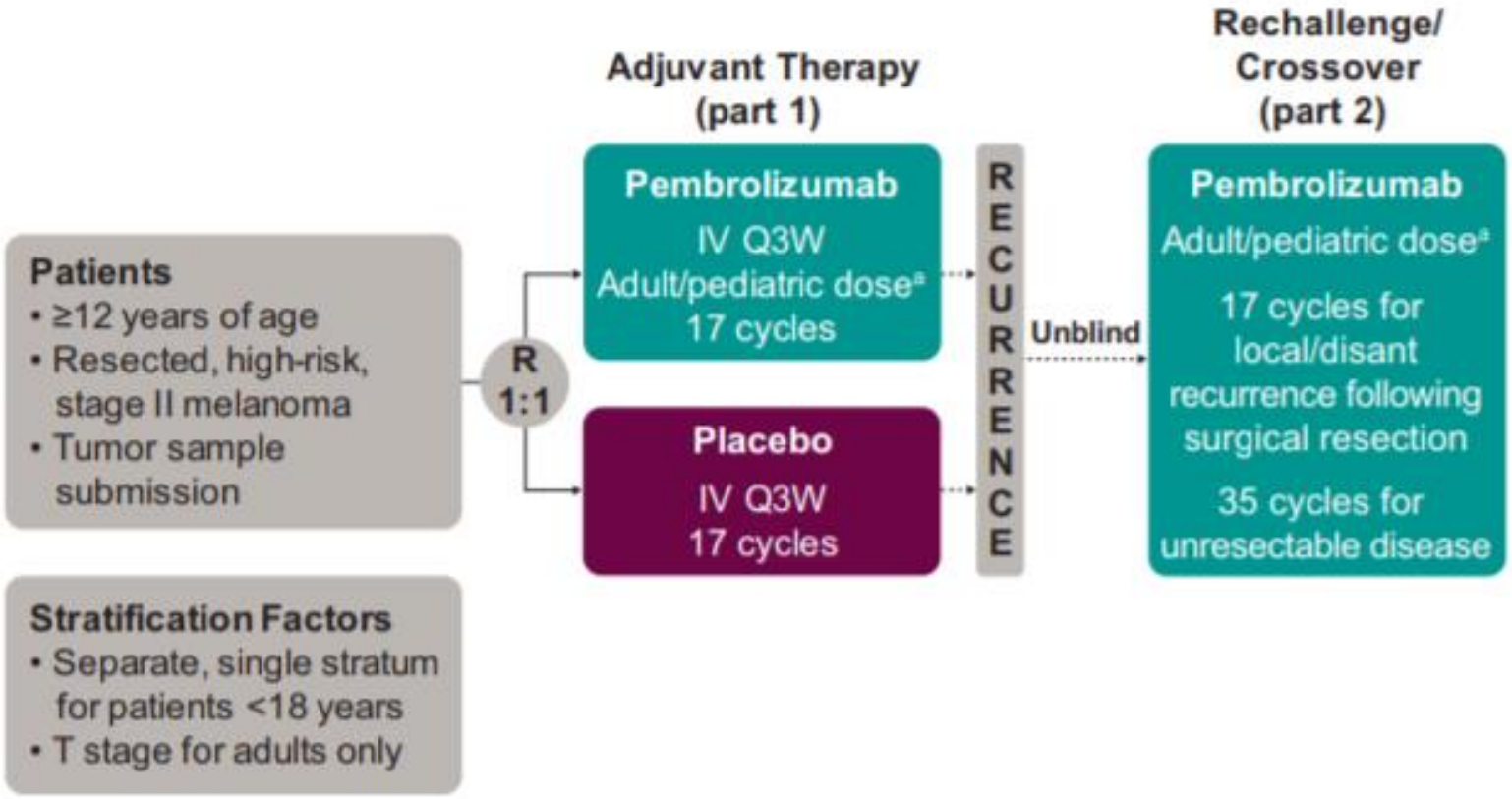
Estimated Primary Completion Date:
November 2020

- Purpose
  - To determine if NIVO+IPI is more effective than NIVO alone in delaying recurrence in patients with complete resection of stage IIIB/C/D or stage IV melanoma
- Primary endpoint
  - RFS measured by time, approximately 30 months
- Secondary endpoints
  - OS measured by time, up to 5 years
  - PD-L1 expression measured by immunoassay, approximately 3 years
- Study-specific eligibility criteria
  - 12 years and older
  - Completely resected stage IIIB/C/D or IV melanoma within 12 weeks of study
  - Patients must be active or, if limited, be able to carry out daily activities
  - No prior anticancer treatment for melanoma (except surgery and/or adjuvant radiation therapy after CNS lesion resection)
  - No history of uveal melanoma
  - No active or known autoimmune disease

CNS = central nervous system; IPI = ipilimumab; IV = intravenous; NIVO = nivolumab; OS = overall survival; PD-L1 = programmed death ligand-1; RFS = recurrence-free survival

www.clinicaltrials.gov. Accessed June 2018.

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



IV, intravenous; Q3W, every 3 weeks; R, randomized.

[a]Adult dose, 200 mg Q3W; pediatric dose, 2 mg/kg Q3W (to a maximum of 200 mg Q3W).

Unanswered questions

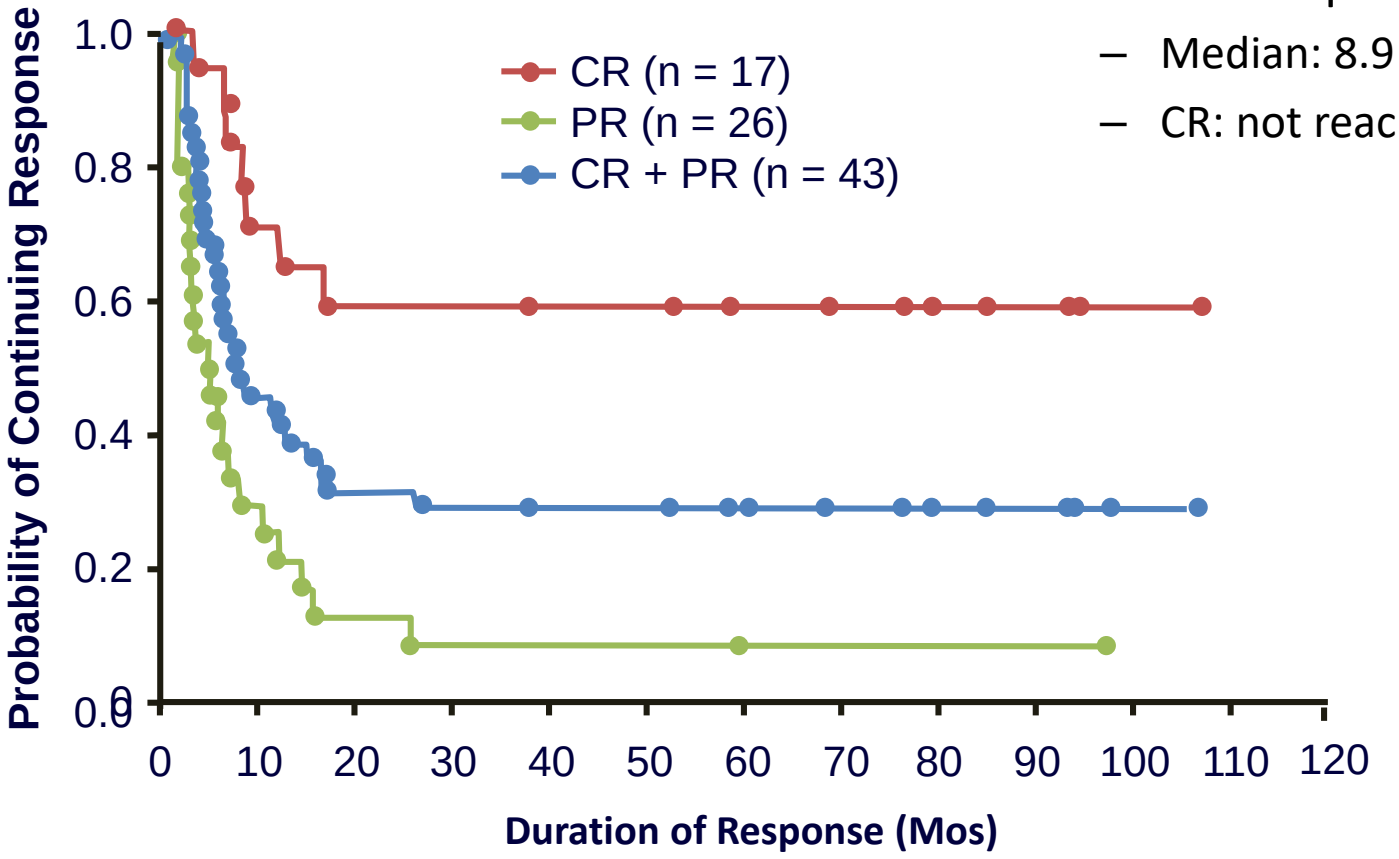
- Direct comparison of ipilimumab with high dose interferon – E1609
- Direct comparison of pembrolizumab with HD IFN or Ipilimumab Induction followed by maintenance therapy
- Mature Survival Data
- Low risk Stage IIIA

April 2019 Metastatic Melanoma What do we know?

- 5yr survival data with anti-PD1 from phase I trials
- 4yr survival data with anti-PD1 from phase III trials
- First report of negative results in melanoma trial
- The plateau in survival curves persists

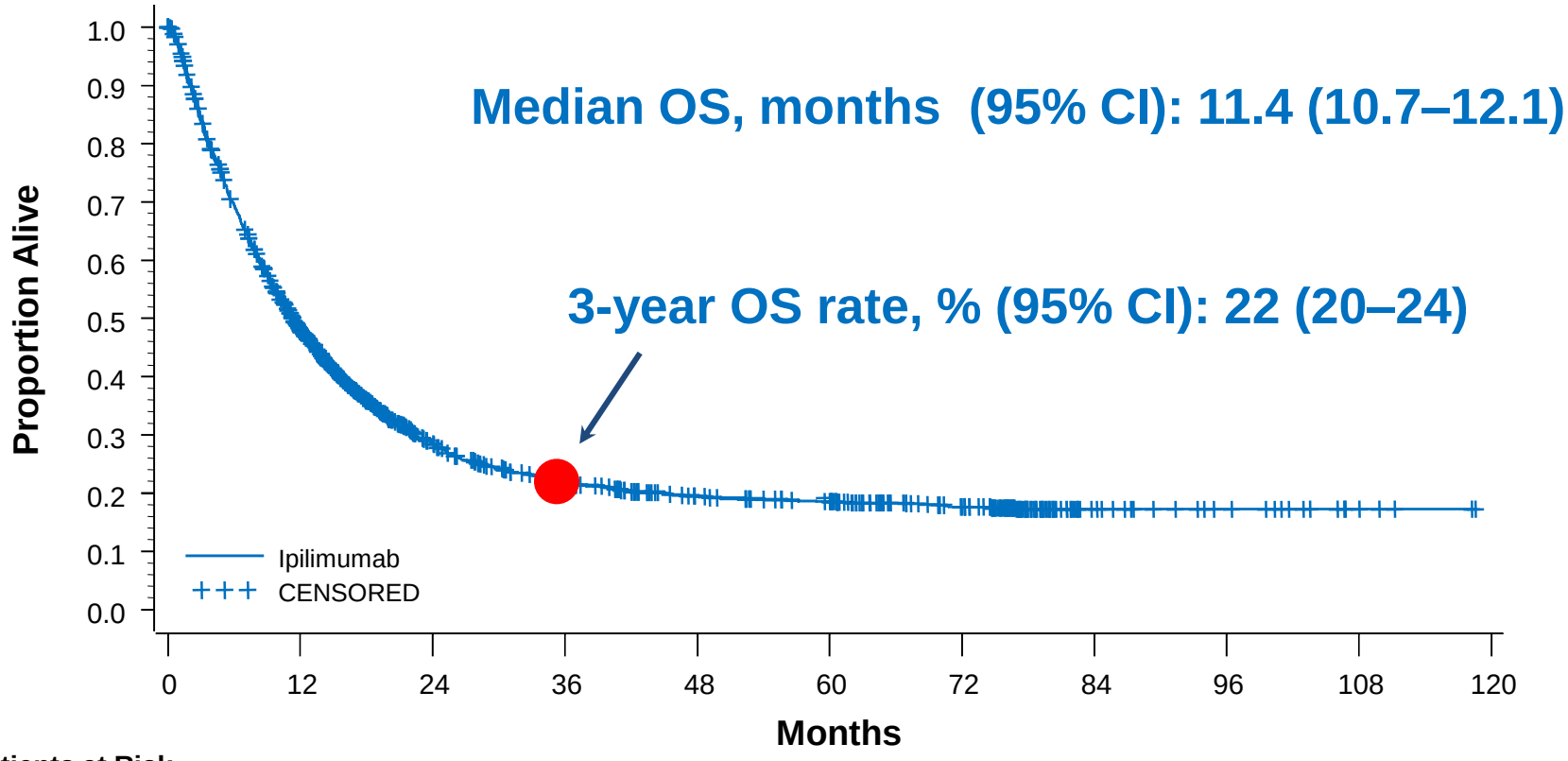
High-Dose IL-2 Therapy

- RR: 16% (43/270)
- Durable responses
  - Median: 8.9 mos
  - CR: not reached

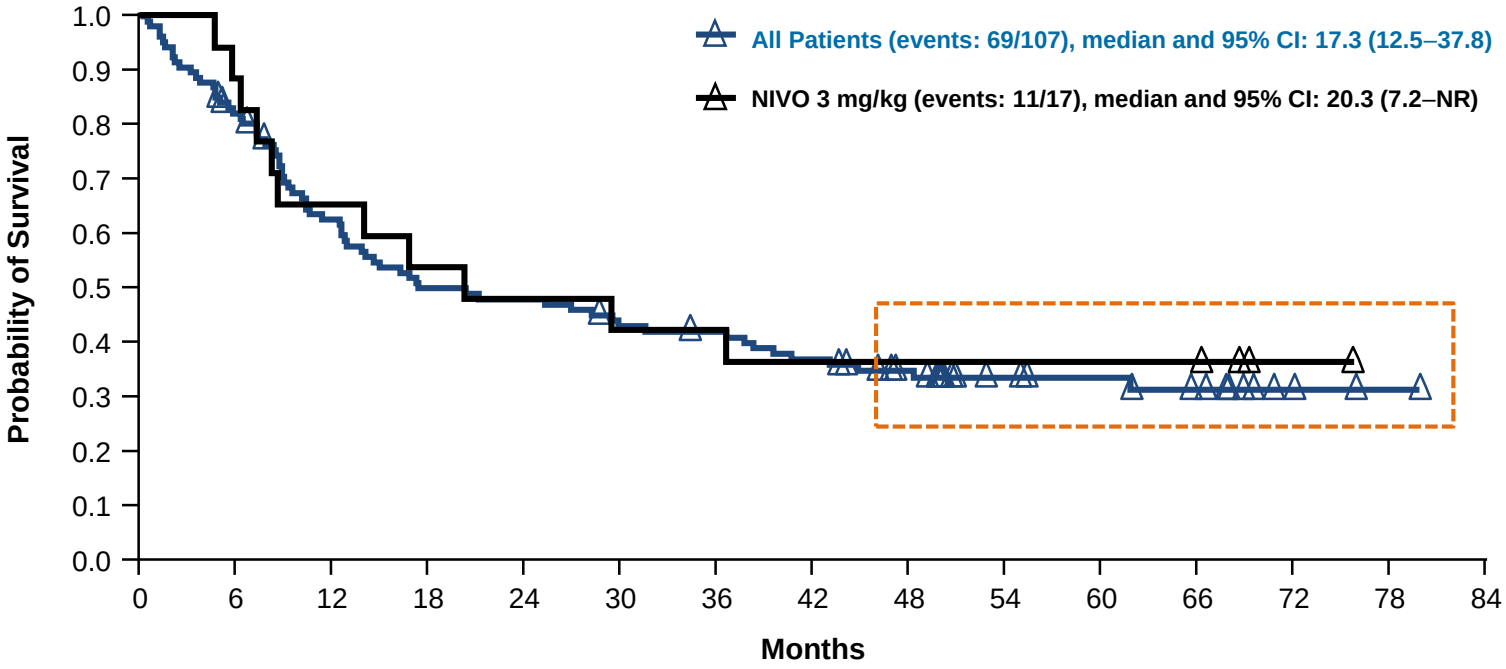


Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116.

Primary Analysis of Pooled OS Data: 1861 Patients



Overall Survival at 5 Years of Follow-up Nivolumab

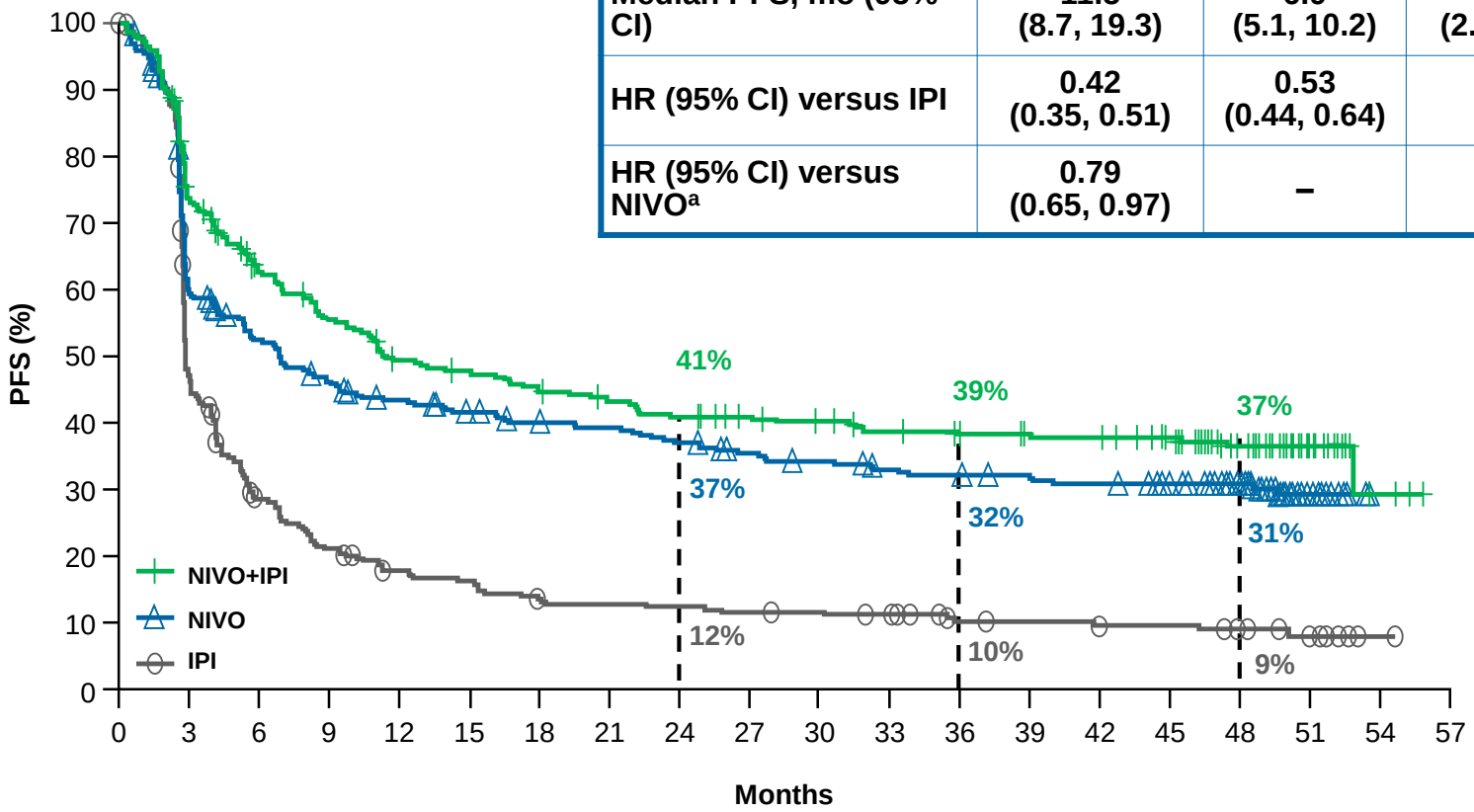


Number of Patients at Risk															
All Patients	107	86	64	51	49	43	41	36	29	17	15	12	3	1	0
NIVO 3 mg/kg	17	15	11	9	8	7	7	6	6	6	6	6	1	0	

Database lock Oct 2015

Progression-Free Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–

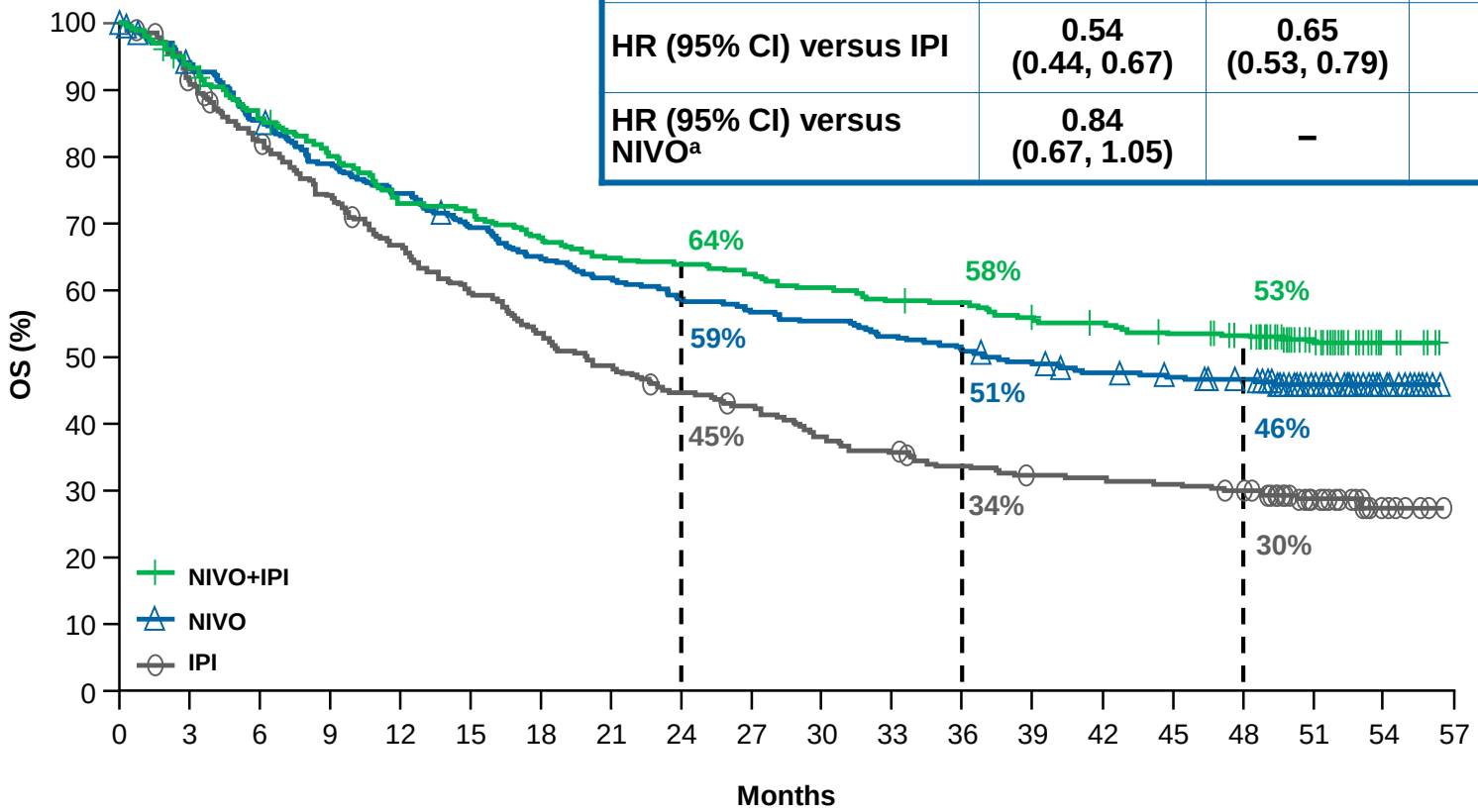


Patients at risk:

NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



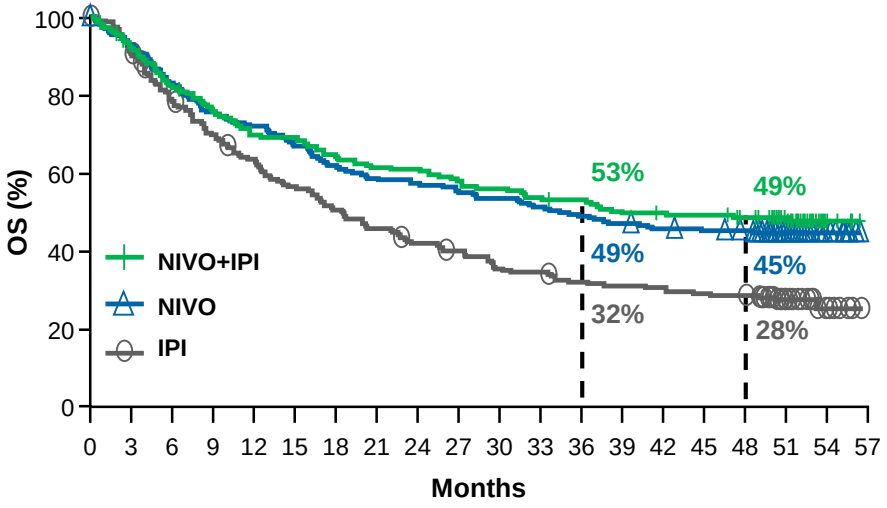
Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

OS in Patients With *BRAF* Wild-type and Mutant Tumors

BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	39.1 (27.5, NR)	34.4 (24.1, NR)	18.5 (14.1, 22.7)
HR (95% CI) versus IPI	0.60 (0.47, 0.77)	0.65 (0.51, 0.83)	–
HR (95% CI) versus NIVO[a]	0.92 (0.71, 1.20)	–	–

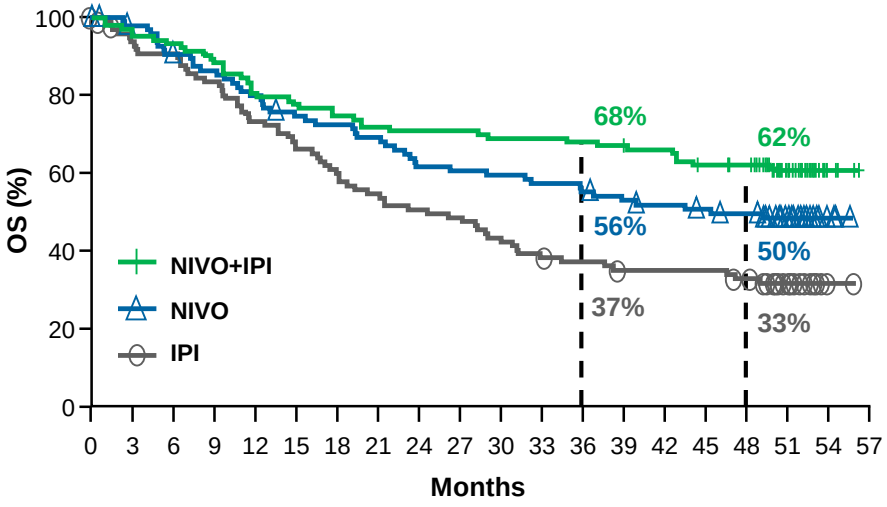


Patients at risk:

NIVO+IPI	211	193	169	156	143	141	132	126	125	119	115	109	108	102	99	98	94	54	6	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	96	93	56	12	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	33	9	0

BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	45.5 (26.4, NR)	24.6 (17.9, 31.0)
HR (95% CI) versus IPI	0.45 (0.30, 0.67)	0.64 (0.44, 0.93)	–
HR (95% CI) versus NIVO[a]	0.70 (0.46, 1.07)	–	–



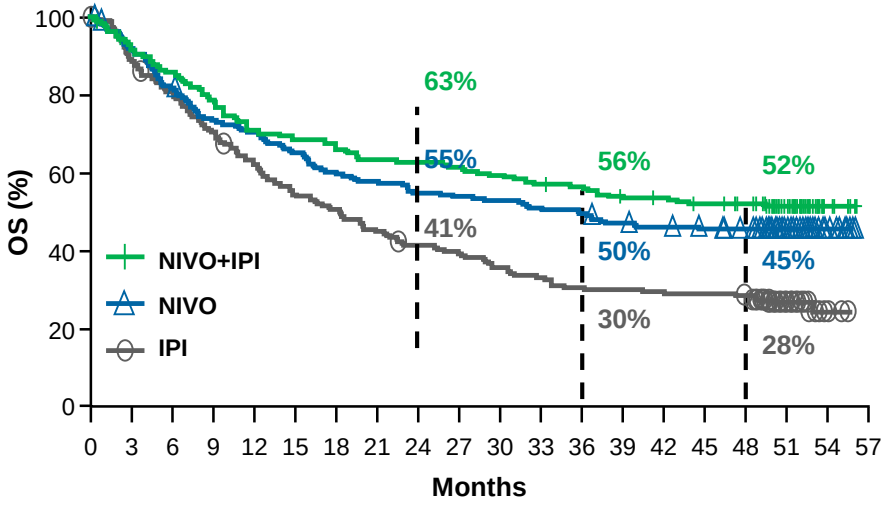
Patients at risk:

NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	62	60	42	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	46	44	42	29	6	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	35	32	32	32	29	17	2	0

OS by Tumor PD-L1 Expression, 5% Cutoff

PD-L1 Expression Level <5%

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (32.7, NR)	35.9 (23.1, NR)	18.4 (13.7, 22.5)
HR (95% CI) versus IPI	0.54 (0.42, 0.69)	0.64 (0.50, 0.82)	–
HR (95% CI) versus NIVO[a]	0.83 (0.64, 1.09)	–	–



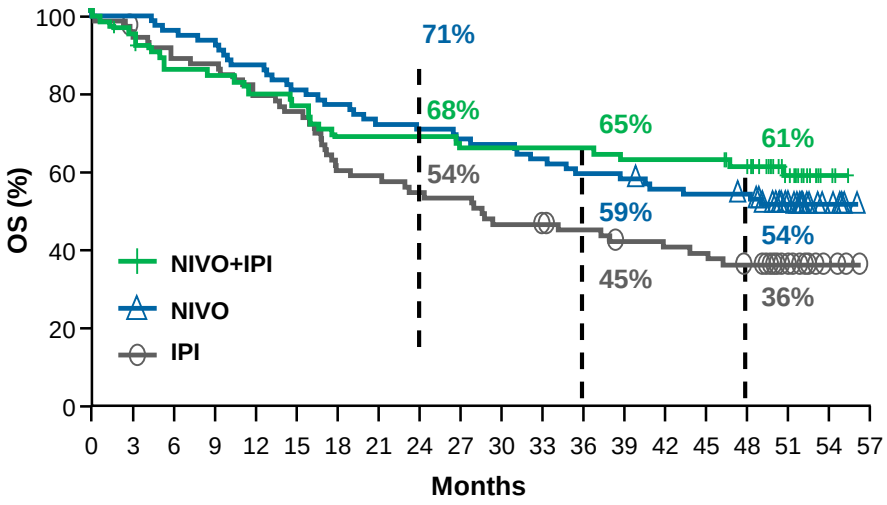
Patients at risk:

NIVO+IPI	210	194	178	163	146	144	139	131	130	127	123	118	116	111	107	103	100	62	9	0
NIVO	208	189	169	151	144	133	123	118	112	110	108	104	102	95	92	89	86	56	10	0
IPI	202	179	158	140	124	107	99	89	80	77	69	64	59	58	57	56	55	31	6	0

[a]Descriptive analysis

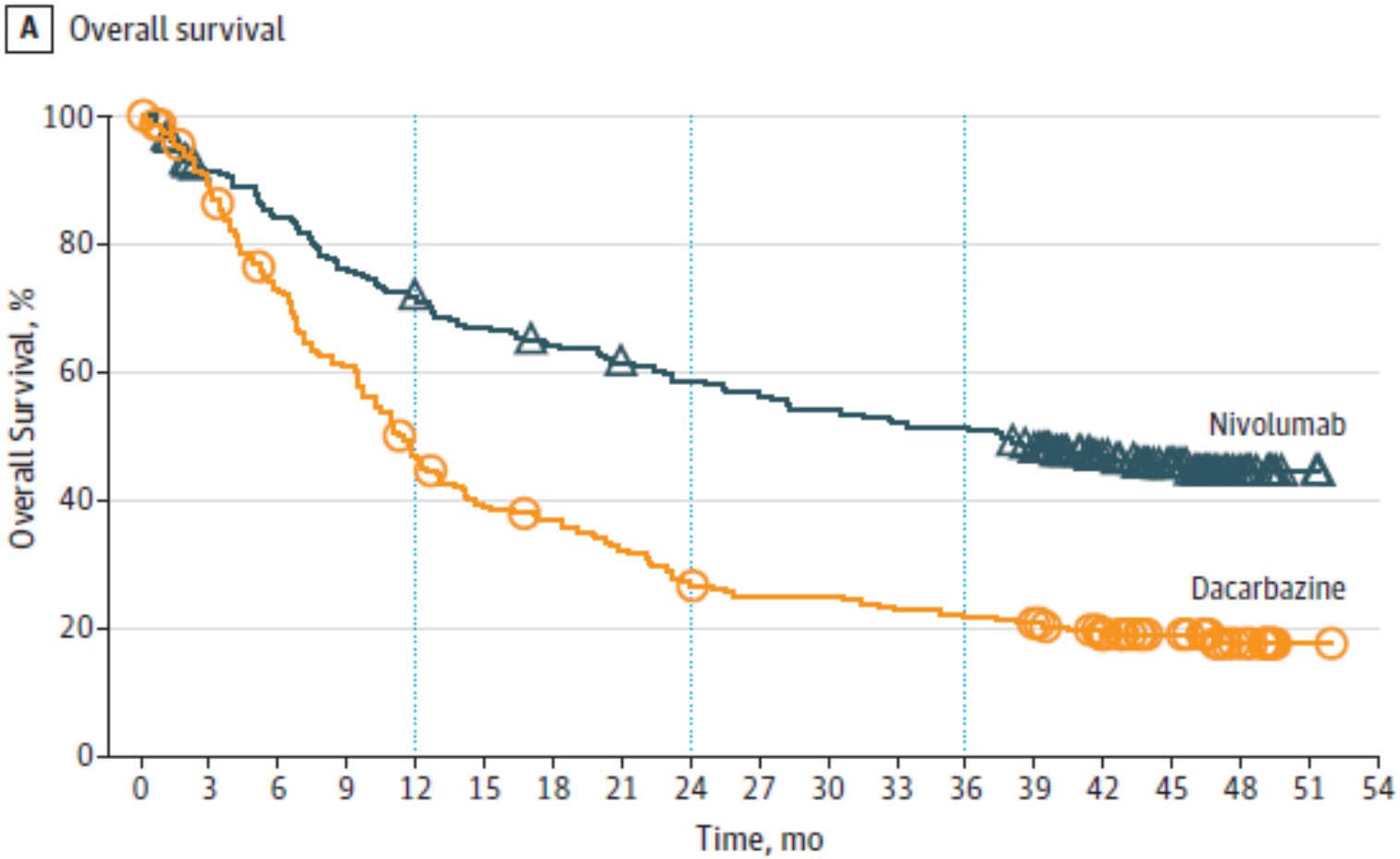
PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (39.1, NR)	NR (33.6, NR)	28.9 (18.1, 44.2)
HR (95% CI) versus IPI	0.56 (0.35, 0.90)	0.65 (0.42, 0.99)	–
HR (95% CI) versus NIVO[a]	0.86 (0.53, 1.41)	–	–



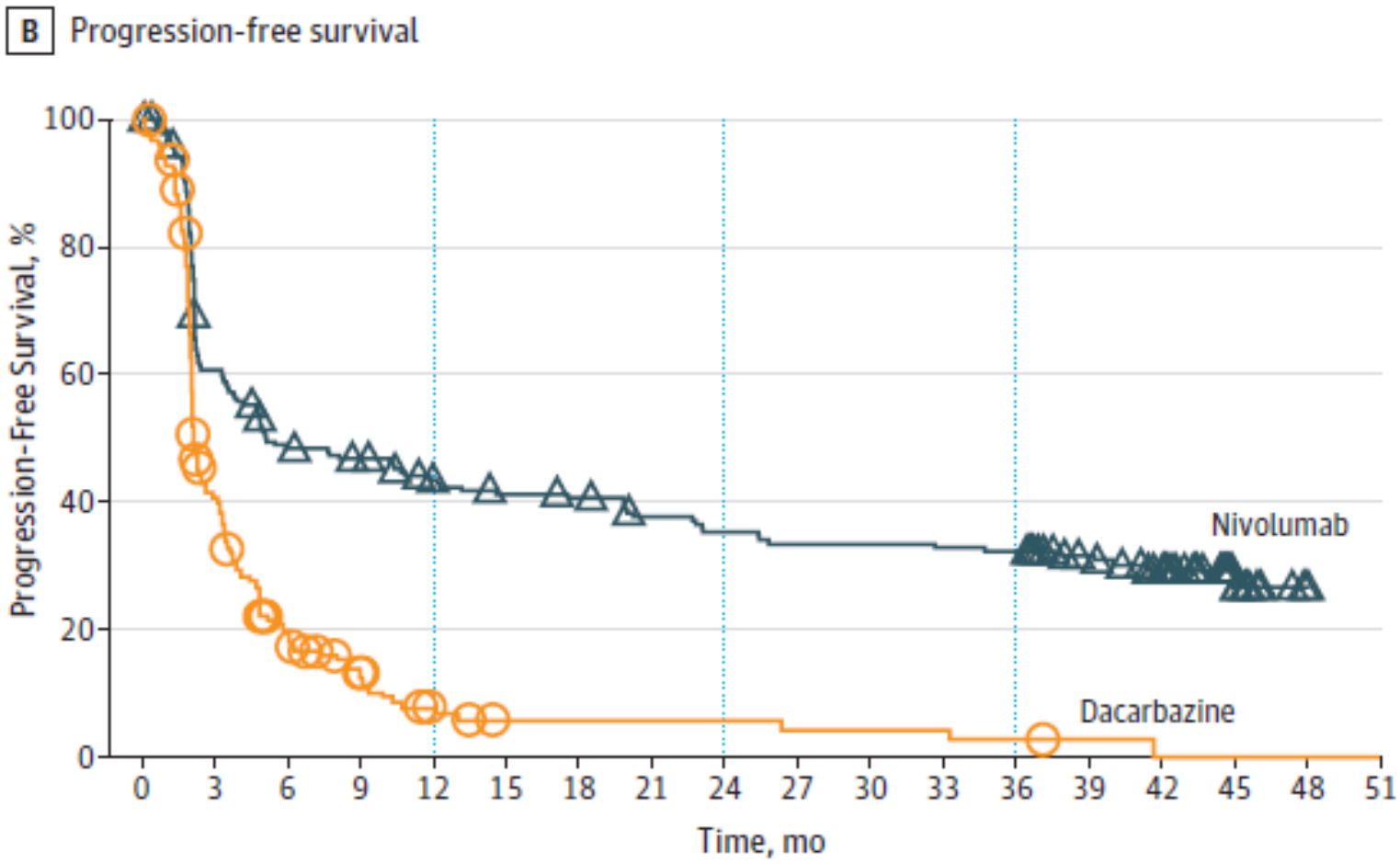
Patients at risk:

NIVO+IPI	68	63	56	55	52	50	45	45	45	44	43	43	43	42	41	41	38	24	3	0
NIVO	80	79	76	74	69	64	61	58	57	54	53	50	47	46	43	42	41	24	6	0
IPI	75	72	66	64	60	55	46	43	40	39	34	34	31	28	28	26	24	13	3	0



No. at risk

Nivolumab	210	186	171	154	143	135	128	122	116	111	107	103	102	92	72	53	16	2	0
Dacarbazine	208	179	146	122	92	76	71	62	51	47	47	43	41	38	26	19	7	1	0



No. at risk

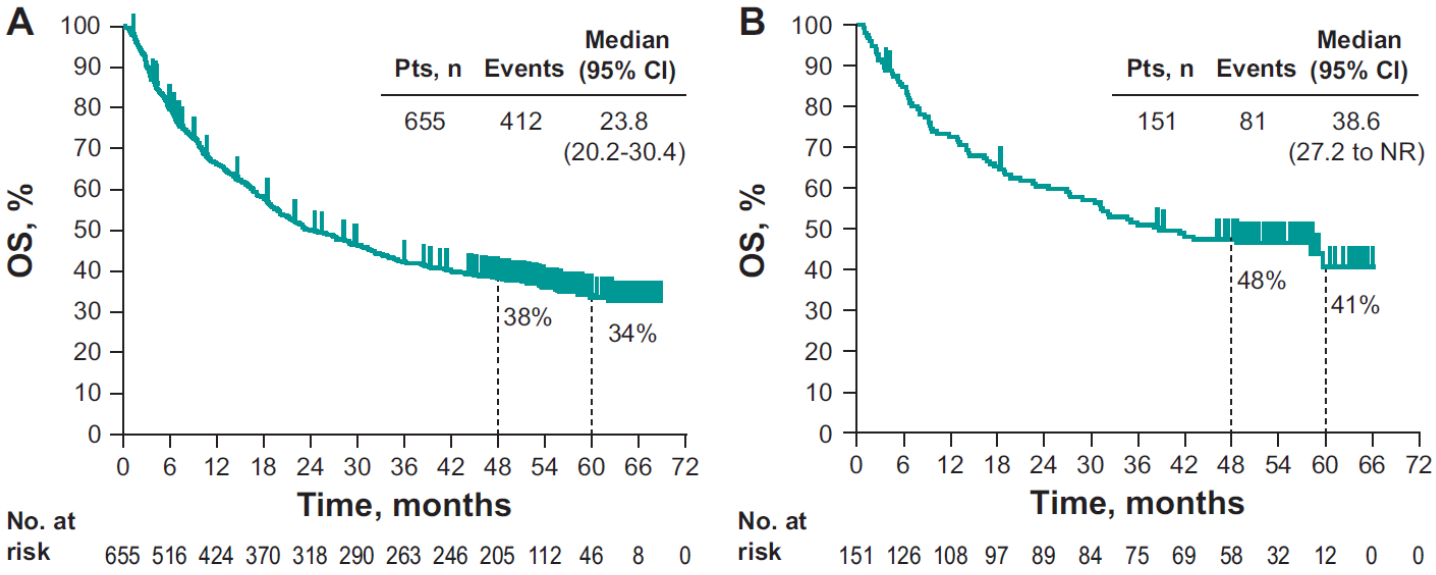
Nivolumab	210	118	92	87	77	72	70	63	59	56	56	55	54	44	32	10	1	0
Dacarbazine	208	75	33	16	7	4	4	4	4	3	3	3	2	1	0	0	0	0

5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001.

ASCO 2018

5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001.

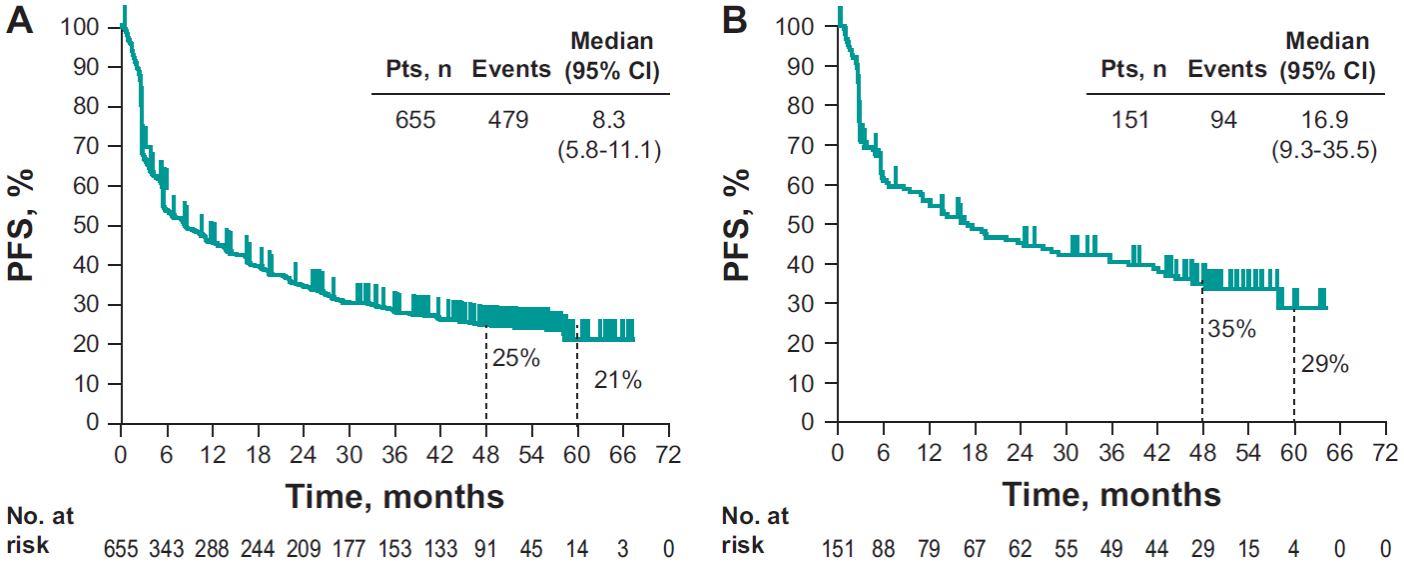
Figure 1. Kaplan-Meier Estimate of OS[a] in the Total Population (A) and in Treatment-Naive Patients (B)



NR, not reached; OS, overall survival; pts, patients. [a]Derived by the product limit (Kaplan-Meier) method of censored data.

5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001.

Figure 2. Kaplan-Meier Estimate of PFS per irRC by Investigator Assessment in the Total Population (A) and in Treatment-Naive Patients (B)



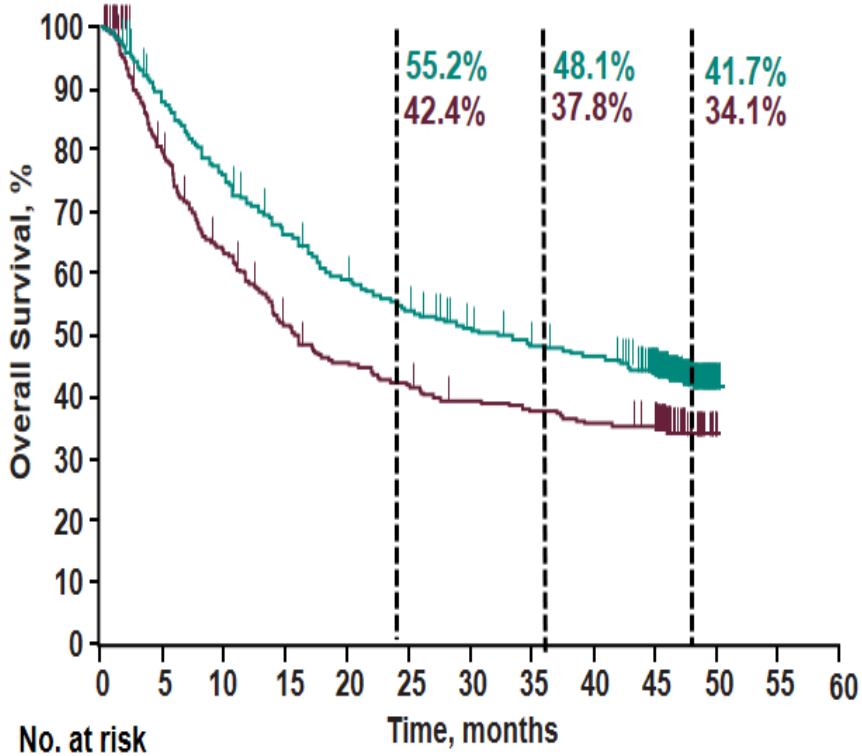
irRC, immune-related response criteria; PFS, progression-free survival; pts, patients. Derived by the product limit (Kaplan-Meier) method of censored data.

Overall Survival

Median Follow-Up 45.9 (0.3-50.0) Months

All Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	309	0.73 (0.61-0.89)	32.7 (24.5-41.6)
Ipi	164	-	15.9 (13.3-22.0)

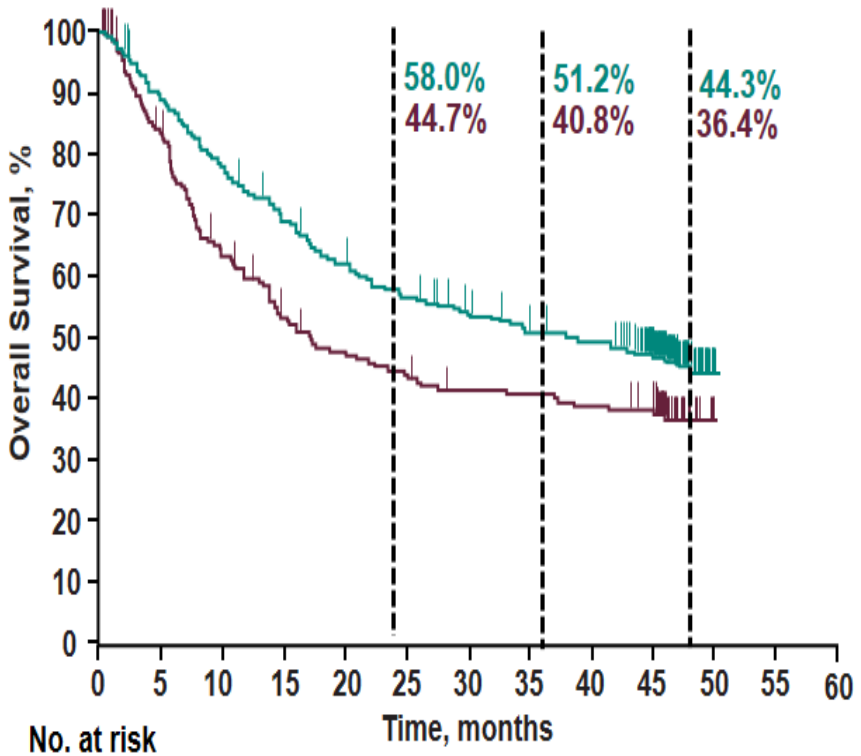


No. at risk

556	481	416	357	317	289	266	250	239	181	0	0	0
278	202	158	127	111	102	94	90	85	76	0	0	0

Treatment-Naive Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	193	0.73 (0.57-0.93)	38.7 (27.3-NR)
Ipi	104	-	17.1 (13.8-26.2)



No. at risk

368	324	284	248	221	201	186	174	167	124	0	0	0
181	140	105	86	76	70	64	63	60	51	0	0	0

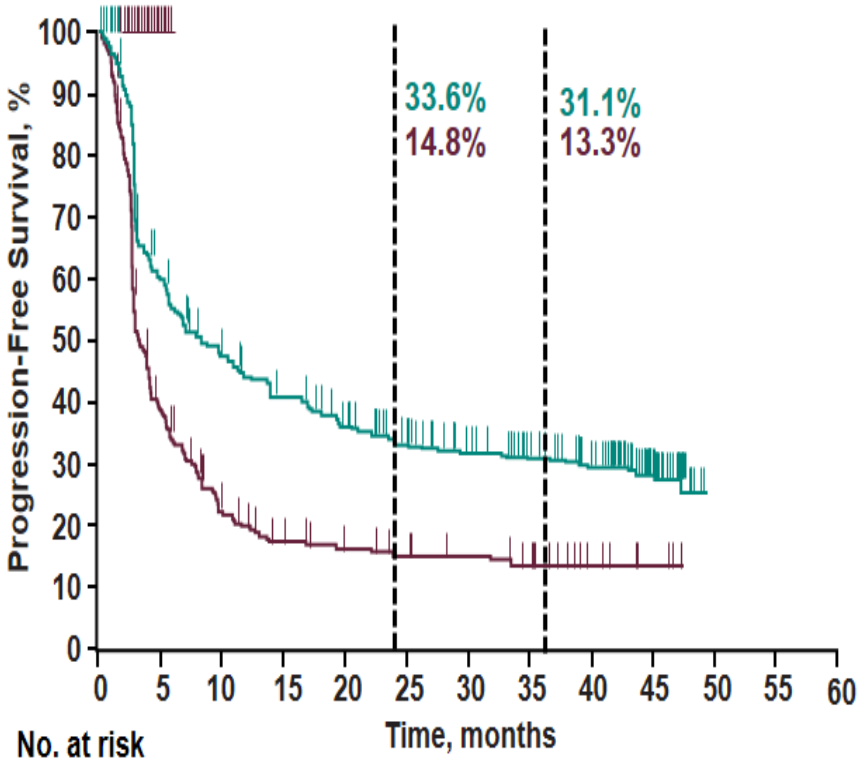
[a]Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. [b]Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.

Progression-Free Survival[a]

Median Follow-Up 45.9 (0.3-50.0) Months

All Patients

	Events, n	HR[b] (95% CI)	Median,[c] mo (95% CI)
Pembro	378	0.56 (0.47-0.67)	8.3 (6.5-11.2)
Ipi	204	-	3.3 (2.9-4.1)

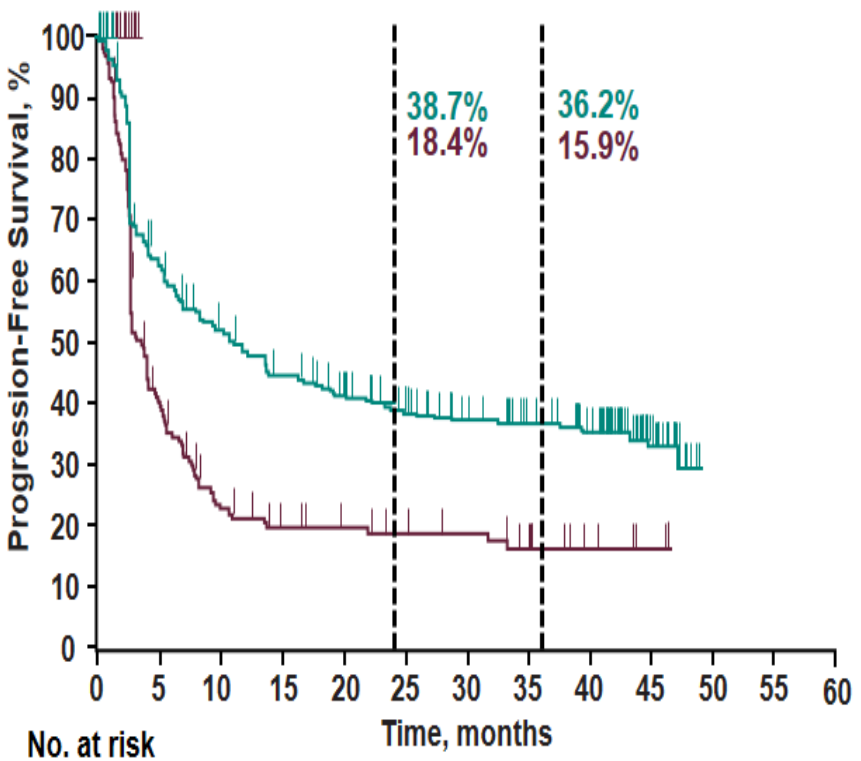


No. at risk

556	324	251	213	183	148	132	115	95	35	0	0	0
278	93	47	32	27	22	20	15	7	3	0	0	0

Treatment-Naive Patients

	Events, n	HR[b] (95% CI)	Median,[c] mo (95% CI)
Pembro	230	0.54 (0.43-0.67)	11.2 (7.1-13.9)
Ipi	130	-	3.7 (2.8-4.3)



No. at risk

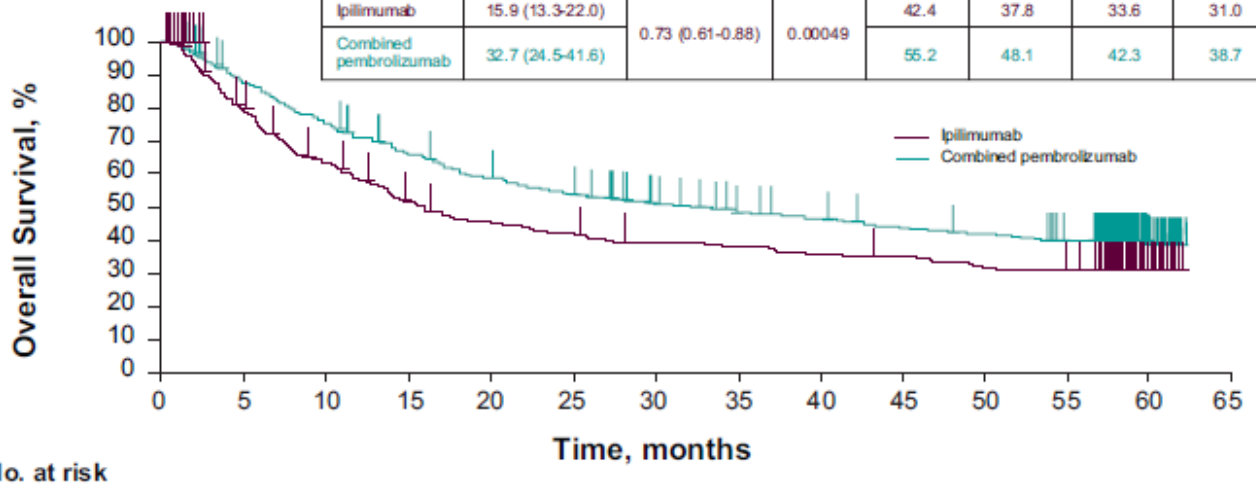
368	222	178	150	133	112	98	88	76	28	0	0	0
181	64	32	23	20	17	15	10	5	2	0	0	0

[a]Per immune-related response criteria by investigator review. [b]Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. [c]Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.

Figure 1. Kaplan-Meier Estimates of Overall Survival (A) in the Total Study Population and (B) in Patients Receiving First-Line Treatment[a]

A

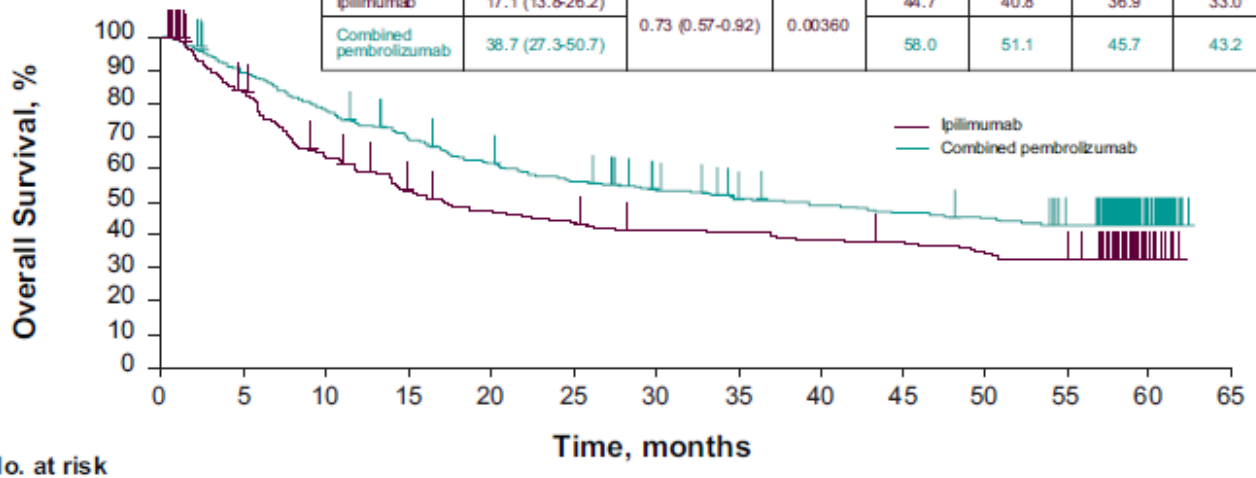
OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	15.9 (13.3-22.0)	0.73 (0.61-0.88)	0.00049	42.4	37.8	33.6	31.0
Combined pembrolizumab	32.7 (24.5-41.6)			55.2	48.1	42.3	38.7



No. at risk														
Ipilimumab	277	202	158	127	111	102	94	90	85	83	75	72	19	0
Combined pembrolizumab	556	481	416	357	317	289	264	245	233	217	208	194	47	0

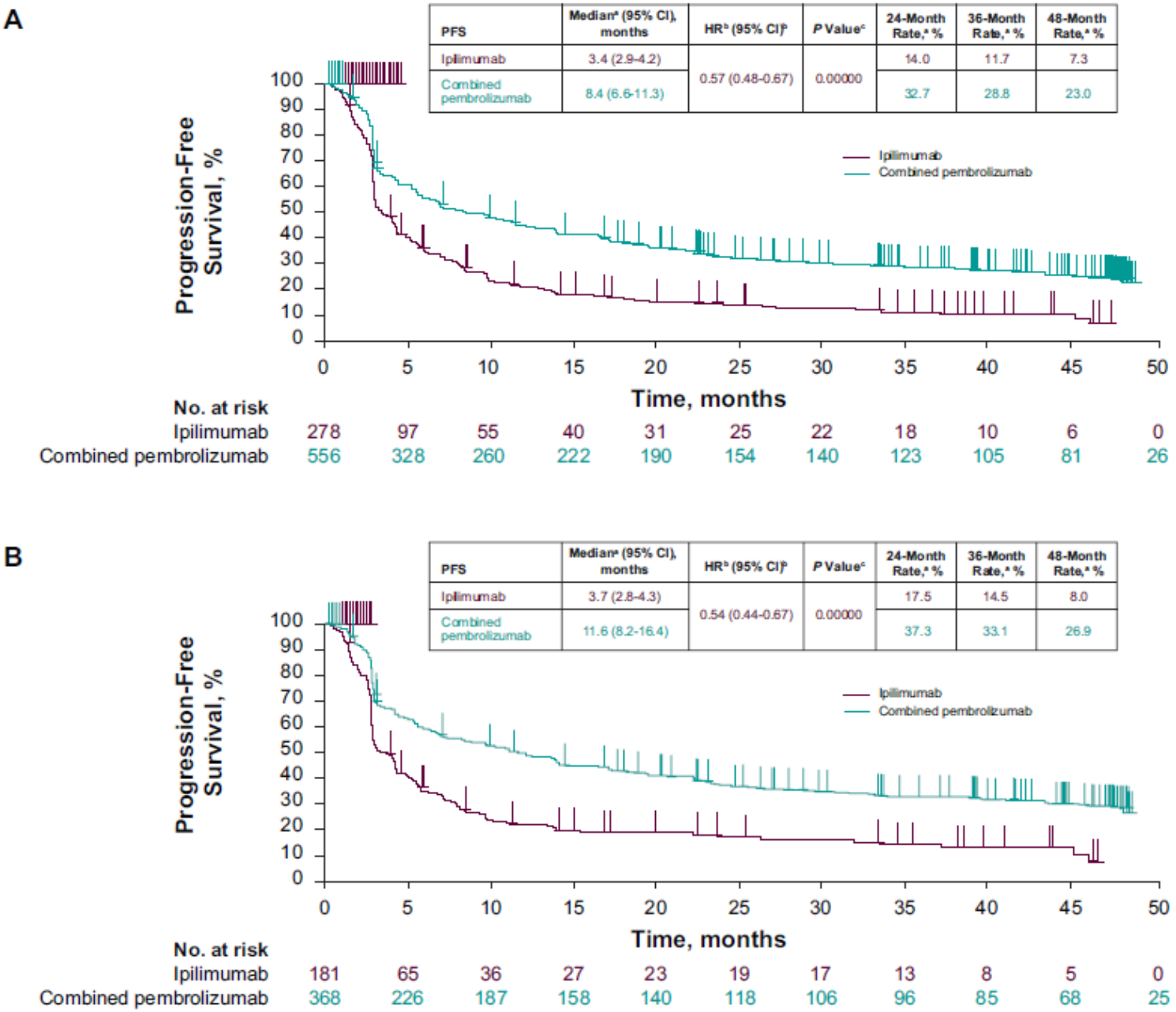
B

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2

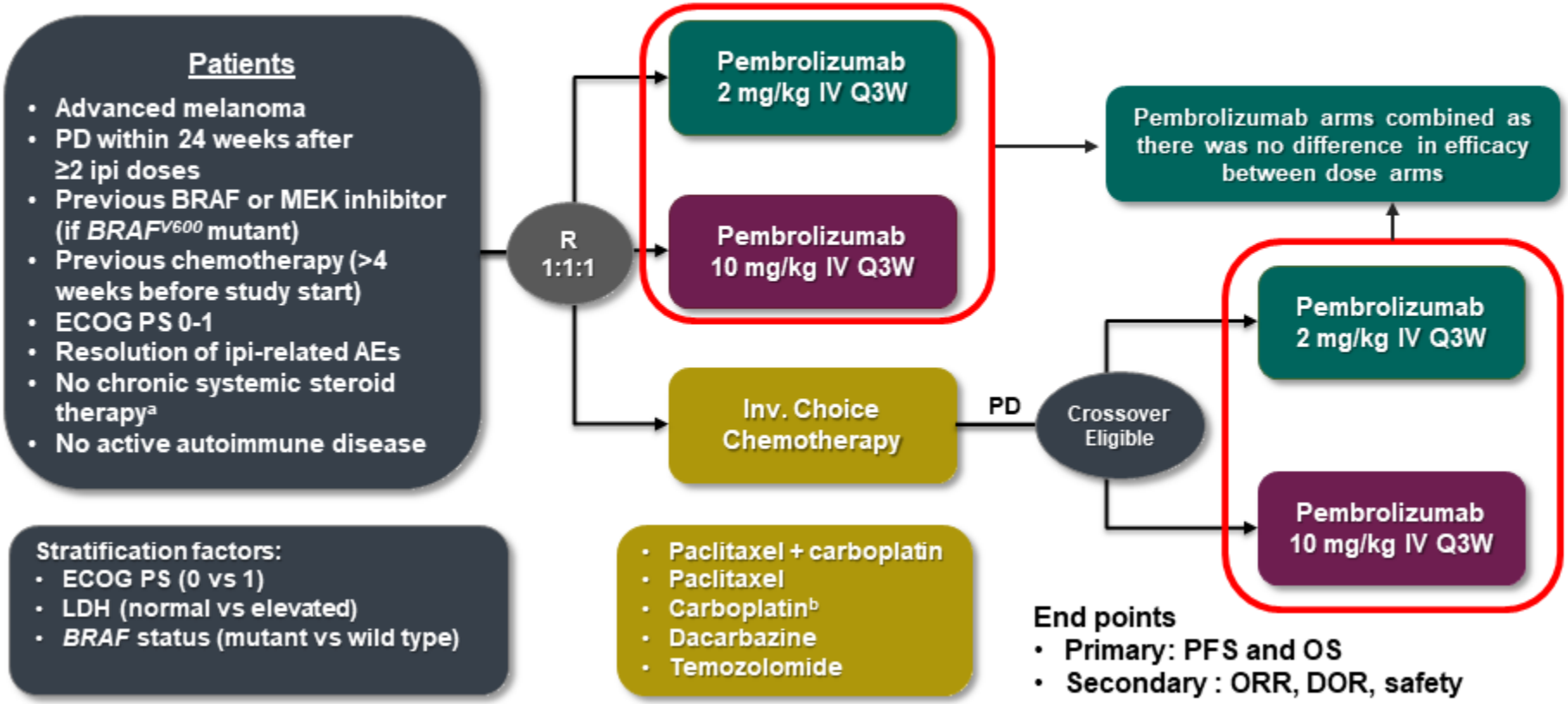


No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

Figure 2. Kaplan-Meier Estimates of PFS per irRC by Investigator Review in (A) the Total Study Population and (B) Patients Receiving First-Line Treatment

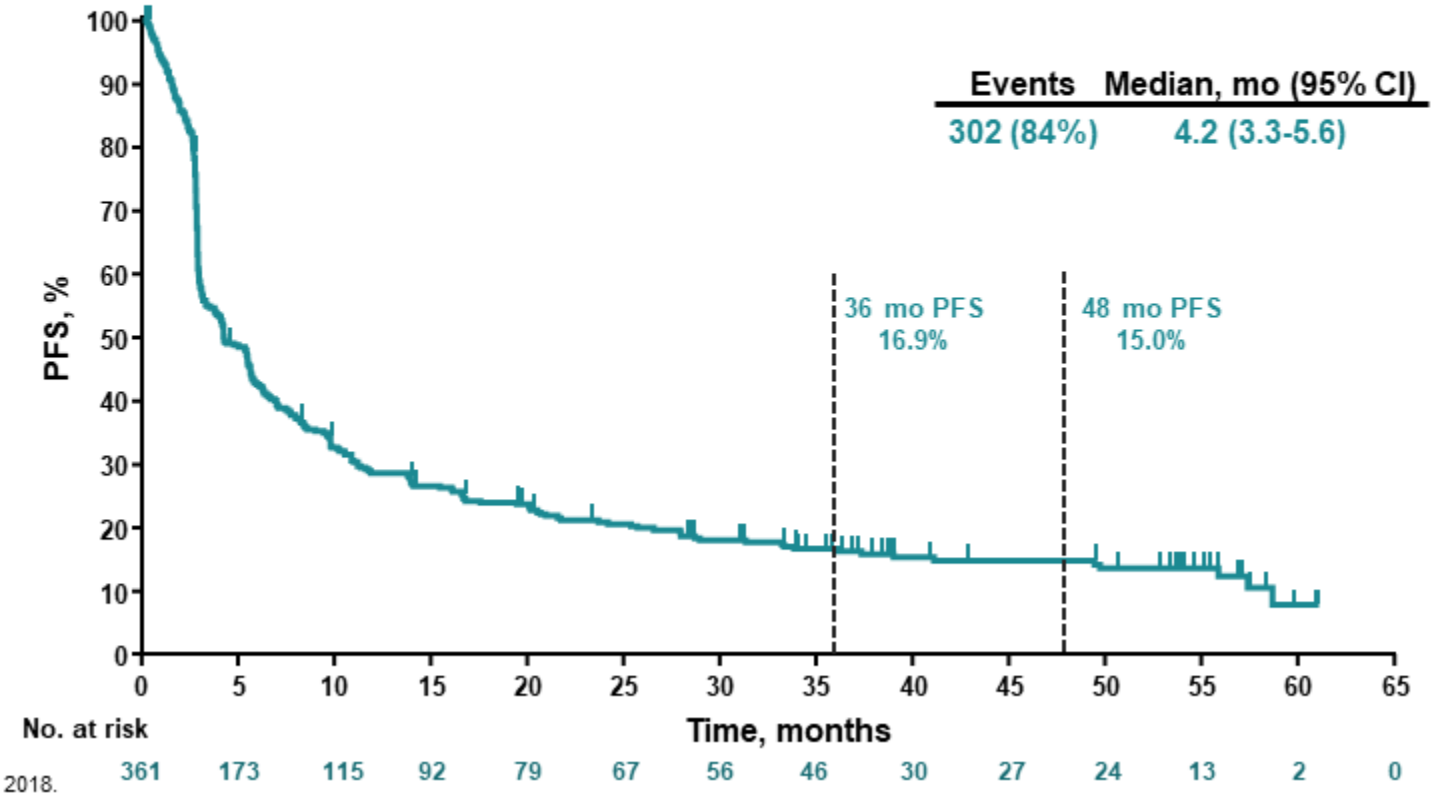


KEYNOTE-002 Study Design (NCT01704287)



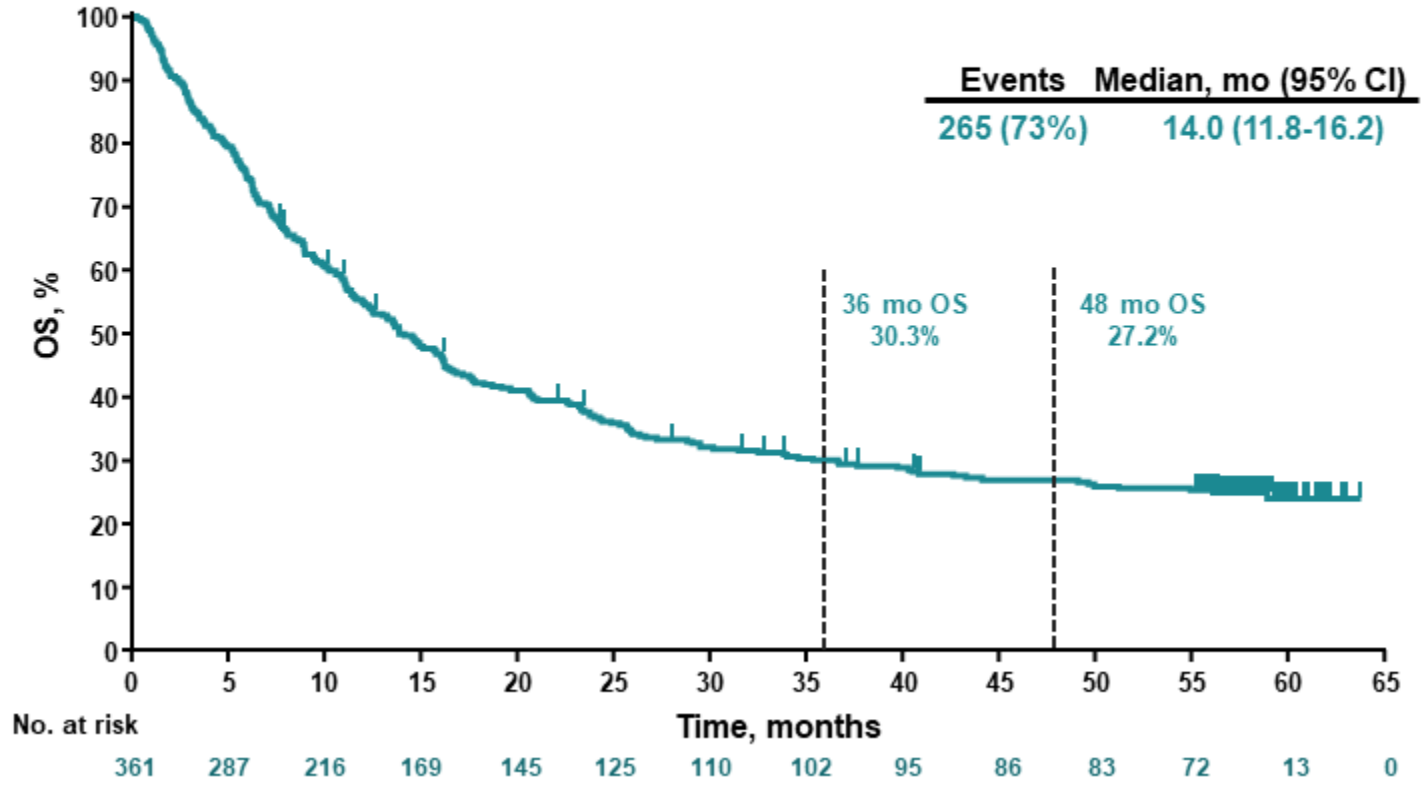
[a]Defined as >10 mg/day prednisone or equivalent.
[b]Carboplatin monotherapy removed early in study by a protocol amendment.

PFS[a] in Patients Randomized to Pembrolizumab



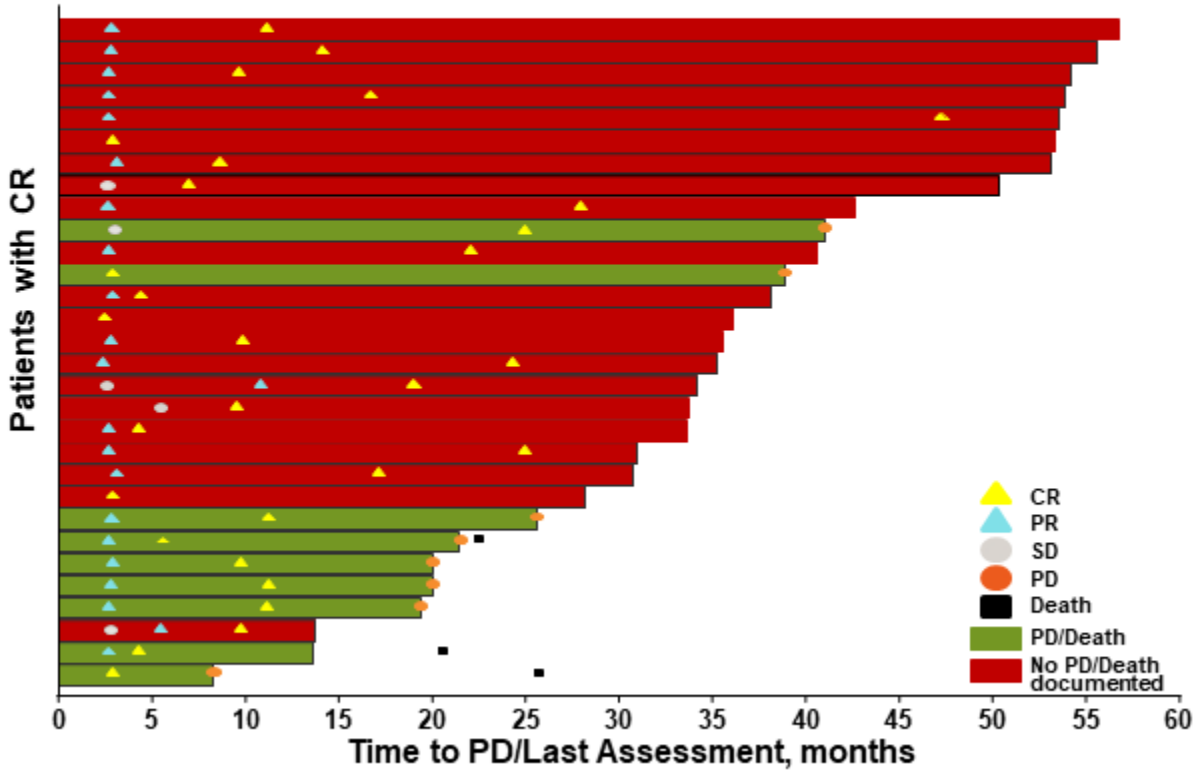
Data cutoff: 30 May 2018.
[a]Assessed by RECIST v1.1, INV.

OS in Patients Randomized to Pembrolizumab



Data cutoff: 30 May 2018.

Characteristics of Complete Response (RECIST v1.1, INV) to Pembrolizumab

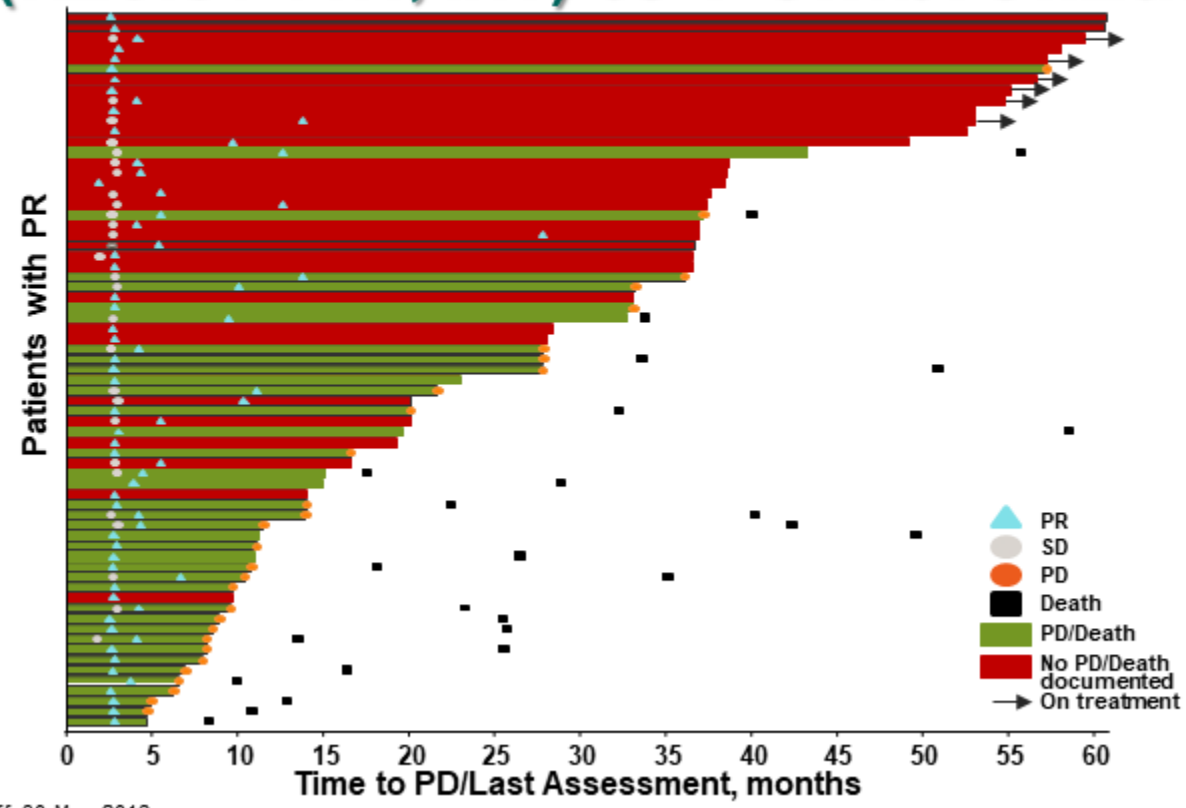


30 patients had best response of CR

- Median time to CR: 2.8 mo (range, 2.4-24.9)
- Median time from SD to CR: 6.9 mo (range, 3.9-21.9) in 5 patients
- Median time from PR to CR: 8.2 mo (1.4-44.4) in 22 patients
- Median duration of CR: not reached (range, 5.5 to 53.9+)

Data cutoff: 30 May 2018.
Of 22 patients without progression, 16 discontinued because of an AE (n = 3) or patient/physician decision (n = 13)..

Characteristics of Partial Response (RECIST v1.1, INV) to Pembrolizumab

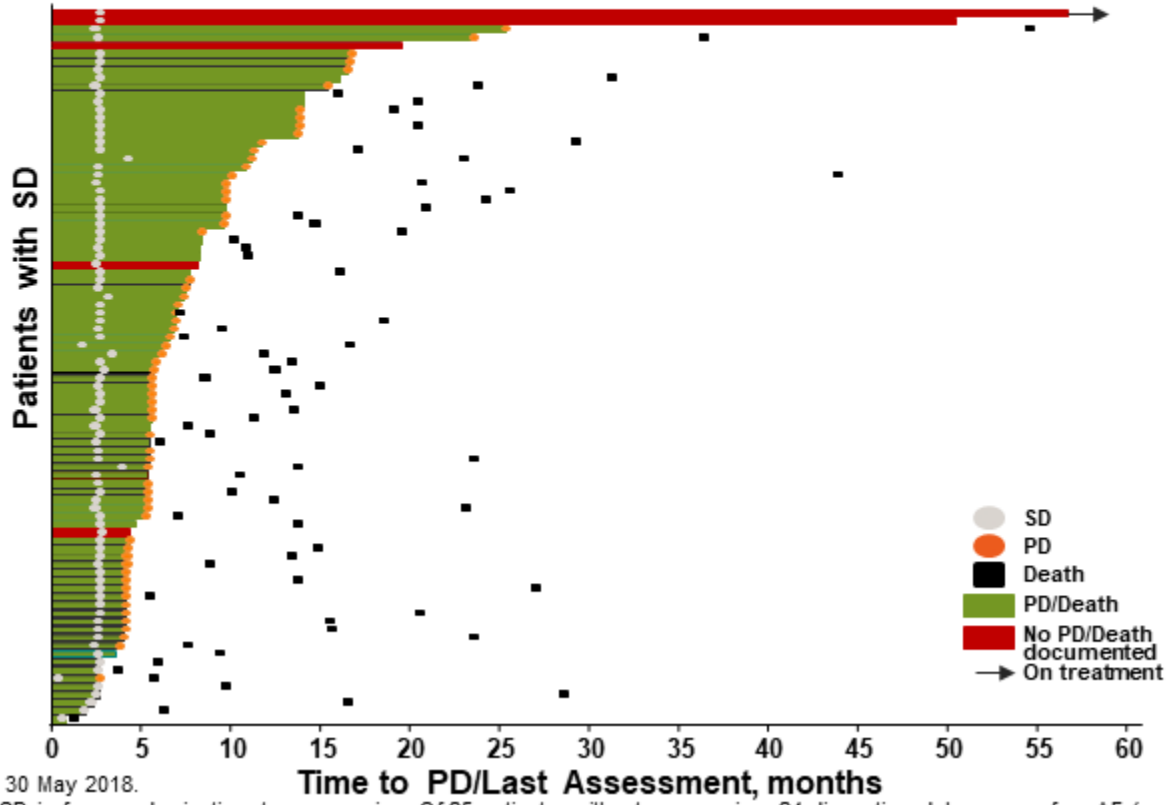


69 patients had best response of PR

- Median time to PR: 2.9 mo (range, 1.9-27.9)
- Median time from SD to PR: 2.7 mo (range, 0.9-25.2) in 28 patients
- Median duration of PR: 54.7 mo (range, 1.9+ to 58.2+)

Data cutoff: 30 May 2018.
Of 40 patients without progression, 31 discontinued because of an AE (n = 15) or physician/patient decision (n = 16)..

Characteristics of Stable Disease to Pembrolizumab



88 patients had best response of SD

- Median duration of SD: 7.8 mo (range, 0.8+ to 56.7+)

Data cutoff: 30 May 2018.

Duration of SD is from randomization to progression. Of 25 patients without progression, 24 discontinued because of an AE (n = 11) or patient/physician decision (n = 13).

Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA.

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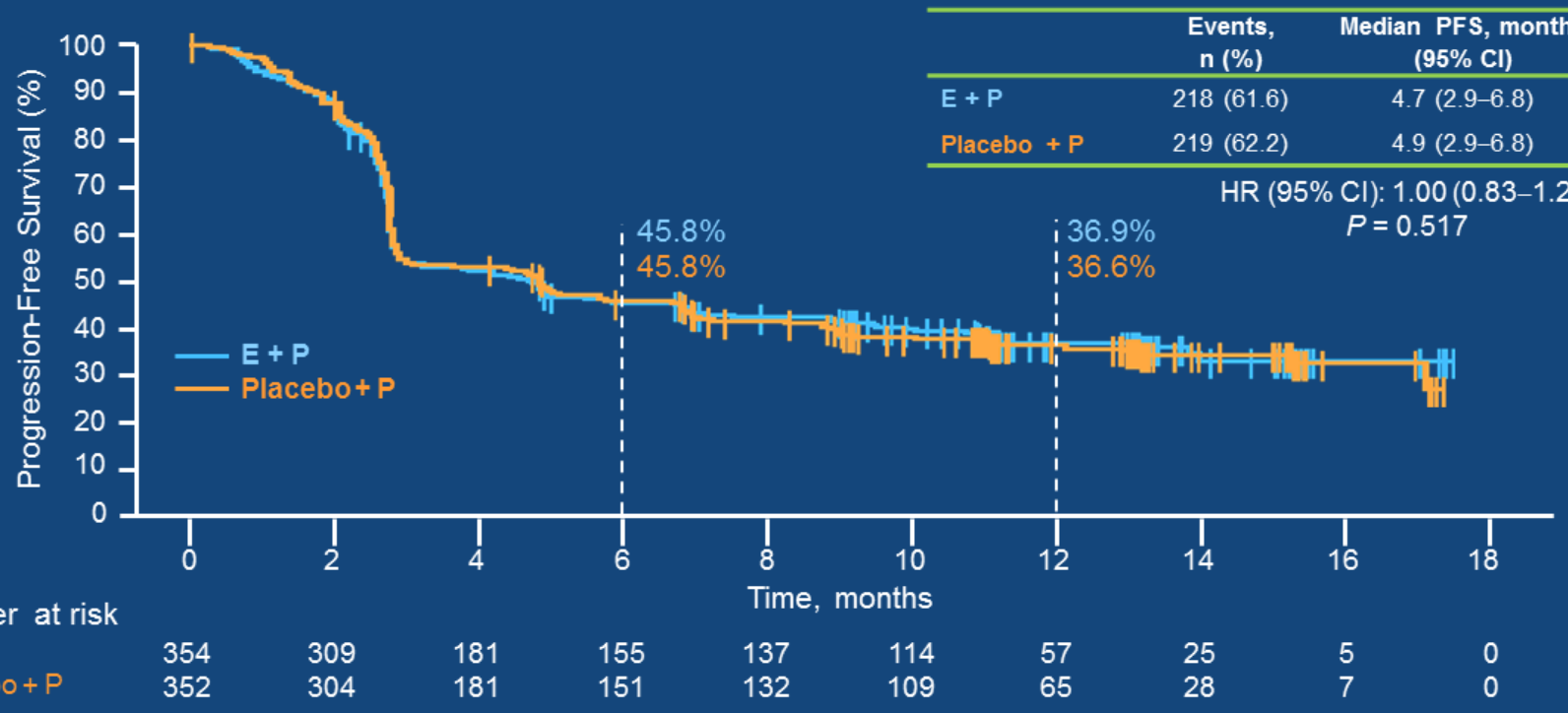
PRESENTED BY: Georgina V. Long

Progression-Free Survival (RECIST v1.1, BICR)



	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517

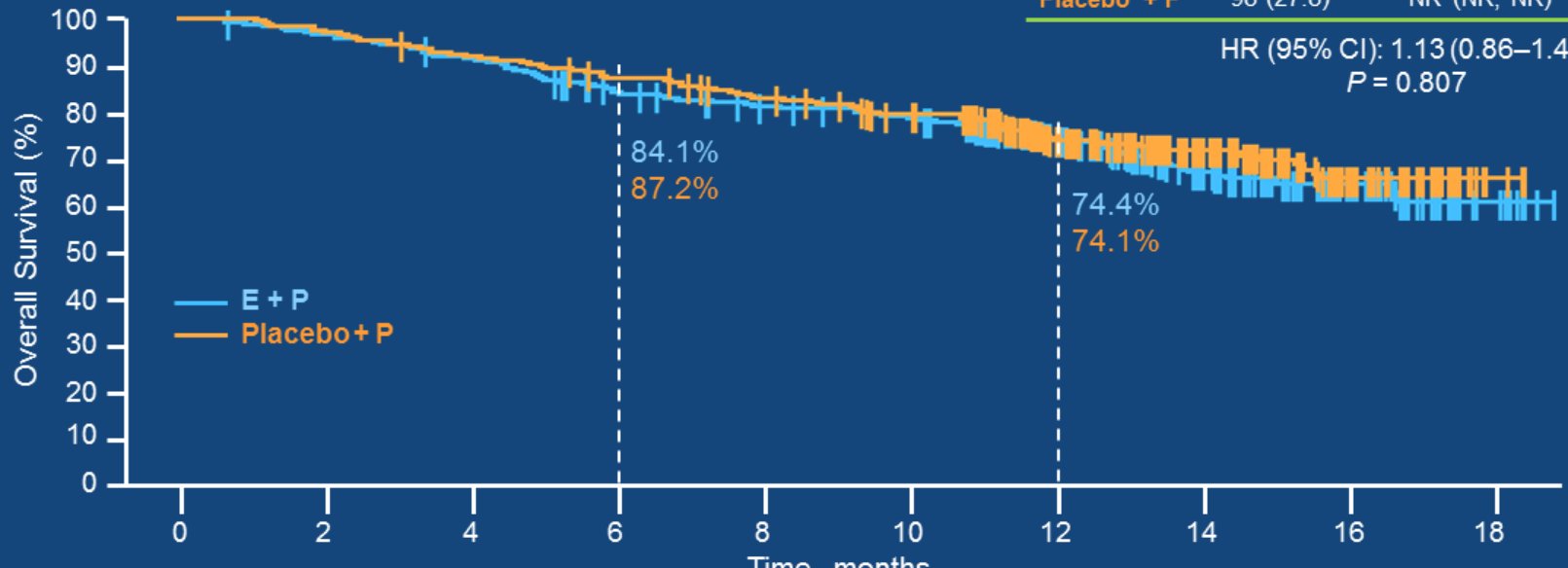
Number at risk										
E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
PFS defined as time from randomization to disease progression or death, whichever occurred first.

Overall Survival

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807

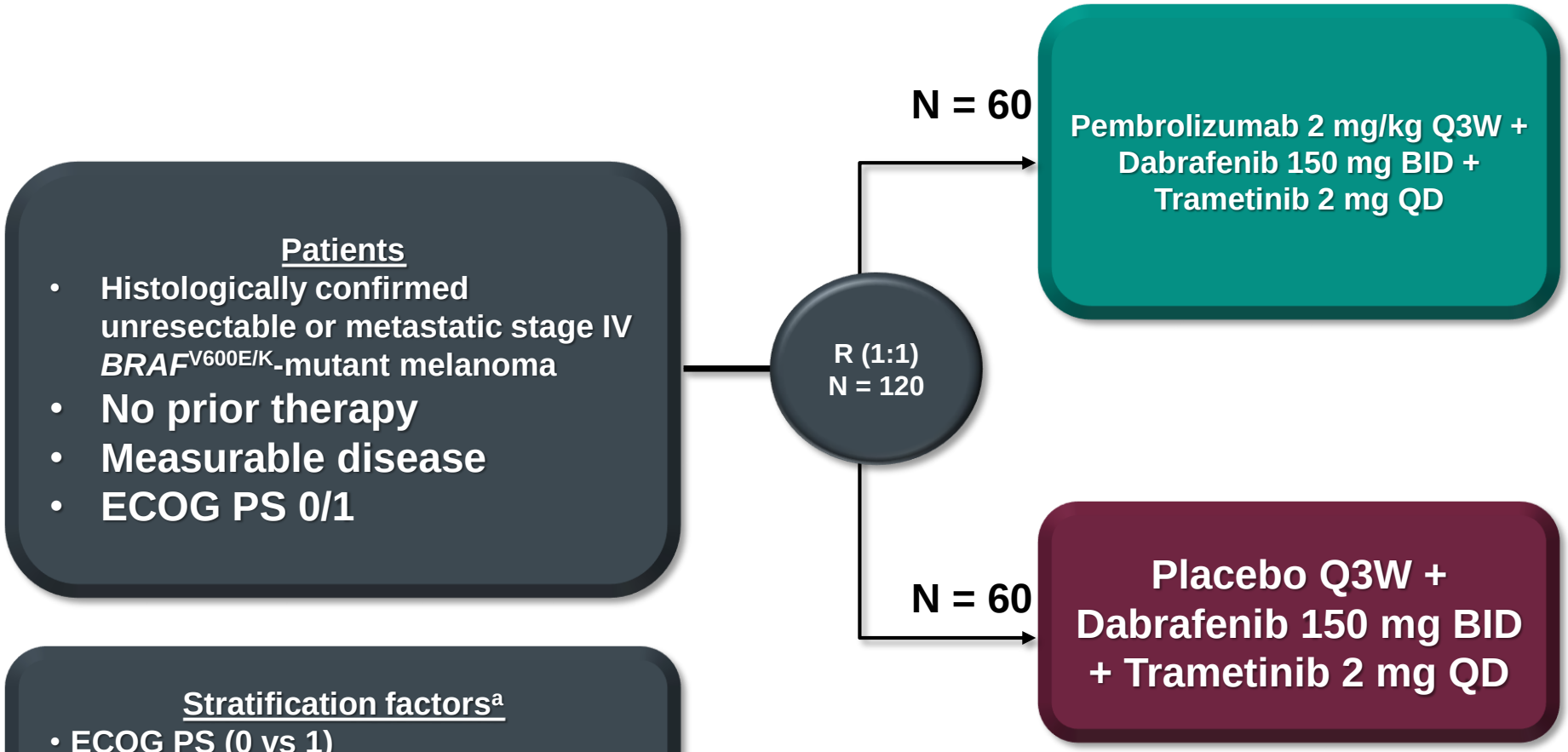


Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

KEYNOTE-022 Part 3 Study Design (NCT02130466)

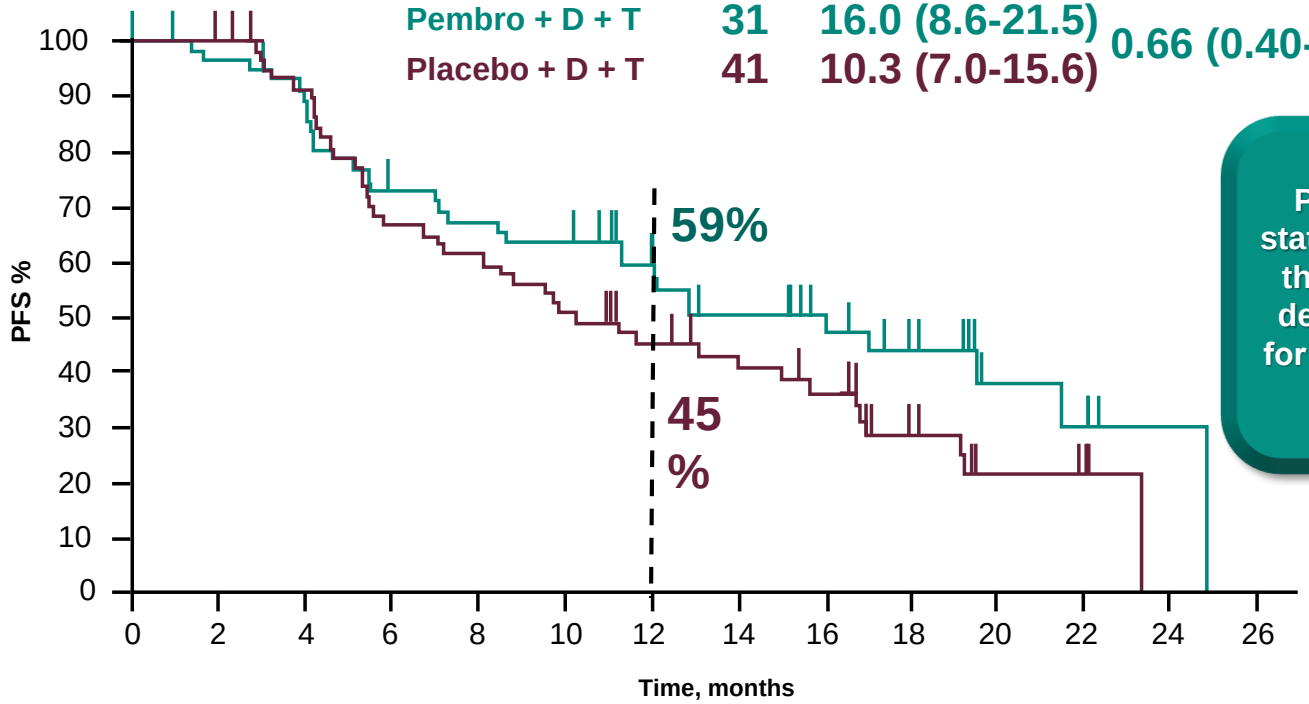


- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, *P* ≤ 0.025)

No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.

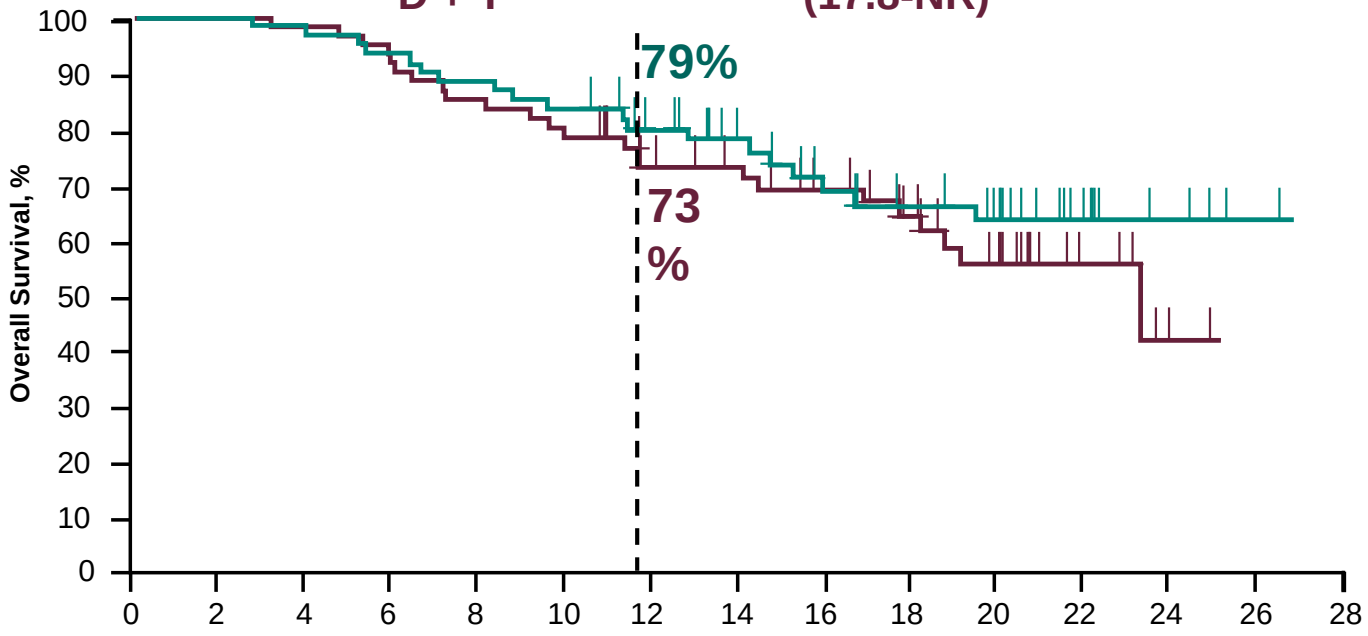
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

[c]One-sided *P* value based on stratified log-rank test.

Data cutoff: Feb 15, 2018.

Overall Survival

	Events, n	Median[a] (95% CI), mo	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	19	NR (19.6-NR)	0.76 (0.41-1.39)	0.18467
Placebo + D + T	24	23.4 (17.8-NR)		



No. at risk

Pembro + D + T	60	60	59	56	53	50	43	35	29	23	18	9	4	1	0
Placebo + D + T	60	60	59	55	51	47	39	36	31	25	18	7	2	0	0

[a]Based on Kaplan-Meier estimate of overall survival.

[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided *P* value based on stratified log-rank test.

Data cutoff: Feb 15, 2018.

MASTERKEY-265 Phase 3 Study Schema

- Unresectable stage IIIB to IV melanoma
- Injectable lesions
- Treatment naive (if *BRAF V600* mutant, prior treatment with BRAF+/- MEK inhibitors is allowed)
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

T-VEC
- Up to 4 mL per treatment
- 1st dose 10^6 PFU/mL, then after 3 weeks, 10^8 PFU/mL Q2W x 4, then Q3W

T-VEC Intralesional
Pembrolizumab 200mg IV Q3W

N = 330

Placebo Intralesional
Pembrolizumab 200mg IV Q3W

N = 330

SAFETY FOLLOW-UP

30 (+7) days after end of treatment

LONG-TERM FOLLOW-UP

Q12W for 5 years from date of last patient randomized

Treatment until whichever occurs first:
- CR
- Progressive disease (PD) per irRC-RECIST
- Intolerance
- All injectable tumors disappear (T-VEC/Placebo only)
- 2 years of treatment

•Primary endpoints:
PFS* and OS

*Centrally reviewed using modified RECIST 1.1

T-VEC: talimogene laherparepvec; irRC-RECIST: immune-related response criteria-response evaluation criteria in solid tumors; IV: intravenous; PFU: plaque-forming unit; Q2W: every 2 weeks; Q3W: every 3 weeks; Q12W: every 12 weeks; AEs: adverse events; OS: overall survival; PFS: progression-free survival

Unanswered Questions

- Metastatic melanoma : Duration of treatment with Anti-PD1
- Monotherapy vs combination therapy
- Long term 5yr follow up data
- Results from ongoing phase-3 trials
- Targeted therapy vs immunotherapy

Annals of Oncology 26 (Supplement 5): v126–v132, 2015
doi:10.1093/annonc/mdv297

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Dummer[1], A. Hauschild[2], N. Lindenblatt[3], G. Pentheroudakis[4] & U. Keilholz[5], on behalf of the ESMO Guidelines Committee*

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Treatment of systemic metastatic disease (stage IV)

- Patients with metastatic melanoma should have metastasis (preferably) or the primary tumour screened for detection of BRAF-V600-mutation. Treatment options for the first- and second-line setting include anti-PD1 antibodies (pembrolizumab, nivolumab), ipilimumab, an anti-CTLA4 antibody, for all patients, and BRAF/MEK inhibitor combinations for patients with BRAF-mutant melanoma [II, B].
- If clinical trials or the approved new targeted compounds are not available, cytotoxic drugs such as DTIC or temozolomide may be administered, with modest activity shown [II, C].

CLINICAL PRACTICE GUIDELINES

An ESMO Product

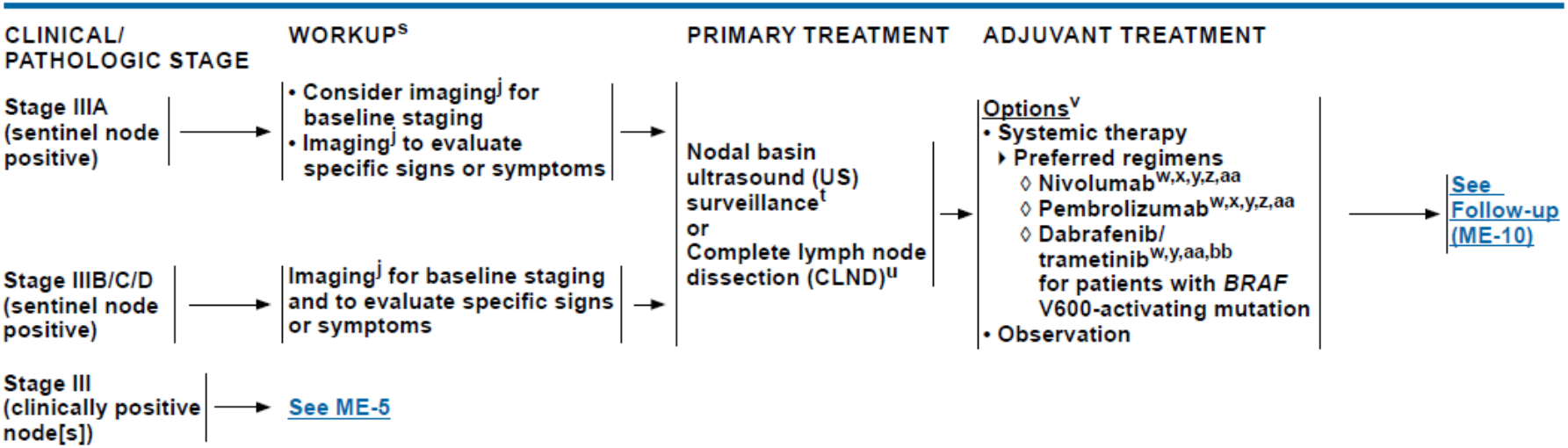
Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan,
on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



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

[s] *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C).

[t] For patients with a positive SLNB who do not undergo CLND, it would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG): at least every 4 months during the first 2 years, then every 6 months during years 3 through 5.

[u] For patients with a positive sentinel node, two prospective randomized phase III studies have demonstrated no improvement in melanoma-specific survival or OS in patients undergoing CLND compared to those who underwent nodal basin US surveillance. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity, including wound complications and long-term lymphedema. Factors that predict non-SLN positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. See Principles of Complete Lymph Node Dissection (ME-G).

[v] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

[w] In patients with very-low-risk stage IIIA disease (non-ulcerated primary, SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit.

[x] 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.

[y] Adjuvant dabrafenib/trametinib and pembrolizumab are category 1 options for patients with AJCC 7th Edition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease. Adjuvant nivolumab is a category 1 option for patients with AJCC 7th Edition stage IIIB/C disease.

[z] Randomized clinical trials testing adjuvant anti-PD-1 therapy included patients with sentinel node-positive disease at high risk: those with ulcerated primary (nivolumab, pembrolizumab) or an SLN metastasis >1 mm (pembrolizumab).

[aa] All patients in the clinical trials studying adjuvant anti-PD-1 or adjuvant dabrafenib/trametinib were required to undergo CLND prior to randomization. In the setting of two prospective trials demonstrating that CLND has no impact on DSS or OS, it is unclear whether CLND should be a factor in the decision to use either adjuvant therapy in sentinel node-positive patients.

[bb] The randomized clinical trial testing adjuvant dabrafenib/trametinib combination therapy for patients with *BRAF* V600E/K mutation included patients with sentinel node-positive disease at high risk: those with ulcerated primary and/or SLN metastasis >1 mm.

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.

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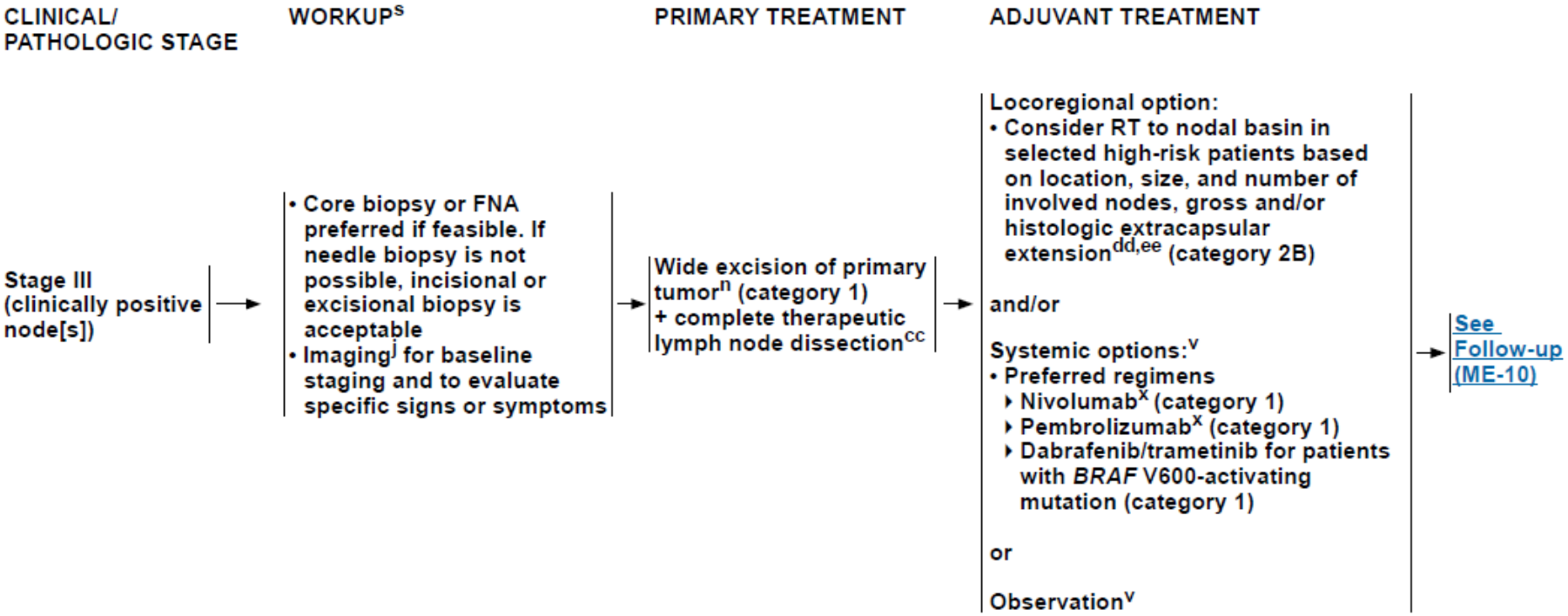
Cutaneous Melanoma



[j] See Principles of Imaging–Workup (ME-D).
[n] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-E).
[s] *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C).
[v] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.
[x] 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.
[cc] In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.
[dd] Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. 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.
[ee] See Principles of Radiation Therapy for Melanoma (ME-H).

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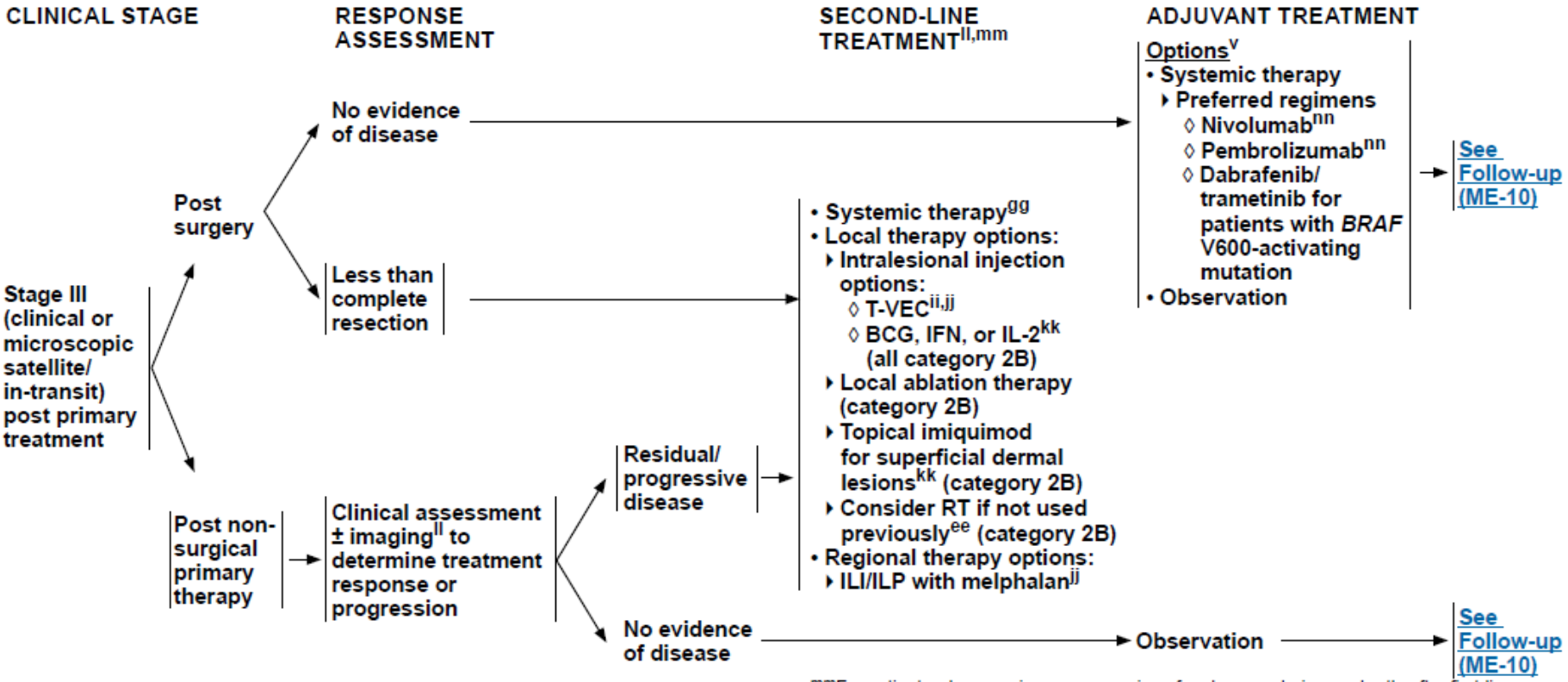

[v]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

[ee]See Principles of Radiation Therapy for Melanoma (ME-H).

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

[ii]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.

[jj]These options have been preference stratified as "Preferred Regimens."

[kk]These options have been preference stratified as "Useful In Certain Circumstances."

[ll]See Principles of Imaging–Treatment Response Assessment (ME-D).

[mm]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.

[nn]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.

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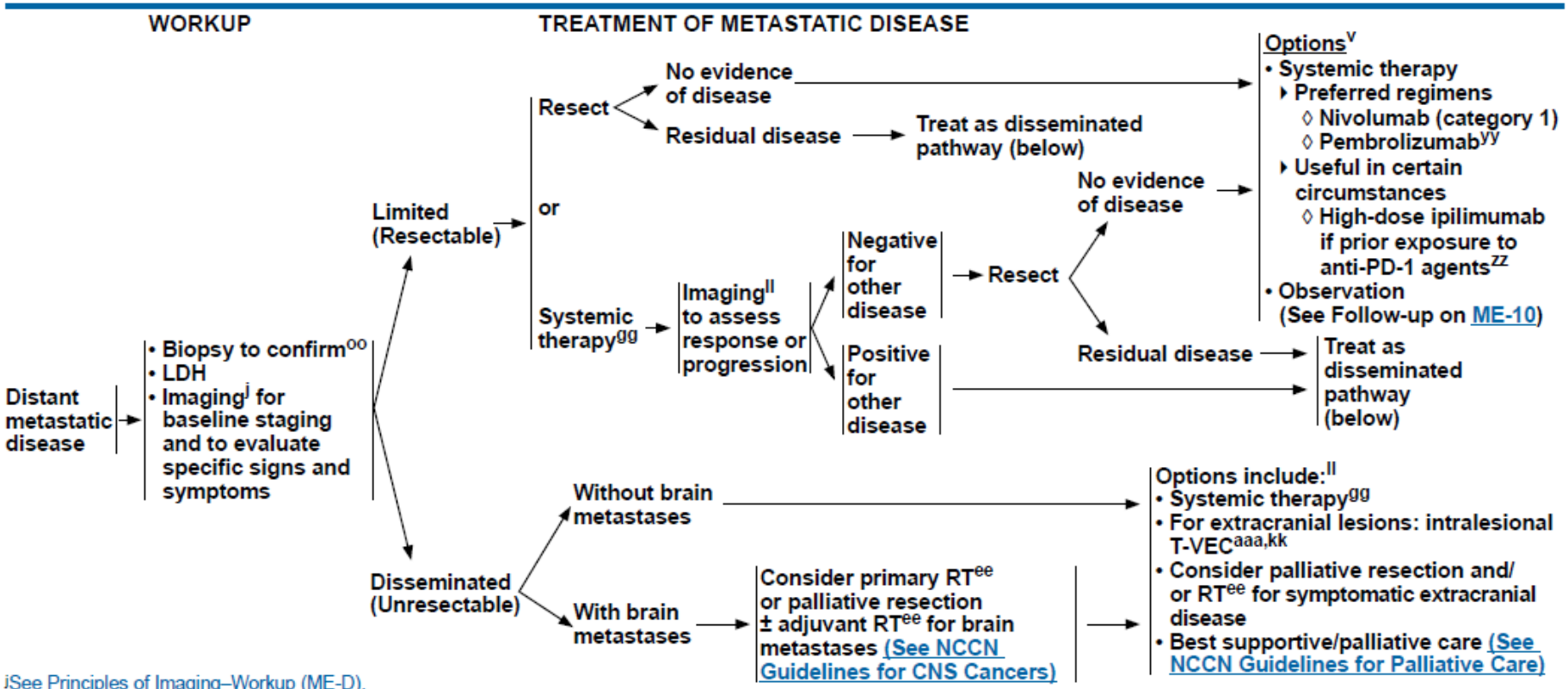

[j] See Principles of Imaging–Workup (ME-D).

[v] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

[ee] See Principles of Radiation Therapy for Melanoma (ME-H).

[gg] See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).

[kk] These options have been preference stratified as "Useful In Certain Circumstances."

[ll] See Principles of Imaging–Treatment Response Assessment (ME-D).

[oo] Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include FNA, core, incisional, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B) and See Principles of Molecular Testing (ME-C).

[yy] Although patients with resected stage IV disease were not included in the phase III prospective randomized trial testing adjuvant pembrolizumab, it is included as an option here because all available evidence suggests that pembrolizumab and nivolumab have highly similar efficacy and safety in patients with melanoma.

[zz] Ipilimumab is included as an adjuvant treatment option for patients with resected stage IV disease who have prior exposure to anti-PD-1 agents based on extrapolation of data demonstrating its efficacy as adjuvant treatment for resected stage III disease and demonstrated efficacy for unresectable stage IV disease.

[aaa] T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with AJCC 7th Edition stage IV-M1a disease (skin, subcutaneous, and/or remote nodes).

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]

FIRST-LINE THERAPY[2]

Metastatic or unresectable disease →

- **Preferred regimens**
  - **Anti PD-1 monotherapy[3,4]**
    - ◊ **Pembrolizumab (category 1)**
    - ◊ **Nivolumab (category 1)**
  - **Combination targeted therapy if *BRAF* V600-activating mutation;[6] preferred if clinically needed for early response[7,8,9,10]**
    - ◊ **Dabrafenib/trametinib (category 1)**
    - ◊ **Vemurafenib/cobimetinib (category 1)**
    - ◊ **Encorafenib/binimetinib (category 1**
- **Useful in certain circumstances**
  - **Nivolumab/ipilimumab (category 1)[3,4,5]**

→ **Disease progression or Maximum clinical benefit from BRAF targeted therapy** →

SECOND-LINE OR SUBSEQUENT THERAPY[11]

- **Systemic therapy**
  - **Preferred regimens**
    - ◊ **Anti PD-1 monotherapy[3,4]**
      - – **Pembrolizumab**
      - – **Nivolumab**
    - ◊ **Nivolumab/ipilimumab[3,4,5]**
    - ◊ **Combination targeted therapy if *BRAF* V600-activating mutation[8,9,10]**
      - ▪ **Dabrafenib/trametinib**
      - ▪ **Vemurafenib/cobimetinib**
      - ▪ **Encorafenib/binimetinib**
  - **Other regimens**
    - ◊ **Ipilimumab[3]**
    - ◊ **High-dose IL-2[12]**
  - **Useful in certain circumstances**
    - ◊ **Ipilimumab[3]/intralesional T-VEC (category 2B)**
    - ◊ **Cytotoxic agents[13]**
    - ◊ **Imatinib for tumors with activating mutations of *KIT***
    - ◊ **Larotrectinib for *NTRK* gene fusion positive tumors**
- **Consider best supportive care for poor performance status (See NCCN Guidelines for Palliative Care)**

[1] See Principles of Imaging – Treatment Response Assessment (ME-D).
[2] The choice of a treatment is based on evaluation of the individual patient.
[3] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[4] The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B).
[5] Nivolumab/ipilimumab combination therapy is associated with improved ORR, PFS, and OS compared with single-agent ipilimumab, at the expense of significantly increased toxicity. Compared to nivolumab, the impact of nivolumab/ipilimumab combination therapy on OS is not known. The phase III trial of nivolumab/ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma. Relative indications for combination nivolumab/ipilimumab in comparison to PD-1 monotherapy include: patient willingness to take on high risk of treatment-related toxicities (irAEs); absence of comorbidities or autoimmune processes that would elevate the risk of irAEs; patient social support and anticipated compliance with medical team to handle toxicities; and absent/low tissue PD-L1.
[6] Positive VE1 IHC results are sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Due to the risk of false positives and false negatives, all VE1 IHC results should be confirmed by sequencing. See Principles of Molecular Testing (ME-C).
[7] Because BRAF/MEK inhibitors have a shorter time to response compared with checkpoint immunotherapies, they may be preferred in patients with rapidly progressing disease and/or symptoms.
[8] See Management of Toxicities Associated with Targeted Therapy (ME-J).
[9] In previously untreated patients with unresectable AJCC 7th Edition stage IIIC or stage IV disease, BRAF/MEK inhibitor combination therapy was associated with improved response rate, PFS, and OS compared to BRAF inhibitor monotherapy.
[10] If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
[11] 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 progressed on single-agent checkpoint immunotherapy, nivolumab/ipilimumab combination therapy is a reasonable treatment option. 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.
[12] High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[13] For a list of cytotoxic regimens, see (ME-I 2 of 5).

Continued

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Thank you