STUDIENERGEBNISSE MELANOM

- OPDIVO® ADJUVANT
- OPDIVO® + YERVOY® Kombination

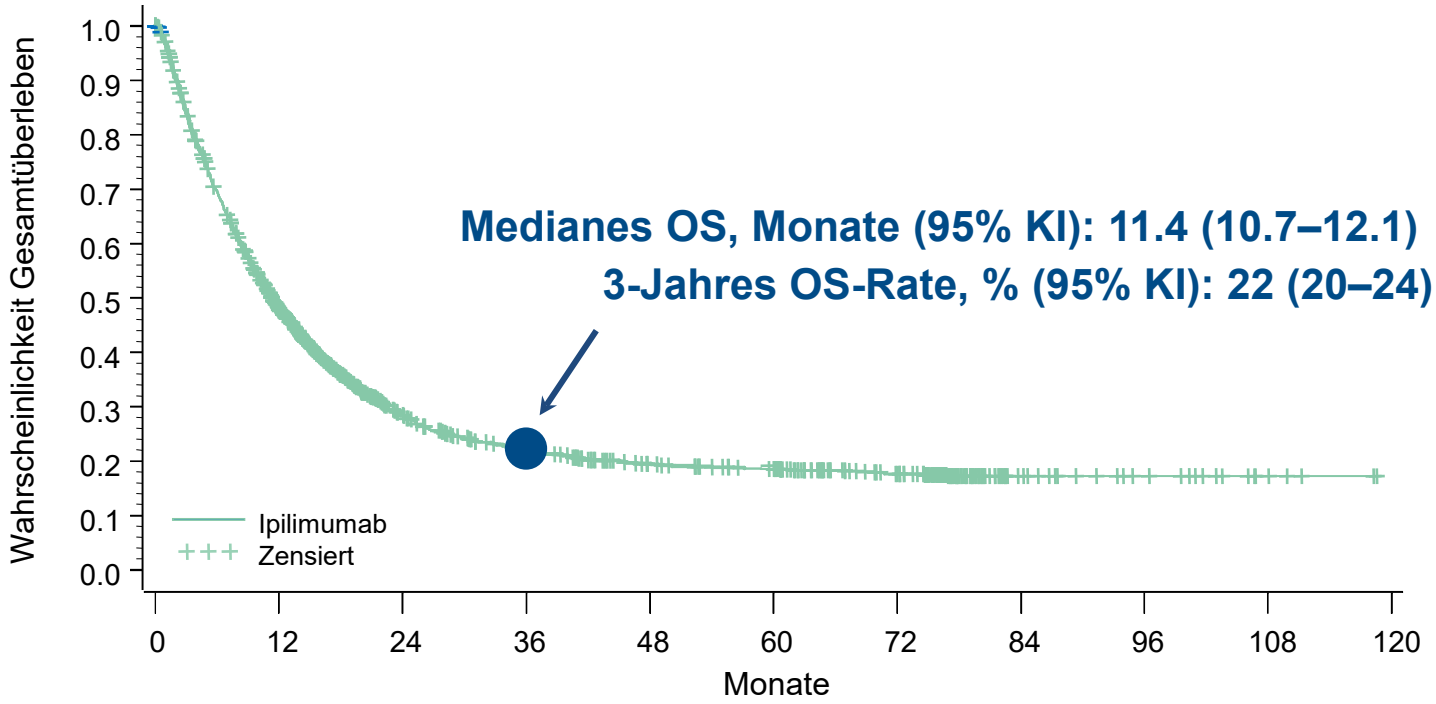
Bristol Myers Squibb™

Immunonkologie

7356-DE-2200225 06/2022

Die Immunonkologie: Proof of Concept

- Langzeitdaten Ipilimumab von 1.861 Melanompatienten (8 Ph. II-, 2 Ph. III-, 2 Ph. IV-Studien)



Patienten unter Progressionsrisiko

Ipilimumab	1.861	839	370	254	192	170	120	26	15	5	0

Schadendorf D et al. JCO, 2015; DOI: 10.1200/JCO.2014.56.2736

Immunonkologie

Inhalte

Immunonkologie

OPDIVO® Adjuvant
Melanom

CheckMate 238

Bristol Myers Squibb™

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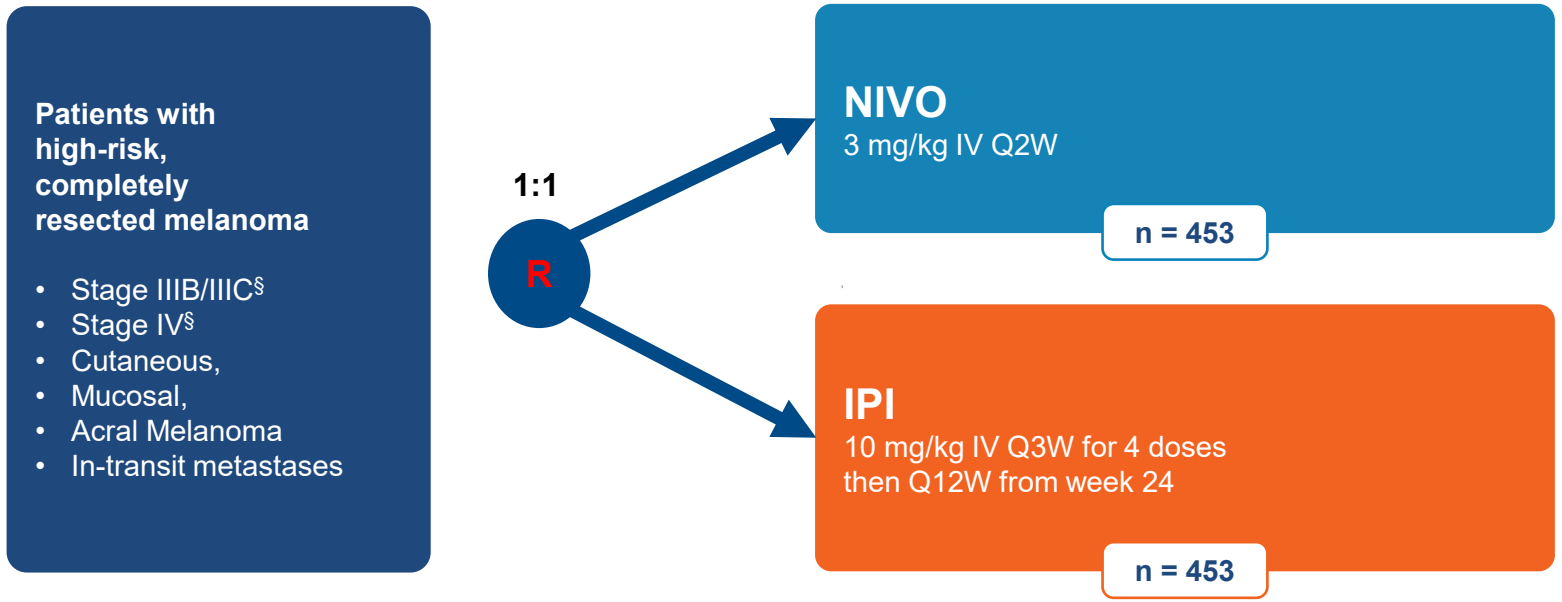
CheckMate 238: Introduction

- A clinical need exists for the adjuvant treatment of high-risk, stage III/IV resected melanoma
  - 5-year recurrence rates are 50%–80%, and most occur within 3 years for stage III melanoma[1–4]
- Interferon is approved in both the USA and the EU as adjuvant therapy for resected high-risk melanoma, but it is not widely used[5]
  - In the phase III EORTC 18071 trial, ipilimumab (IPI) 10 mg/kg demonstrated a significant improvement in recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS) vs placebo[5, 6]
  - RFS began to plateau after 3 years, with IPI RFS rates of 52%, 46%, 43%, and 41% at 2, 3, 4, and 5 years, respectively
  - However, > 50% of patients treated with ipilimumab experienced a grade 3–4 adverse event[6]
  - IPI 10 mg/kg received FDA approval in 2015 for the adjuvant treatment of completely resected stage III melanoma and is not approved in Europe
- The phase III CheckMate 238 trial demonstrated significantly longer recurrence-free survival (RFS) for nivolumab (NIVO) and a lower rate of grade 3/4 adverse events compared with IPI 10 mg/kg in patients with resected stage IIIB/IIIC or IV melanoma[7]
  - In July 2018, the EMA approved NIVO treatment in patients with melanoma with lymph node involvement or metastatic disease who had undergone complete resection, in the adjuvant setting

1. Leiter U et al. *J Am Acad Dermatol*. 2012;66:37–45. 2. Romano E et al. *J Clin Oncol*. 2010;28:3042–3047. 3. Meyers MO et al. *Ann Surg Oncol*. 2009;16:941–947. 4. Tas F et al. *Melanoma Res.* 2017;27:134–139. 5. Eggermont AMM et al. *Lancet Oncol*. 2015;16:522–530. 6. Eggermont AMM et al. *N Engl J Med.* 2016;375: 1845–1855. 7. Weber J et al. *N Engl J Med*. 2017;377:1824–1835.

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: A Randomized, Double-blind, Phase 3 Trial (CheckMate 238)



Follow-up
Maximum treatment duration of 1 year

Primary endpoint
RFS#

Secondary endpoint
OS, Safety and tolerability, RFS by PD-L1 tumor expression, HRQoL

Exploratory endpoint
Distant metastasis-free survival (DMFS)s

Stratified by:

- Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c*
- PD-L1 status at a 5% cutoff in tumor cells

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

* ECOG PS 0-1, # RFS: time from randomization until first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, § Stadieneinteilung AJCC-Classifikation, 7th Edition 2007.

Weber J et al. *N Engl J Med*, 2017;377:1824-35

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CheckMate 238: Key Eligibility Criteria

- At least 15 years of age
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Histologically confirmed melanoma metastatic to regional lymph nodes or with distant metastases surgically rendered free of disease
  - Stage IIIB, IIIC, or stage IV melanoma by the American Joint Committee on Cancer 2009 classification, 7th edition
  - Complete regional lymphadenectomy or resection was required within 12 weeks of randomization
- Patients with ocular/uveal melanoma, systemic corticosteroid use > 10 mg/day of prednisone or equivalent, or previous systemic therapy for melanoma were excluded
  - Acral and mucosal melanoma were allowed

Weber J et al. ASCO, 2018; Oral Presentation

Baseline Patient Characteristics and Treatment Summary

	NIVO (n = 453)	IPI (n = 453)
Median age, years	**56**	**54**
Male, %	**57**	**59**
Stage, IIIB+IIIC, %	**81**	**81**
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	**18**	**19**
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression ≥ 5%,[a] %	**34**	**34**
BRAF mutation, %	**41**	**43**
LDH ≤ ULN, %	**91**	**91**
Melanoma subtype, %		
Cutaneous	86	83
Mucosal	4	3
Acral	4	4

- Median doses were **24** (1–26) in the NIVO group and **4** (1–7) in the IPI group[1]
- 61% of patients in the NIVO group and 27% in the IPI group completed 1 year of treatment[1]

[a]PD-L1 IHC 28-8 pharmDx assay. LDH, lactate dehydrogenase; ULN, upper limit of normal.

1. Weber J et al. ASCO, 2018; Oral Presentation
Modified to Weber J et al. ESMO, 2019; Oral Presentation

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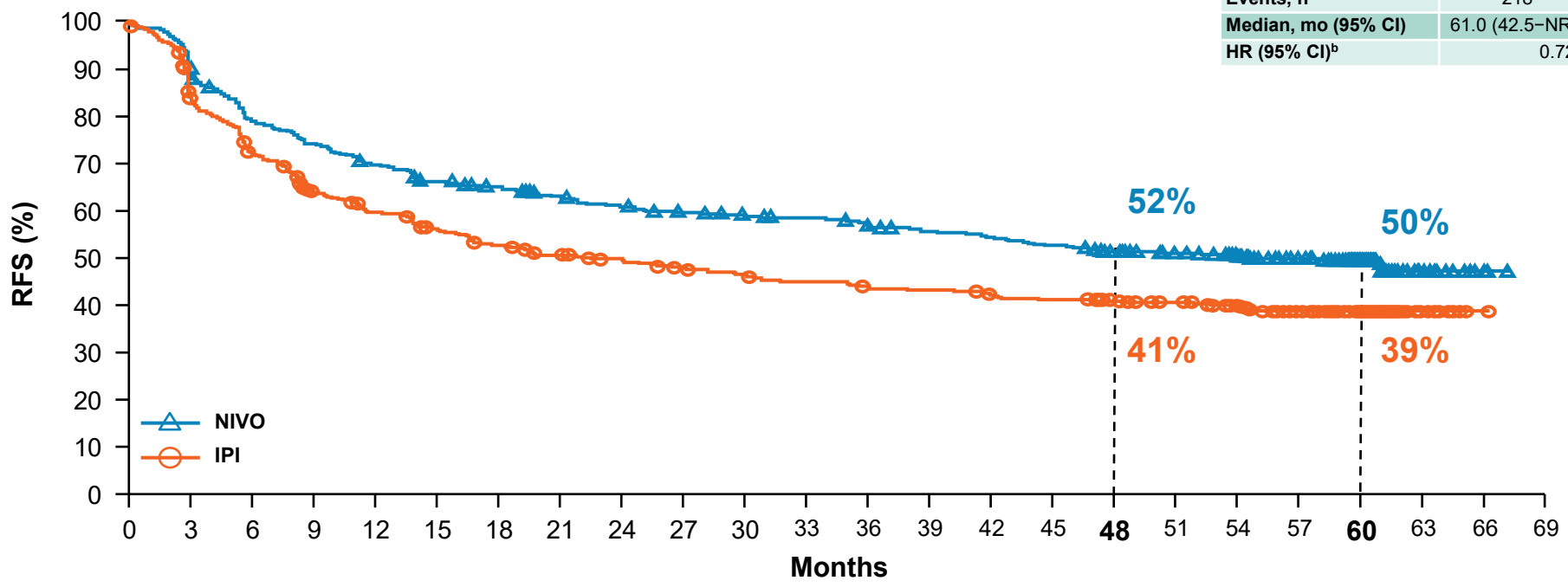
CheckMate 238: Primary endpoint: 60-month RFS update in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	218	257
Median, mo (95% CI)	61.0 (42.5–NR)[a]	24.1 (16.6–35.1)
HR (95% CI)[b]	0.72 (0.60–0.86)	



No. at risk																							
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	234	225	220	213	202	191	176	147	94	17	4	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	178	173	170	165	159	152	145	134	114	78	18	1	0

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

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen.

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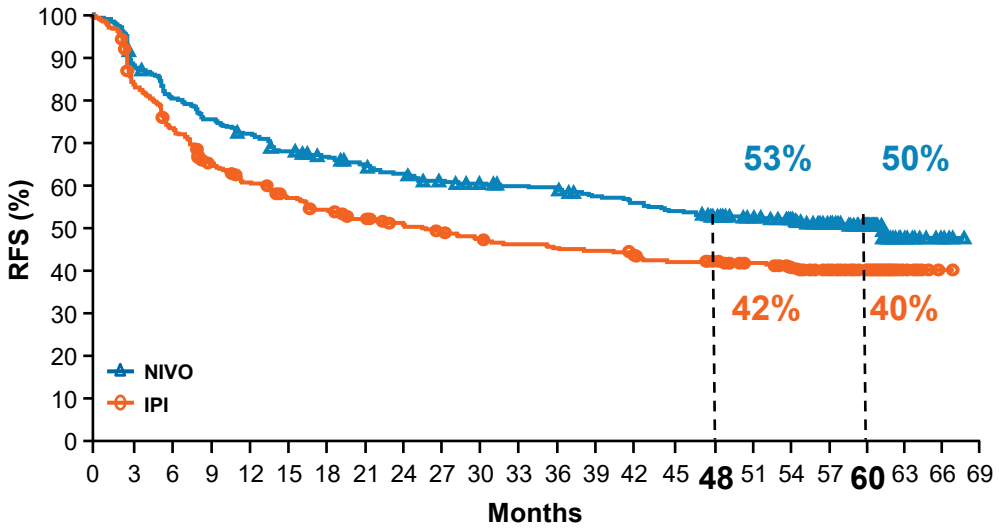
CheckMate 238: Subgroup analysis: 60–month RFS update by disease stages IIIB–C and IV

Stage IIIB–C

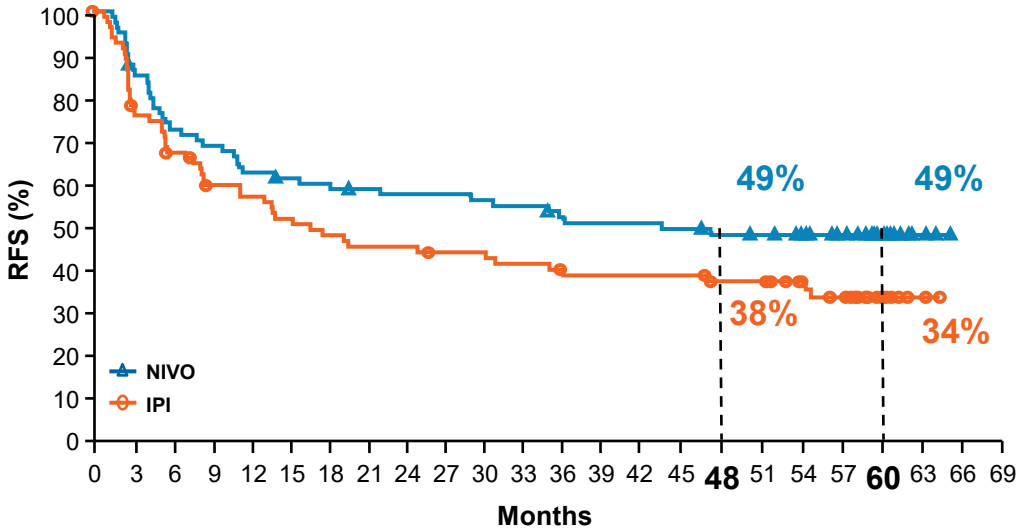
	NIVO (n = 370)	IPI (n = 366)
Events, n	176	205
Median, mo (95% CI)	61.0 (42.9–NR)	25.5 (16.6–38.0)
HR (95% CI)[a]	0.73 (0.60–0.89)	



No. at risk																									
NIVO 3 mg/kg	370	323	294	275	260	244	235	225	217	205	201	197	194	186	181	175	166	156	143	119	78	14	4	0
IPI 10 mg/kg	366	301	261	226	208	193	182	172	165	157	151	146	143	141	136	130	126	119	111	96	68	16	1	0

Stage IV

	NIVO (n = 82)	IPI (n = 87)
Events, n	41	52
Median, mo (95% CI)	47.4 (15.9–NR)	16.8 (8.5–47.2)
HR (95% CI)[a]	0.71 (0.47–1.06)	



No. at risk																									
NIVO 3 mg/kg	82	71	59	56	51	49	48	46	45	45	44	43	40	39	39	38	36	35	33	28	16	3	0	0
IPI 10 mg/kg	87	65	55	47	45	41	38	36	36	34	34	32	30	29	29	29	26	26	23	18	10	2	0	0

[a]Unstratified.

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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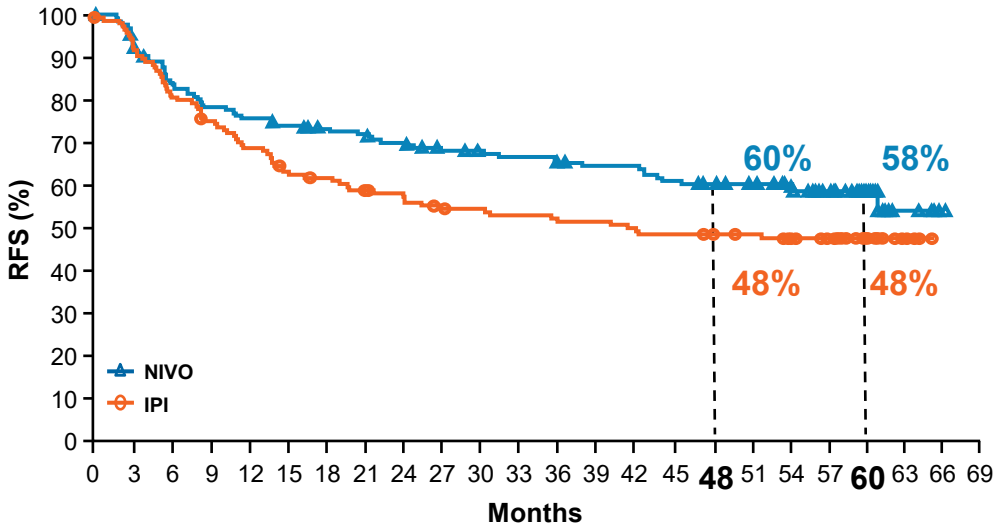
CheckMate 238: Subgroup analysis: 60–month RFS update by disease stages IIIB and IIIC

Stage IIIB

	NIVO (n = 166)	IPI (n = 147)
Events, n	65	74
Median, mo (95% CI)	NR (61.1–NR)	41.7 (21.8–NR)
HR (95% CI)[a]	0.72 (0.52–1.01)	

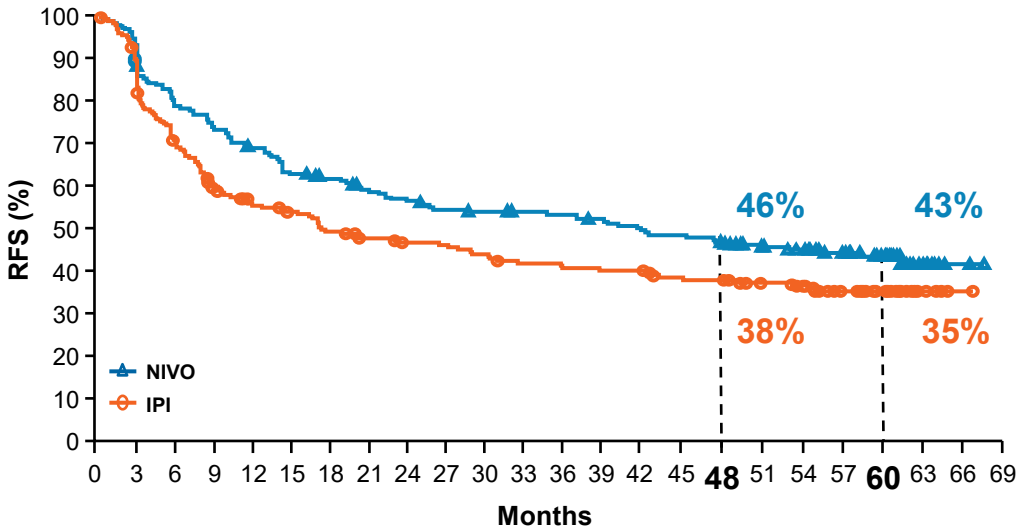


No. at risk

NIVO 3 mg/kg	166	149	134	125	121	117	113	111	107	100	98	96	94	91	91	86	83	80	73	58	36	5	1	0
IPI 10 mg/kg	147	133	117	107	98	89	86	82	79	73	72	70	69	68	66	64	63	60	57	50	35	8	0	0

Stage IIIC

	NIVO (n = 202)	IPI (n = 219)
Events, n	111	131
Median, mo (95% CI)	40.9 (22.1–61.0)	16.8 (10.8–29.6)
HR (95% CI)[a]	0.76 (0.59–0.97)	



No. at risk

NIVO 3 mg/kg	202	172	158	148	137	125	120	112	108	103	101	99	98	93	88	87	81	74	68	59	40	9	3	0
IPI 10 mg/kg	219	168	144	119	110	104	96	90	86	84	79	76	74	73	70	66	63	59	54	46	33	8	1	0

[a]Unstratified.

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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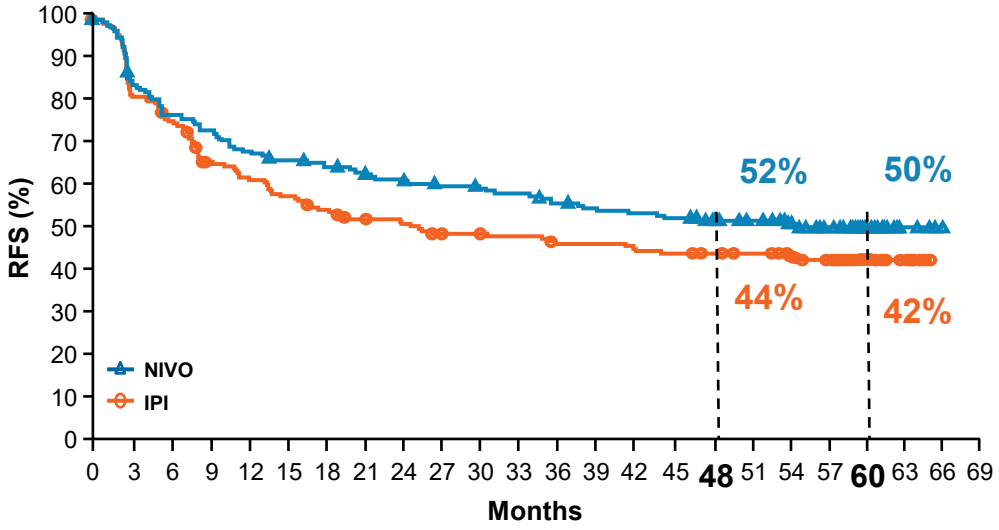
CheckMate 238: Subgroup analysis: 60–month RFS update by BRAF mutation status

BRAF Mutant[a]

	NIVO (n = 187)	IPI (n = 194)
Events, n	90	106
Median, mo (95% CI)	NR (35.0–NR)	25.5 (15.9–55.1)
HR (95% CI)[b]	0.80 (0.60–1.05)	

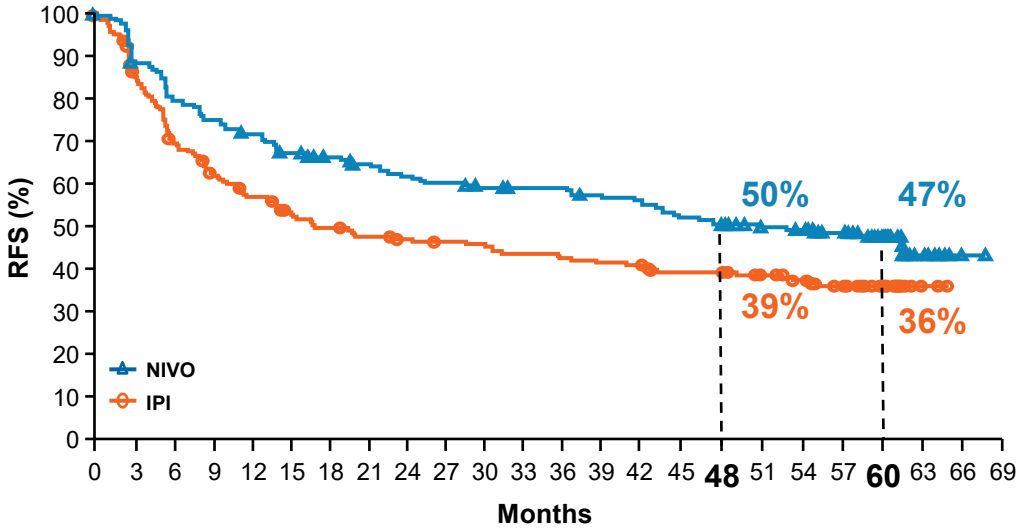


No. at risk

NIVO 3 mg/kg	187	157	142	135	126	121	119	114	110	104	103	100	95	92	90	88	83	79	72	57	37	6	2	0
IPI 10 mg/kg	194	156	143	120	113	105	98	92	91	84	83	81	78	77	76	73	70	68	66	56	40	12	0	0

BRAF wild-type

	NIVO (n = 197)	IPI (n = 212)
Events, n	100	125
Median, mo (95% CI)	50.2 (36.3–NR)	16.6 (11.6–35.1)
HR (95% CI)[a]	0.69 (0.53–0.90)	



No. at risk

NIVO 3 mg/kg	197	173	155	145	137	128	121	116	111	108	104	102	101	97	94	89	84	78	73	64	40	8	1	0
IPI 10 mg/kg	212	173	139	122	110	99	93	88	85	83	81	78	76	74	70	67	64	61	54	46	31	3	0	0

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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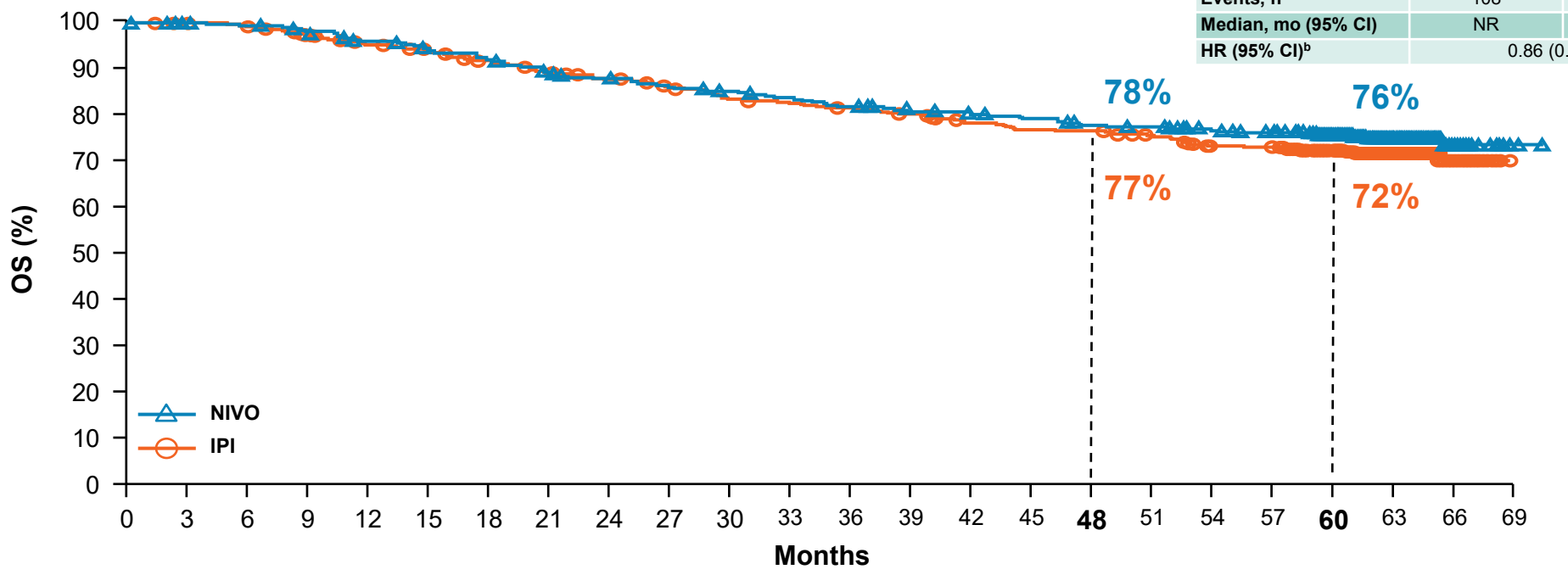
CheckMate 238: Secondary endpoint: 60-month OS update in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	108	120
Median, mo (95% CI)	NR	NR
HR (95% CI)[b]	0.86 (0.66–1.12)	



No. at risk																								
NIVO 3 mg/kg	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	321	312	305	280	178	42	0	0
IPI 10 mg/kg	453	447	442	430	416	407	395	382	373	362	350	345	340	333	322	316	315	306	294	292	261	155	36	0	0

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

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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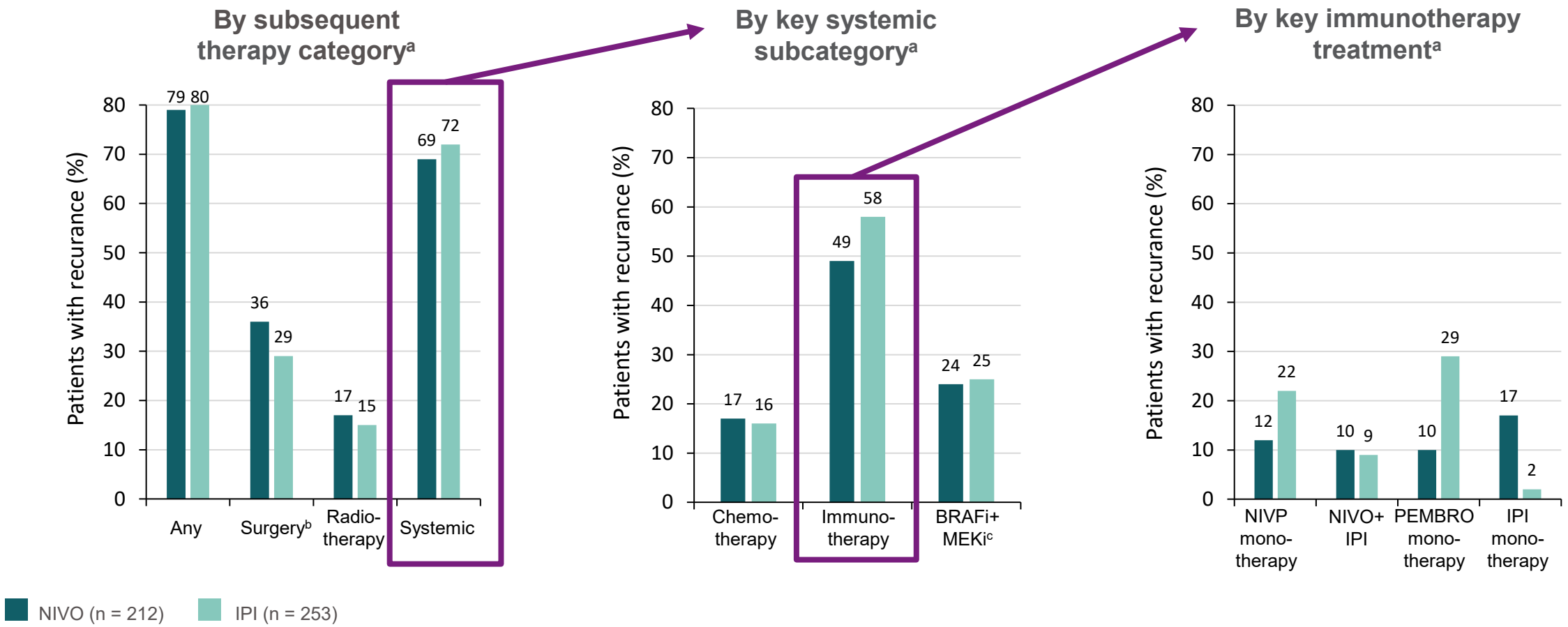
CheckMate 238: Subsequent therapy in patients with recurrence

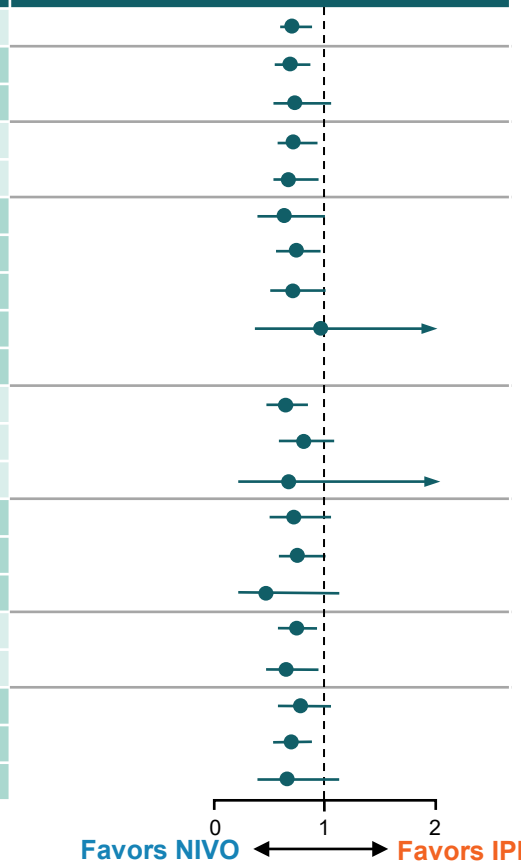


[a]Some patients received >1 post-protocol therapy type/agent; [b]Includeddiagnostic checks and biopsy; [c]Dabrafeniband trametinib and/or cobimetiniband vemurafenib. PEMBRO, pembrolizumab.

Modified to Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

CheckMate 238: 60-Month RFS update: pre-specified subgroup analysis

Subgroup		NIVO 3 mg/kg n/N	IPI 10 mg/kg n/N	Unstratified HR (95% CI)
Overall	Overall	218/453	257/453	0.73 (0.61–0.87)
Age	< 65 years	147/333	184/339	0.70 (0.57–0.88)
	≥ 65 years	71/120	73/114	0.76 (0.55–1.06)
Sex	Male	131/258	157/269	0.74 (0.59–0.93)
	Female	87/195	100/184	0.71 (0.54–0.95)
Stage	IIIB	65/166	74/147	0.72 (0.52–1.01)
	IIIC	111/202	131/219	0.76 (0.59–0.97)
	IV M1a–M1b	32/62	43/66	0.64 (0.40–1.01)
	IV M1c	9/20	9/21	0.98 (0.39–2.47)
	Not reported	1/1	0/0	–
Stage III: ulceration	Absent	81/201	115/213	0.65 (0.49–0.87)
	Present	89/155	83/137	0.81 (0.60–1.09)
	Not reported	6/14	7/16	0.67 (0.22–2.02)
Stage III: lymph node involvement	Microscopic	58/128	72/134	0.75 (0.53–1.06)
	Macroscopic	109/217	122/214	0.75 (0.58–0.98)
	Not reported	9/25	11/18	0.47 (0.19–1.13)
Tumor PD-L1 status[b]	< 5% or indeterminate	161/300	183/299	0.75 (0.61–0.93)
	≥ 5%	57/153	74/154	0.66 (0.47–0.94)
***BRAF* mutation status[c]**	Positive	90/187	106/194	0.80 (0.60–1.05)
	Negative	100/197	125/212	0.69 (0.53–0.90)
	Not reported	28/69	26/47	0.66 (0.39–1.13)

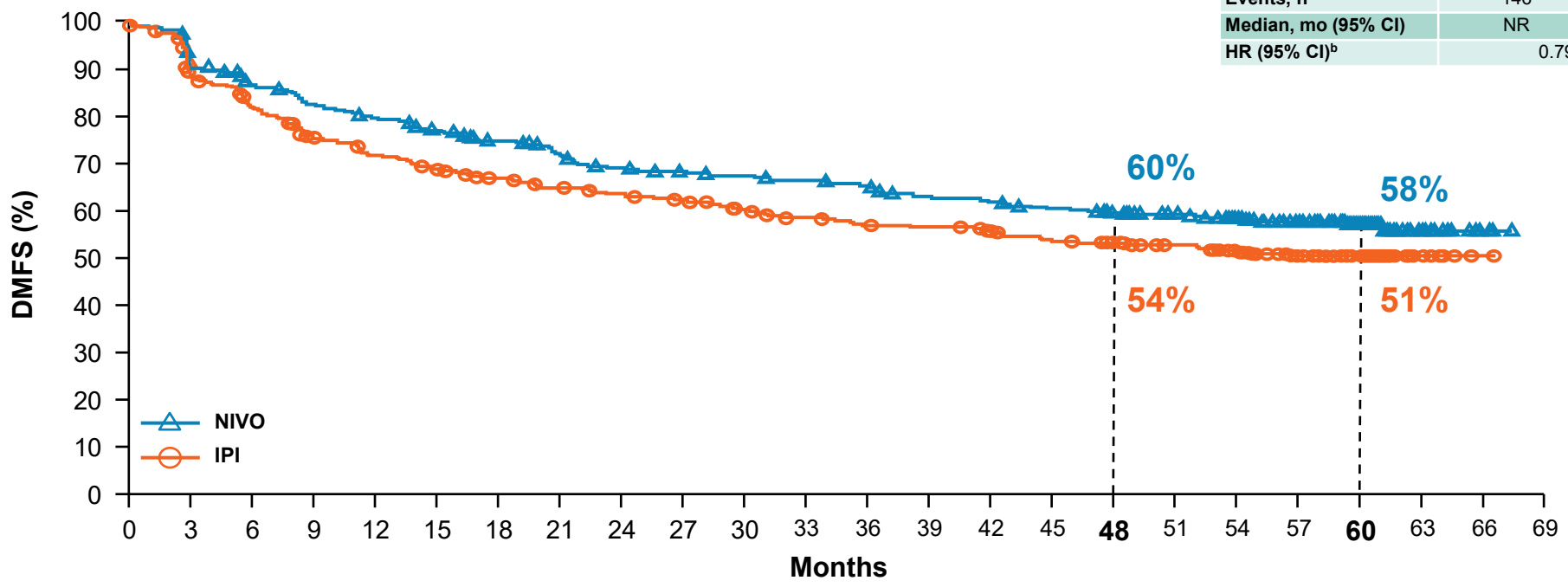


[a]Stratified HR = 0.72 (95% CI, 0.60–0.86); [b]PD–L1 IHC 28–8 pharmDx assay; status determined as percentage of tumor cells; [c]V600E/K.

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

CheckMate 238: Exploratory endpoint: 60-month DMFS update in stage IIIB–C patients

	NIVO (n = 370)	IPI (n = 366)
Events, n	146	164
Median, mo (95% CI)	NR	NR (42.4–NR)
HR (95% CI)[b]	0.79 (0.63–0.99)	



No. at risk																							
NIVO 3 mg/kg	370	334	312	295	284	272	256	243	232	223	220	216	210	200	197	191	182	172	156	130	87	20	4	0
IPI 10 mg/kg	366	314	287	257	244	233	222	213	206	200	188	180	173	171	163	156	150	139	130	111	76	17	2	0

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

Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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CheckMate 238: Post-protocol Treatment

Treatment, n (%)[a]	NIVO (n = 453)	IPI (n = 453)
Any	141 (31.1)	186 (41.1)
Systemic therapy	100 (22.1)	151 (33.3)
Chemotherapy	28 (6.2)	30 (6.6)
Immunotherapy	60 (13.2)	119 (26.3)
Nivolumab[b]	20 (4.4)	52 (11.5)
Pembrolizumab	13 (2.9)	72 (15.9)
Anti-PD-1 agent	1 (0.2)	2 (0.4)
Ipilimumab[b]	44 (9.7)	19 (4.2)
Other CTLA-4 inhibitor	1 (0.2)	1 (0.2)
BRAF inhibitor[c]	47 (10.4)	45 (9.9)
MEK inhibitor[c]	38 (8.4)	1 (0.2)
Surgery[d]	73 (16.1)	68 (15.0)
Radiotherapy	26 (5.7)	27 (6.0)

a Patients may have received more than one type of post-protocol therapy and more than one agent within each type. All percentages are based on total number of patients in each group.
b May include patients treated with NIVO+IPI combination. c May include patients treated with BRAF+MEK combination. d Includes tumor resection for diagnostic purposes and biopsies

Weber J et al. ASCO, 2018; Oral Presentation

CheckMate 238: Safety Summary

	NIVO (n = 452)		IPI (n = 453)	
	Any AE n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
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

Weber J et al. ESMO, 2017; Oral Presentation

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CheckMate 238: Treatment-Related Select Adverse Events

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

- Median time to onset of treatment-related select AEs was generally shorter for patients receiving IPI (range 2.6–10 weeks) than for those receiving NIVO (range 3.3–14.2 weeks)

Weber J et al. ESMO, 2017; Oral Presentation

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CheckMate 238: Conclusions

- Nivolumab continues to be an effective adjuvant treatment for patients with resected high-risk melanoma at 5 years, with sustained recurrence free- and distant metastasis-free survival benefit versus the active comparator ipilimumab
  - RFS HR, 0.72 (95% CI, 0.60−0.86); DMFS HR, 0.79 (95% CI, 0.63−0.99)
  - The RFS benefit was observed across patient subgroups

- OS data continue to be immature
  - The HR for OS (0.86 [95% CI, 0.66–1.12]) was similar to the 48-month follow-up, with 17 additional events
  - 5-year OS rates were 76% (NIVO) and 72% (IPI), compared with the 4-year 78% and 77% rates

- More patients treated with IPI received subsequent immunotherapy
- Safety data within 100 days after last dose were published previously[1]
- These data further support the use of NIVO in resected stage III/IV melanoma

RFS = recurrence-free survival

Modified to Weber J, Larkin J, Mandalá M et al. Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB-C or IV melanoma (CheckMate 238). SMR 2021, Oral Presentation

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

Immunonkologie

OPDIVO® Adjuvant

Overall Survival, Cure Rate and RFS of Nivolumab vs. Placebo (indirect comparisons)

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Introduction adjusted indirect comparison CheckMate 238 vs EORTC 18071[1,2]

- The phase 3, randomized controlled trial (RCT) CheckMate 238 demonstrated the safety and efficacy of nivolumab as an adjuvant treatment for stage IIIB/C or IV melanoma (based on American Joint Committee on Cancer [AJCC] 7th edition staging criteria) versus ipilimumab[3]
- Because CheckMate 238 used an active comparator, there are currently no data directly comparing the efficacy of nivolumab versus routine surveillance (ie, placebo) in this indication. EORTC 18071 is a phase 3 RCT comparing ipilimumab with placebo in patients with resected stage IIIA–IIIC melanoma (based on AJCC 6th edition staging criteria)[4]
- Indirect treatment comparisons (ITCs) of nivolumab versus placebo were constructed to evaluate the relative efficacy of treatments in terms of recurrence-free survival (RFS) using data from CheckMate 238 and study EORTC 18071[2]

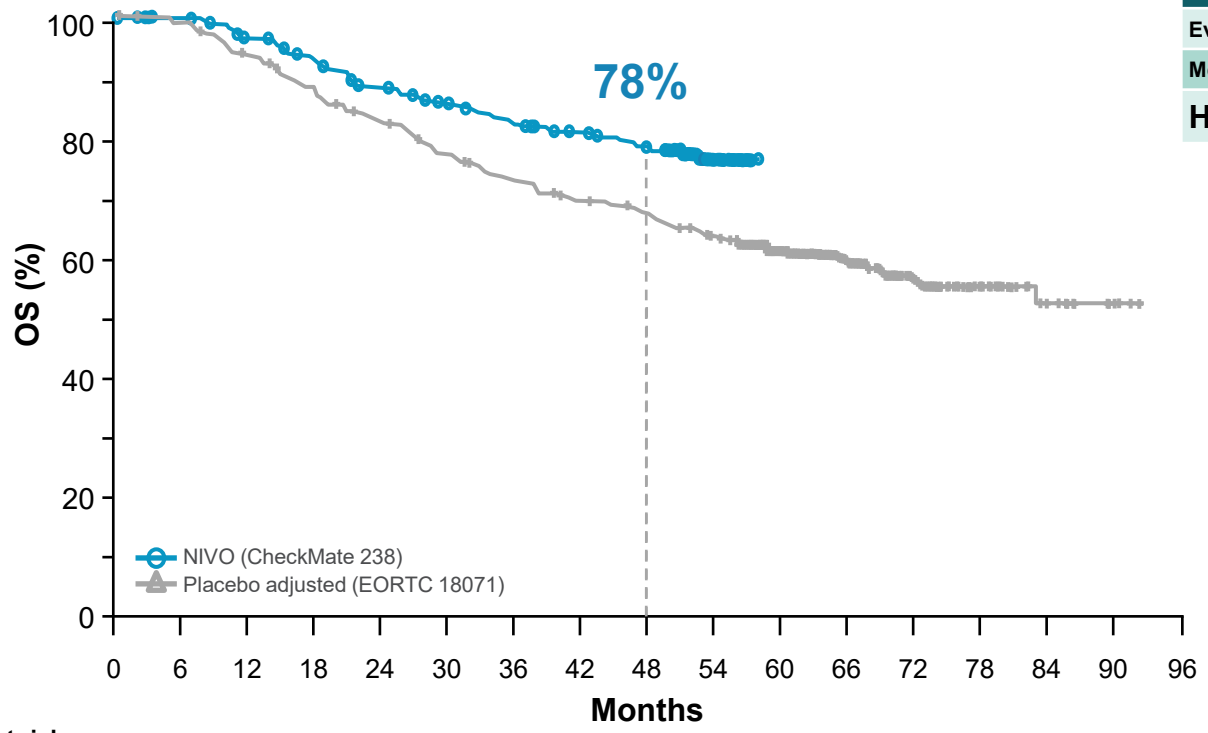
1. Modified to Hemstock M et al. SMR Congress 2018; Poster Presentation, 2. Weber J et al. SITC 2020, Poster Presentation #308,
3. Weber J, et al. N Engl J Med 2017;377:1824–1835., 4. Eggermont AM, et al. *N Engl J Med* 2016;375:1845–1855.

Immunonkologie

Overall Survival (OS) of Nivolumab vs Placebo

Indirect adjusted comparison from CheckMate 238 & EORTC 18071 *,#,1

OS in the NIVO arm in CheckMate 238 and the adjusted placebo arm in EORTC 18071[a, 1]



No. at risk

NIVO (CheckMate 238)	453	447	427	405	383	366	350	337	324	45	0	0	0	0	0	0	0
Placebo adjusted (EORTC 18071)	476	468	439	406	382	355	333	316	301	279	226	143	80	38	14	2	0

	NIVO (CheckMate 238)	Placebo adjusted (EORTC 18071)
Events, n	100/453	193/476
Median, mo (95% CI)	NR (NR–NR)	NR (81.7–NR)
HR (95% CI)[a]	**0.65 (0.45–0.91)**	

* Adjustierter indirekter Vergleich der beiden randomisierten, kontrollierten Studien CheckMate 238 und EORTC 18071 durch die Bucher Methode (Bucher HC et al. J Clin Epidemiol, 1997; 50(6): 683–691); minimale Nachbeobachtungszeit CheckMate 238 betrug 4 Jahre, mediane Nachbeobachtungszeit EORTC 18071 betrug 4,5 Jahre; Unter der Annahme einer Post-Rezidiv Überlebensrate von 63 % im Placebo-Arm, ausgeschlossen sind die Neuentwicklungen von Primärmelanomen in der CheckMate 238-Studie

Indirect Comparison; no Head-to-Head comparison

[a]Assuming a post-recurrence survival increase of 63% in the placebo arm. NR, not reached.

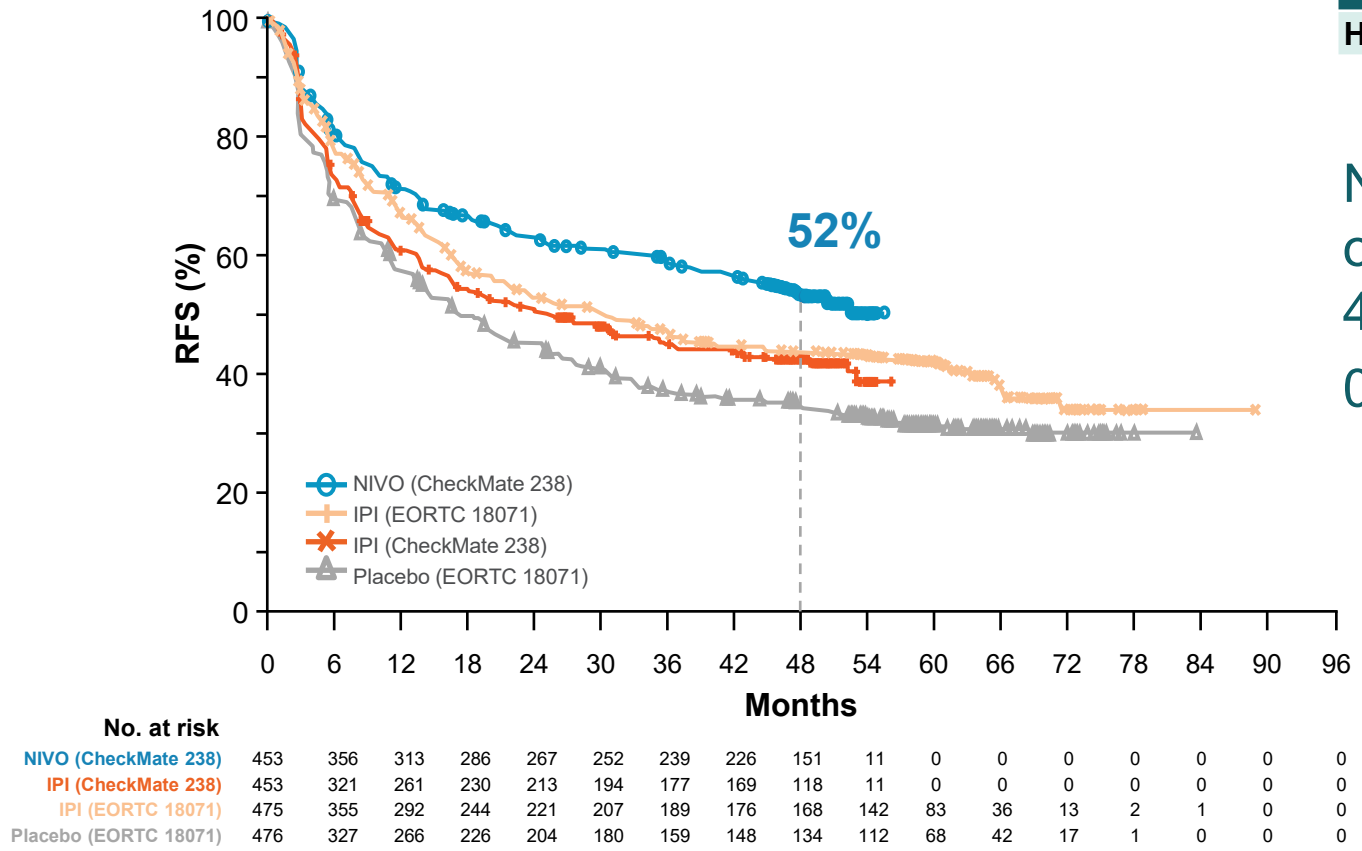
Modified to Weber J et al.: SITC 2020, Poster Presentation #308, 1. Weber J et al.: SITC 2020, Poster Presentation #308

Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen

Recurrence Free Survival (RFS) of Nivolumab vs Placebo

Indirect comparison from CheckMate 238 & EORTC 18071*,#,1

RFS in CheckMate 238 and EORTC 18071[1]



No. at risk																	
NIVO (CheckMate 238)	453	356	313	286	267	252	239	226	151	11	0	0	0	0	0	0	0
IPI (CheckMate 238)	453	321	261	230	213	194	177	169	118	11	0	0	0	0	0	0	0
IPI (EORTC 18071)	475	355	292	244	221	207	189	176	168	142	83	36	13	2	1	0	0
Placebo (EORTC 18071)	476	327	266	226	204	180	159	148	134	112	68	42	17	1	0	0	0

	NIVO vs Placebo*
HR (95% CI)	0.54 (0.43–0.69)

Nivolumab reduces the risk of recurrence vs placebo by 46%, HR (95% CI):

0,54 (0.43, 0.69)*, 1

* Indirekter Vergleich der beiden randomisierten, kontrollierten Studien CheckMate 238 und EORTC 18071 durch die Bucher Methode (Bucher HC et al. J Clin Epidemiol, 1997; 50(6): 683–691); minimale Nachbeobachtungszeit CheckMate 238 betrug 4 Jahre, mediane Nachbeobachtungszeit EORTC 18071 betrug 4,5 Jahre; Unter der Annahme einer Post-Rezidiv Überlebensrate von 63 % im Placebo-Arm, ausgeschlossen sind die Neuentwicklungen von Primärmelanomen in der CheckMate 238-Studie

Indirect Comparison; no Head-to-Head comparison

Modified to Weber J et al.: SITC 2020, Poster Presentation #308, 1. Weber J et al.: SITC 2020, Poster Presentation #308

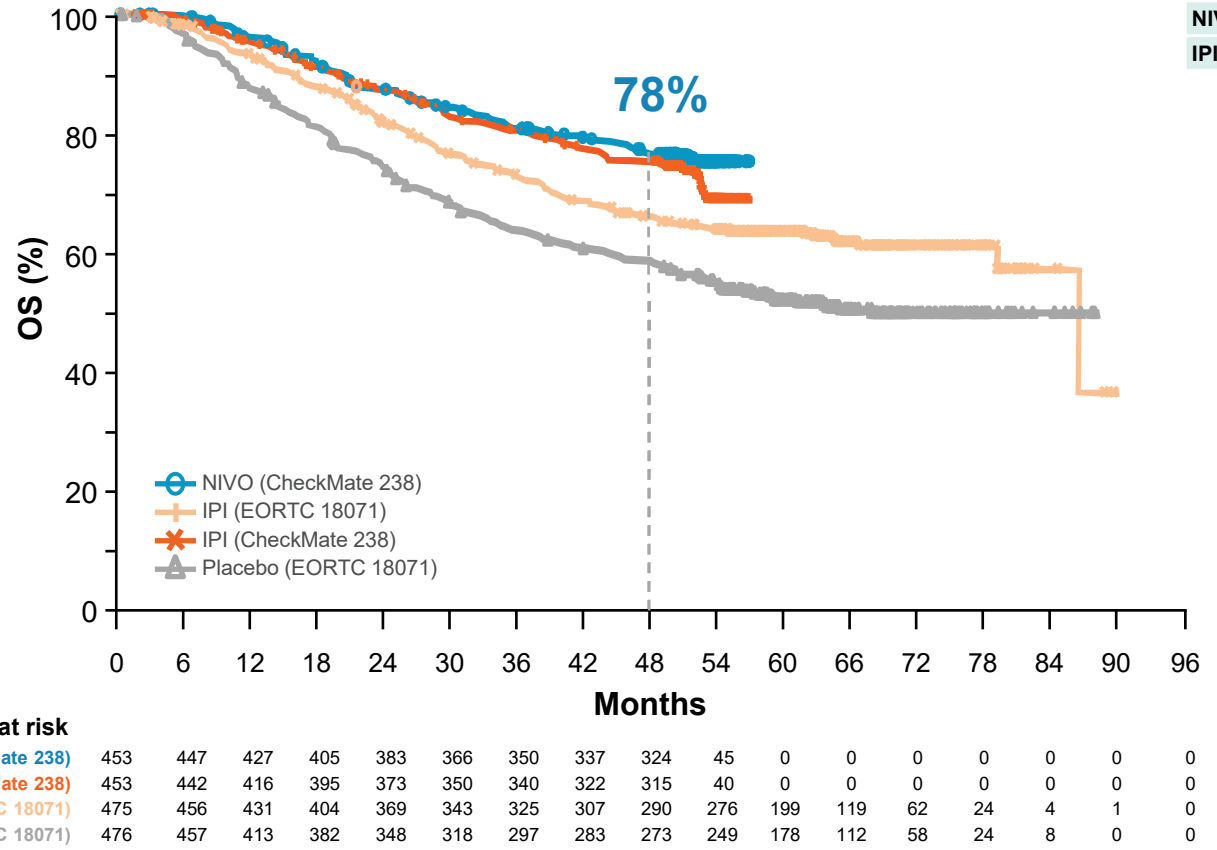
Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen

Immunonkologie

Overall Survival (OS) of Nivolumab vs Placebo

Indirect adjusted comparison from CheckMate 238 & EORTC 18071*,#,1

OS in CheckMate 238 and EORTC 18071[1, a]



No. at risk																	
NIVO (CheckMate 238)	453	447	427	405	383	366	350	337	324	45	0	0	0	0	0	0	0
IPI (CheckMate 238)	453	442	416	395	373	350	340	322	315	40	0	0	0	0	0	0	0
IPI (EORTC 18071)	475	456	431	404	369	343	325	307	290	276	199	119	62	24	4	1	0
Placebo (EORTC 18071)	476	457	413	382	348	318	297	283	273	249	178	112	58	24	8	0	0

	OS HR (95% CI)[a]
NIVO vs IPI (CheckMate 238)	0.87 (0.66–1.14)
IPI vs placebo (EORTC 18071)	0.72 (0.58–0.88)

* Adjustierter indirekter Vergleich der beiden randomisierten, kontrollierten Studien CheckMate 238 und EORTC 18071 durch die Bucher Methode (Bucher HC et al. J Clin Epidemiol, 1997; 50(6): 683–691); minimale Nachbeobachtungszeit CheckMate 238 betrug 4 Jahre, mediane Nachbeobachtungszeit EORTC 18071 betrug 4,5 Jahre; Unter der Annahme einer Post-Rezidiv Überlebensrate von 63 % im Placebo-Arm, ausgeschlossen sind die Neuentwicklungen von Primärmelanomen in der CheckMate 238-Studie

Indirect Comparison; no Head-to-Head comparison

[a]Assuming a post-recurrence survival increase of 63% in the placebo arm. NR, not reached.

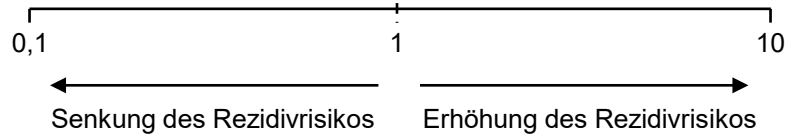
Modified to Weber J et al.: SITC 2020, Poster Presentation #308, 1. Weber J et al.: SITC 2020, Poster Presentation #308

Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen

Immunonkologie

Reduktion des Rezidivrisikos mit adjuvanten Therapien vs. Placebo im indirekten adjustierten Hazard Ratio-Vergleich[1]

Behandlungseffekt vs. Placebo aus Longo et al. 2019	Hazardrate HR für Rezidiv, Mittelwert (95 % Konfidenzintervall)
Ipilimumab*	0,60 (0,50 – 0,72)
Dabrafenib + Trametinib	0,45 (0,35 – 0,59)
Nivolumab	**0,37 (0,27 – 0,52)**
Pembrolizumab	0,48 (0,37 – 0,62)
Vemurafenib#	0,61 (0,42 – 0,88)



Unter den im adjuvanten Setting untersuchten Therapieoptionen gibt es nur für Nivolumab vs. Ipilimumab einen „Head-to-head"-Vergleich, alle anderen Therapien vergleichen sich vs. Placebo.

Eine Bayessche Netzwerk-Metaanalyse ist ein analytischer Ansatz, mit dem die neuen adjuvanten Behandlungen in Bezug auf ihre Effektivität und Sicherheit indirekt verglichen werden können. Beim Vergleich von Studien, die unterschiedliche Patientenkollektive beinhalten (BRAF-Mutationsstatus und TNM-Stadium), findet diese Methode Anwendung.[1]

Ein Ergebnis dieser Analyse zeigt, dass alle Behandlungsoptionen einen klaren RFS-Vorteil gegenüber Placebo erbringen.[1]

Ein weiteres Ergebnis zeigt für Nivolumab die höchste Wahrscheinlichkeit, das Rückfallrisiko am effektivsten zu senken (SUCRA-Analyse §). Stadium-IV-Patienten mithöherem Risiko waren nur in der CheckMate 238 eingeschlossen – dies unterstreicht die Bedeutung der Ergebnisse für Nivolumab im indirekten Vergleich zu anderen Therapien.[1]

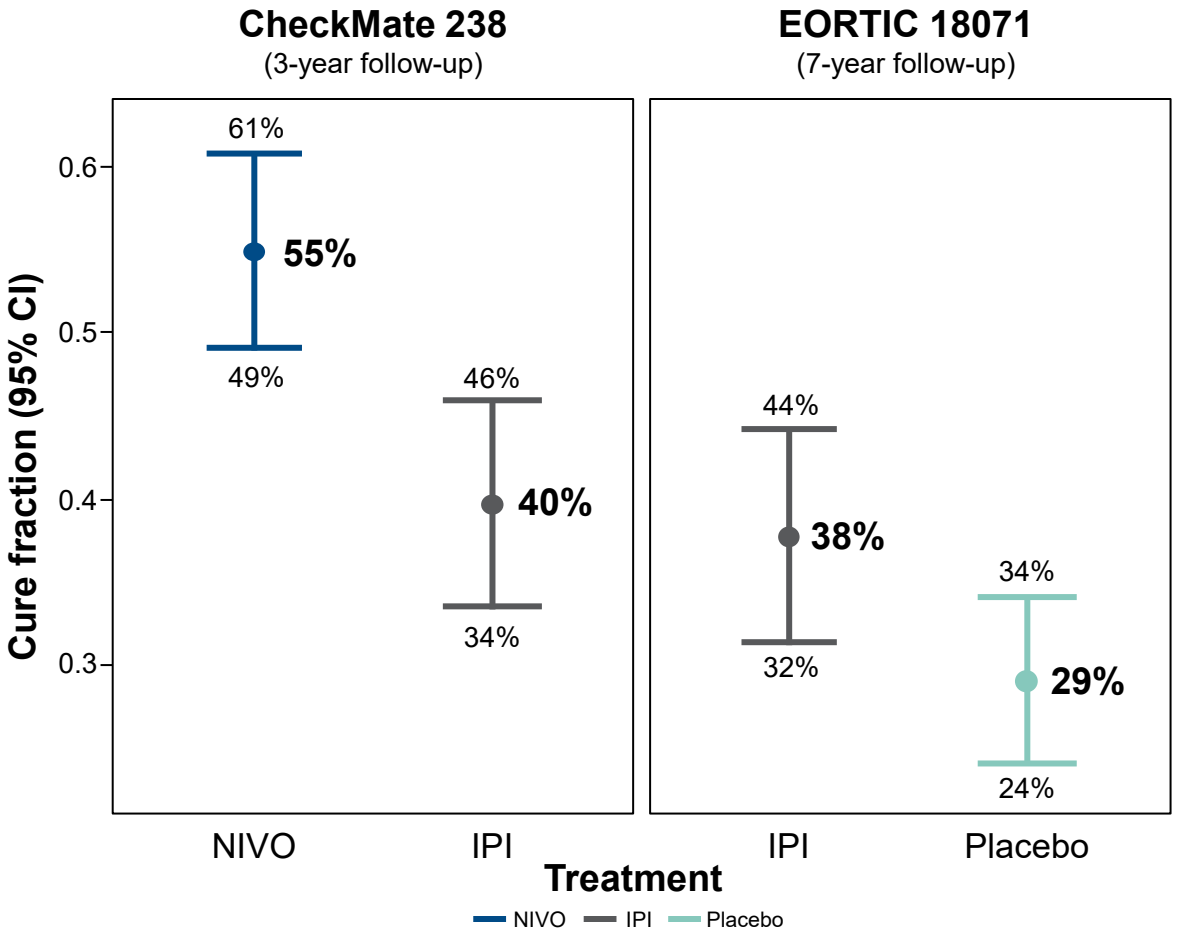
Bestes Sicherheitsprofil für Nivolumab für unerwünschte Ereignisse vom Grad 3/4 bei Patienten im Stadium III und auch IV im unabhängigen indirekten adjustierten Vergleich[1]

* Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen. # Vemurafenib ist nicht zur adjuvanten Behandlung des Melanoms zugelassen. § Surface under the cumulative ranking area

1. Modifiziert nach: Longo C et al. J Eur Acad Dermatol Venereol, 2019; DOI: 10.1111/jdv.16074

Mixture-Cure Modeling for Resected Stage III/IV Melanoma*

- Estimated cure fractions in CheckMate 238 and EORTC 18071
- Analysis of hazard rates from CheckMate 238 in comparison to mortality rates in the general population suggests the likely emergence of a plateau in the RFS distribution in both arms by year 3; this supports the assumption of the existence of a cure fraction
- Findings from CheckMate 238 showed higher cure-fraction estimates in the NIVO arm compared with the IPI arm (55% vs 40%) at the 3-year follow-up



*Mixture Cure Modeling: Nivolumab vs. Ipilimumab (Datenbasis: CheckMate 238, 3-Jahres-Daten) sowie Ipilimumab vs. Placebo (Datenbasis: EORTC 18071, 7-Jahres-Daten), 55 % (95 % KI: 49–61 %) vs. 40 % (95 % KI: 34–46 %) unter Ipilimumab; Ipilimumab 38 % vs. Placebo 29 %, Ipilimumab ist in Europa nicht zur adjuvanten Behandlung des Melanoms zugelassen Modified to Weber J et al. ESMO, 2019; Poster Presentation #1331P

Immunonkologie

Verträglichkeit von Nivolumab 480 mg alle 4 Wochen als Fixdosierung im adjuvanten Setting

CheckMate 915

Bristol Myers Squibb™

Immunonkologie

Safety of Nivolumab in the Adjuvant Setting

Nivolumab adjuvant 480mg every 4 weeks (Q4W) CheckMate 915[1]

	NIVO (n = 917) 480mg Q4W	
	Any AE n (%)	Grade 3/4 n (%)
Any AE	888 (97)	211 (23)
Treatment-related AE	**788 (86)**	**117 (13)**
Any AE leading to discontinuation	108 (12)	62 (7)
Treatment-related AE leading to discontinuation	**95 (10)**	**54 (6)**

Nivolumab adjuvant 3mg/kg every 2 weeks (Q2W) CheckMate 238[2]

	NIVO (n = 452) 3mg/kg Q2W	
	Any AE n (%)	Grade 3/4 n (%)
Any AE	438 (97)	115 (25)
Treatment-related AE	**385 (85)**	**65 (14)**
Any AE leading to discontinuation	44 (10)	21 (5)
Treatment-related AE leading to discontinuation	**35 (8)**	**16 (4)**

There were no treatment-related deaths in the NIVO group in both studies CheckMate 915 and CheckMate 238[1,2]

Results for Nivolumab from CheckMate 238 were reproduced with Nivolumab 480 mg every 4 weeks (Q4W) in CheckMate 915 with over 900 patients.[1] Nivolumab 480mg every 4 weeks is well tolerable and no new safety signals were observed with this dosing regimen.[1]

1 Long et al., AACR 2021, Oral Presentation 2 Weber J et al. ESMO, 2017; Oral Presentation

OPDIVO® + YERVOY®

Fortgeschrittenes Melanom

CheckMate 067

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Immunonkologie

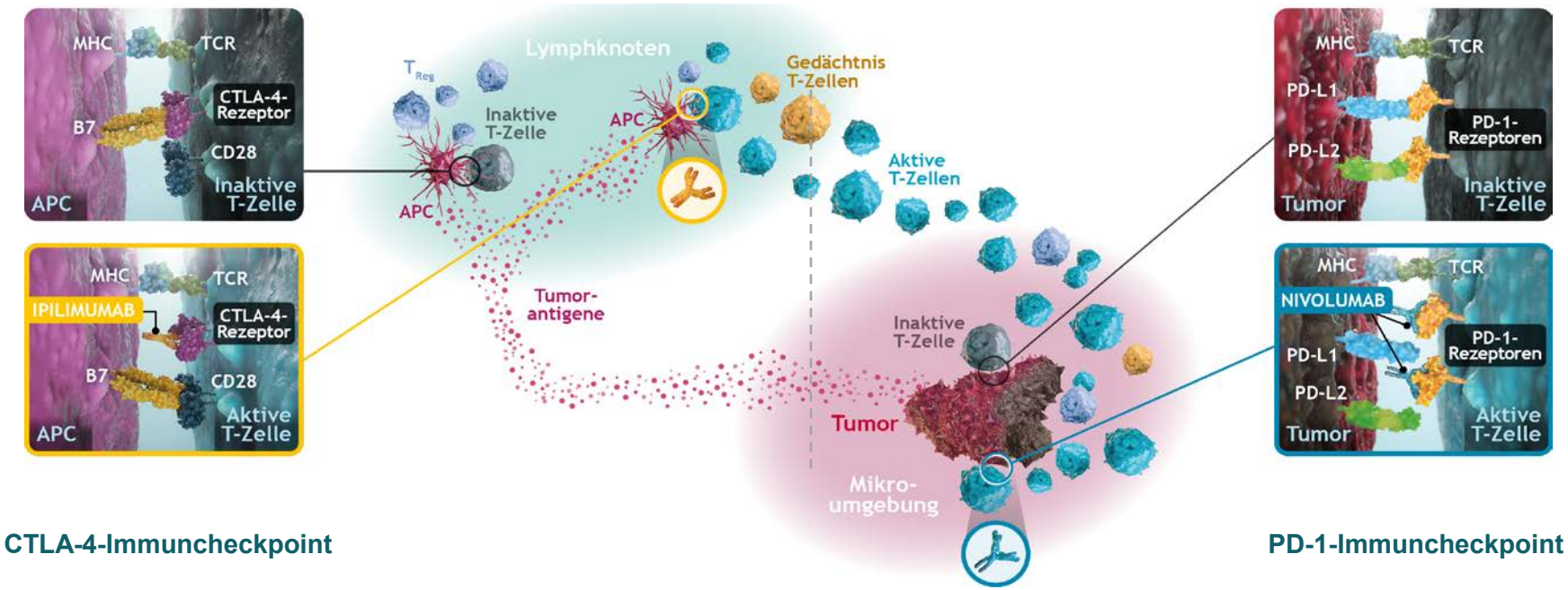
Nivolumab + Ipilimumab – ein kluges immunologisches Zusammenspiel[1–14]

Ipilimumab (anti–CTLA-4)

- **Blockade des CTLA-4-Immuncheckpoints kann eine effektivere Immunantwort ermöglichen durch:**
  - Verstärkte Aktivierung neuer T-Zellen
  - Bildung von Gedächtnis-T-Zellen
  - Verringerung immunsuppressiver regulatorischer T-Zellen

Nivolumab (anti–PD-1)

- **Blockade des PD-1-Immuncheckpoints kann Immune-Escape von Tumorzellen stoppen:**
  - Verhinderung der PD-L1-vermittelten Inaktivierung von T-Zellen durch den Tumor



CTLA-4-Immuncheckpoint

PD-1-Immuncheckpoint

APC = Antigen-präsentierende Zelle, **CTLA-4** = Cytotoxic T-Lymphocyte-Associated Protein[4], **MHC** = Major Histocompatibility Complex, **PD-1** = Programmed Cell Death Protein[1], **PD-L1** = Programmed Death Ligand [1], **PD-L2** = Programmed Death Ligand[2],**TCR** = T-Zell-Rezeptor, **TReg** = regulatorische T-Zelle

Modifiziert nach Wolchok, Peggs, Blank, Hamaishi, Nurieva[1–5]

1. Wolchock J et al. J Clin Oncol, 2013; ASCO Annual Meeting Abstracts 31: 15_suppl 2. Peggs KS et al. Curr Opin Immunol, 2006; 18(2): 206–13 3. Blank C et al. Cancer Immunol Immunother, 2007; 56(5): 739–45 4. Hamanishi J et al. Proc Natl Acad Sci USA, 2007; 104(9): 3360–5 5. Nurieva RI et al. Immunol Rev, 2009; 229(1): 88–100 6. Wei SC et al. Cancer Discov, 2018; 8(9): 1069–1086 7. Wei SC et al. PNAS, 2019; 116(45): 22699–22709 8. Pardoll DM. Nat Rev Cancer, 2012; 12(4): 252–264 9. Rowshanravan B. Blood, 2018; 131(1): 58–67 10. Weber JS et al.J Immunother, 2012; 35(1): 89–97 11. Ribas A. N Engl J Med, 2012; 366(26): 2517–2519 12. Darvin P et al. Exp Mol Med, 2018; 50(12): 1–11 13. de Coana YP et al. Oncotarget, 2017; 8(13): 21539–21553 14. Curran MA et al. Proc Natl Acad Sci USA, 2010; 107(9): 4275–4280

Introduction CheckMate 067

- CheckMate 069 and 067 established the combination of NIVO (1 mg/kg) and IPI (3 mg/kg) as a standard of care for patients with metastatic melanoma[1–3]
- In the phase 3 CheckMate 067 trial, a durable and sustained clinical benefit was achieved with both NIVO + IPI and NIVO alone vs IPI at 7.5 years of follow-up in patients with previously untreated, unresectable, stage III/IV melanoma[3]
  - Median OS was not reached with NIVO + IPI and 5-year OS rates were 52%, 44%, and 26%, respectively
  - 5-year OS rates for patients with BRAF-mutated tumors were 60%, 46%, and 30%, respectively
- Here we present 7.5-year efficacy and safety outcomes from CheckMate 067

IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.

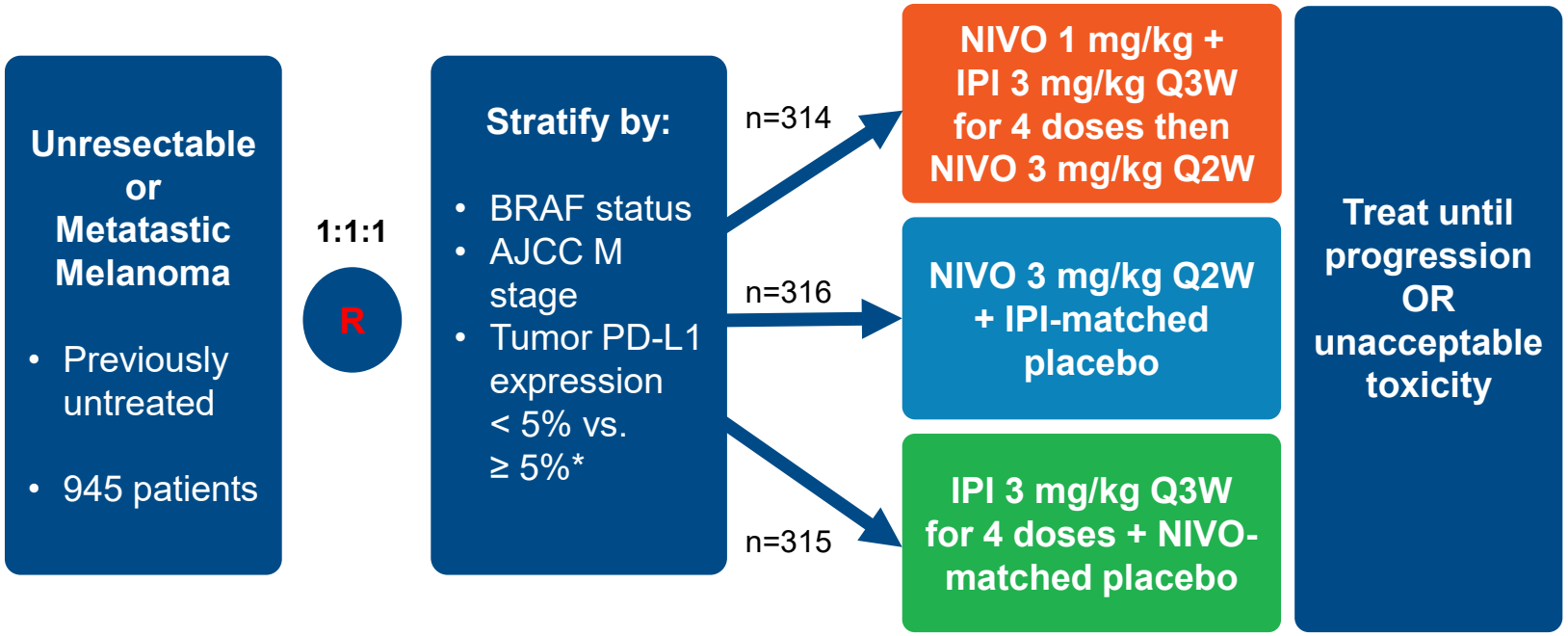
1. Hodi FS, et al. Lancet Oncol. 2016;17:1558–1568. 2. Larkin J, et al. N Engl J Med. 2015;373:23–34. 3. Larkin J, et al. N Engl J Med. 2019;381:1535–1546.

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone[a]
Co-primary endpoints were PFS and OS in the NIVO-containing arms versus IPI alone



Database lock: Oct 19, 2020;
minimum follow-up of 77 months for all patients

NCT01844505
[a]The study was not powered for a comparison between NIVO+IPI and NIVO. AJCC, American Joint Committee on Cancer.
Modified to Wolchok JD et al. ASCO, 2021, Abstract #9506

CheckMate 067: Key Eligibility Criteria

- Histologically confirmed stage III (unresectable) or stage IV melanoma
- No prior systemic therapy for unresectable or metastatic melanoma
  – Prior adjuvant therapy allowed
- Age ≥ 18 years
- ECOG performance status of 0 or 1
- Tumor tissue available for assessment of PD-L1 expression
- Known BRAF V600 mutational status
- No active brain metastases, ocular melanoma, or autoimmune disease

Wolchok et al. LBA 1, ASCO, 2015; Plenary Session

CheckMate 067: Best Response to treatment

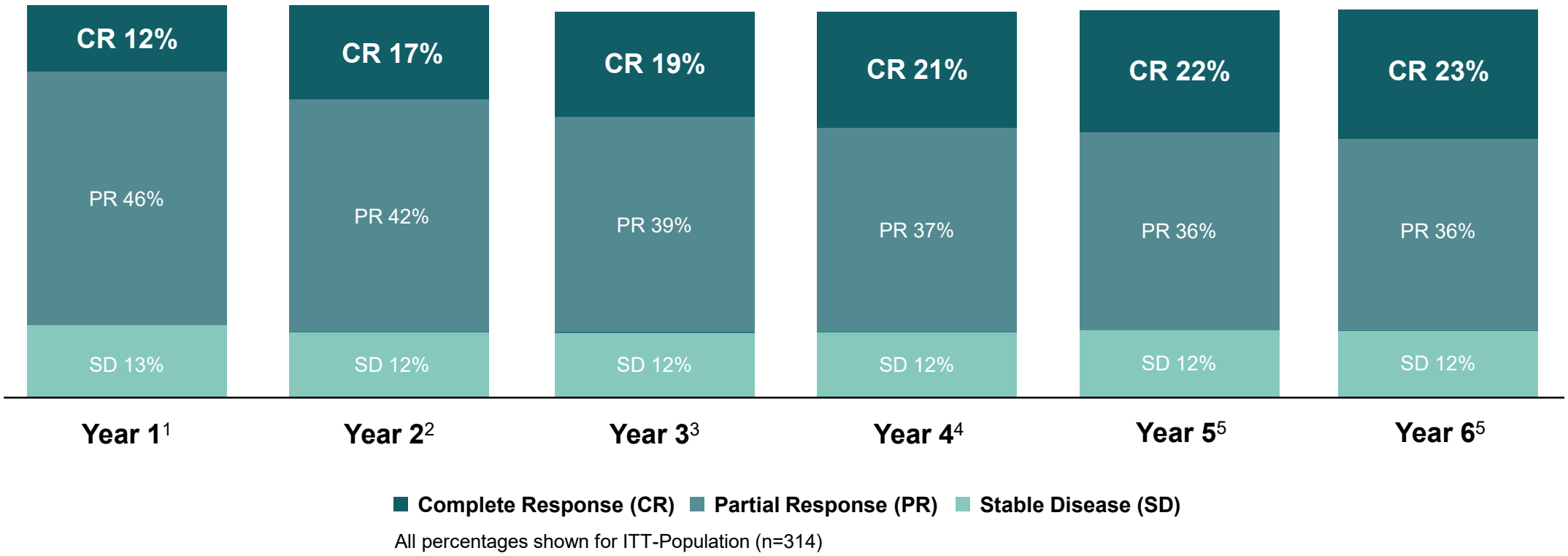
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NR (61.9-NR)**	**NR (45.7–NR)**	**19.2 (8.8–47.4)**

- While ORR has remained stable, rates of CR have increased over the 3-, 4-, 5-year analysis and at the 6.5-year analysis for NIVO+IPI[1,2,3]
  - 19%, 21%, 22%, and 23% for NIVO+IPI
  - 16%, 18%, 19%, and 19% for NIVO
  - 5%, 5%, 6% and 6% for IPI

1. Wolchok JD, et al. N Engl J Med 2017;377:1345–1356; 2. Hodi FS, et al. Lancet Oncol 2018;19:1480–1492 3. Wolchok JD et al. ASCO, 2021, 2019; Oral Presentation

Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

CheckMate 067: Best Response for NIVO + IPI over Time



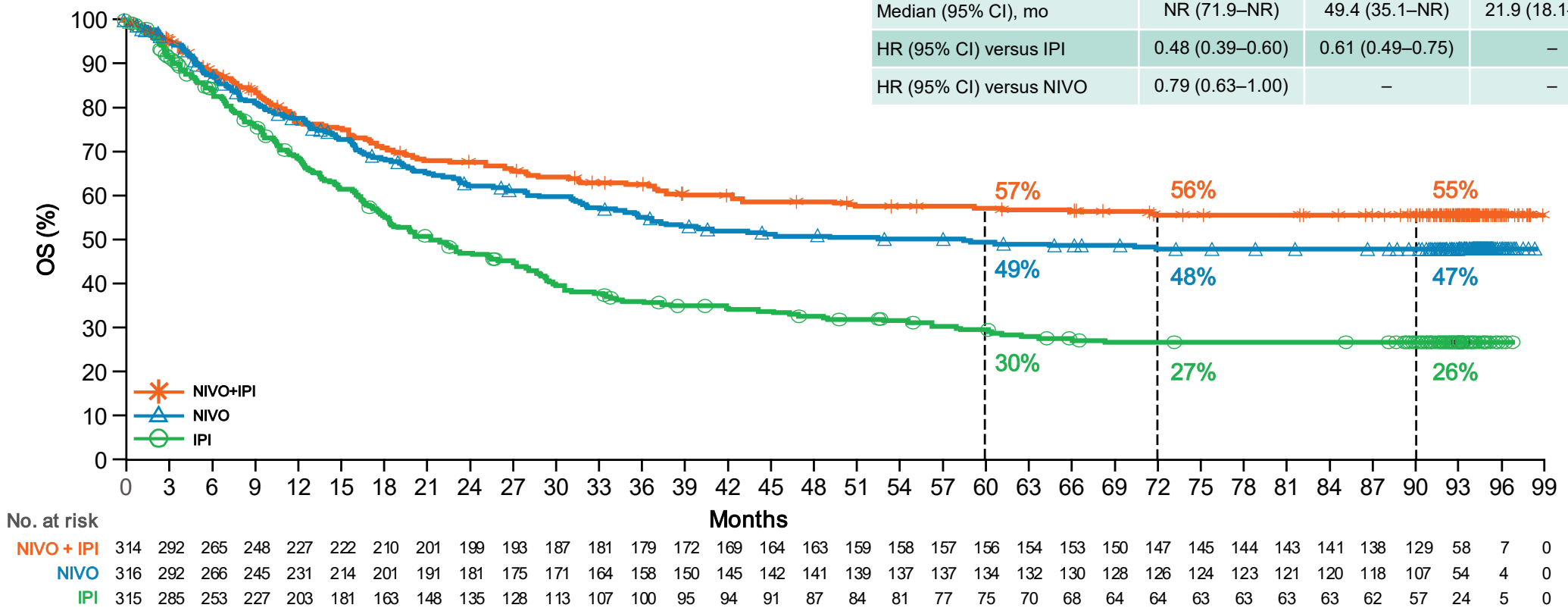
All percentages shown for ITT-Population (n=314)

1. Larkin J et al. N Engl J Med, 2015; 373: 23–34
2. Larkin J et al. AACR, 2017; Abstract CT075, Oral Presentation
3. Wolchok JD et al. N Engl J Med, 2017; 377: 1345–56
4. Hodi FS et al. Lancet Oncol, 2018; 19: 1480–92
5. Larkin J et al. N Engl J Med, 2019; 381: 1535-1546
6. Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

Immunonkologie

CheckMate 067: Melanoma-specific survival[a]

	NIVO + IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median (95% CI), mo	NR (71.9–NR)	49.4 (35.1–NR)	21.9 (18.1–27.4)
HR (95% CI) versus IPI	0.48 (0.39–0.60)	0.61 (0.49–0.75)	–
HR (95% CI) versus NIVO	0.79 (0.63–1.00)	–	–



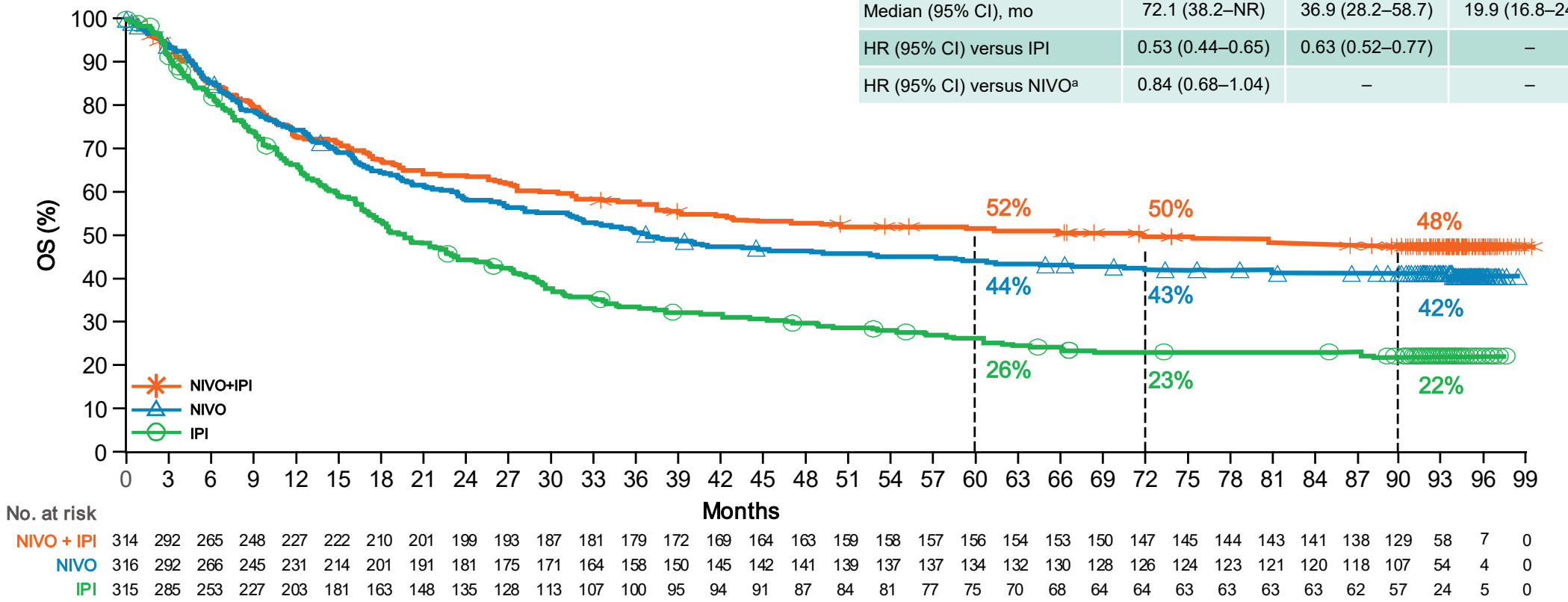
[a]In this descriptive post hoc analysis, an event was defined as death due to melanoma and deaths for any other reason were censored.

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: Overall Survival

	NIVO + IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median (95% CI), mo	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) versus IPI	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–
HR (95% CI) versus NIVO[a]	0.84 (0.68–1.04)	–	–



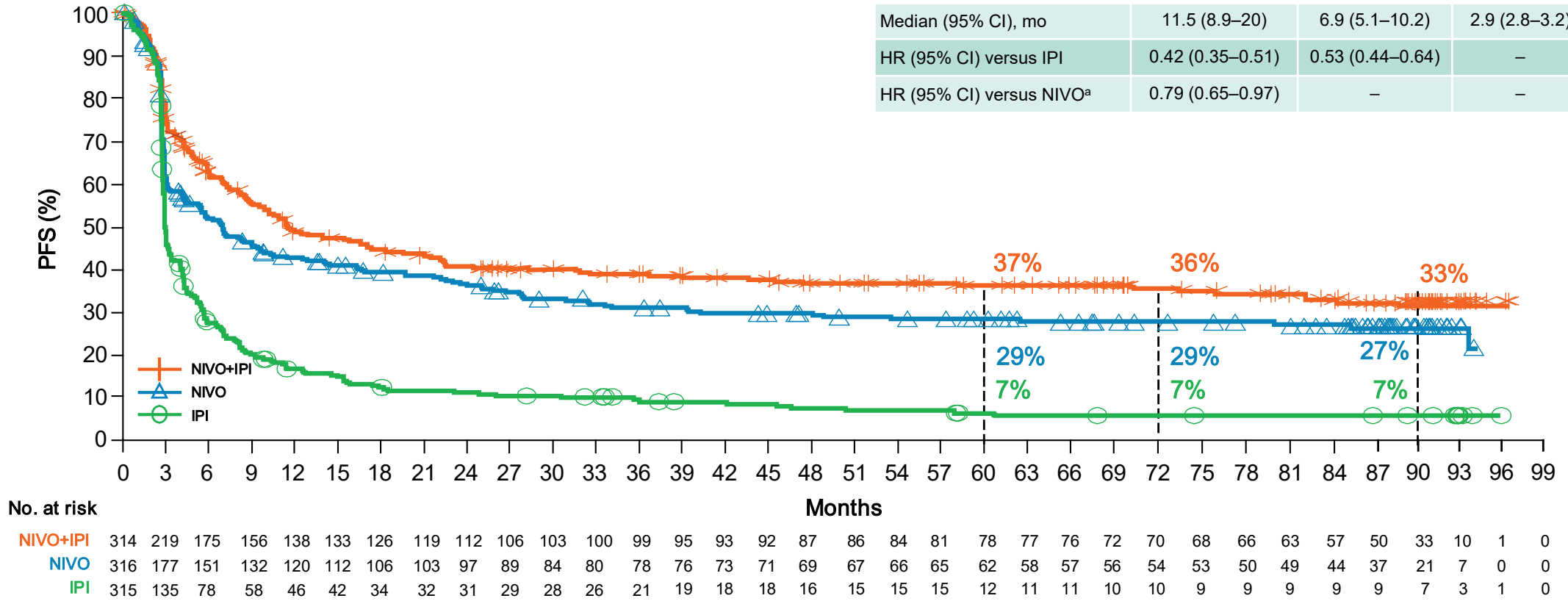
[a]Descriptive analysis

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: Progression-free survival after 7.5 years

	NIVO + IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median (95% CI), mo	11.5 (8.9–20)	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)	–	–



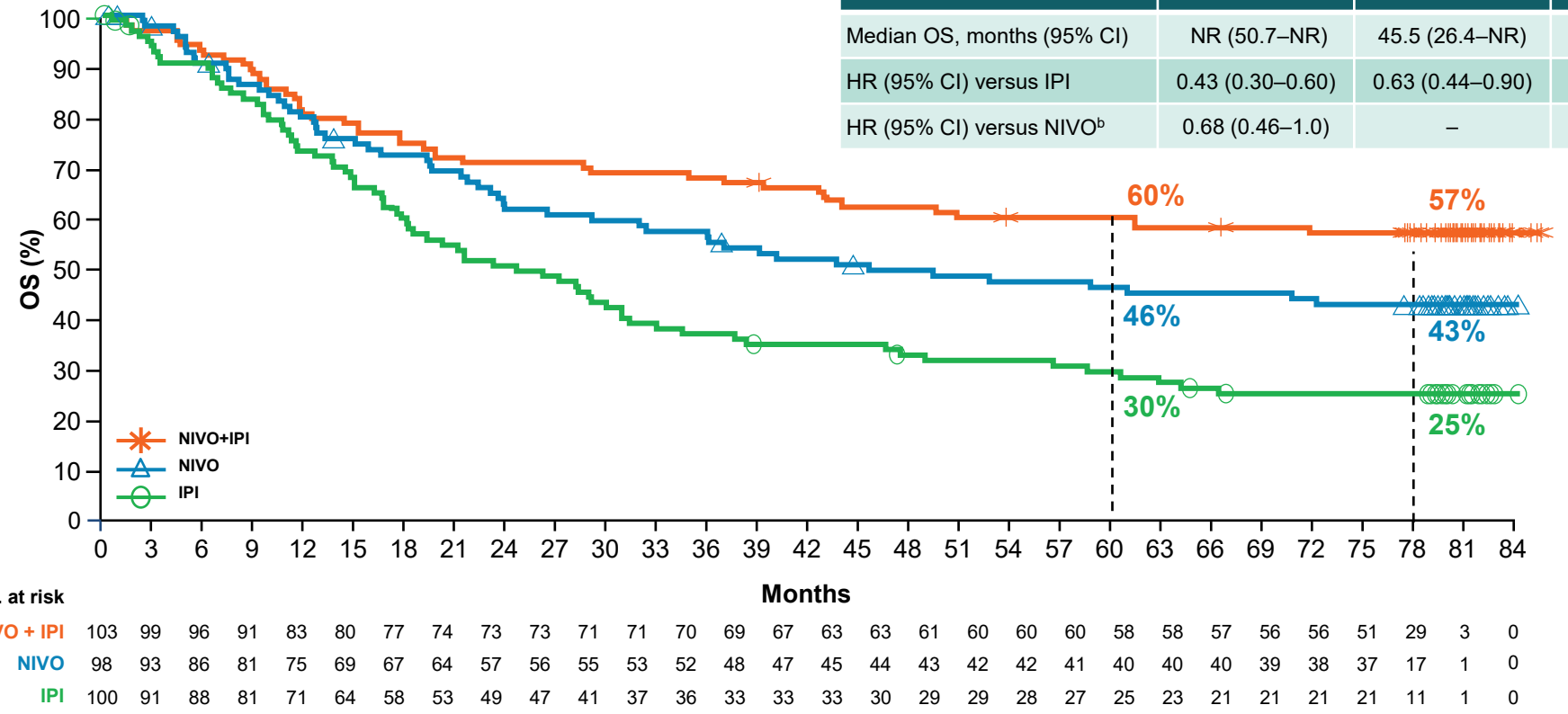
[a]Descriptive analysis.

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: OS in Patients with BRAF-Mutant Tumors[a]

	NIVO + IPI (n=103)	NIVO (n=98)	IPI (n=100)
Median OS, months (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) versus IPI	0.43 (0.30–0.60)	0.63 (0.44–0.90)	–
HR (95% CI) versus NIVO[b]	0.68 (0.46–1.0)	–	–



No. at risk

NIVO + IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	60	60	58	58	57	56	56	51	29	3	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	42	41	40	40	40	39	38	37	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	25	23	21	21	21	21	11	1	0

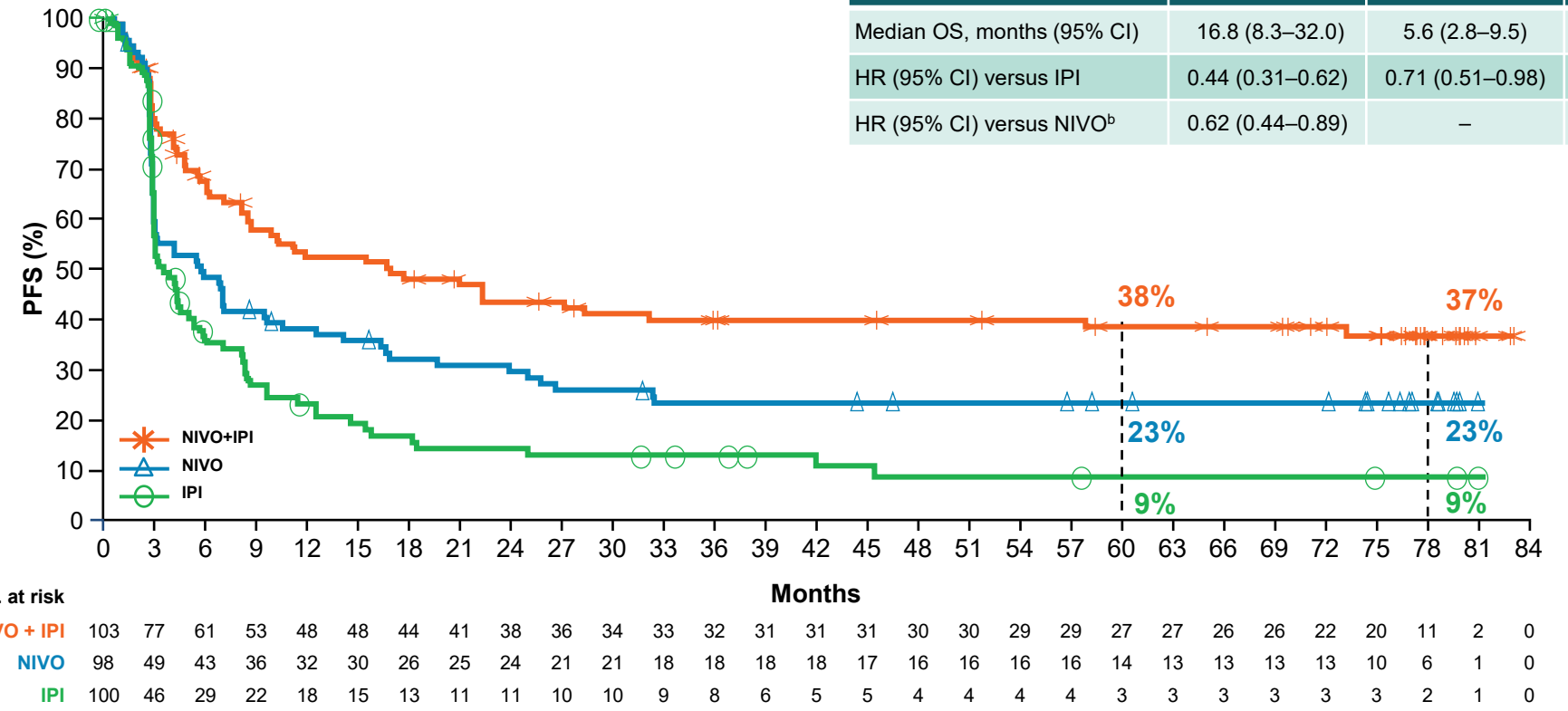
[a]Patients with BRAF status results were 314 for NIVO + IPI, 316 for NIVO, and 315 for IPI. [b]Descriptive analysis.

Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

Immunonkologie

CheckMate 067: PFS in Patients with BRAF-Mutant Tumors[a]

	NIVO + IPI (n=103)	NIVO (n=98)	IPI (n=100)
Median OS, months (95% CI)	16.8 (8.3–32.0)	5.6 (2.8–9.5)	3.4 (2.8–5.2)
HR (95% CI) versus IPI	0.44 (0.31–0.62)	0.71 (0.51–0.98)	–
HR (95% CI) versus NIVO[b]	0.62 (0.44–0.89)	–	–



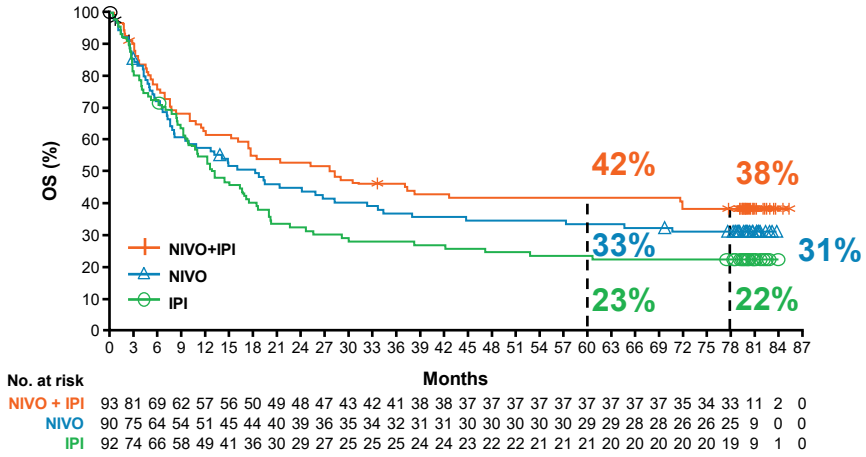
[a]Patients with BRAF status results were 314 for NIVO + IPI, 316 for NIVO, and 315 for IPI. [b]Descriptive analysis.
Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

Immunonkologie

CheckMate 067: OS by presence of baseline liver metastases

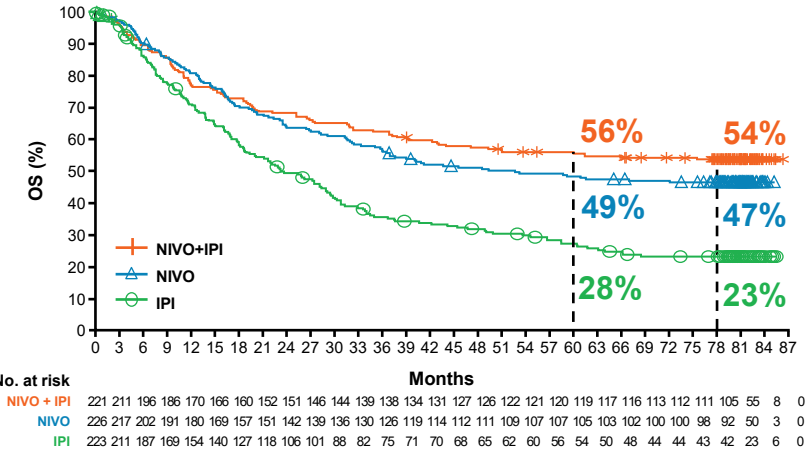
With liver metastases

	NIVO + IPI (n=93)	NIVO (n=90)	IPI (n=92)
Median OS, months (95% CI)	28.2 (15.2–71.9)	18.2 (8.1–32.3)	13.1 (9.6–18.4)
HR (95% CI) versus IPI	0.66 (0.46–0.93)	0.81 (0.58–1.14)	–
HR (95% CI) versus NIVO*	0.81 (0.56–1.16)	–	–



Without liver metastases

	NIVO + IPI (n=221)	NIVO (n=226)	IPI (n=223)
Median OS, months (95% CI)	NR (50.7–NR)	52.7 (36.0–NR)	23.5 (18.6–29.4)
HR (95% CI) versus IPI	0.47 (0.37–0.60)	0.56 (0.44–0.71)	–
HR (95% CI) versus NIVO*	0.84 (0.64–1.09)	–	–



[a]Descriptive analysis.

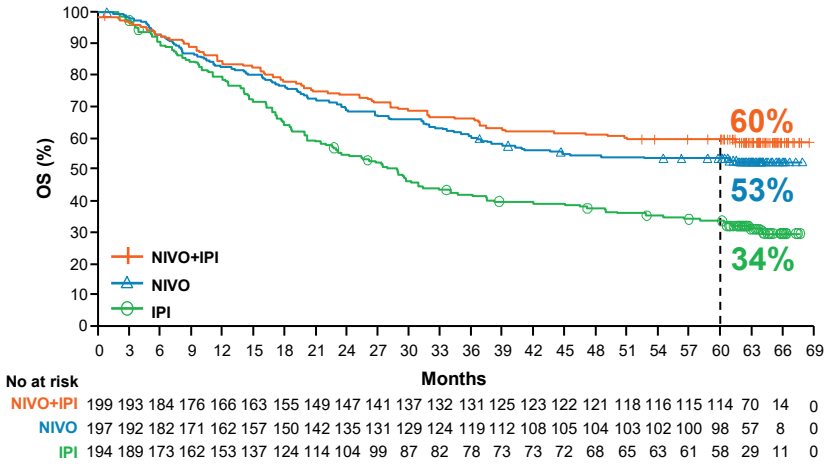
Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

Immunonkologie

CheckMate 067: OS by LDH Level

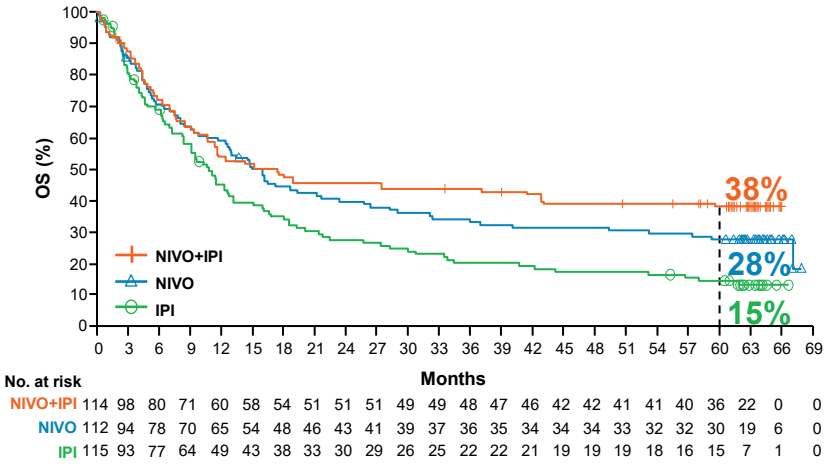
LDH ≤ ULN

	NIVO + IPI (n=199)	NIVO (n=197)	IPI (n=194)
Median OS, months (95% CI)	NR	NR (40.2–NR)	28.8 (22.7–34.0)
HR (95% CI) versus IPI	0.48 (0.37–0.64)	0.58 (0.44–0.76)	–
HR (95% CI) versus NIVO*	0.83 (0.62–1.12)	–	–



LDH > ULN

	NIVO + IPI (n=114)	NIVO (n=112)	IPI (n=115)
Median OS, months (95% CI)	17.4 (10.7–42.6)	16.0 (11.7–21.7)	10.9 (8.4–13.1)
HR (95% CI) versus IPI	0.58 (0.43–0.79)	0.71 (0.53–0.96)	–
HR (95% CI) versus NIVO*	0.82 (0.59–1.13)	–	–



[a]Descriptive analysis. LDH, lactate dehydrogenase; ULN, upper limit of normal.

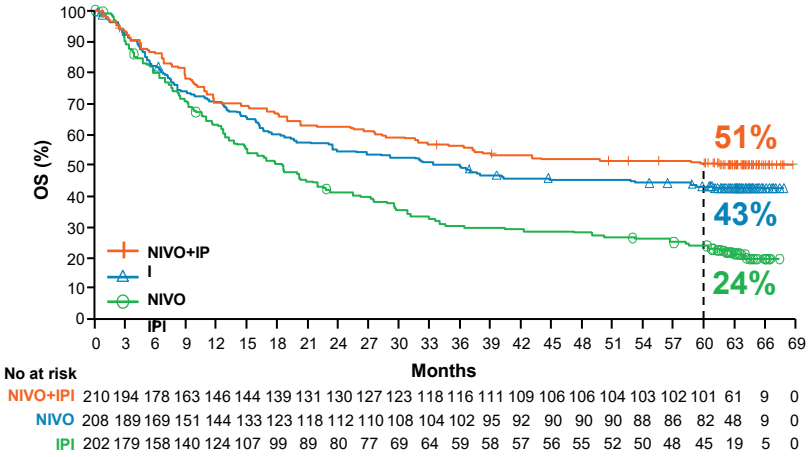
Modified to Larkin J et al. ESMO, 2019; Oral Presentation

Immunonkologie

CheckMate 067: OS by Tumor PD-L1 Expression, 5% Cutoff

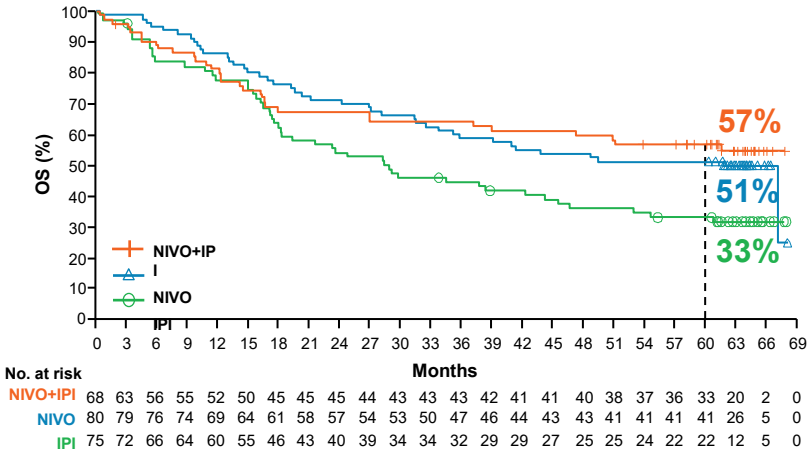
PD-L1 < 5%

	NIVO + IPI (n=210)	NIVO (n=208)	IPI (n=202)
Median, mo (95% CI)	NR (32.7–NR)	35.9 (23.1–59.2)	18.4 (13.7–22.5)
HR (95% CI) vs IPI	0.50 (0.39–0.65)	0.62 (0.49–0.79)	–
HR (95% CI) vs NIVO[a]	0.81 (0.62–1.06)	–	–



PD-L1 ≥ 5%

	NIVO + IPI (n=68)	NIVO (n=80)	IPI (n=75)
Median, mo (95% CI)	NR (39.1–NR)	61.6 (33.6–NR)	28.9 (18.1–44.2)
HR (95% CI) vs IPI	0.58 (0.37–0.91)	0.63 (0.42–0.96)	–
HR (95% CI) vs NIVO[a]	0.91 (0.57–1.46)	–	–

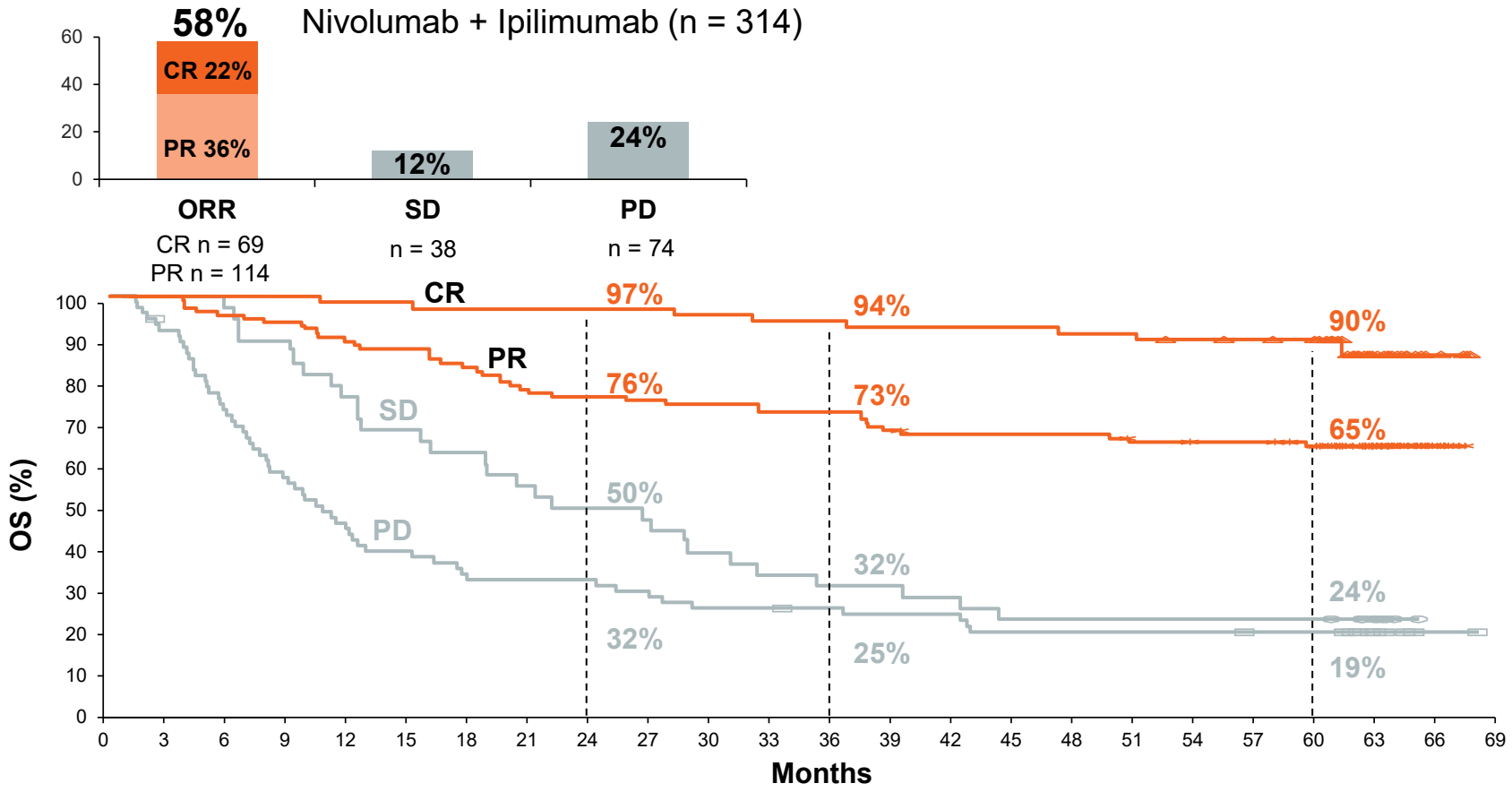


[a]Descriptive analysis.

Modified to Larkin J et al. ESMO, 2019; Oral Presentation

Immunonkologie

CheckMate 067: OS by Best Overall Response NIVO+IPI



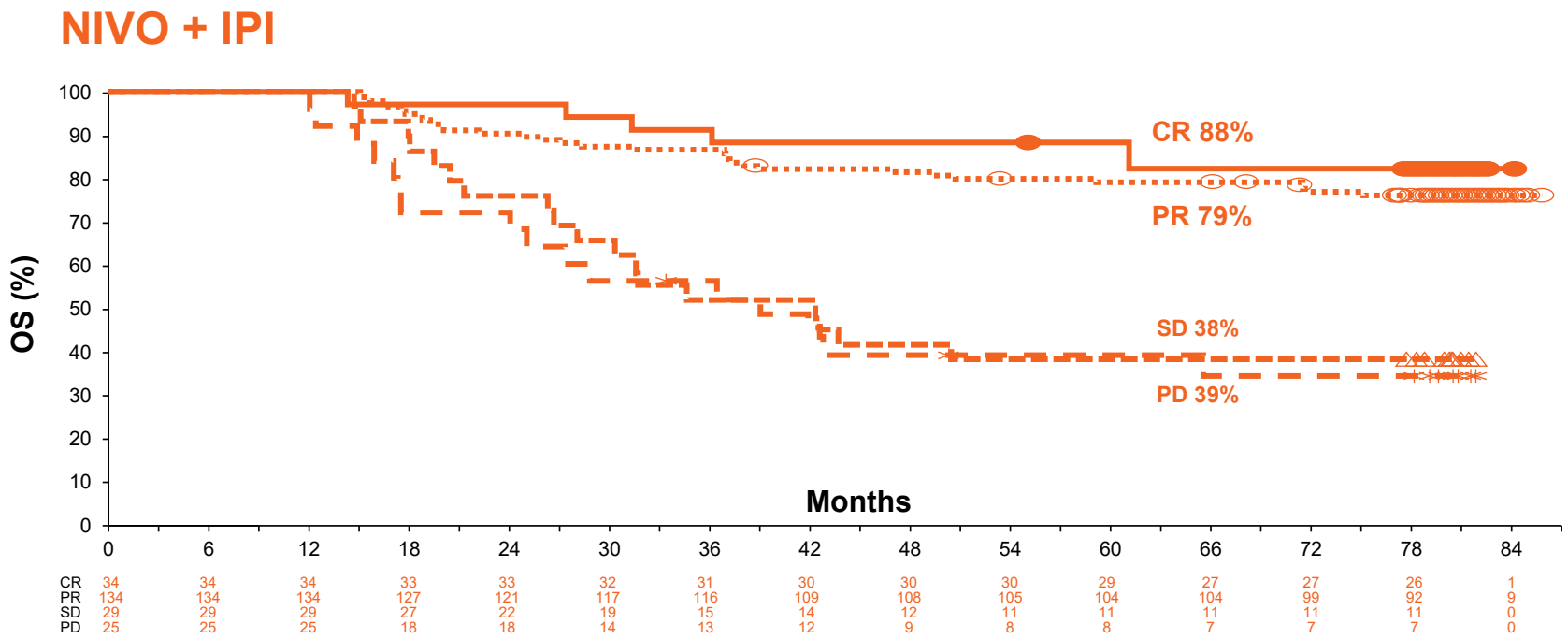
Median, mo (95% CI)	
CR	NR
PR	NR
SD	23.7 (14.8–31.8)
PD	10.0 (7.1–12.5)

Modified to Long et al. SMR, 2019; Oral Presentation

Immunonkologie

CheckMate 067: OS by best overall response NIVO+IPI

12-month landmark analysis[a]



[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.

PD, progressive disease.

Modified to Wolchok JD et al. ASCO, 2021, Abstract #9506

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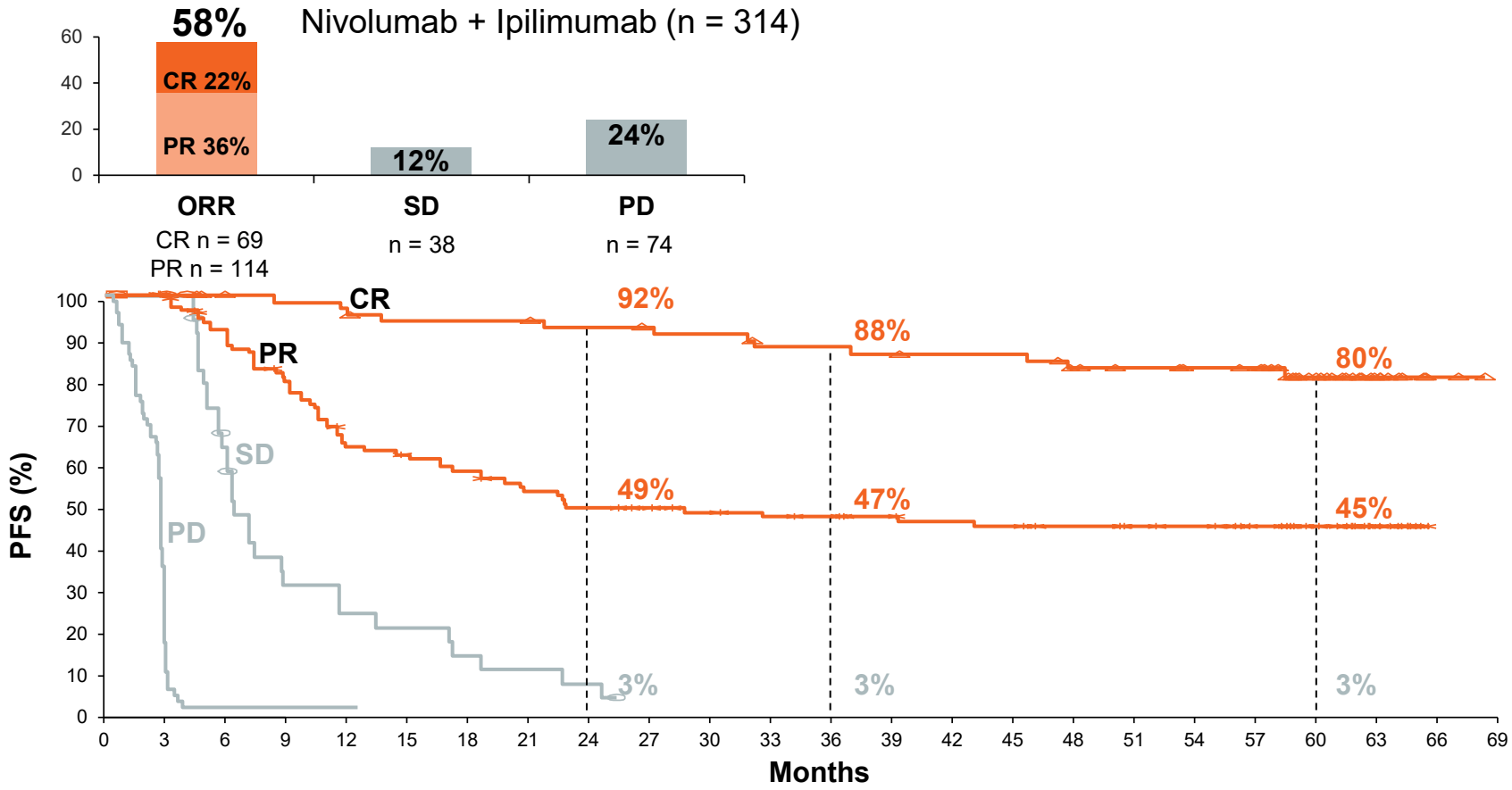
CheckMate 067: PFS by Best Overall Response NIVO+IPI

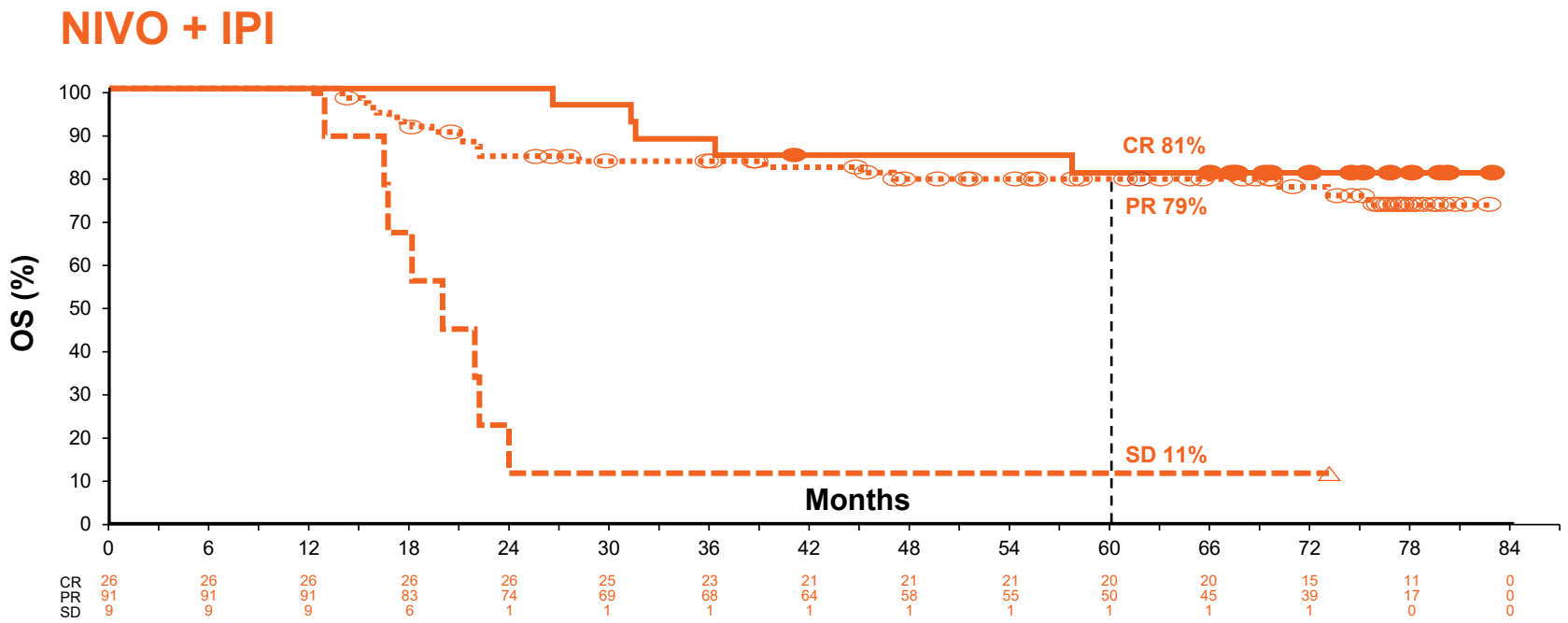


Median, mo (95% CI)	
CR	NR
PR	22.2 (15.5–NR)
SD	5.9 (5.3–8.3)
PD	2.6 (2.5–2.6)

Modified to Long et al. SMR, 2019; Oral Presentation

CheckMate 067: OS by best overall response NIVO+IPI

12-month landmark analysis[a]



[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
[b]Since PD is a PFS event, patients with a best overall response of PD were excluded from this analysis.
CR, complete response; PR, partial response; SD, stable disease.
Modified to Wolchok JD et al. ASCO, 2021, Abstract #9506

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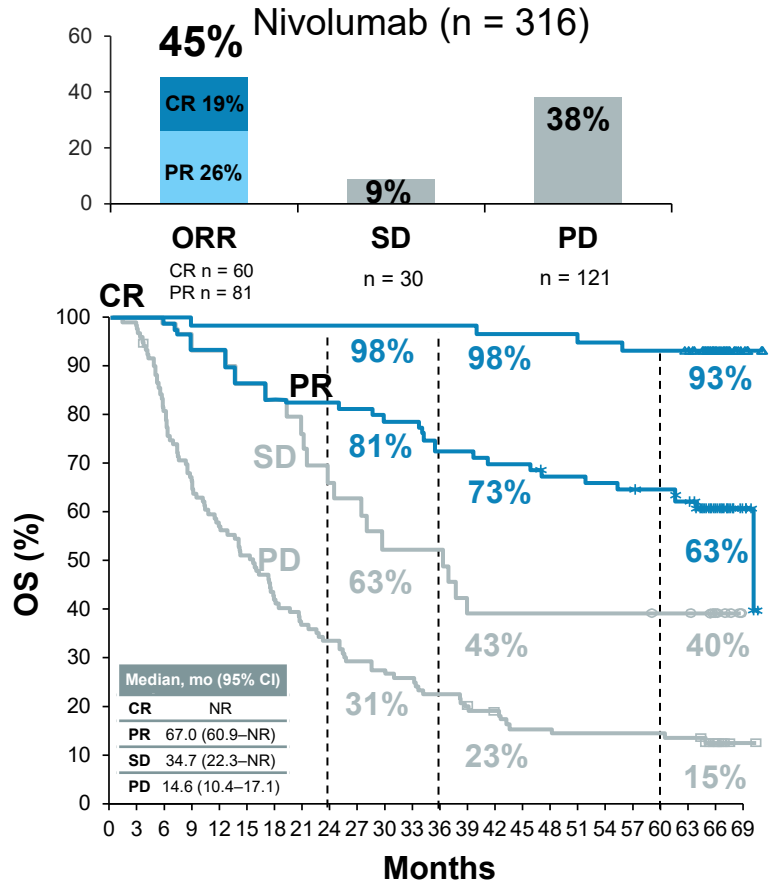
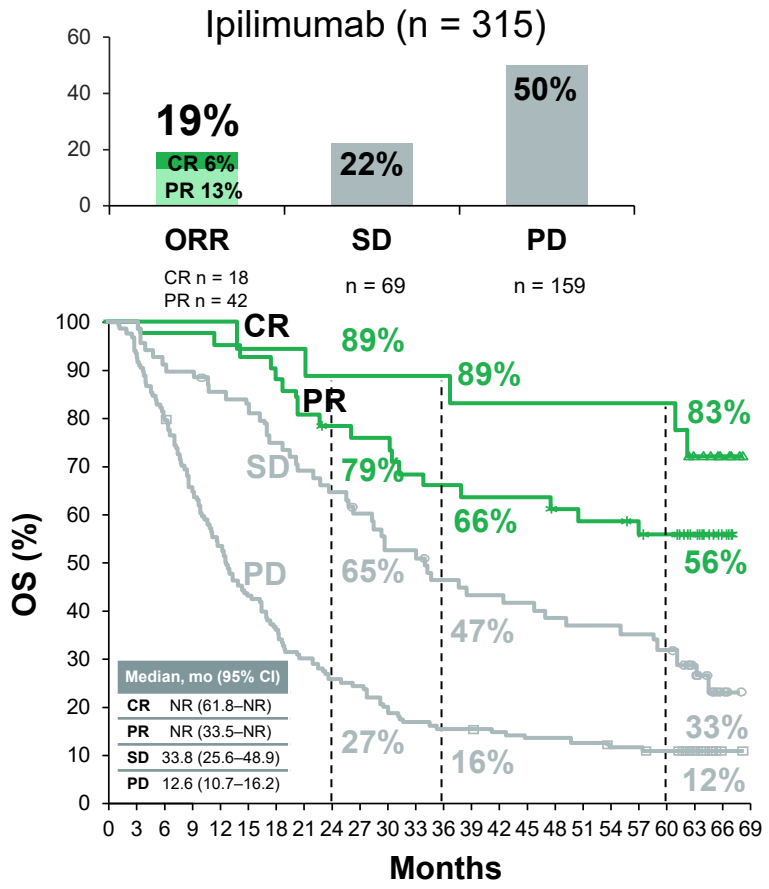
CheckMate 067: OS by Best Overall Response





Modified to Long et al. SMR, 2019; Oral Presentation

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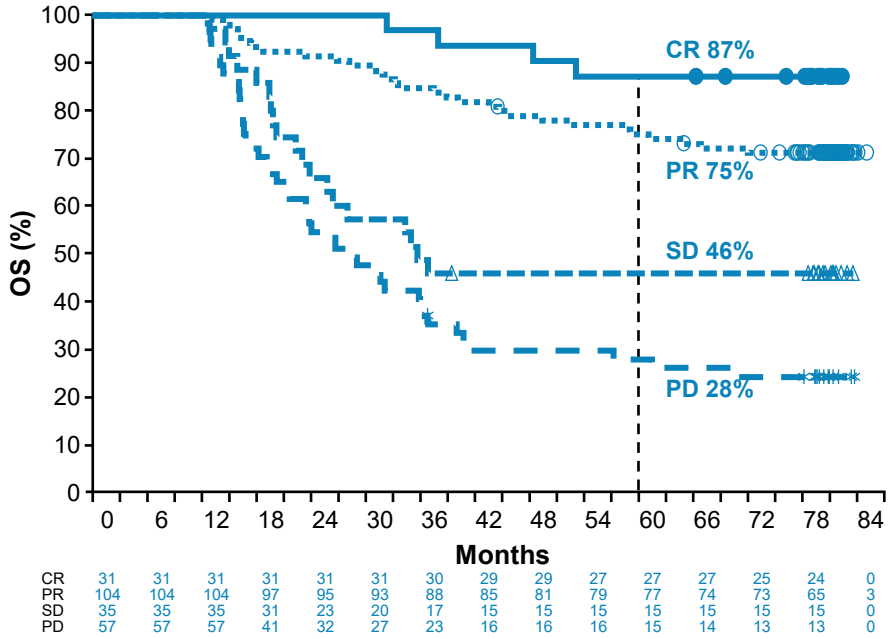
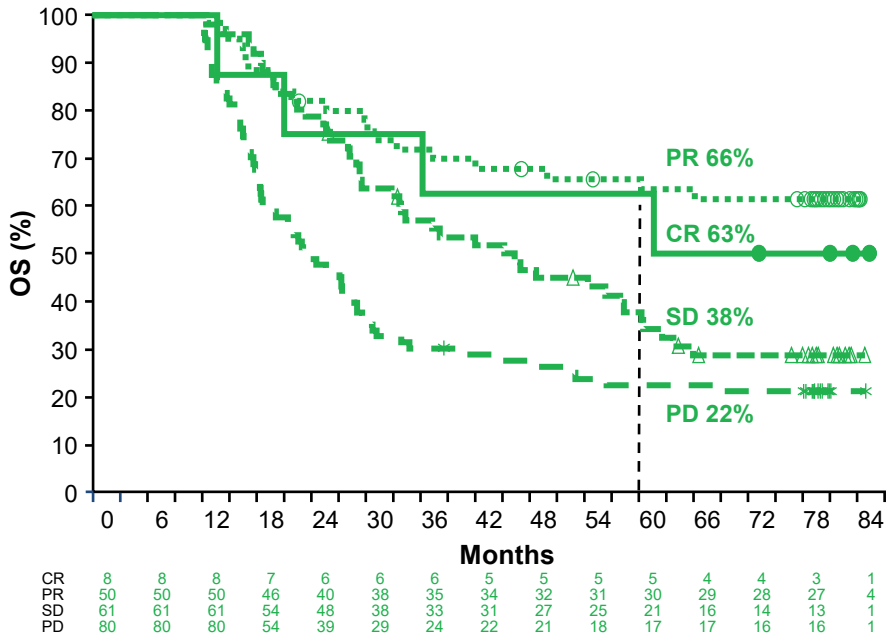
CheckMate 067: OS by best overall response, 12-month landmark analysis[a]

NIVO



IPI



[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.

PD, progressive disease.

Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

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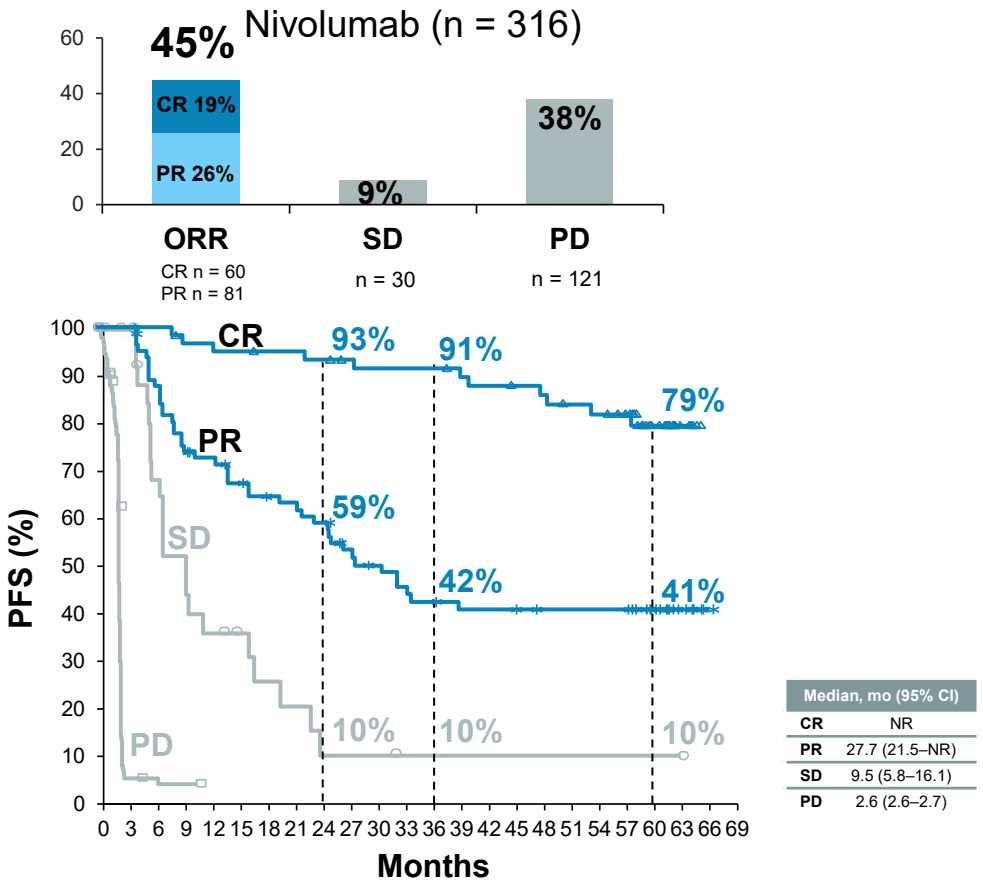
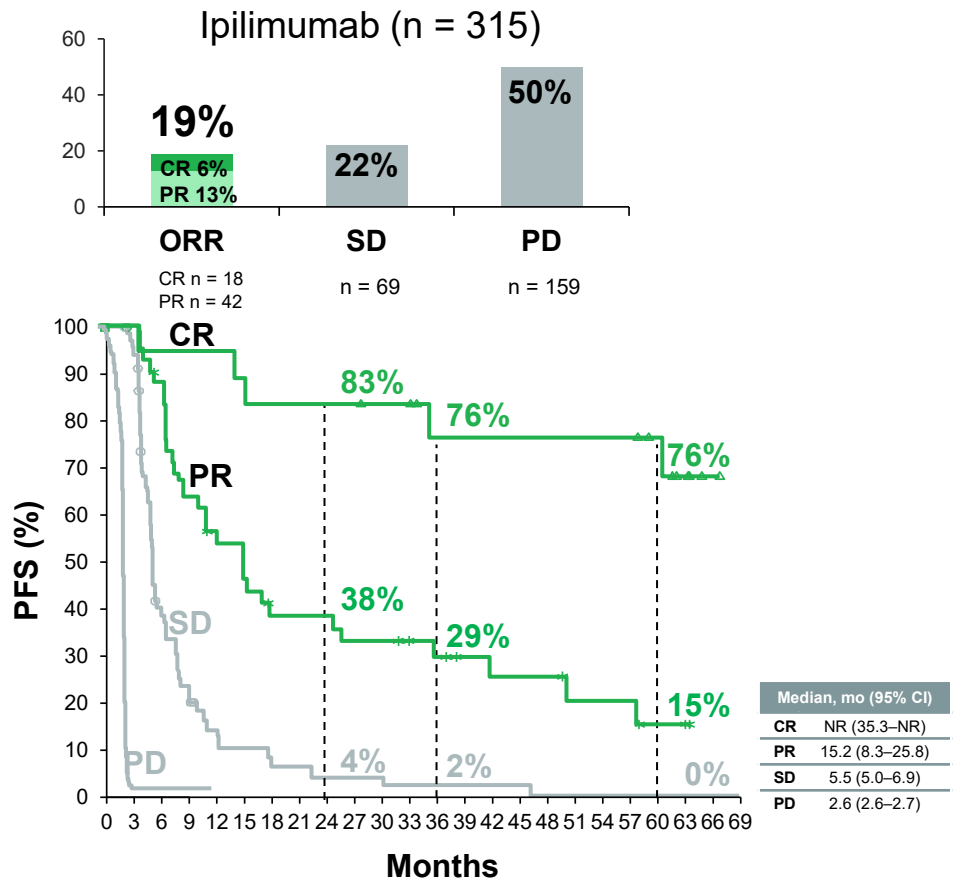
CheckMate 067: PFS by Best Overall Response



Median, mo (95% CI)	
CR	NR
PR	27.7 (21.5–NR)
SD	9.5 (5.8–16.1)
PD	2.6 (2.6–2.7)



Median, mo (95% CI)	
CR	NR (35.3–NR)
PR	15.2 (8.3–25.8)
SD	5.5 (5.0–6.9)
PD	2.6 (2.6–2.7)

Modified to Long et al. SMR, 2019; Oral Presentation

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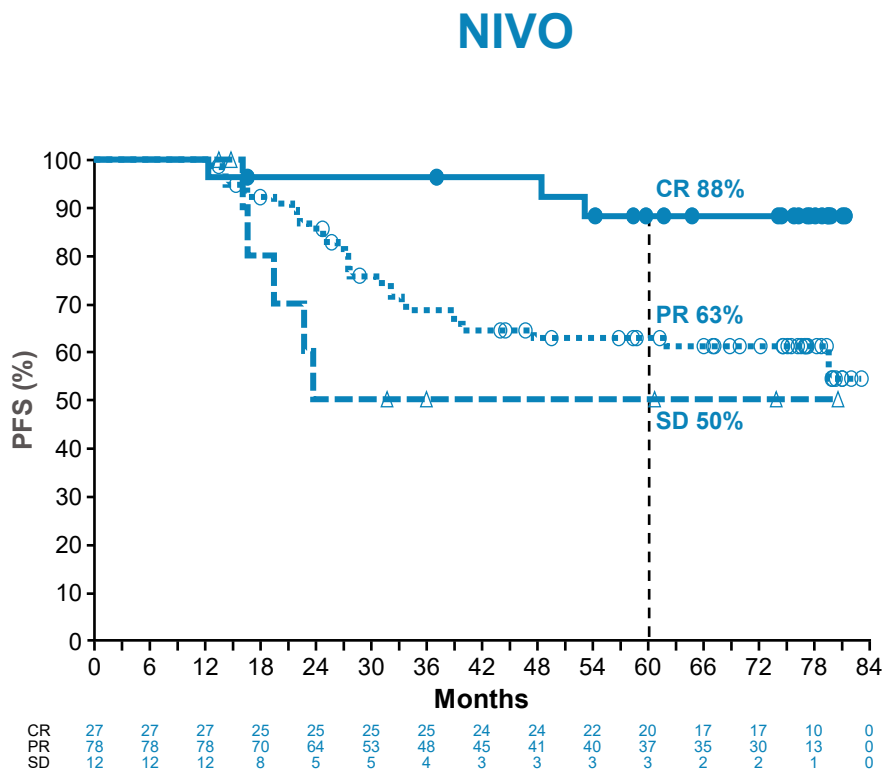
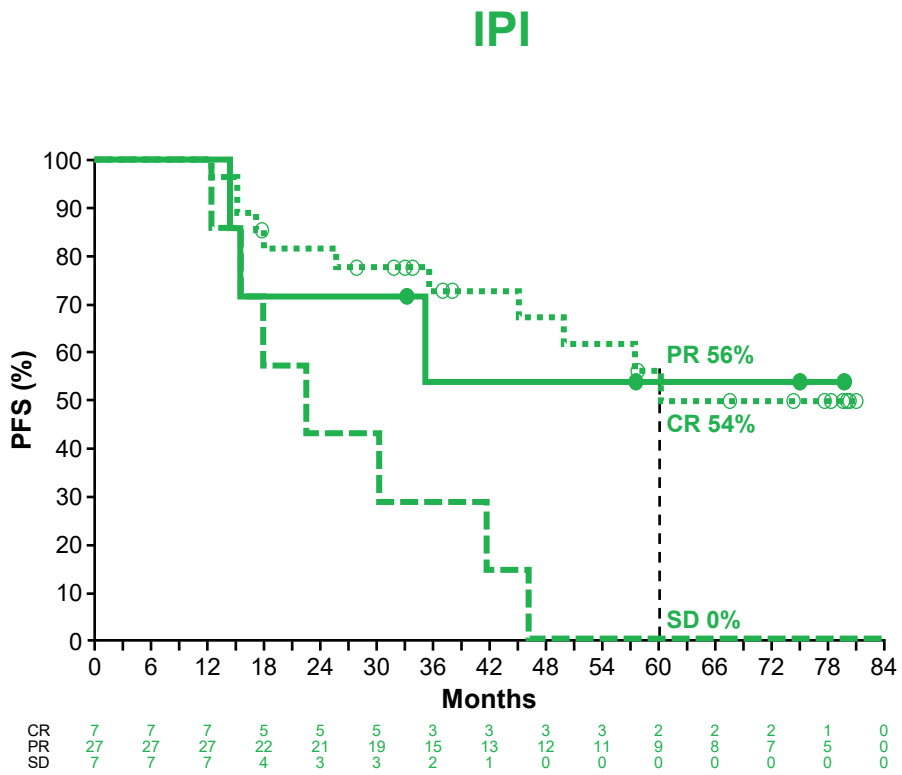
CheckMate 067: PFS by best overall response

12-month landmark analysis[a]

- Patients with a best overall response of a CR, PR, or SD at 12 months were followed for PFS[b]





[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
[b]Since PD is a PFS event, patients with a best overall response of PD were excluded from this analysis.
CR, complete response; PR, partial response; SD, stable disease.
Modified to Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

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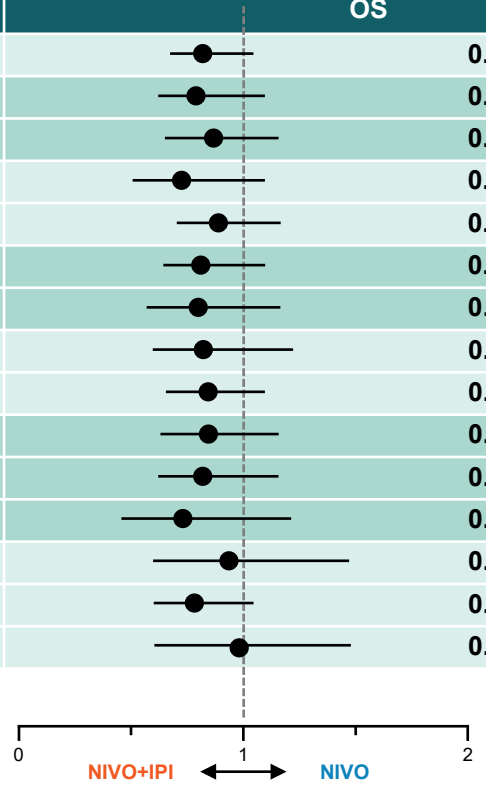
CheckMate 067: OS Subgroup Analyses

Overall Survival: Nivolumab Plus Ipilimumab Versus Nivolumab

	No. of patients		5-Year OS Rate, % (95% CI)		Unstratified HR (95% CI)
	NIVO+IPI	NIVO	NIVO+IPI	NIVO	OS
Overall	314	316	**52 (46, 57)**	**44 (39, 50)**	**0.83 (0.66, 1.03)**
Age <65 years	185	198	**54 (47, 61)**	**45 (38, 52)**	**0.80 (0.60, 1.06)**
Age ≥65 years	129	118	**48 (39, 57)**	**43 (34, 52)**	**0.86 (0.62, 1.20)**
BRAF mutant	103	98	**60 (50, 69)**	**46 (36, 56)**	**0.70 (0.46, 1.05)**
BRAF wild-type	211	218	**48 (41, 54)**	**43 (37, 50)**	**0.89 (0.69, 1.15)**
ECOG PS 0	230	237	**57 (51, 63)**	**49 (42, 55)**	**0.82 (0.53, 1.06)**
ECOG PS ≥1	83	79	**36 (26, 47)**	**30 (20, 40)**	**0.81 (0.55, 1.18)**
M0/M1a/M1b	129	132	**64 (55, 72)**	**58 (49, 66)**	**0.82 (0.56, 1.21)**
M1c	185	184	**43 (35, 50)**	**35 (28, 41)**	**0.82 (0.53, 1.07)**
LDH ≤ULN	199	197	**60 (52, 66)**	**53 (46, 60)**	**0.83 (0.52, 1.12)**
LDH >ULN	114	112	**38 (29, 47)**	**28 (20, 36)**	**0.82 (0.59, 1.13)**
LDH >2 × ULN	37	37	**28 (15, 43)**	**14 (5, 28)**	**0.73 (0.43, 1.24)**
Lesion sites: 1	89	80	**64 (53, 73)**	**61 (49, 70)**	**0.92 (0.57, 1.50)**
Lesion sites: 2 or 3	165	176	**49 (41, 57)**	**40 (33, 48)**	**0.78 (0.58, 1.03)**
Lesion sites: >3	60	59	**40 (27, 52)**	**33 (21, 45)**	**0.97 (0.51, 1.53)**



Modified to Supplement to Larkin et al. N Engl J Med 2019; 381:1535-1546

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CheckMate 067: Subsequent therapy at 6.5 years

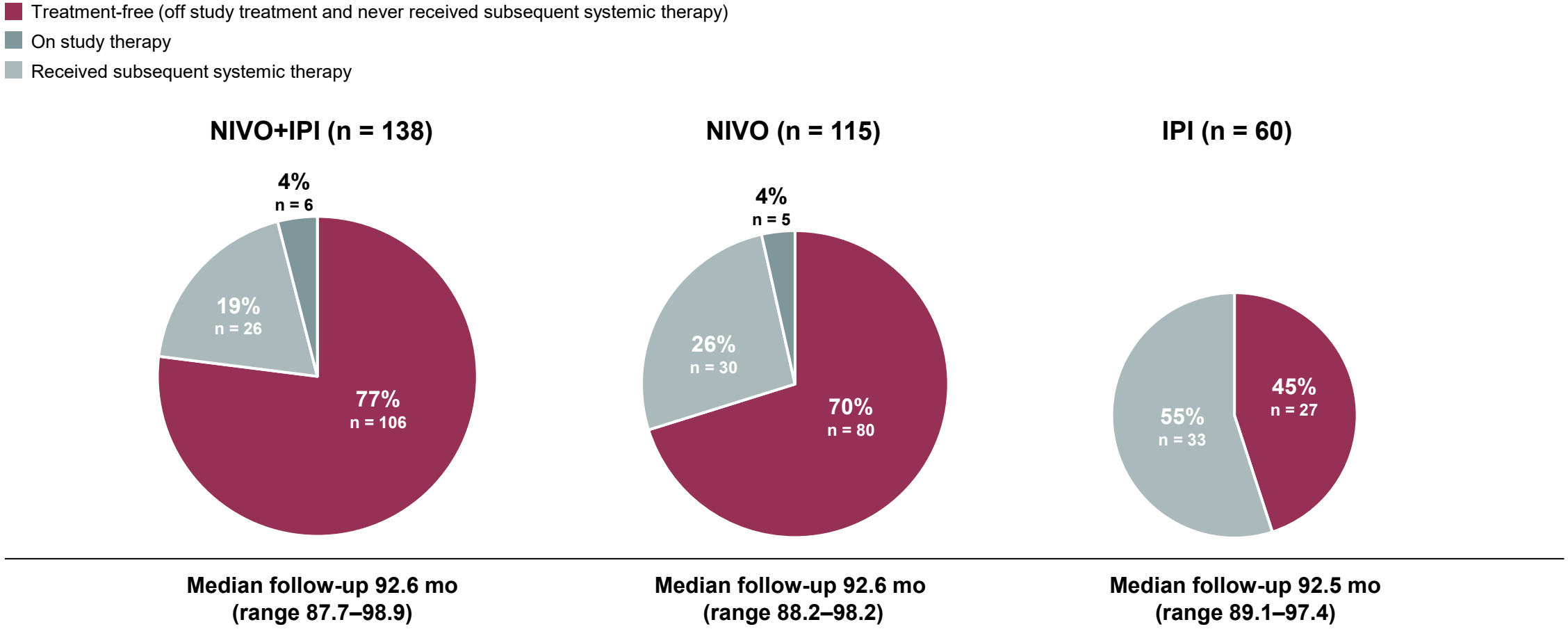
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Any subsequent therapy, n (%)[a]	**146 (46.5)**	**188 (59.5)**	**238 (75.6)**
Subsequent systemic therapy	**112 (36)**	**154 (49)**	**209 (66)**
Subsequent immunotherapy	**59 (19)**	**107 (34)**	**151 (48)**
Anti-PD-1 agents	**43 (14)**	**52 (16)**	**146 (46)**
Anti-CTLA-4 agents	**23 (7)**	**92 (29)**	**19 (6)**
BRAF inhibitor	**43 (14)**	**61 (19)**	**72 (23)**
MEK/NRAS inhibitor	**34 (11)**	**44 (14)**	**42 (13)**
Subsequent radiotherapy, n (%)	**71 (23)**	**96 (30)**	**128 (41)**
Subsequent surgery, n (%)	**69 (22)**	**75 (24)**	**97 (31)**
Median time from randomization to subsequent systemic therapy, (95% CI(, months	**NR (59.6–NR)**	**25.2 (16.0–43.2)**	**8.0 (6.5–8.7)**

[a]Patients may have received more than one type of subsequent therapy, and more than one agent within each type.

CTLA-4, cytotoxic T-lymphocyte-associated-4; MEK, mitogen-activated protein kinase kinase; NRAS, neuroblastoma RAS viral oncogene homolog; PD-1, programmed death[1].

Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

CheckMate 067: Patients alive and treatment-free at 7.5 years



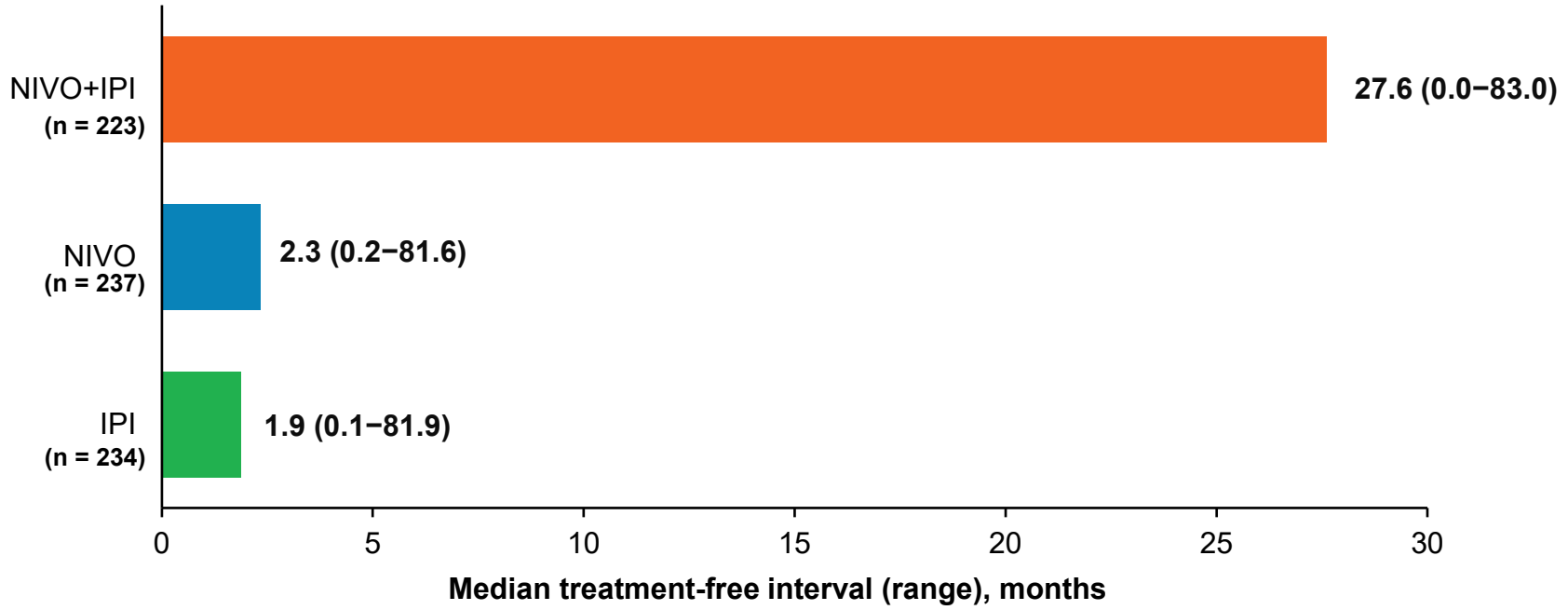
[a]Post-hoc analysis.

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: Treatment-free interval following study therapy discontinuation

- Patients analyzed were those who (1) were alive or (2) who died following subsequent systemic therapy
- Median duration of treatment was 3.6 mo (range, 0–80.1) with NIVO + IPI, 8.6 mo (0–79.8) with NIVO, and 3.7 mo (0–49.9) with IPI

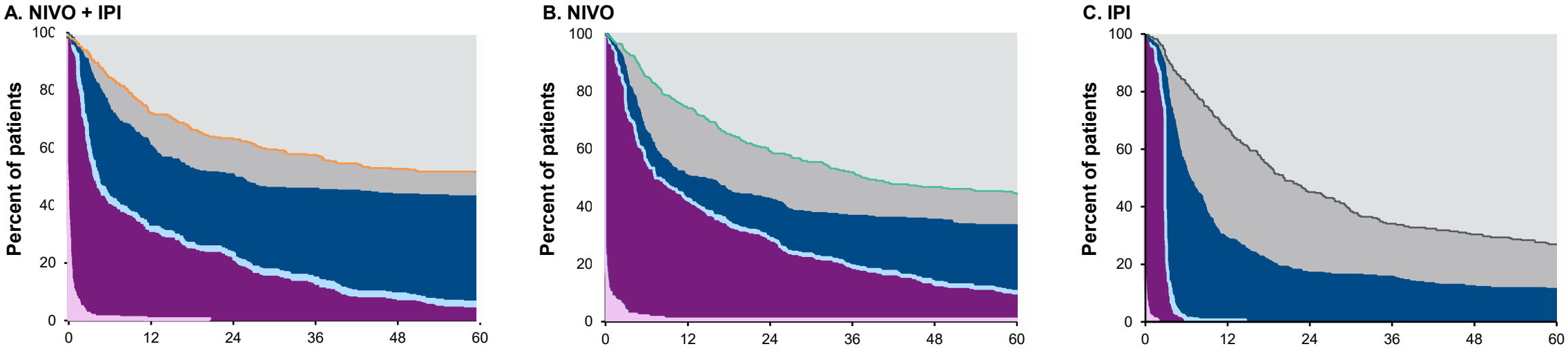


[a]Post-hoc analysis; [b]93 patients excluded: 12 on study treatment, 53 had died without receiving subsequent systemic therapy, and 28 were no longer in follow-up and never received subsequent therapy; [c]87 patients excluded: 24 on study treatment, 45 had died without receiving subsequent systemic therapy, and 18 were no longer in follow-up and never received subsequent therapy; [d]76 patients excluded: 57 had died without receiving subsequent systemic therapy and 19 were no longer in follow-up and never received subsequent therapy.

Wolchok JD et al. ASCO, 2021, Abstract #9506, Oral Presentation

Immunonkologie

CheckMate 067: Treatment Free Survival and survival states over the 60-month follow-up period



Survival state	NIVO + IPI		NIVO		Difference (95% CI): NIVO+IPI vs NIVO (mo)	IPI		Difference (95% CI): NIVO+IPI vs IPI (mo)
	60-mo mean time (mo)	Percent of 60-mo period	60-mo mean time (mo)	Percent of 60-mo period		60-mo mean time (mo)	Percent of 60-mo period	
Overall survival	38.6	64 %	36.1	60 %	2.5 (−1.1 to 6.2)	28.4	47%	10.2 (6.6 to 13.9)
Survival after subsequent therapy initiation	6.6	11 %	9.3	15 %	−2.7 (−4.9 to −0.4)	13.9	23%	−7.3 (−9.8 to −4.8)
TFS Without grade ≥ 3 TRAE With grade ≥ 3 TRAE	19.7 18.1 1.6	**33 %** 30 % 3 %	9.9 9.0 0.9	**17 %** 15 % 2 %	9.8 (6.7 to 12.8) 9.0 (6.1 to 12.0) 0.7 (−0.4 to 1.8)	11.9 11.7 0.2	20% 19% < 1%	7.8 (4.6 to 11.0) 6.4 (3.3 to 9.5) 1.4 (0.5 to 2.3)
Time on protocol therapy Without grade ≥ 3 TRAE With grade ≥ 3 TRAE	12.3 11.8 0.5	21 % 20 % 1 %	16.9 16.2 0.7	28 % 27 % 1 %	−4.6 (−7.3 to −1.8) −4.4 (−7.1 to −1.7) −0.2 (−0.8 to 0.5)	2.6 2.5 0.1	4% 4% < 1%	9.8 (7.9 to 11.6) 9.3 (7.5 to 11.1) 0.4 (0.2 to 0.6)

Regan M. et al., ASCO 2020, Abstract Number 10043

CheckMate 067 Treatment Free Survival: Authors' conclusions

- The sustained long-term OS benefit observed with NIVO-containing regimens compared with IPI was accompanied by sustained TFS, which represented an increasing percentage of time spent after NIVO+IPI and NIVO, but not after IPI
- On average, patients treated with NIVO+IPI have been treatment-free for one-third of the entire 7.5-year period since ICI initiation
- Patients treated with NIVO+IPI continued to have TFS twice as long as those treated with NIVO alone, due to earlier therapy cessation for toxicity and subsequent resolution of many of those toxicities without disease progression
- The majority of TFS time was spent without grade ≥ 3 TRAEs after all 3 treatment regimens

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Immunonkologie

CheckMate 067: Post-treatment Tumor Assessments in All Randomized Patients With Progressive Disease

	NIVO + IPI (n=74)	NIVO (n=121)	IPI (n=159)
Patients with at least one existing lesion, n (%)	18 (24)	31 (26)	39 (25)
Patients with at least one new lesion, n (%)	56 (76)	90 (74)	120 (75)
Site of new lesion, n (%)			
Bone	12 (16)	11 (9)	12 (8)
Central nervous system	8 (11)	21 (17)	23 (14)
Intestine	4 (5)	5 (4)	5 (3)
Liver	10 (14)	25 (21)	38 (24)
Lung	17 (23)	29 (24)	46 (29)
Lymph node	8 (11)	15 (12)	27 (17)
Other	5 (7)	4 (3)	9 (6)
Skin	3 (4)	10 (8)	8 (5)
Soft tissue	8 (11)	15 (12)	21 (13)
Visceral, other	7 (9)	18 (15)	30 (19)
No. of sites with at least one new lesion, n (%)			
1	35 (47)	53 (44)	57 (36)
2	16 (22))	18 (15)	36 (23)
3	5 (7)	13 (11)	19 (12)
4	0	5 (4)	7 (4)
≥ 5	0	1 (1)	1 (1)

Supplement to: Wolchok JD et al. N Engl J Med, 2017; DOI: 10.1056/NEJMoa1709684

CheckMate 067: Safety Summary

	NIVO+IPI (n=313)		NIVO (n=313)		IPI (n=311)	
Patients reporting event	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Treatment-related AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death[a], n (%)	2 (1)		1 (< 1)		1 (< 1)	

- No change to the safety summary was observed during additional follow-up
- In addition to the 4 deaths due to melanoma progression, there were 6 deaths since the 6.5-year follow-up, none of which were treatment-related

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO + IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1).

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

AE, adverse event.

Immunonkologie

CheckMate 067: Grade ≥ 2 Treatment-Related Select AEs Across Organ Categories

Number of organ categories impacted, n (%)*	All treated patients		
	NIVO + IPI (n=313)	NIVO (n=313)	IPI (n=311)
0	91 (29)	236 (75)	171 (55)
1	125 (40)	61 (20)	112 (36)
2	77 (25)	14 (5)	24 (8)
3	15 (5)	2 (1)	4 (1)
> 3	5 (2)	0 (0)	0 (0)

- A higher proportion of patients who received the combination experienced at least two grade 2–4 AEs across organ categories during treatment

* Organ categories: Skin, gastrointestinal, endocrine, hepatic, pulmonary, renal

Larkin et al. ESMO, 2015; Abstract 3303, oral presentation

CheckMate 067: Most Common Treatment-related Select AEs (≥ 5 %)[1]

	NIVO+IPI (n=313)		NIVO (n=313)		IPI n=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin and subcutaneous AEs, n (%)	194 (62)	20 (6)	146 (47)	6 (2)	174 (56)	9 (3)
Pruritus	112 (36)	6 (2)	69 (22)	1 (< 1)	113 (36)	1 (< 1)
Rash	93 (30)	10 (3)	74 (24)	1 (< 1)	69 (22)	5 (2)
Vitiligo	28 (9)	0	31 (10)	1 (< 1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	16 (5)	2 (1)	38 (12)	1 (< 1)
Gastrointestinal AEs, n (%)	150 (48)	48 (15)	72 (23)	11 (4)	117 (38)	36 (12)
Diarrhea	142 (45)	30 (10)	69 (22)	9 (3)	105 (34)	18 (6)
Colitis	40 (13)	26 (8)	8 (3)	3 (1)	35 (11)	24 (8)
Endocrine AEs, n (%)	106 (34)	20 (6)	53 (17)	6 (2)	37 (12)	8 (3)
Hypothyroidism	54 (17)	1 (< 1)	32 (10)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (5)	0	3 (1)	0
Hypophysitis	24 (8)	5 (2)	2 (1)	1 (< 1)	12 (4)	5 (2)
Hepatic AEs, n (%)	102 (33)	62 (20)	25 (8)	9 (3)	23 (7)	5 (2)
Increased AST	52 (17)	19 (6)	14 (5)	3 (1)	12 (4)	2 (1)
Increased ALT	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Hypersensitivity/ infusion reactions, n (%)	14 (4)	0	14 (5)	1 (< 1)	8 (3)	1 (< 1)
Infusion-related reaction	10 (3)	o	8 (3)	1 (<1)	8 (3)	1 (< 1)
Pulmonary AEs, n (%)	25 (8)	3 (1)	6 (2)	1 (< 1)	6 (2)	1 (< 1)
Pneumonitis	23 (7)	3 (1)	5 (2)	1 (< 1)	5 (2)	1 (< 1)
Renal AEs, n (%)	22 (7)	6 (2)	6 (2)	2 (1)	8 (3)	1 (< 1)
Increased blood creatinine	14 (4)	1 (< 1)	3 (1)	1 (< 1)	5 (2)	0

[1]Modified to Supplement to Larkin et al. N Engl J Med 2019; 381:1535-1546

.

Immunonkologie

CheckMate 067: Resolution to Baseline of Grade 3–5 Treatment-Related Select AEs in Patients Treated with Immune Modulators[1]

Select AEs organ category	NIVO + IPI (n=313)		NIVO (n=313)	
	Pts with resolution of select AEs*, n (%)	Median time to resolution, weeks (range)	Pts with resolution of select AEs*, n (%)	Median time to resolution, weeks (range)
Skin	15/15 (100)	3.1 (0.6–54.6)	3/4 (75)	4.1 (0.9–208.0+)
Gastrointestinal	44/45 (98)	3.1 (0.3–33.1+)	5/8 (63)	12.4 (0.9–231.3+)
Endocrine	7/14 (50)	18.6 (1.6–264.6+)	0/3 (0)	NR (225.9+–255.7+)
Hepatic	38/38 (100)	4.1 (0.3–26.0)	6/6 (100)	7.0 (2.0–27.1)
Pulmonary	2/2 (100)	4.2 (1.1–7.3)	1/1 (100)	2.3 (2.3–2.3)
Renal	3/3 (100)	1.7 (0.4–3.6)	1/2(50)	NR (15.4–218.9+)

AE, adverse event

* The total number of patients with resolution of event was the number of treated patients experiencing resolution or improvement to the baseline grade for the longest AE belonging to the select AE category.

[1]Modified to Supplement to Larkin et al. N Engl J Med 2019; 381:1535-1546

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CheckMate 067: Summary

- CheckMate 067, with a minimum 7.5-year follow-up, continues to demonstrate durable, long-term survival outcomes with NIVO + IPI combination therapy
  - 7.5-year OS rates were 48%, 42%, and 22% for NIVO + IPI, NIVO, and IPI respectively
  - Median MSS is still not reached for NIVO +IPI, and 7.5-year rates were 55%, 47%, and 26% for the treatment arms, respectively
  - Median DOR remains NR in patients treated with NIVO + IPI, was reached for NIVO (90.8 months), and remains 19.2 months for IPIO
  - 4 deaths across the 3 treatment arms were due to disease progression since the last database lock
- Patients treated with NIVO + IPI spent more time treatment-free and were less likely to receive subsequent systematic therapy
- Median time to subsequent therapy was NR, 24.7 months, and 8.0 months respectively
- HRQoL remains similar to the 5-year analysis, with no sustained deterioration during treatment, following treatment discontinuation, or during the treatment-free period

Hodi S.F. et al. ASCO, 2022, Abstract #9522, Poster Presentation

Larkin J et al. N Engl J Med 2019; 381:1535-1546.

DSMC decided to **stop DREAMseq study ahead of schedule** because of 2 yrs **clinically meaningful superior survival for NIVO + IPI Firstline**
- in order to give all DAB + TRAM Firstline patients the option to **switch to NIVO + IPI** arm even without progression.[1]

1. Atkins MB et al. J Clin Oncol 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

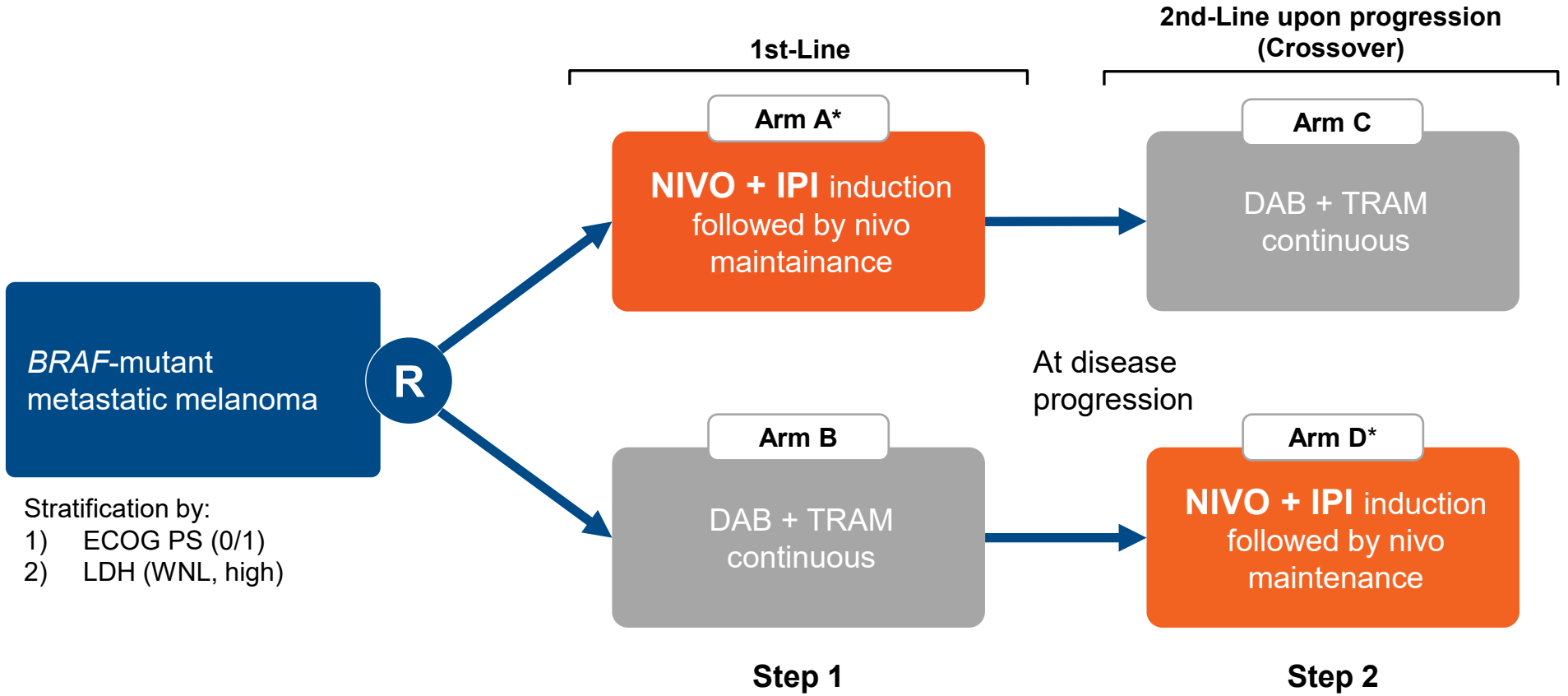
DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) – A Phase III Trial: ECOG-ACRIN EA6134

Michael B. Atkins, Sandra Lee, Bartosz Chmielowski, Antoni Ribas, Ahmad A. Tarhini, Thach-Giao Truong, Diwakar Davar, Mark O'Rourke, Brendan D. Curti, Joanna M. Brell, Kari L. Kendra, Alexandra P. Ikeguchi, Jedd D. Wolchok, John M. Kirkwood

Bristol Myers Squibb

Immunonkologie

DREAMseq Trial Treatment Schema



Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

* NIVO + IPI Induction = 12 wks; NIVO maintenance = 72 wks; NIVO = Nivolumab; IPI = Ipilimumab; DAB = Dabrafenib; TRAM = Trametinib; WNL = within normal limit; PS = Performance Status

DREAMseq Objectives

Primary Objective: 2 year landmark OS (70 % vs 50 %*)

- 300 patients (270 evaluable)

Secondary Objectives:

- 3 year landmark OS
- HR for death at specified time points
- ORRs and PFS and safety of NIVO + IPI in BRAF mutant population
- Activity of DAB + TRAM after NIVO + IPI vs DAB + TRAM upfront
- Activity of NIVO + IPI after DAB + TRAM vs NIVO + IPI upfront
- Feasibility of crossover
- Platform for correlative studies

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473
NIVO = Nivolumab; IPI = Ipilimumab; DAB = Dabrafenib; TRAM = Trametinib
* 90% Power 2-Year OS rate of 70% in Arm A to C sequence vs. 50% in Arm B to D, two-sided type I error rate of 0.05

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DREAMseq Accrual

- Activated on July, 13 2015
- Suspended/Reactivated: Feb, 2 2016 – April, 11 2016
- Terminated: Sept, 30 2021

	1st-Line only Step 1		**2nd-Line upon disease progression (Crossover)** Step 2	
	Arm A N + I 1st-Line	**Arm B** D + T 1st-Line	**Arm C** N + I 1st-Line D + T 2nd-Line	**Arm D** D + T 1st-Line N + I 2nd-Line
As of July, 16 2021* (DSMC 4th data cut-off date)	133	132	27	46

Median follow-up 27.7 months

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473
DSMC: Data and Safety Monitoring Committee

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DREAMseq Demographics (1st-Line only, Step 1)

Characteristic	Arm A N + I 1st-Line (n = 133)	Arm B D + T 1st-Line (n = 132)
Age (years)	61 (range: 25-85)	61 (range: 30-84)
Sex % Male	61 %	65 %
ECOG PS 0 (%)	68 %	67 %
Stage III unresectable M1A M1B M1C	(n = 130) 9 (7 %) 16 (12 %) 24 (18 %) 81 (62 %)	(n = 130) 17 (13 %) 14 (11 %) 23 (18 %) 76 (58 %)
LDH > ULN (%)	53 (40 %)	53 (40 %)
Prior Treatment (adjuvant)*	16 (12 %)	21 (17 %)

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

* Almost exclusively IFN; No CPI or BRAF/MEKi therapy; CPI = Checkpoint inhibitor

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DREAMseq Toxicity By Treatment Arm

	Step 1		Step 2	
	Arm A N + I 1st-Line (n = 126)	**Arm B** D + T 1st-Line (n = 130)	**Arm C** N + I 1st-Line D + T 2nd-Line (n = 26)	**Arm D** D + T 1st-Line N + I 2nd-Line (n = 42)
Grade 3+ TRAEs (95 % CI)	60 % (51 %, 69 %)	52 % (43 %, 61 %)	54 % (33 %, 73 %)	50 % (34 %, 66 %)
Grade 5 AEs (CTEP)^	11	10	3	3
Grade 5 TRAE	2*	0	1#	0

^ CTEP Grade 5 AEs = death from any cause within 30 days of last treatment

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* Myocarditis, GI; # Thromboembolic-CVA;

CTEP: NCI Cancer Therapy Evaluation Program

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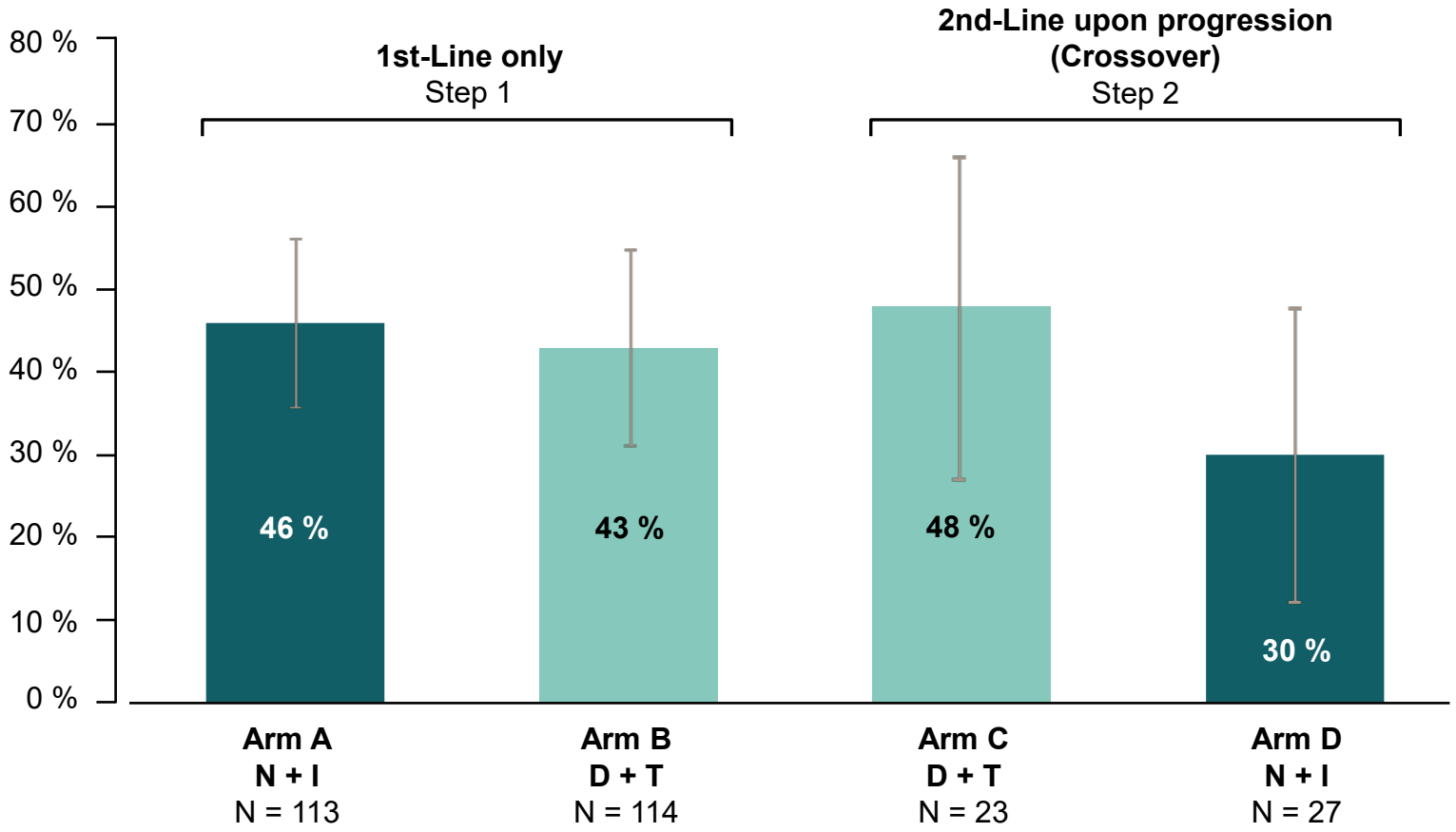
DREAMseq ORR (%) By Treatment Arm*



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* Bars represent 95 % CI; Data missing on ~ 15 % of pts

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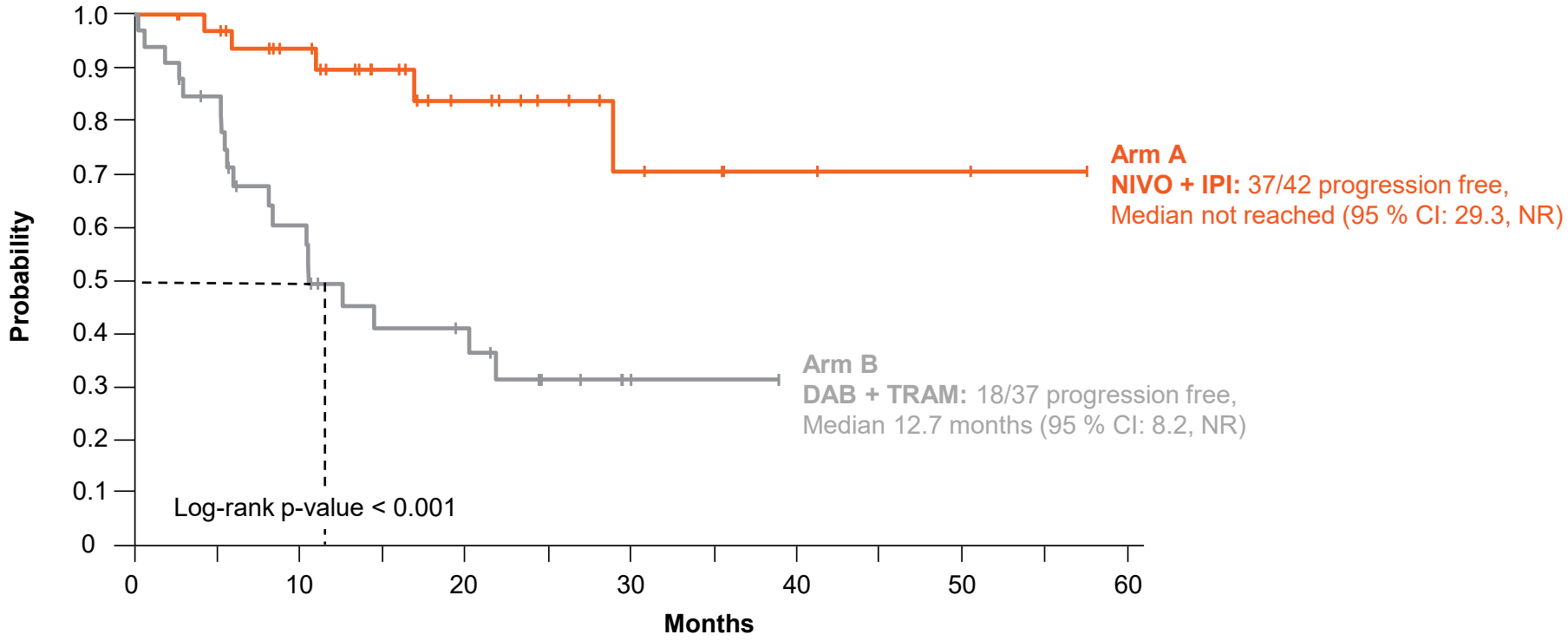
DREAMseq Duration of Response, DOR* (1st-Line only, Step 1)



	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	(Time Intervall)
Arm A: NIVO + IPI	42	31	23	14	10	6	4	2	2	1	(# at risk)
Arm B: DAB + TRAM	37	23	14	12	8	2	1	0	0	0	

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

* DOR: time from PR or CR to progression or last assessed

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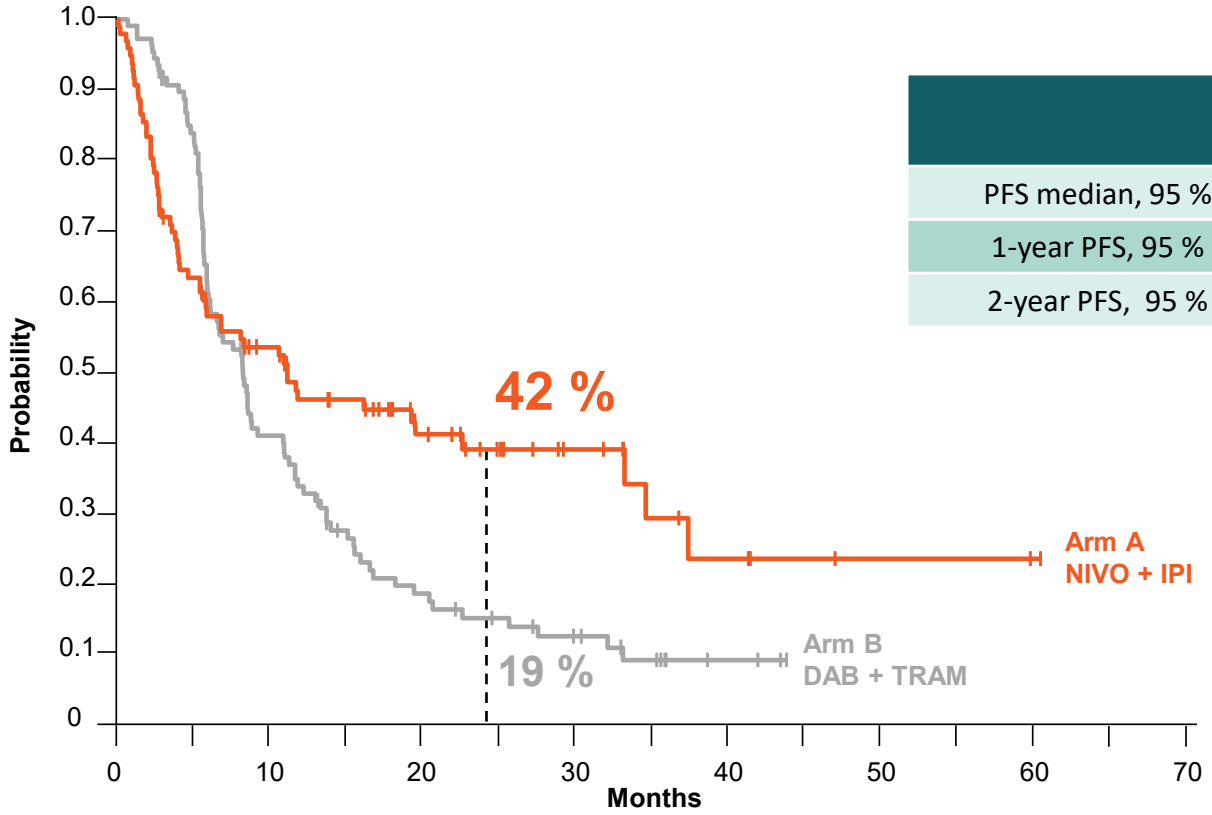
DREAMseq Progression Free Survival, PFS (1st-Line only, Step1, n = 214)



	Arm A NIVO + IPI	Arm B DAB + TRAM
PFS median, 95 % CI	**11.8 mo** (5.9, 33.5)	**8.8 mo** (6.5, 11.3)
1-year PFS, 95 % CI	**49 %** (38 %, 58 %)	**36%** (28 %, 46 %)
2-year PFS, 95 % CI	**42 %** (31 %, 52 %)	**19%** (12 %, 27 %)

Log-rank p-value = 0.054

	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	(Time Intervall)
Arm A: NIVO + IPI	101	57	40	32	19	12	7	3	2	2	2	(# at risk)
Arm B: DAB + TRAM	113	66	38	23	17	13	6	3	0	0	0	

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

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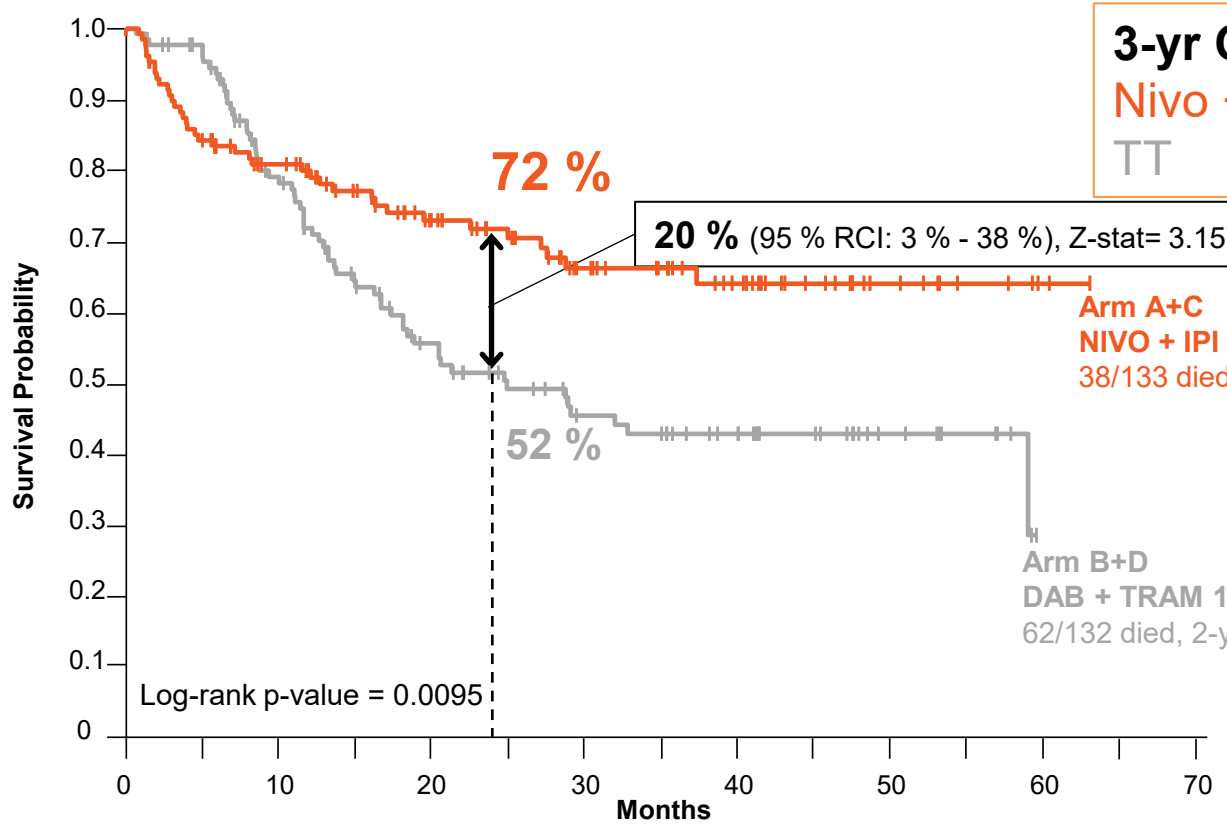
DREAMseq Overall Survival, OS (1st-Line only and 1st-Line followed by 2nd-Line upon progression (Crossover) Step 1+2)



3-yr OS-Rate*

Nivo + IPI +/-TT		66.2% (56.0,74.6)
TT	+/- TT	42.8% (32.9,52.4)

20 % (95 % RCI: 3 % - 38 %), Z-stat= 3.157 >2.743

Arm A+C
NIVO + IPI 1L & NIVO + IPI 1L → DAB + TRAM:
38/133 died, 2-yr OS rate 72 % (95 % CI: 62 %, 79 %)

Arm B+D
DAB + TRAM 1L & DAB + TRAM 1L → 2L NIVO + IPI:
62/132 died, 2-yr OS rate 52 % (95 % CI: 42 %, 60 %)

	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	(Time Intervall)
Arm A + C: NIVO + IPI +/- DAB + TRAM	133	99	87	71	55	42	33	23	15	6	3	(# at risk)
Arm B + D: DAB + TRAM +/- NIVO + IPI	132	115	78	60	47	35	30	18	15	6	1	

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

* Atkins et al. ASCO Plenary Series 2022, Updates on Abstract 356154

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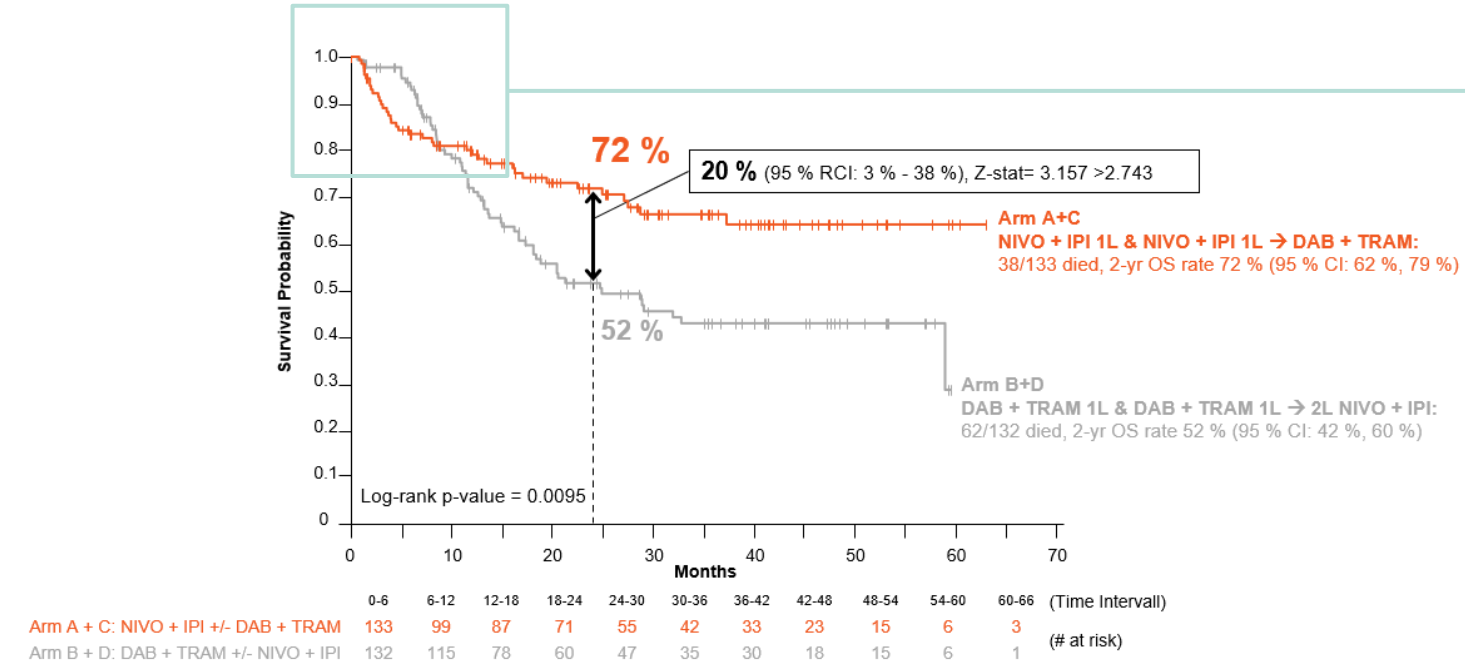
DREAMseq: Early Deaths (<10 mos) on Arm-A Nivo/Ipi; N=24



Med OS: 3 mos (0.9-8.4 mos)

PS 1 (42%); **LDH-high** (58%); Stage M1c (71%)

Median Rx Duration < 6 weeks

Off Rx Reason

- PD= 39%
- AE = 30%
- Death= 26%
- Other= 4%

Crossover to Arm C-TT = 0

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

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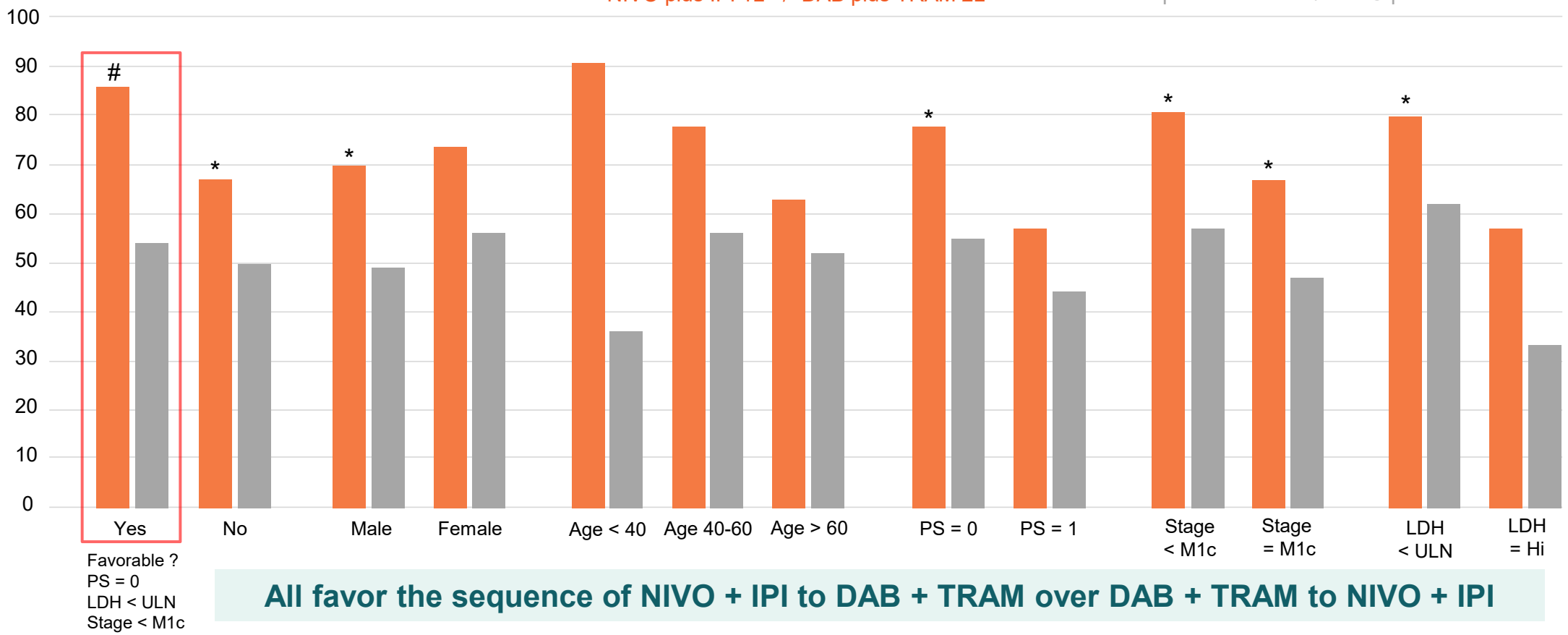
DREAMseq 2-yr OS Rate Subgroup Analyses by Sequence

Log-rank test, multiple analysis not adjusted

Arm A+/-C
NIVO plus IPI 1L +/- DAB plus TRAM 2L

Arm B+/-D
DAB plus TRAM 1L +/- NIVO plus IPI 2L



All favor the sequence of NIVO + IPI to DAB + TRAM over DAB + TRAM to NIVO + IPI

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473

* Log-rank p-value < 0.05; # Log-rank p-value = 0.054

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DREAMseq Summary/Conclusion

- NIVO + IPI followed by DAB + TRAM is associated with greater OS at 2 years and likely beyond than the converse sequence
  - NIVO + IPI results in more durable and ongoing responses
  - OS benefit for NIVO + IPI initial sequence was seen in all subgroups
  - 2nd-Line DAB + TRAM is a critical contributor to overall efficacy

- PFS and OS curves were biphasic with curves crossing at 6 and 10 months
  - Pts dying early on NIVO + IPI had worse prognosis, AEs and never received DAB + TRAM
  - Efforts underway to further identify and best manage this small subset of pts

NIVO + IPI followed by BRAF/MEKi (if necessary) should be the preferred treatment sequence for pts with BRAF mutant melanoma.

DSMC decided to **stop DREAMseq study ahead of schedule** because of 2 yrs **clinically meaningful superior survival for NIVO + IPI Firstline** - in order to give all DAB + TRAM Firstline patients the option to **switch to NIVO + IPI** arm even without progression.

Modified to Atkins MB et al. *J Clin Oncol* 39, 2021 (suppl 36; abstr 356154) https://meetings.asco.org/asco-plenary-series/14130?presentation=204473
DSMC: Data and Safety Monitoring Committee

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CheckMate 067, 069

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Background[1]

- Combination immunotherapies with checkpoint inhibitors and combination targeted therapies with BRAF-MEK inhibitors are 2 therapeutic approaches for treatment-naïve patients with *BRAF*-mutant advanced melanoma, which constitutes ~45% of the advanced melanoma population
- Combination of BRAF (dabrafenib or vemurafenib) and MEK (trametinib or cobimetinib) inhibitors has significantly improved outcomes for patients with advanced melanoma[2]; however, acquired resistance to agents that target the mitogen-activated protein kinase pathway remains problematic[3]
- Combination immunotherapy with checkpoint inhibitors such as nivolumab and ipilimumab or with nivolumab monotherapy resulted in superior long-term survival outcomes compared with ipilimumab alone in patients with advanced melanoma[4]
- As data from head-to-head studies between these 2 treatment approaches are not yet available, clinicians and payers must rely for the present on indirect cross-trial comparisons to assess the long-term outcomes of BRAF-mutant patients on immunotherapy and targeted therapies[5]

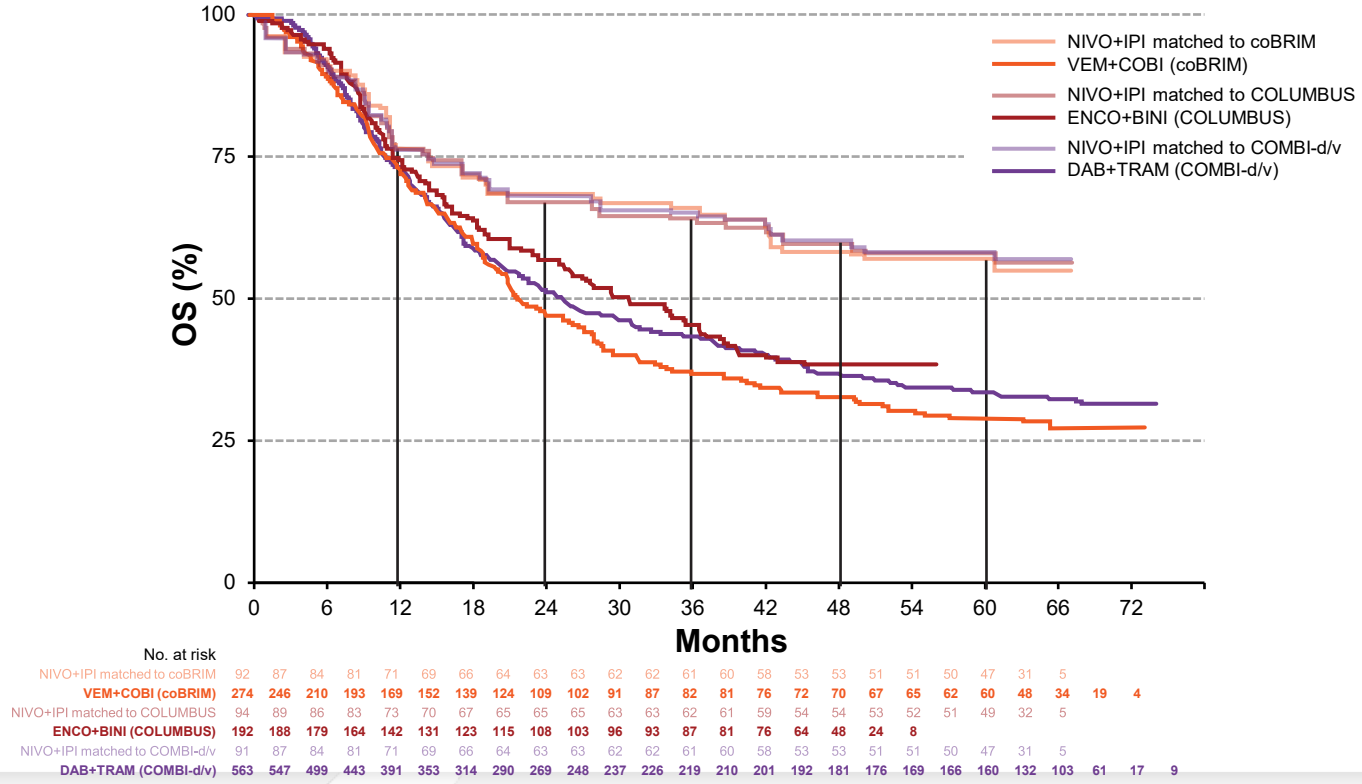
1. Modified to Atkins MB et al. AACR, 2018; Poster Presentation #3639, 2. Schadendorf D et al. *Eur J Cancer.* 2017;82:45-55. 3. Welsh SJ et al. *Eur J Cancer.* 2016;62:76-85. 4. Modified to Larkin J et al. ESMO, 2019; Oral Presentation, 5. Tarhini et al. ESMO Open, Vol. 6, Issue 2, 2021

Overall Survival for Patients with BRAF Mutant Melanoma

Indirect comparison of immunotherapy & targeted therapy

Nivolumab + Ipilimumab First-Line and BRAF + MEK-Inhibition First-Line *,[1,2]

No Head-to-Head Comparison; adjusted indirect overall survival comparison



NIVO + IPI versus	HR (95% CI)
VEM + COBI	0.50 (0.36–0.70)
ENCO + BINI	0.60 (0.42–0.85)
DAB + TRAM	0.53 (0.39–0.73)

* Matching-adjusted indirect comparison (MAIC) of Patients from CheckMate 067 and 069 (Nivolumab + Ipilimumab) as well as COMBI-v and COMBI-d (Dabrafenib + Trametinib) Mean Follow-up (estimated) CheckMate 067 38.4 Months, CheckMate 069 16.7 Months, COMBI-d 32.3 Months, COMBI-v 32.3 Months

1. Atkins MB et al. Immunotherapy, 2019; 11(7): 617–29, 2. Modified to Tarhini et al. ESMO Open, Vol. 6, Issue 2, 2021

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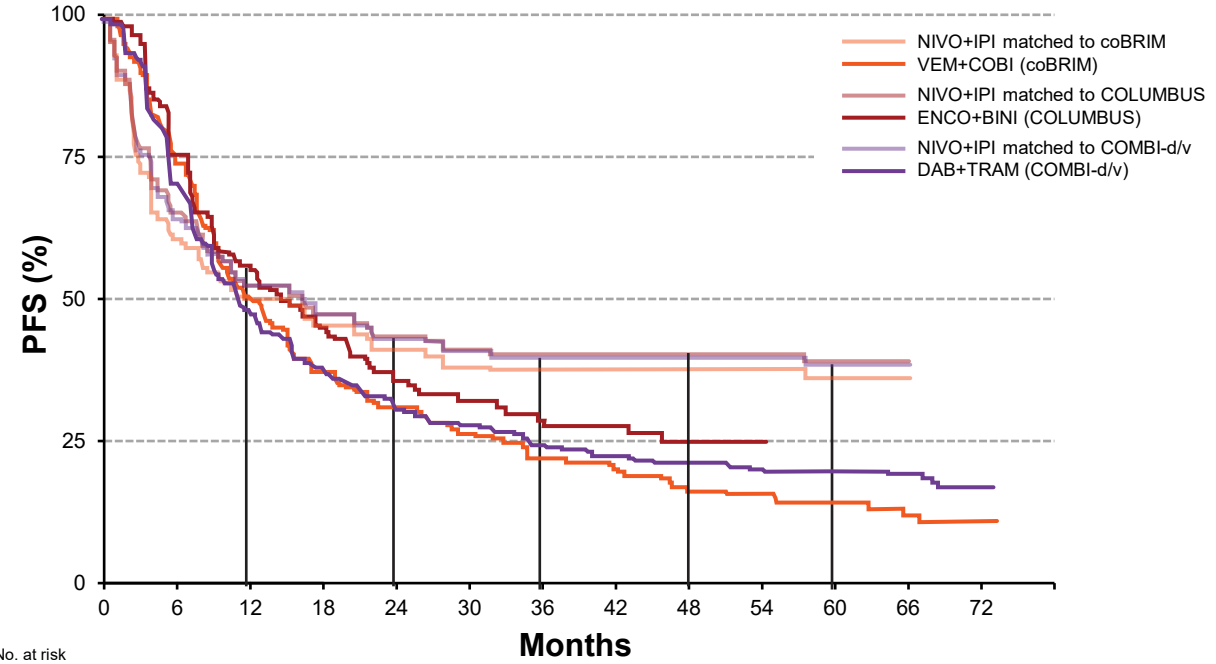
Progression Free Survival for Patients with BRAF Mutant Melanoma

Indirect comparison of immunotherapy & targeted therapy

Nivolumab + Ipilimumab First-Line and BRAF + MEK-Inhibition First-Line *,[1,2]

No Head-to-Head Comparison; adjusted indirect progression free survival comparison



No. at risk

NIVO+IPI matched to coBRIM	92	65	50	45	41	41	37	34	32	31	28	28	27	26	26	26	24	23	23	23	15	5	1		
VEM+COBI (coBRIM)	**274**	**220**	**175**	**144**	**117**	**103**	**85**	**78**	**69**	**61**	**54**	**50**	**44**	**39**	**36**	**33**	**28**	**27**	**24**	**21**	**19**	**15**	**10**	**6**	**2**
NIVO+IPI matched to COLUMBUS	94	66	52	46	42	42	38	35	33	31	29	28	28	26	26	26	24	24	24	23	16	5	1		
ENCO+BINI (COLUMBUS)	**192**	**174**	**129**	**105**	**87**	**75**	**68**	**58**	**50**	**36**	**27**	**26**	**24**	**23**	**23**	**21**	**16**	**8**	**4**						
NIVO+IPI matched to COMBI-d/v	92	65	50	45	41	41	37	34	32	31	28	28	27	26	26	26	24	23	23	23	15	5	1		
DAB+TRAM (COMBI-d/v)	**563**	**506**	**371**	**307**	**243**	**215**	**188**	**169**	**148**	**134**	**125**	**118**	**105**	**97**	**91**	**86**	**81**	**78**	**71**	**65**	**59**	**45**	**32**	**21**	**2**

NIVO + IPI versus	HR (95% CI)
VEM + COBI	0.74 (0.55–0.99)
ENCO + BINI	0.88 (0.63–1.21)
DAB + TRAM	0.73 (0.55–0.96)

* Matching-adjusted indirect comparison (MAIC) of Patients from CheckMate 067 and 069 (Nivolumab + Ipilimumab) as well as COMBI-v and COMBI-d (Dabrafenib + Trametinib) Mean Follow-up (estimated) CheckMate 067 38.4 Months, CheckMate 069 16.7 Months, COMBI-d 32.3 Months, COMBI-v 32.3 Months

1. Atkins MB et al. Immunotherapy, 2019; 11(7): 617–29, 2. Modified to Tarhini et al. ESMO Open, Vol. 6, Issue 2, 2021

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Discussion[1,2]

- After adjusting for baseline characteristics, NIVO+IPI had a significant OS benefit over DAB+TRAM, VEM+COBI and ENCO+BINI for the treatment of BRAF-mutant advanced melanoma patients
- Short-term (<12 months) outcomes were similar between NIVO+IPI and BRAF+MEK inhibitors, with OS and PFS benefits emerging for NIVO+IPI after 12 months of treatment
  - Landmark PFS and OS at 48 months were 17% and 20% higher, respectively, for NIVO+IPI compared with DAB+TRAM[1]
  - After 5 years NIVO+IPI reduced the risk of death vs. BRAF+MEK inhibitors by 40-50%[2]
- Ongoing randomized studies (NCT02224781; NCT02631447) comparing the outcomes for patients initiating treatment with NIVO+IPI and those treated with targeted therapies are important to validate these results

1. Modified to Tarhini et al. SMR 2019; Poster Presentation; 2. Modified to Tarhini et al. ESMO Open, Vol. 6, Issue 2, 2021

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Melanom-bedingte Hirnmetastasen

CheckMate 204

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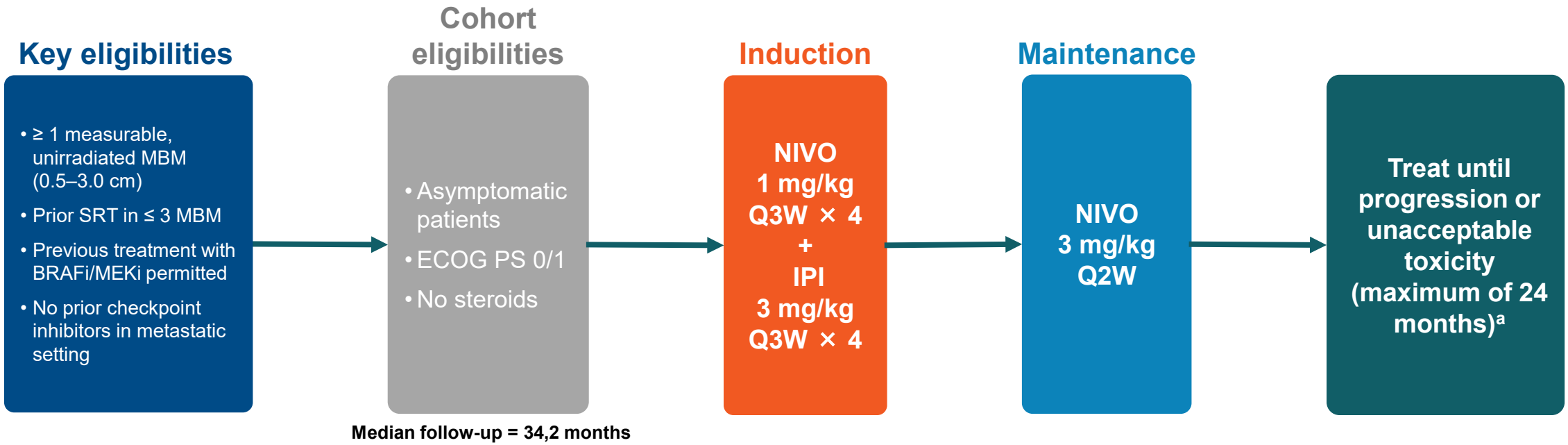
CheckMate 204: Background[1]

- Brain metastases are a major cause of morbidity/death from melanoma[2]
  - More than half of all patients with metastatic melanoma are expected to have a brain metastasis during the course of their disease
  - Historically, patients with melanoma metastatic to the brain have had a median overall survival (OS) of ~4−5 months[2]
  - Strategies for managing brain metastases have traditionally been limited to surgery and radiation therapy[3]
- In patients with melanoma brain metastases (MBM) who are asymptomatic and do not require steroids, immunotherapy has been proven tolerable, and has clinical benefit:
  - Single agent ipilimumab (IPI) has a CNS ORR of 16%[4]
  - Both nivolumab (NIVO) and pembrolizumab have a CNS ORR of ~ 20%[5,6]

RECIST = Response Evaluation Criteria In Solid Tumors

1. Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, 2. Davies MA, et al. *Cancer.* 2011;117:1687−1696,
3. Chukwueke U, et al. J Oncol Pract. 2016;12:536−542, 4. Margolin K, et al. Lancet Oncol. 2012;13:459−465,
5. Long GV, et al. Lancet Oncol. 2018;19:672−681, 6. Kluger HM, et el. J Clin Oncol. 2019;37:52−60

CheckMate 204: Study Design – Asymptomatic Cohort



Median follow-up = 34,2 months

- **Primary objective**: intracranial clinical benefit rate (CR + PR + SD ≥ 6 months) using modified RECIST
- **Secondary objectives**: safety, overall survival, extracranial and global clinical benefit rate
- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease

Data cutoff date of December 18, 2020

a Patients with grade 3–4 adverse events (AEs) during NIVO + IPI induction could resume NIVO when toxicity resolved and all patients who discontinued proceeded to follow-up
b Using modified RECIST v1.1.

Q2W = every 2 weeks; Q3W = every 3 weeks; CBR = clinical benefit rate; CR = complete response; EC = extracranial; IC =intracranial; MBM = melanoma brain metastases; PR = partial disease; SD = stable disease; SRT = stereotactic radiosurgery.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

CheckMate 204 – Asymptomatic Cohort: Demographic and Patient Characteristics

	Patients (n = 101)[a]
Male, n/N (%)	68/101 (67)
Median age, years (range)	59.0 (22–81)
BRAF mutation, n/N (%)	66/99 (67)
NRAS mutation, n/N (%)	7/26 (27)
LDH > ULN, n/N (%)	41/101 (41)
LDH > 2 × ULN, n/N (%)	11/101 (11)
PD-L1 expression, n/N (%)	
≥ 1%	44/81 (54)
< 1%	37/81 (46)
Prior SRT, n/N (%)	9/101 (9)
Median of sum of intracranial target lesion diameters, mm (range)	15 (5–91)
Intracranial target lesions, n/N (%)	
1–2 lesions	78/100 (78)
≥ 3 lesions	22/100 (22)

a Nine patients did not have extracranial disease.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Asymptomatic Cohort: Response to Treatment

	Patients (n = 101)		
	Intracranial (ESMO 2021)*	Extracranial (ASCO 2019)	Global (ASCO 2019)
Best overall response, n (%)			
Complete response	33 (33)	11 (11)	11 (11)
Partial response	21 (21)	38 (38)	40 (40)
Stable disease ≥ 6 months	4 (4)	6 (6)	4 (4)
Progressive disease	30 (30)	16 (16)	28 (28)
Not evaluable	13 (13)	30 (30)[a]	18 (18)
ORR, n/N (%)	55/101 (53)	49/101 (49)	51/101 (51)
(95% CI)	(43–64)	(38–59)	(40–61)
CBR[b], n/N (%)	58/101 (57)	55/101 (54)	59/101 (54)
(95% CI)	(47–67)	(44–64)	(44–64)

- Median duration of response was not yet reached at 36 months
- ORR and CBR for extracranial and global disease were similar to those for intracranial disease

ORR = Objective Response Rate, * Investigator assesed

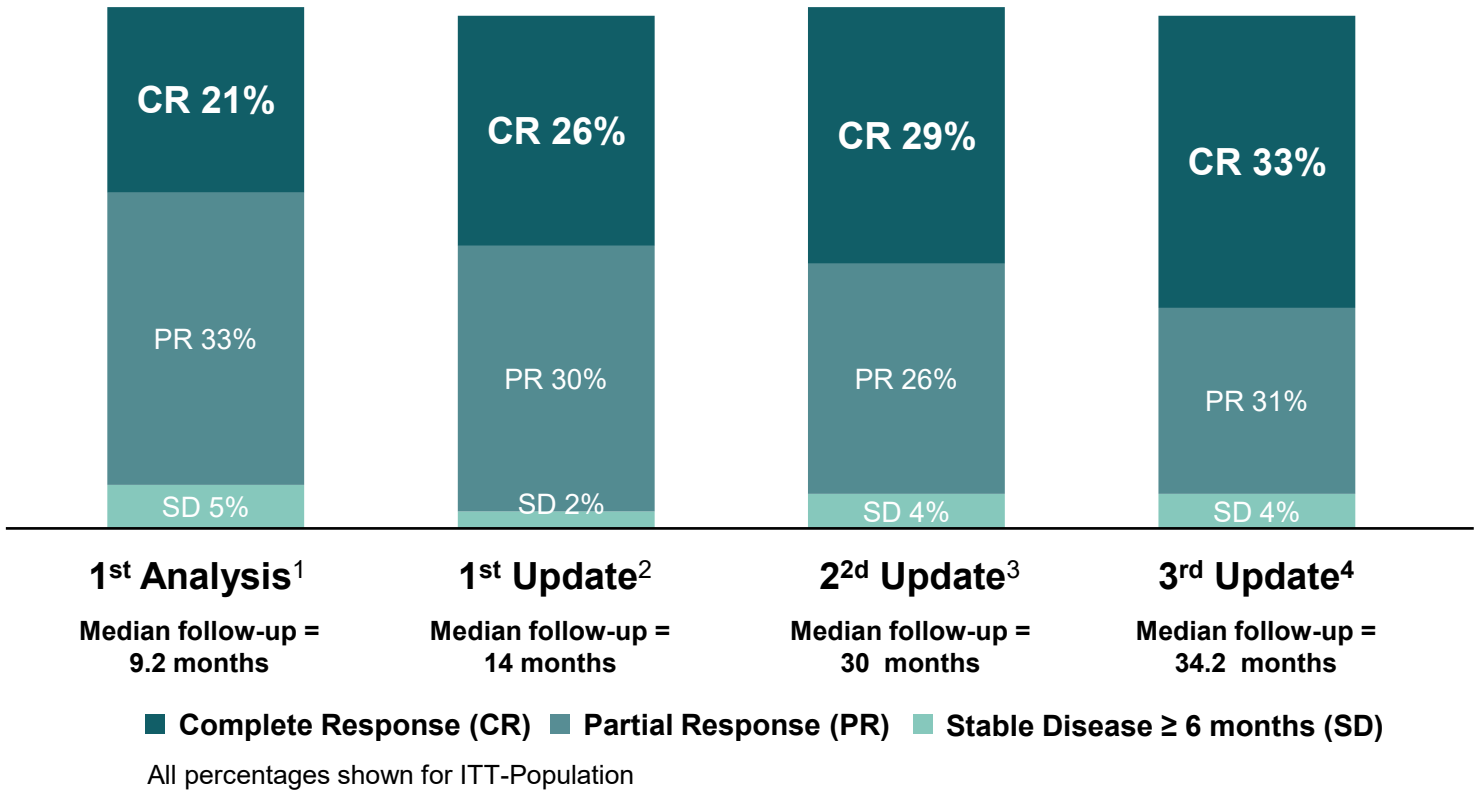
[a] Seven of these patients did not have extracranial disease at baseline

[b] Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

For investigator: BOR Not evaluable: death prior to assessment (n = 2), early discontinuation due to toxicity (n = 1), SD < 6 months (n = 6), other (n = 4); reasons for BICR-assessed were not captured in the clinical database. Data for 6 patients was not available because the patients died, progressed, or withdrew consent before evaluation.

CheckMate 204 – Asymptomatic Cohort: Best Response for NIVO + IPI over Time



1. Tawbi HA et al. ASCO, 2017; Abstract #9507, Oral Presentation.
2. Tawbi HA et al. N Engl J Med, 2018; 379: 722-730.
3. Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.
4. Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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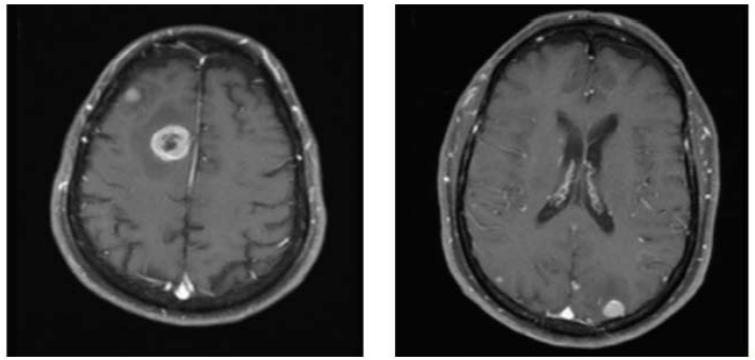
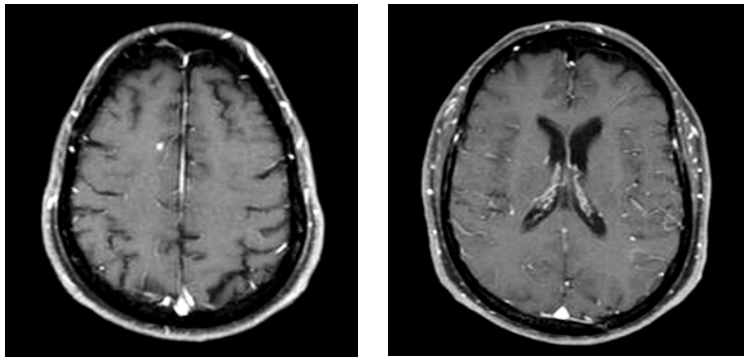
CheckMate 204 – Asymptomatic Cohort: Patient Case

- 71 year old male with BRAF V600E-mutated MEL, ~7 brain mets, no steroids or SRT

Baseline



1 year

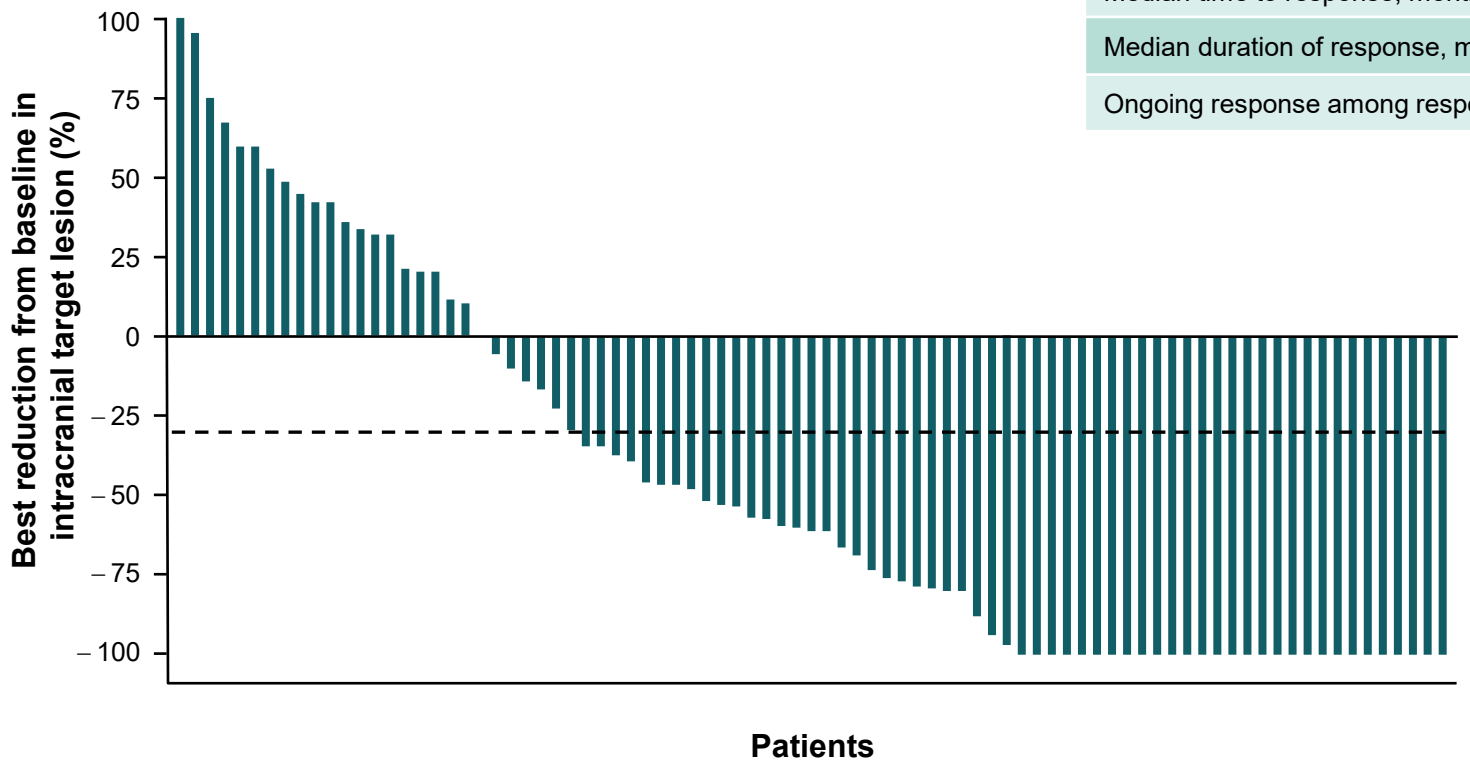


Tawbi HA et al. ASCO, 2017; Abstract #9507, Oral Presentation.

CheckMate 204 – Asymptomatic Cohort:

Intracranial Tumor Burden Change and Characteristics of Intracranial Response

	n = 101
Median time to response, months (range)	1,6 (1.1-12.5)
Median duration of response, months (95% CI)	NR (NR–NR)
Ongoing response among responders, n/N (%)	48/55 (87%)



Median change: -57.1%

CI = confidence interval

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

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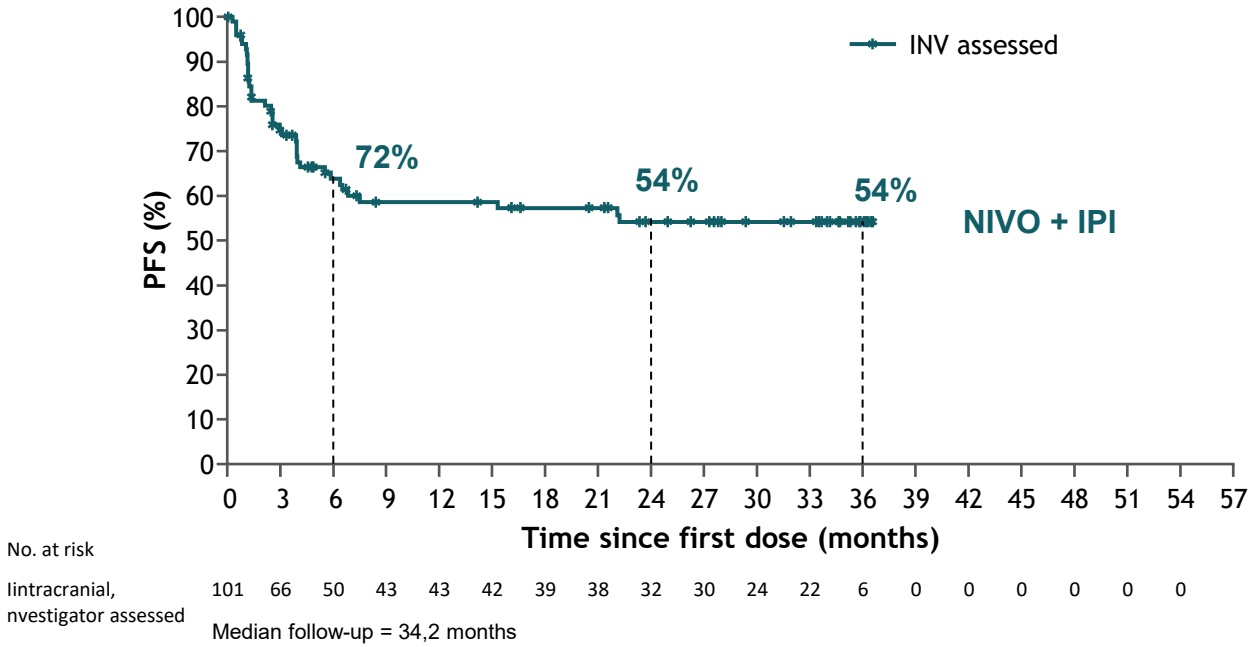
CheckMate 204 – Asymptomatic Cohort: Progression-Free Survival



- PFS rates for extracranial and global disease were similar
- Extracranial 24-month rates were 59%; 36-month rates were 53%
- Global 24-month rates were 50%; 36-month rates were 45%

CI = confidence interval; NR = not reached; PFS = progression-free survival

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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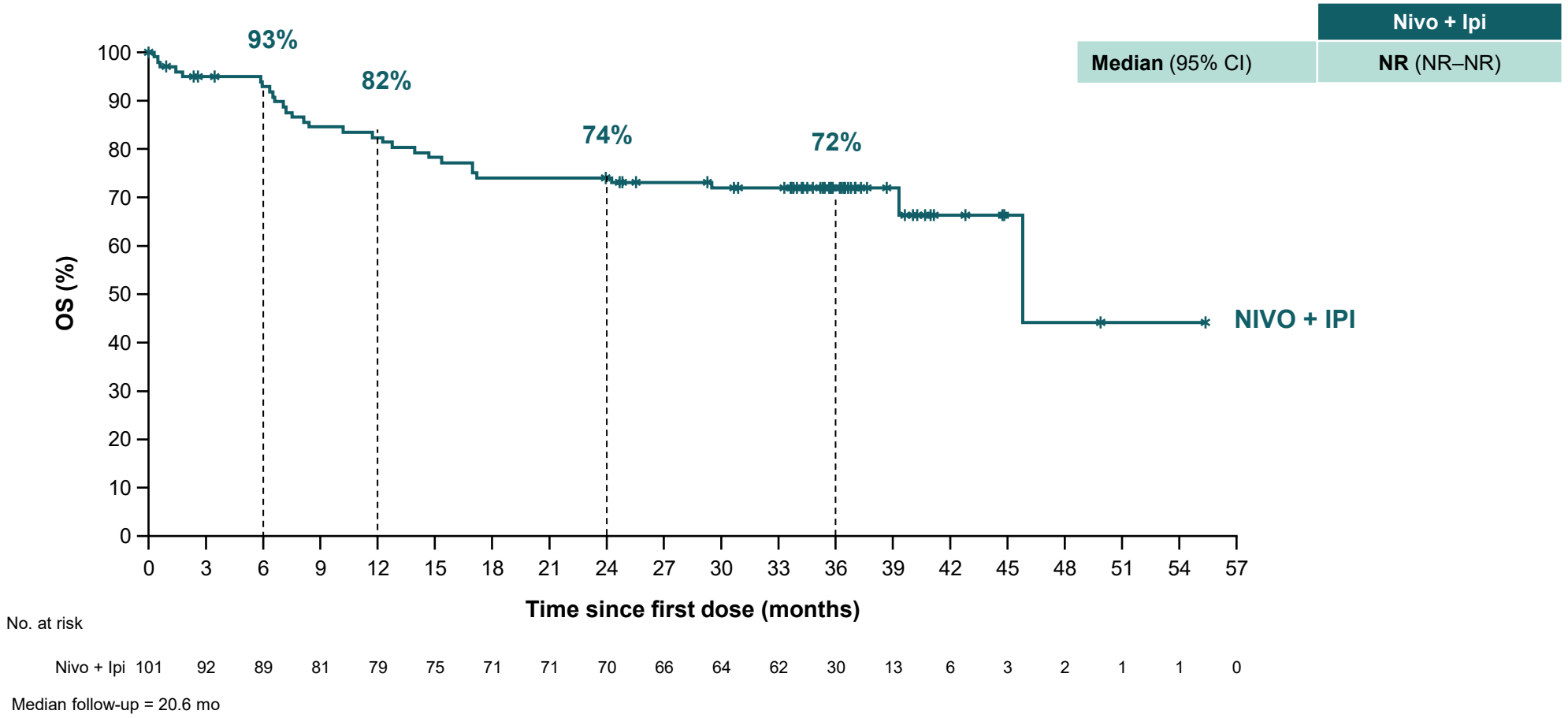
CheckMate 204 – Asymptomatic Cohort: Overall Survival



CI = confidence interval; NR = not reached; OS = overall survival

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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CheckMate 204 – Asymptomatic Cohort: Safety Summary

n (%)	Asymptomatic[a] (n = 101)	
	Any grade	Grade 3–4
Treatment-related AEs	97 (96)	55 (54)
Treatment-related nervous system AEs	35 (35)	7 (7)
Treatment-related AEs leading to discontinuation	29 (29)	19 (19)
Treatment-related nervous system AEs leading to discontinuation	2 (2)	2 (2)

a One death reported: treatment-related grade 5 myocarditis (previously reported).[1]

1. Johnson DB et al. N Engl J Med. 2016;375:1749–1755.

Modified to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Asymptomatic Cohort: Treatment-Related Nervous System AEs[1]

Events reported in ≥ 2% of patients, n (%)	Asymptomatic[a] (n = 101)	
	Any grade	Grade 3–4
Patients with any AEs	35 (35)	7 (7)
Headache	20 (20)	3 (3)
Paresthesia	4 (4)	0
Dysgeusia	3 (3)	0
Peripheral sensory neuropathy	3 (3)	0
Aphasia	2 (2)	0
Brain edema	2 (2)	2 (2)
Intracranial hemorrhage	2 (2)	1 (1)
Seizure	2 (2)	0
Amnesia	0	0
Dysarthria	0	0
Lethargy	0	0
Partial seizures	0	0
Syncope	1 (1)	1 (1)

a One death reported: treatment-related grade 5 myocarditis (previously reported).[2]

1. Modified to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.
2. Johnson DB et al. N Engl J Med. 2016;375:1749–1755.

CheckMate 204 – Asymptomatic Cohort: Summary/Conclusions[1]

- Final 3-year results support the continued use of standard-dose NIVO 1 + IPI 3 as first line therapy for neurologically asymptomatic, steroid-free patients with advanced melanoma and untreated brain metastases
- ORR was 54%, with an estimated stable 24-month and 36-month PFS rate of 54%
- At a median follow-up of 34.2 months, median OS has not yet been reached and is 72% at 36 months
- The safety profile of NIVO+IPI for symptomatic patients with MBM was similar to that of patients without brain metastases[2,3]
- These results are paralleled and confirmed in an independent Australian study[4]
- Patients in this study cohort were a select population without any neurologic symptoms or steroid therapy

1. Modified to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO
2. Hodi FS et al. Lancet Oncol. 2016;17:1558−1568.
3. Hodi FS et al. Lancet Oncol. 2018;19:1480−1492.
4. Long GV et al. Lancet Oncol, 2018; 19: 672–81.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.

Tawbi HA et al. N Engl J Med, 2018; 379: 722-730

CheckMate 204: Background – Symptomatic Cohort

- Patients with symptomatic MBM are more challenging to treat
  - Patients tend to deteriorate quickly
  - Steroid use may reduce the effectiveness of immunotherapy

	IPI[1]	NIVO[2]	Dabrafenib + Trametinib[3]
Patients, n	21	16	17[a]
ORR,%	5	6	59
DOR, months	Not reported	Not reported	4.5

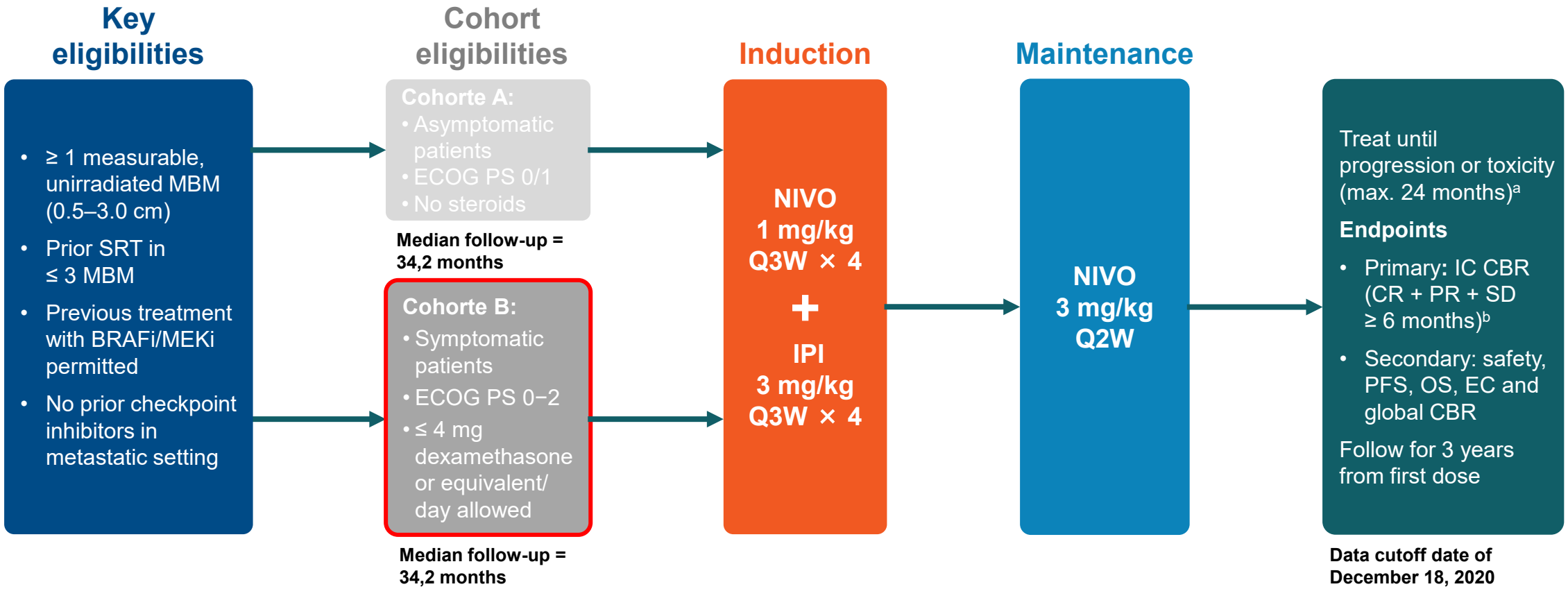
a BRAF mutant patients.

- Here we provide the first report of safety and efficacy of NIVO+IPI in patients with MBM who are **symptomatic and/or on steroids**

ORR = Objective Response Rate; DOR = Duration of Response

1. Margolin K et al. Lancet Oncol, 2012;13:459−465.
2. Long GV et al. Lancet Oncol, 2018;19:672−681.
3. Davies MA et al. Lancet Oncol, 2017;18:863−873.

CheckMate 204: Study Design – Symptomatic Cohort



a Patients with grade 3–4 adverse events (AEs) during NIVO + IPI induction could resume NIVO when toxicity resolved and all patients who discontinued proceeded to follow-up
b Using modified RECIST v1.1.

Q2W = every 2 weeks; Q3W = every 3 weeks; CBR = clinical benefit rate; CR = complete response; EC = extracranial; IC =intracranial; MBM = melanoma brain metastases; PR = partial disease; SD = stable disease; SRT = stereotactic radiosurgery.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation., Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

CheckMate 204 – Symptomatic Cohort: Demographic and Patient Characteristics

	Patients (n = 18)[a]
Male, n/N (%)	13/18 (72)
Median age, years (range)	59.5 (29–80)
BRAF mutation, n/N (%)	8/16 (50)
NRAS mutation, n/N (%)	1/2 (50)
LDH > ULN, n/N (%)	8/17 (47)
LDH > 2 × ULN, n/N (%)	2/17 (12)
PD-L1 expression, n/N (%)	
≥ 1%	6/10 (60)
< 1%	4/10 (40)
Prior SRT, n/N (%)	0
Median of sum of intracranial target lesion diameters, mm (range)	26 (7–86)
Intracranial target lesions, n/N (%)	
1–2 lesions	11/18 (61)
≥ 3 lesions	7/18 (39)
Steroid use at baseline, n/N (%)	11/18 (61)

a One patient did not have extracranial disease.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Symptomatic Cohort: Response to Treatment

	Patients (n = 18)		
	Intracranial (ESMO 2021)*	Extracranial (ASCO 2019)	Global (ASCO 2019)
Best overall response, n (%)			
Complete response	3 (17)	0	0
Partial response	0	4 (22)	4 (22)
Stable disease ≥ 6 months	0	0	0
Progressive disease	11 (61)	6 (33)	8 (44)
Not evaluable	4 (22)	8 (44)[a]	6 (33)
ORR, n/N (%)	3/18 (17)	4/18 (22)	4/18 (22)
(95% CI)	(4-41)	(6−48)	(6−48)
CBR[b], n/N (%)	3/18 (17)	4/18 (22)	4/18 (22)
(95% CI)	(4-41)	(6−48)	(6−48)

- Median duration of response was not yet reached at 36 months
- ORR and CBR for extracranial and global disease were the same as for intracranial disease

ORR = Objective Response Rate, * Investigator assesed

[a] Seven of these patients did not have extracranial disease at baseline

[b] Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months.

Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation, Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

For investigator: BOR Not evaluable: death prior to assessment (n = 2), early discontinuation due to toxicity (n = 1), SD < 6 months (n = 6), other (n = 4); reasons for BICR-assessed were not captured in the clinical database. Data for 6 patients was not available because the patients died, progressed, or withdrew consent before evaluation.

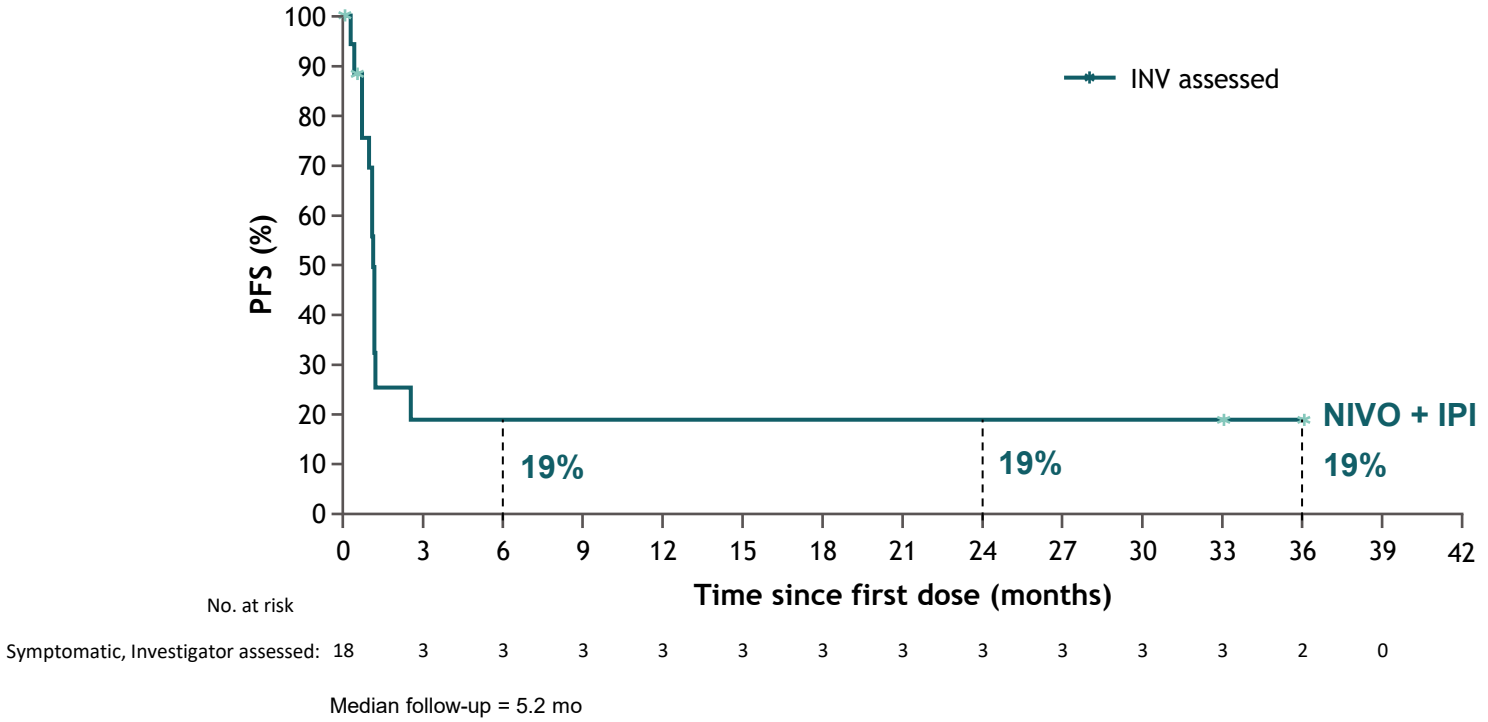
CheckMate 204 – Symptomatic Cohort: Responders

Intracranial response	BRAF status	NIVO+IPI induction doses	Maintenance doses	Steroid use at baseline
CR	Mutant	4	37	Yes
CR	Wild type	1	23	No
PR	Mutant	4	23	No
PRs	Not reported	3	0[a]	No

- Median time to intracranial response of 4.1 (1.0−6.9) months; median duration of response not reached
- 3 of 4 (75%) with ongoing responses

CR = Complete Response; PR = Partial Response
a Patient discontinued treatment due to toxicity.
Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Symptomatic Cohort: Progression-Free Survival



Median follow-up = 5.2 mo

- PFS rates for extracranial and global disease were similar
- Extracranial 24- and 36-month rates were 28%
- Global 24- and 36-month rates were 24%

CI = confidence interval; NR = not reached; PFS = progression-free survival

Tawbi HA et al. N Engl J Med. 2018; 379: 722–730.
Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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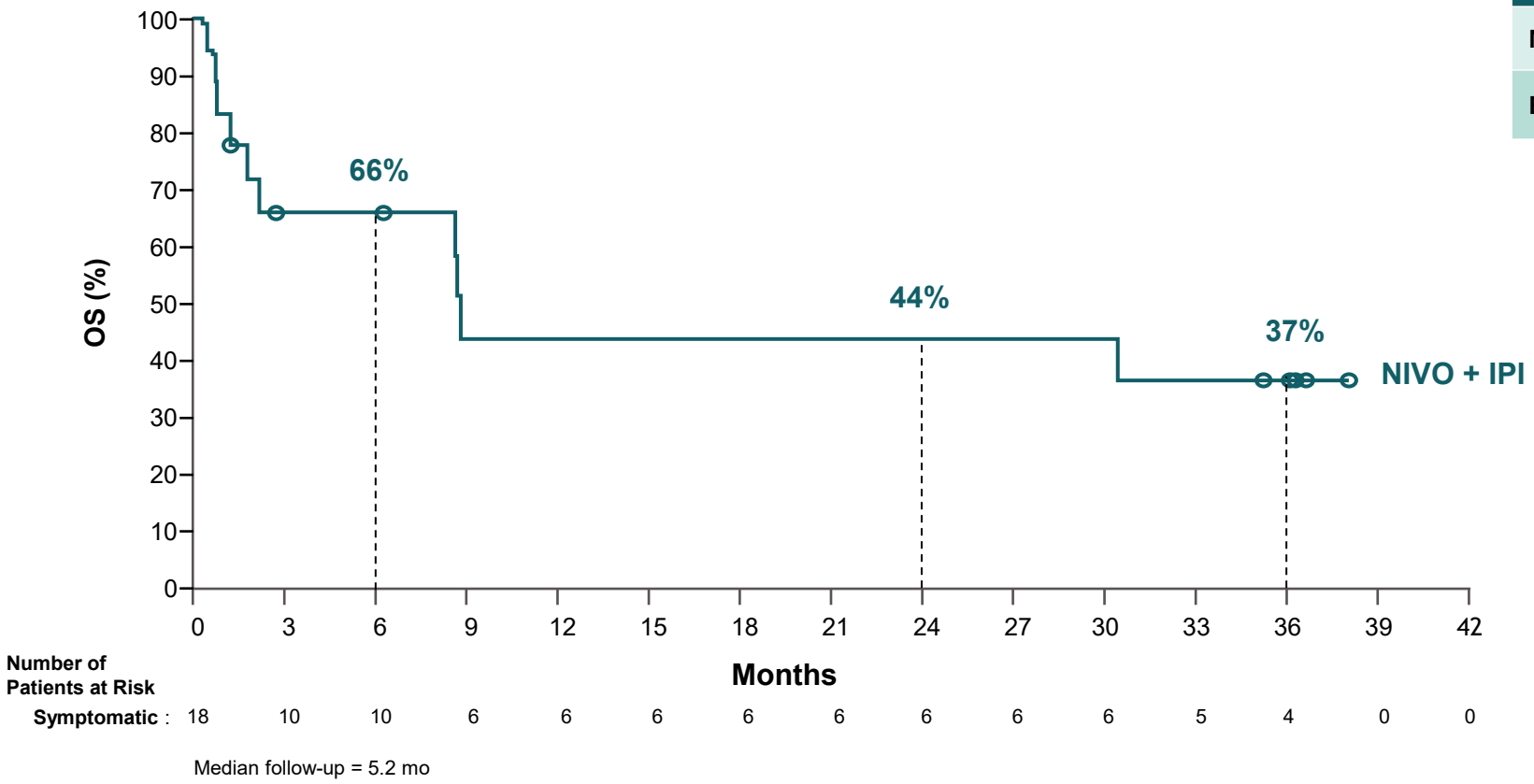
CheckMate 204 – Symptomatic Cohort: Overall Survival



Median follow-up = 5.2 mo

	Symptomatic
Median (95% CI)	**8.7** (1.8–NR)
Events/patients n/N	**8/18**

CI = confidence interval; NR = not reached; OS = overall survival

Tawbi HA et al. N Engl J Med. 2018; 379: 722–730.

Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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CheckMate 204 – Symptomatic Cohort: Safety Summary

n (%)	Symptomatic (n = 18)	
	Any grade	Grade 3–4
Treatment-related AEs	16 (89)	10 (56)
Treatment-related nervous system AEs	3 (17)	3 (17)
Treatment-related AEs leading to discontinuation	2 (11)	0
Treatment-related nervous system AEs leading to discontinuation	0	0

Modified to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Symptomatic Cohort: Treatment-Related Nervous System AEs

Events reported in ≥ 2% of patients, n (%)	Symptomatic (n = 18)	
	Any grade	Grade 3–4
Patients with any AEs	3 (17)	3 (17)
Headache	1 (6)	1 (6)
Paresthesia	0	0
Dysgeusia	0	0
Peripheral sensory neuropathy	0	0
Aphasia	0	0
Brain edema	0	0
Intracranial hemorrhage	0	0
Seizure	0	0
Amnesia	1 (6)	1 (6)
Dysarthria	1 (6)	1 (6)
Lethargy	1 (6)	0
Partial seizures	1 (6)	1 (6)
Syncope	1 (6)	1 (6)

1. Johnson DB et al. N Engl J Med. 2016;375:1749–1755.
2. Supplement to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation.

CheckMate 204 – Symptomatic Cohort: Conclusions[1]

- NIVO+IPI showed intracranial antitumor activity in symptomatic patients
  - ORR was 17% (3 CRs)
  - Median OS was 8.7 months, with a 6-month survival rate of 66% and 36-month survival rate of 37%
- Median number of NIVO+IPI doses received was 1 (range 1−4; 10 of 18 patients with one dose)
  - 4 patients entered the maintenance phase
- The safety profile of NIVO+IPI for symptomatic patients with MBM was similar to that of patients without brain metastases[2,3]
- Symptomatic patients remain difficult to treat, but some can benefit from NIVO+IPI
- Further studies in patients with **symptomatic** brain metastases need to
  - Facilitate and accelerate the screening phase to enable rapid treatment
  - Evaluate the incorporation or sequencing of radiation therapy
  - Incorporate targeted therapies and/or steroid-sparing agents

Modified to Tawbi HA et al. ASCO, 2019; Abstract #9501, Oral Presentation .
Hodi FS et al. Lancet Oncol. 2016;17:1558−1568.
Hodi FS et al. Lancet Oncol. 2018;19:1480−1492.
Tawbi HA et al. ESMO 2021; Oral Presentation #1039MO

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The Anti-PD1 Brain Collaboration (ABC)

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A Randomized Phase II Study of Nivolumab plus Ipilimumab or Nivolumab in Patients with Melanoma Brain Metastases: The Anti-PD1 Brain Collaboration (ABC)

Australian investigator-led, randomized, open label phase II study conducted by the Australia and New Zealand Melanoma Trials Group (ANZMTG)

- Melanoma Brain Metastases
  - ≥ 5 mm & < 40 mm
- No previous
  - Anti-CTLA-4
  - Anti-PD-1 or -PD-L1 agents
- Previous BRAFi+MEKi allowed
- ECOG PS 0–2
- No serious autoimmune disease
- No corticosteroids
  (Cohort C > 10mg prednisone allowed)

R 30:24

A: No prior local brain Rx & asymptomatic (n=35)
Nivolumab + Ipilimumab (NIVO+IPI)

B: No prior local brain Rx & asymptomatic (n=25)
Nivolumab (NIVO)

C: Previously treated or symptomatic or leptomeningeal, with MRI progression (n=16)
Nivolumab (NIVO)

Total 76 Patients Recruited

Primary Endpoint: Intracranial Response Rate ≥ 12 weeks

Secondary Endpoints: Extracranial Response Rate, Overall Response Rate, PFS (Intracranial, Extracranial, Overall), OS, Safety

Data cutoff 31 December 2020; All 76 patients enrolled with follow up; min 43.3 months, max 71.5 months
Median follow up 52.8 months (IQR 48.0-61.2 months)

Modified to Long GV et al. ESMO, 2019; Oral presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Immunonkologie

Patient Characteristics

	A: NIVO+IPI (n=35)	B: NIVO (n=25)	C: NIVO* (n=16)
Age, median (range)	59 (29–76)	63 (31–86)	51 (28–73)
Sex male, n (%)	29 (83)	19 (76)	11 (69)
ECOG performance status, n (%)			
1	34 (97)	25 (100)	15 (94)
2	1 (3)	0	1 (6)
LDH > ULN, n (%)	18 (51)	14 (58)	3 (19)
V600 BRAF mutation-positive, n (%)	19 (54)	14 (56)	13 (81)
Target brain metastases, n (%)			
1	11 (31)	6 (24)	1 (6)
2–4	10 (29)	14 (56)	7 (44)
> 4	14 (40)	5 (20)	8 (50)
Extracranial metastases, n (%)	30 (86)	21 (84)	12 (75)
Prior BRAFi+MEKi	8 (23)	6 (24)	12 (75)

* Previous local treatment (n=16), neurological symptoms (n=10), Leptomeningeal disease (n=4)

Long GV et al. ESMO, 2019; Oral Presentation, Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Immunonkologie

Best Intracranial RECIST Response

	All patients			Drug treatment-naïve patients§	
	A: NIVO+IPI (n=35)	B: NIVO (n=25)	C: NIVO* (n=16)	A: NIVO+IPI (n=27)	B: NIVO (n=19)
Intracranial Response, n (%)	**18 (51%)**	**5 (20%)**	**1 (6%)**	**16 (59%)**	**4 (21%)**
CR	9 (26%)	4 (16%)	0 (0%)	8 (30%)	3 (16%)
PR	9 (26%)	1 (4%)	1 (6%)	8 (30%)	1 (5%)
SD	2 (6%)	0 (0%)	2 (13%)	2 (7%)	0 (0%)
PD	14 (40%)	19 (76%)	13 (81%)	8 (30%)	14 (74%)
NE#	1 (3%)	1 (4%)	0 (0%)	1 (4%)	1 (5%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable

* Leptomeningeal, previous local treatment or symptoms # Patients who deceased prior to week 12 = PD
§ Drug naive refers to combined MEK and BRAF inhibitor therapy-naive patients

Modified to Long GV et al. ESMO, 2019; Oral Presentation, Long GV et al ASCO 2021 Abstract #9508, Oral presentation

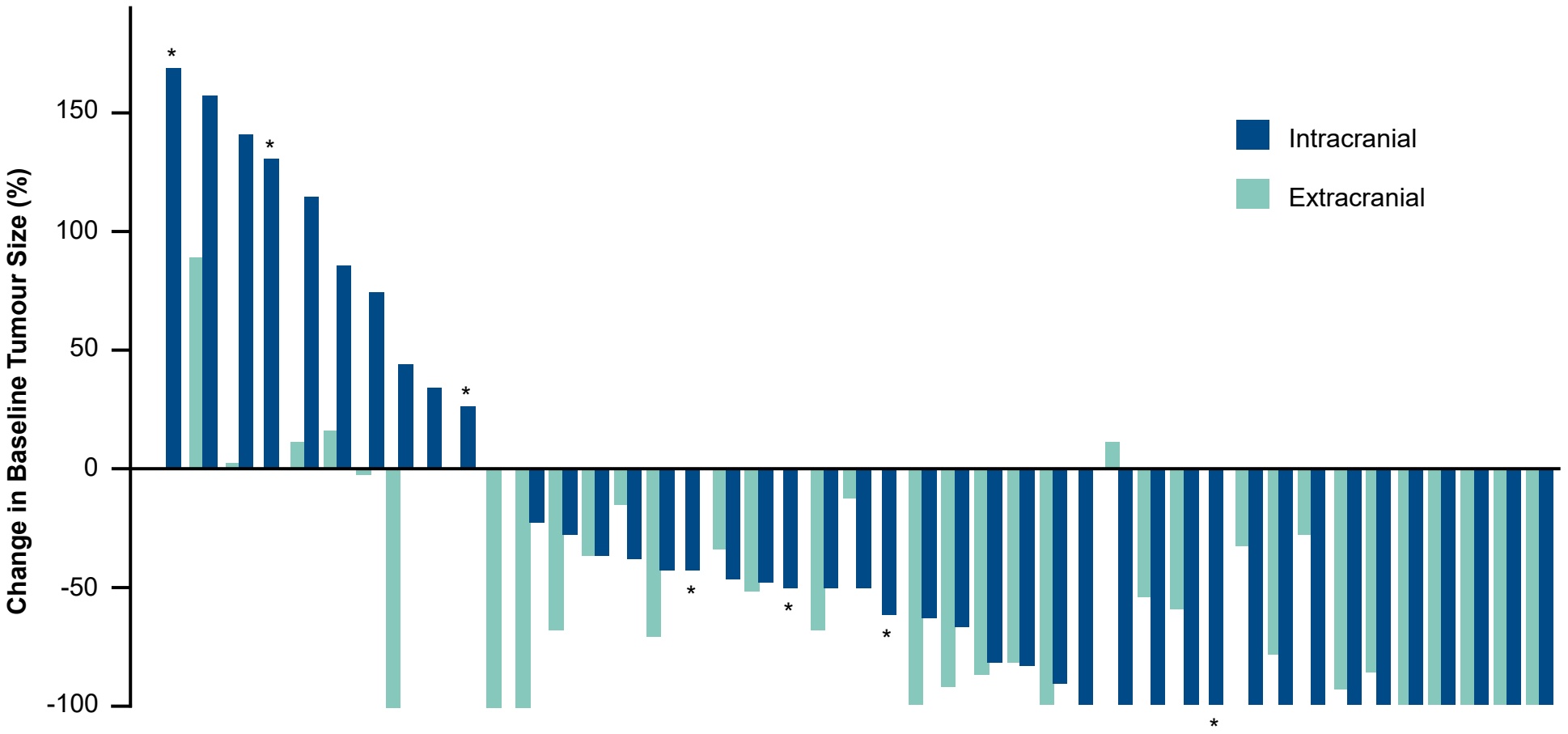
Best Extracranial[#] RECIST Response

	A: NIVO+IPI (n=30)	B: NIVO (n=21)	C: NIVO↑ (n=12)
Extracranial Response Rate, n (%)	**17 (57%)**	**6 (29%)**	**3 (25%)**
CR	5 (13%)	4 (19%)	2 (8%)
PR	12 (43%)	2 (10%)	1 (17%)
SD	4 (13%)	2 (10%)	1 (8%)
PD	8 (27%)	11 (52%)	7 (58%)
NE*	1 (3%)	2 (10%)	1 (8%)

#63 of 76 (83%) patients had extracranial melanoma metastases at baseline NE = Not Evaluable
* Pts who deceased prior to wk 12 = PD, ↑Leptomeningeal, previous local treatment or symptoms Long GV et al. ESMO, 2019; Oral presentation, ,

Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Cohorts A & B: Concordant Intra- & Extra-cranial Response*



* Intracranial metastases only

Supplement to: Long GV et al. Lancet Oncol, 2018; 19: 672–81

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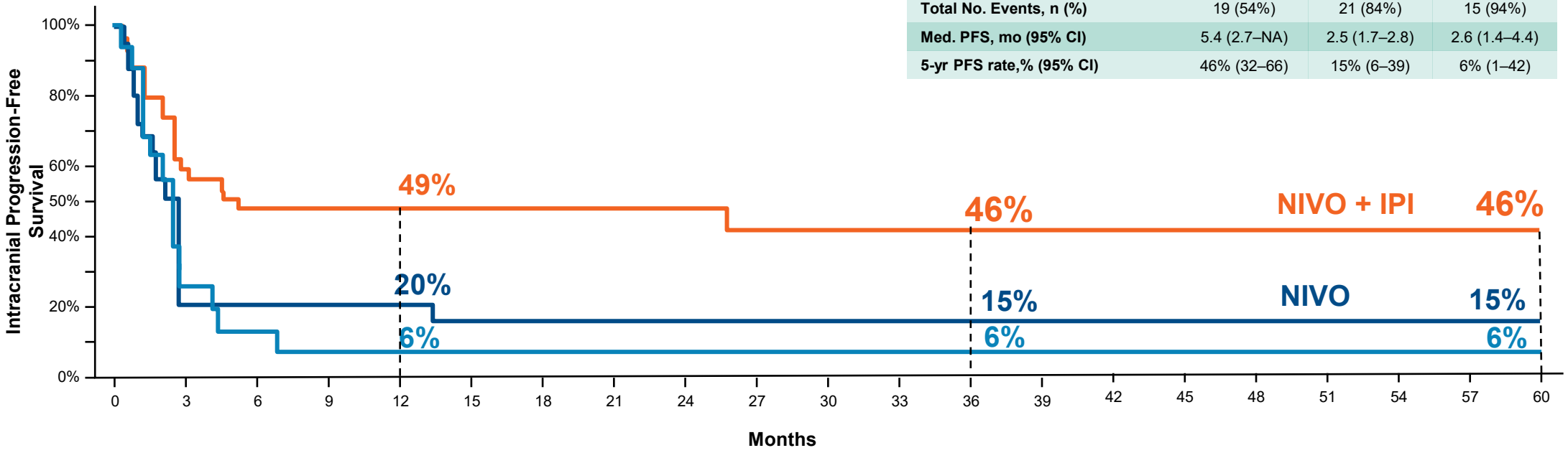
Intracranial Progression-Free Survival
All Patients

	A: NIVO+IPI (n=35)	B: NIVO (n=25)	C: NIVO (n=16)
Total No. Events, n (%)	19 (54%)	21 (84%)	15 (94%)
Med. PFS, mo (95% CI)	5.4 (2.7–NA)	2.5 (1.7–2.8)	2.6 (1.4–4.4)
5-yr PFS rate,% (95% CI)	46% (32–66)	15% (6–39)	6% (1–42)



Number at risk (cumulative number of censored)

A Nivo+Ipi	35 (0)	21 (0)	17 (0)	16 (1)	16 (1)	16 (1)	16 (1)	16 (1)	16 (7)	15 (1)	15 (1)	15 (1)	14 (2)	14 (2)	13 (3)	9 (7)	6 (10)	5 (11)	4 (12)	4 (12)	3 (12)
B Nivo	25 (0)	5 (0)	5 (0)	4 (1)	4 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	2 (2)	2 (2)	2 (2)	2 (2)
C Nivo	16 (0)	4 (0)	2 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)

Long GV et al. ESMO, 2019; Oral presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

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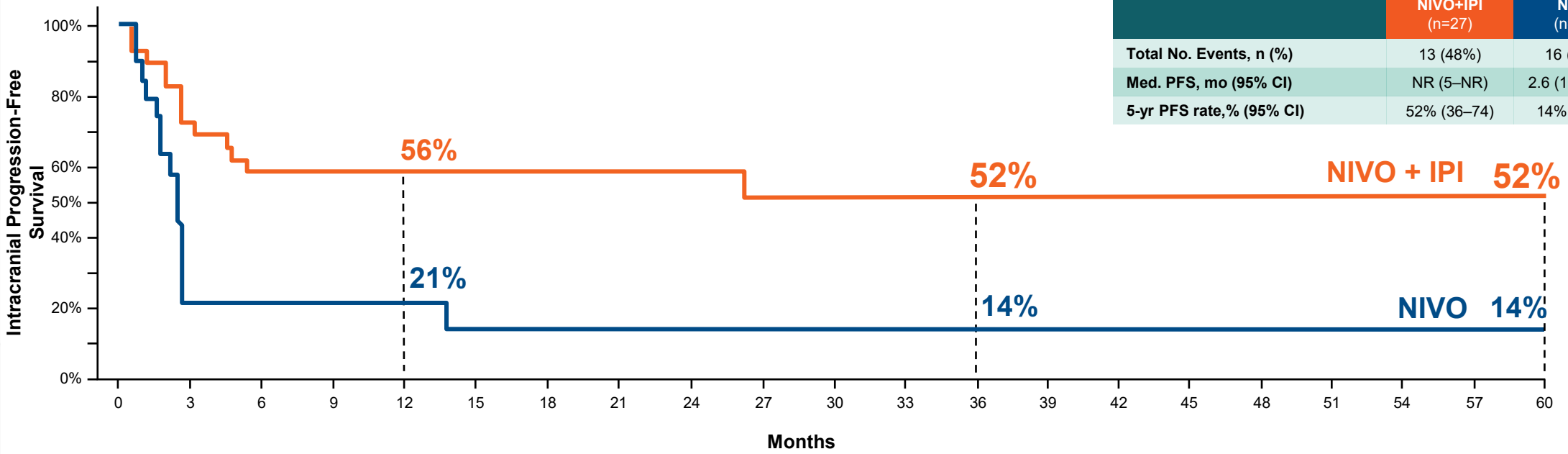
Intracranial Progression-Free Survival
Drug-treatment Naïve Patients

	A: NIVO+IPI (n=27)	B: NIVO (n=19)
Total No. Events, n (%)	13 (48%)	16 (84%)
Med. PFS, mo (95% CI)	NR (5–NR)	2.6 (1.8–13.8)
5-yr PFS rate,% (95% CI)	52% (36–74)	14% (4–46)



Number at risk (cumulative number of censored)

A Nivo+Ipi	27 (0)	19 (0)	15 (0)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	13 (1)	13 (1)	13 (1)	12 (1)	12 (1)	11 (3)	7 (7)	5 (9)	4 (10)	3 (11)	3 (11)	2 (13)
B Nivo	19 (0)	4 (0)	4 (0)	3 (1)	3 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	1 (2)	1 (2)	1 (2)	1 (2)

Long GV et al. ESMO, 2019; Oral presentation
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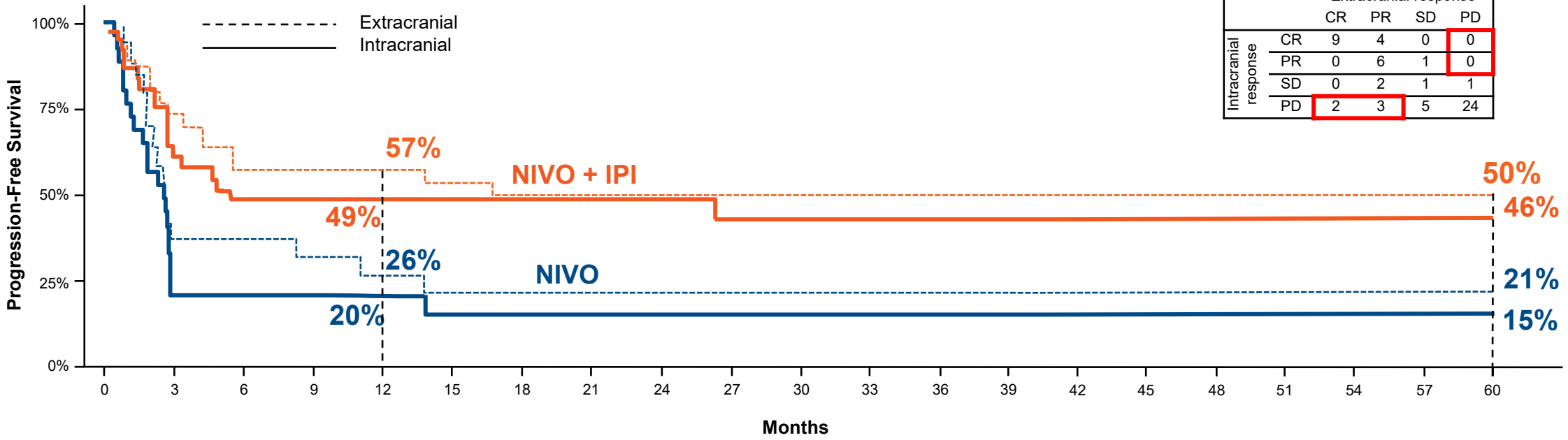
Intracranial and Extracranial Concordance
All patients Cohort A and B



Intracranial response	Extracranial response: CR	PR	SD	PD
CR	9	4	0	0
PR	0	6	1	0
SD	0	2	1	1
PD	2	3	5	24

Number at risk

Nivo+Ipi	30 (0)	22 (0)	17 (0)	16 (1)	16 (1)	15 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	13 (2)	13 (2)	13 (2)	13 (2)	8 (7)	6 (9)	4 (11)	3 (12)	3 (12)	2 (14)
Nivo+Ipi	35 (0)	21 (0)	17 (0)	16 (1)	16 (1)	16 (1)	16 (1)	16 (1)	16 (1)	15 (1)	15 (1)	15 (1)	14 (2)	14 (2)	13 (3)	9 (7)	6 (10)	5 (11)	4 (12)	4 (12)	3 (13)
Nivo	20 (0)	7 (1)	7 (1)	6 (1)	5 (1)	4 (1)	4 (1)	4 (1)	3 (2)	3 (2)	3 (2)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	1 (4)	1 (4)	1 (4)	1 (4)
Nivo	25 (0)	5 (0)	5 (0)	4 (1)	4 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	2 (2)	2 (2)	2 (2)	2 (2)

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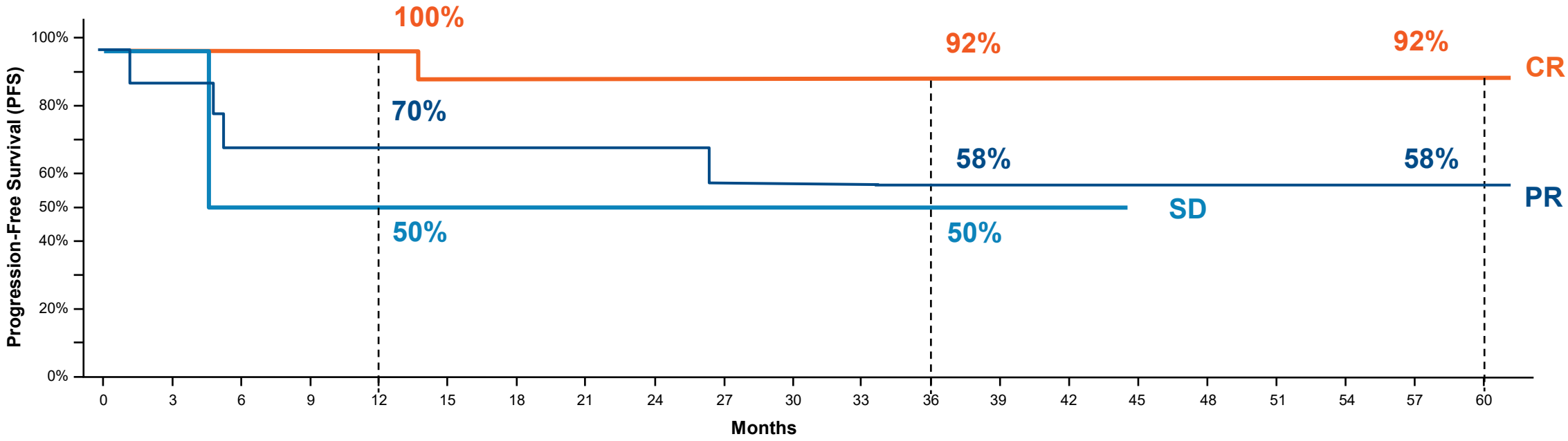
Intracranial Progression-Free Survival by Intracranial Best Response (Cohort A+B)



Number at risk (cumulative number censored)

CR	13 (0)	13 (0)	13 (0)	12 (1)	12 (1)	11 (1)	11 (1)	11 (1)	11 (1)	11 (1)	11 (1)	11 (1)	10 (2)	10 (2)	9 (3)	6 (6)	5 (7)	4 (8)	4 (8)	4 (8)	3 (9)
PR	10 (0)	9 (0)	7 (0)	6 (1)	6 (1)	6 (1)	6 (1)	6 (1)	6 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	4 (2)	3 (3)	2 (4)	2 (4)	2 (4)	2 (5)
SD	2 (0)	2 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

Long GV et al. ESMO, 2019; Oral presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Subsequent Therapy After Intracranial PD

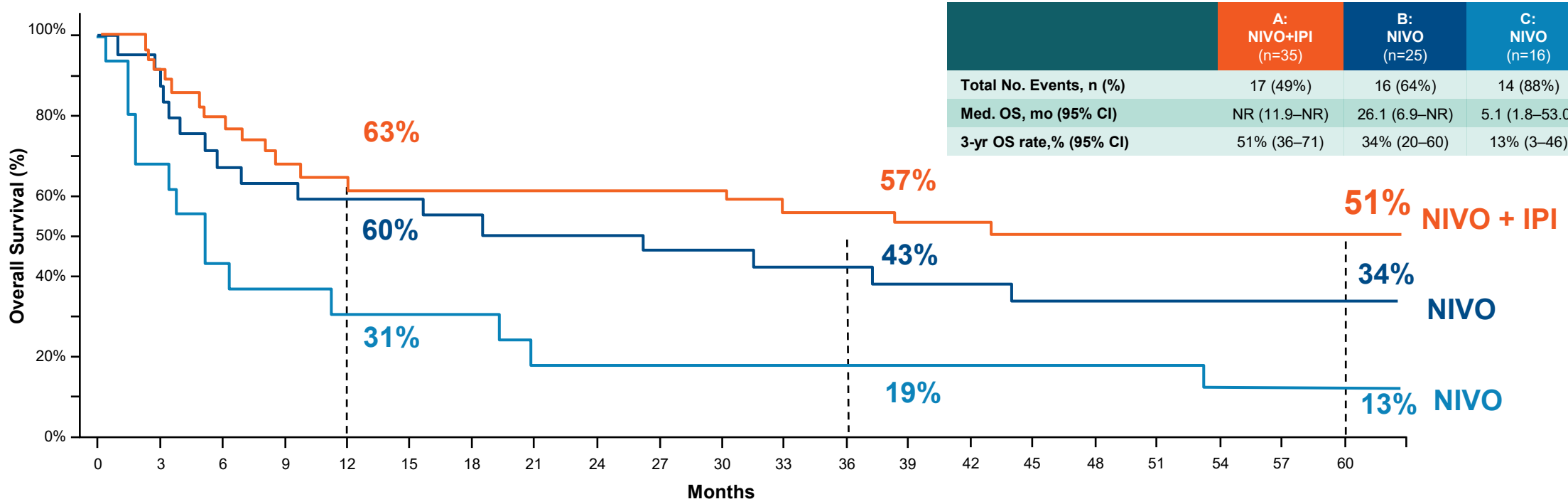
	A: NIVO+IPI (n=19)	B: NIVO (n=21)	C: NIVO (n=15)
Any treatment, n (%)	**14 (74%)**	**16 (76%)**	**8 (53%)**
Local therapy tp brain*	**6 (32%)**	**13 (62%)**	**4 (27%)**
Stereotactic Radiotherapy	3 (16%)	6 (29%)	1 (7%)
Whole Brain Radiotherapy	4 (21%)	7 (33%)	1 (7%)
Surgery	3 (16%)	2 (10%)	2 (13%)
Systemic therapy	12 (63%)	14 (67%)	6 (40%)
BRAF/MEKi	7 (37%)	9 (43%)	5 (33%)
Iplimumab	2 (11%)	2 (10%)	1 (7%)
Anti-PD-1	4 (21%)	2 (24%)	1 (7%)
Iplimumab + Anti-PD-1	1 (5%)	6 (29%)	1 (7%)
Chemotherapy	2 (11%)	0 (0%)	0 (0%)

* Some patients may have had multiple modalities of local therapy to the brain.

Long GV et al. ESMO, 2019; Oral presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Overall Survival

	A: NIVO+IPI (n=35)	B: NIVO (n=25)	C: NIVO (n=16)
Total No. Events, n (%)	17 (49%)	16 (64%)	14 (88%)
Med. OS, mo (95% CI)	NR (11.9–NR)	26.1 (6.9–NR)	5.1 (1.8–53.0)
3-yr OS rate,% (95% CI)	51% (36–71)	34% (20–60)	13% (3–46)



Number at risk (cumulative number of censored)

A Nivo+IPI	35 (0)	32 (0)	28 (0)	23 (1)	21 (1)	21 (1)	21 (1)	21 (1)	21 (1)	21 (1)	21 (1)	19 (1)	19 (1)	18 (1)	18 (1)	11 (7)	8 (10)	6 (12)	5 (13)	5 (13)	4 (15)
B Nivo	25 (0)	23 (0)	17 (0)	15 (1)	14 (1)	14 (1)	13 (1)	12 (1)	12 (1)	11 (1)	11 (1)	10 (1)	10 (1)	9 (1)	9 (1)	8 (1)	7 (2)	6 (3)	6 (3)	4 (5)	3 (6)
C Nivo	16 (0)	11 (0)	7 (0)	6 (0)	5 (0)	5 (0)	5 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)	2 (0)	2 (0)

- Death solely due to interacranial progression in 8/76 (17%) patients (1 Cohort A, 4 Cohort B, 3 Cohort C)

Long GV et al. ESMO, 2019; Oral presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

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Treatment-Related Adverse Events

	A: NIVO+IPI (n=35)	B: NIVO (n=25)	C: NIVO (n=16)
Treatment-related AEs, n (%)	34 (97%)	17 (68%)	8 (50%)
Grade ¾ treatment-related AEs, n (%)	19 (54%)	5 (20%)	2 (13%)
Treatment-related SAE, n (%)	16 (46%)	1 (4%)	2 (13%)
Discontinuation due to AE*	5 (14%)	1 (4%)	0 (0%)

- No new or unexpected AEs
- 4/76 (5%) pts had neurological SAE: 1 radionecrosis^, 1 seizure, 2 headache
- No deaths due to treatment-related AE

SAE; Serious Adverse Event

*Pts with grade 3/4 treatment related AE in Cohort A were allowed to continue nivolumab monotherapy if recovered and deemed due to ipilimumab; ^ Pt in cohort C, prior SRS

Long GV et al. ESMO, 2019; Oral presentation, Long GV et al ASCO 2021 Abstract #9508, Oral presentation

Treatment-Related Adverse Events Stratified by System Organ Class*

	A: NIVO+IPI (n=35)	B: NIVO (n=25)
Treatment-related AEs, n (%)[1]	34 (97)	17 (68)
Gastrointestinal	27 (77)	14 (56)
Skin	26 (74)	7 (28)
Fatigue	21 (60)	9 (36)
Endocrine	13 (37)	3 (12)
Musculoskeletal	12 (34)	4 (16)
Nervous system	11 (31)	6 (24)
Respiratory	10 (29)	3 (12)
Other	5 (14)	4 (16)
Eye disorders	3 (9)	1 (4)
Infections and infestations	2 (6)	2 (8)
Renal and urinary disorders	2 (6)	0 (0)
Vascular disorders	1 (3)	0 (0)

- 14/60 (23%) patients in cohort A and B had neurological AE: 9 headache, 3 peripheral neuropathy, 1 diaphragmatic weakness, 1 seizure[2]

AE = Adverse Event

* There were no treatment-related grade 5 events (deaths)

1. Supplement to: Long GV et al. Lancet Oncol, 2018; 19: 672–81 2. Long GV et al. Lancet Oncol, 2018; 19: 672

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Summary/Conclusion

- Nivolumab + ipilimumab has enduring activity in patients with untreated asymptomatic melanoma brain metastases, no prior local therapy or BRAF/MEK inhibitors
  - **Nivo+Ipi intracranial: Response Rate = 59%; 5-year PFS 52%; 5-year OS 51%**
  - **Nivo alone intracranial: Response Rate = 21%; 5-year PFS 14%; 5-year OS 34%**
- Intracranial and extracranial responses were mostly concordant
- Activity of nivo+/- ipi is **low** after BRAF/MEKi, after multiple modality therapy, or in pts with leptomeningeal/symptomatic intracranial melanoma
- There were no unexpected toxicities and quality of life was maintained
- **NIVO combined with IPI has high activity in melanoma brain metastases and may be considered for upfront therapy in such patients.[1]**

1 Long GV et al. ASCO 2017; Oral presentation
Modified to Long GV et al. ESMO, 2019; Oral Presentation
Long GV et al ASCO 2021 Abstract #9508, Oral presentation

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CheckMate 067: long-term outcomes in patients with mucosal melanoma – Background

- Mucosal melanoma is a rare but aggressive malignancy with a poor prognosis and 5-year survival rates of 14%–25%, depending on the stages considered[1,2]
- Practice-changing clinical trial results led to the approval of checkpoint inhibitors in the treatment of metastatic melanoma, including nivolumab (NIVO) monotherapy and combination therapy with nivolumab plus ipilimumab (NIVO+IPI)
- Although response was lower than in the overall population, limited short-term data indicated clinical benefit with NIVO+IPI, NIVO, and IPI in patients with mucosal melanoma in a pooled study that included data from CheckMate 067[3]
- Other trials also showed activity of NIVO or pembrolizumab treatment in patients with mucosal melanoma, but without long-term follow-up[4–6]
- Here we report 5-year outcomes in the subgroup of patients with mucosal melanoma treated with NIVO+IPI, NIVO alone, or IPI alone in the phase 3 CheckMate 067 trial

Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019

1.Tyrrell H, Payne M. Melanoma Manag 2018;5:MMT11., 2. Lerner BA, et al. Oncology (Williston Park) 2017;31:e23–e32., 3. D'Angelo SP, et al. J Clin Oncol 2017;35:226–235., 4. Shoushtari AN, et al. Cancer 2016;122:3354–3362., 5. Hamid O, et al. Br J Cancer 2018;119:670–674., 6. Kim HJ, et al. Front Oncol 2019;9:835.

CheckMate 067: Baseline characteristics in the mucosal and ITT populations

	NIVO+IPI		NIVO		IPI	
	Mucosal (n = 28)	ITT (n = 314)[7]	Mucosal (n = 23)	ITT (n = 316)[7]	Mucosal (n = 28)	ITT (n = 315)[7]
Median age, years (range)	64 (35–84)	61 (18–88)	61 (27–88)	60 (25–90)	61 (39–77)	62 (18–89)
Male,n (%)	13 (46)	206 (66)	11 (48)	202 (64)	15 (54)	202 (64)
ECOG PS 0, n (%)	18 (64)	230 (73)	17 (74)	237 (75)	19 (68)	224 (71)
BRAF mutation, n (%)	2 (7)	101 (32)	0	100 (32)	3 (11)	97 (31)
LDH, n (%)						
≤ ULN	13 (46)	199 (63)	12 (52)	197 (62)	14 (50)	194 (62)
> ULN	15 (54)	114 (36)	11 (48)	112 (35)	13 (46)	115 (37)
> 2 x ULN	6 (21)	37 (12)	5 (22)	37 (12)	4 (14)	30 (10)
Not reported	0	1 (< 1)	0	7 (2)	1 (4)	6 (2)
PD-L1 expression, n (%)						
< 5%	21 (75)	210 (67)	16 (70)	208 (66)	21 (75)	202 (64)
≥ 5%	4 (14)	68 (22)	3 (13)	80 (25)	1 (4)	75 (24)
Not reported	3 (11)	36 (11)	4 (17)	28 (9)	6 (21)	38 (12)
History of brain metastas, n (%)	3 (11)	11 (4)	0	7 (2)	0	15 (5)
M stage, n (%)						
M0, M1A, or M1B	9 (32)	133 (42)	7 (30)	132 (42)	12 (43)	132 (42)
M1C	19 (68)	181 (58)	16 (70)	184 (58)	16 (57)	183 (58)
Sum of diameters of target lesions (mm), median (range)[a]	59 (10–153)	54 (10–372)	57 (10–200)	54 (10–384)	61 (14–240)	55 (10–283)
Number of lesion sites, n (%)						
1	4 (14)	89 (28)	5 (22)	80 (25)	10 (36)	84 (27)
2–3	18 (64)	165 (53)	13 (57)	176 (56)	15 (54)	170 (54)
> 3	6 (21)	60 (19)	5 (22)	59 (19)	3 (11)	61 (19)

[a]Primary site data were not collected. ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.
Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019. Lerner BA, et al. Oncology (Williston Park) 2017;31:e23–e32.

CheckMate 067: Results

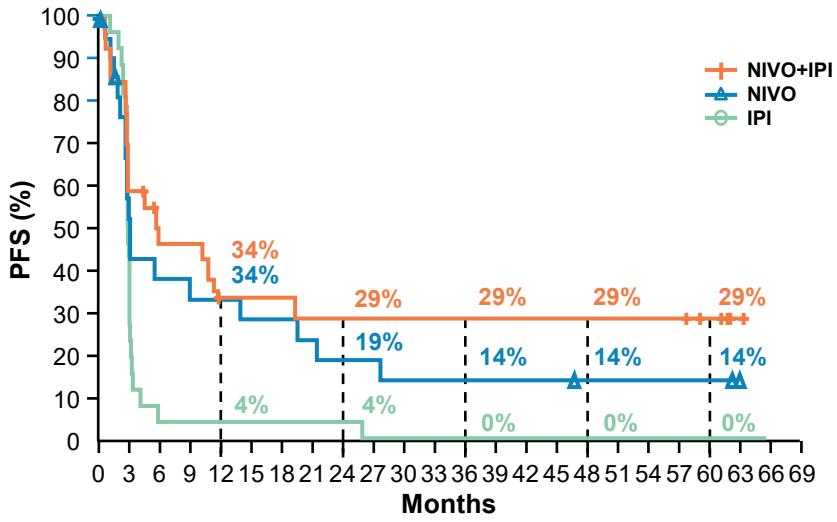
Efficacy

1. In the mucosal melanoma population, NIVO+IPI treatment (compared with NIVO or IPI alone) was associated with
   - Higher 5-year PFS (29% vs 14% and 0%, respectively; Figure 3)
   - Higher 5-year OS (36% vs 17% and 7%; Figure 4)
2. In patients with mucosal melanoma, ORR was higher for NIVO+IPI than for NIVO or IPI alone, similar to the ITT population (Table 2)
3. ORR differences between the mucosal and ITT populations were similar for all treatment groups
   - ORR rates for the mucosal and ITT populations were 43% and 58% for NIVO+IPI, 30% and 45% for NIVO, and 7% and 19% for IPI, respectively
     - The difference in complete response (CR) rates between the mucosal and ITT populations was greater for NIVO-treated patients than for NIVO+IPI-treated patients (4% and 19% vs 14% and 22%, respectively)
4. Median duration of response
   - Has not yet been reached for NIVO+IPI-treated patients with mucosal melanoma or the ITT population, nor for the NIVO-treated patients in the ITT population
   - Was 18.7 months for NIVO-treated patients with mucosal melanoma

Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019. D'Angelo SP, et al. J Clin Oncol 2017;35:226–235.

CheckMate 067: PFS in the mucosal and ITT populations

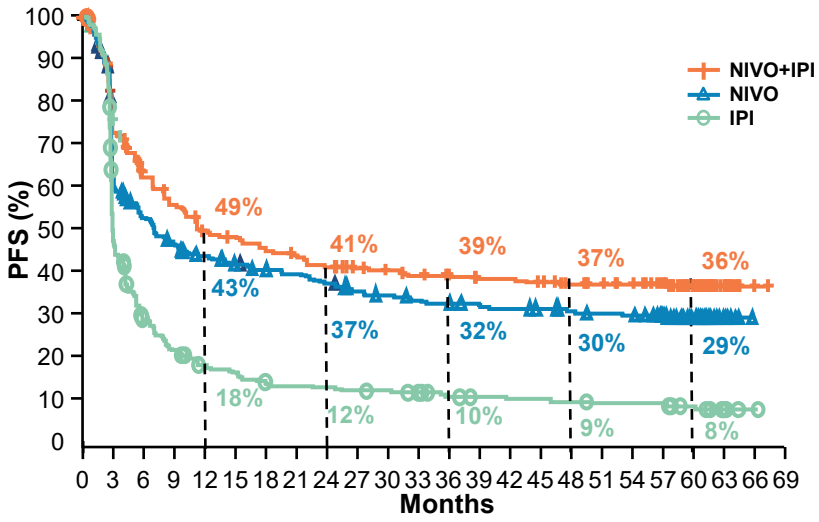
Mucosal	NIVO + IPI (n = 28)	NIVO (n = 23)	IPI (n = 28)
Median PFS, mo (95% CI)	5.8 (2.7–19.3)	3.0 (2.5–13.9)	2.6 (2.6–2.8)
HR (95% CI) vs IPI	0.34 (0.18–0.64)	0.49 (0.26–0.92)	-
HR (95% CI) vs NIVO[a]	0.69 (0.36–1.33)	-	-



No. at risk

NIVO+IPI	28	16	11	11	7	7	7	6	6	6	6	6	6	6	6	6	6	6	6	4	1	0	0
NIVO	23	9	8	7	7	6	6	5	4	4	3	3	3	3	3	2	2	2	2	2	1	0	0
IPI	28	5	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

ITT[1,b]	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) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.64–0.96)	-	-



No. at risk

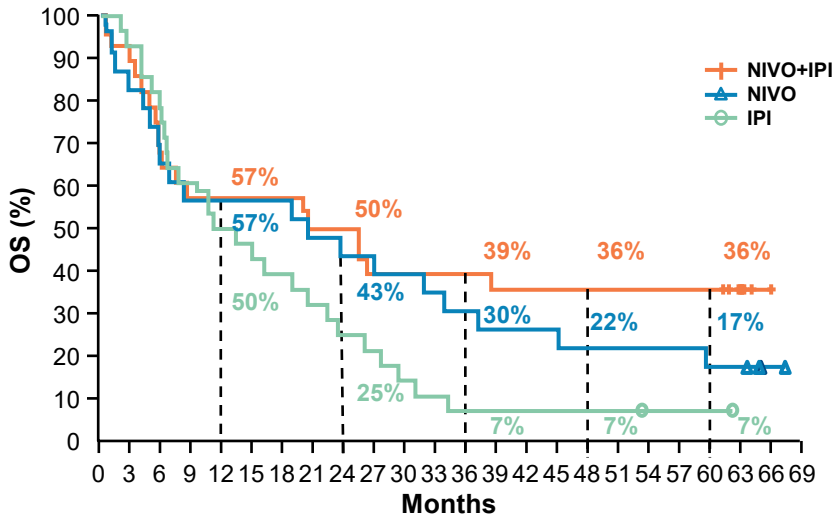
NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

[a]Descriptive analysis; [b]12-, 24-, 36-, and 48-month rates are data on file. CI, confidence interval; HR, hazard ratio; NR, not reached.

1. Larkin J, et al. N Engl J Med 2019:381:1535–1546.
Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019.

CheckMate 067: OS in the mucosal and ITT populations

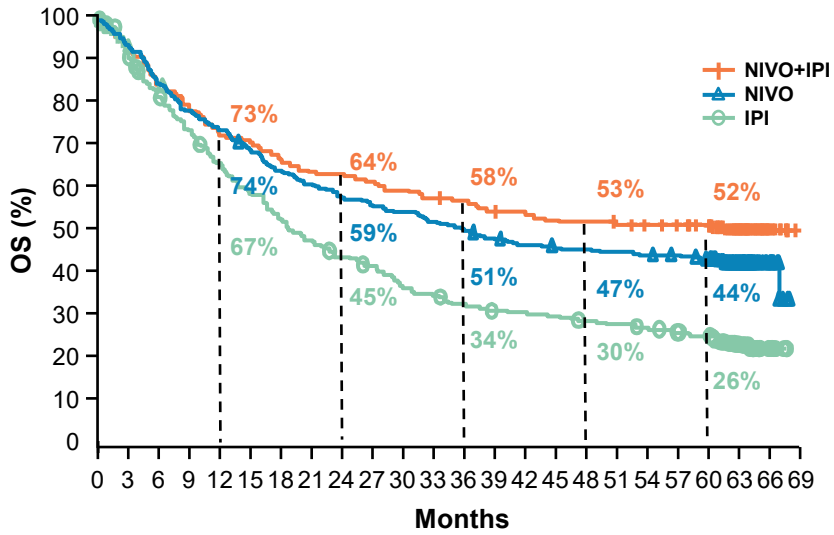
Mucosal	NIVO + IPI (n = 28)	NIVO (n = 23)	IPI (n = 28)
Median PFS, mo (95% CI)	22.7 (5.6–NR)	20.2 (5.6–33.6)	12.1 (6.4–20.2)
HR (95% CI) vs IPI	0.52 (0.28–0.96)	0.71 (0.39–1.30)	-
HR (95% CI) vs NIVO[a]	0.73 (0.38–1.39)	-	-



No. at risk

NIVO+IPI	28	25	18	17	16	16	16	14	14	11	11	11	11	10	10	10	10	10	10	10	10	2	0	0
NIVO	23	19	15	13	13	13	13	11	10	9	9	8	7	6	6	5	5	5	5	5	4	4	1	0
IPI	28	26	21	16	14	12	11	9	7	6	4	3	2	2	2	2	2	2	1	1	1	0	0	0

ITT[1,b]	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	-
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	-	-



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis; b12-, 24-, 36-, and 48-month rates are data on file.

1. Larkin J, et al. N Engl J Med 2019:381:1535–1546.
Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019.

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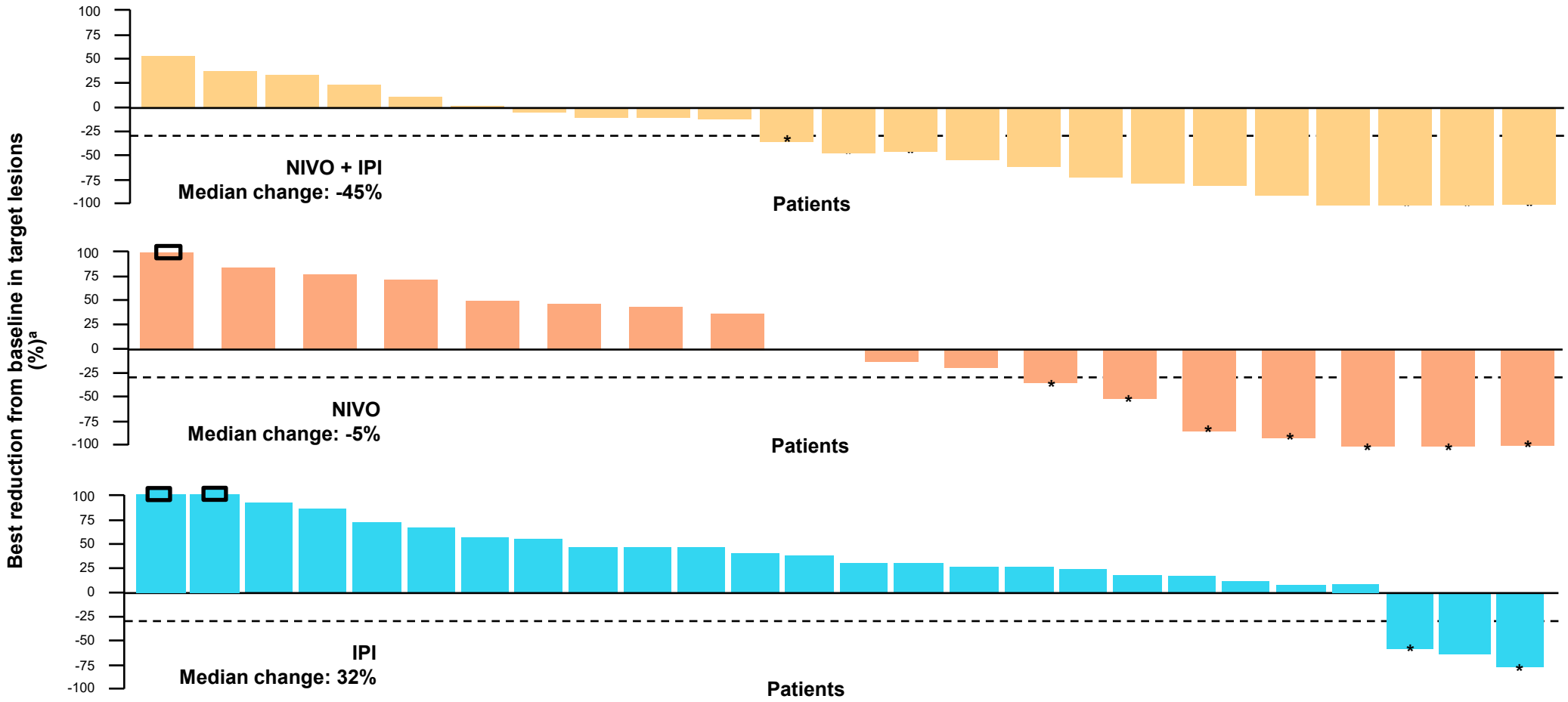
CheckMate 067: Response in the mucosal and ITT populations

	NIVO+IPI		NIVO		IPI	
	Mucosal (n = 28)	ITT[1] (n = 314)	Mucosal (n = 23)	ITT[1] (n = 316)	Mucosal (n = 28)	ITT[1] (n = 315)
ORR, % (95% CI)	43 (24–63)	58 (53–64)	30 (13–53)	45 (39–50)	7 (1–24)	19 (15–24)
Best overall response, n (%) Complete response Partial response Stable disease Progressive disease Unknown	4 (14) 8 (29) 4 (14) 9 (32) 3 (11)	69 (22) 114 (36) 38 (12) 74 (24) 19 (6)	1 (4) 6 (26) 2 (9) 11 (48) 3 (13)	60 (19) 81 (26) 30 (9) 121 (38) 24 (8)	0 (0) 2 (7) 1 (4) 25 (89) 0 (0)	18 (6) 42 (13) 69 (22) 159 (50) 27 (9)
Median duration of response, mo (95% CI)	NR (7.6–NR)	NR	18.7 (2.8–NR)	NR (50.4–NR)	11.1 (3.0–19.2)	14.4 (8.3–53.6)
Median time to response, mo (range)	2.9 (1.9–9.9)	2.8 (1.1–27.8)[a]	2.8 (2.4–6.9)	2.8 (2.3–42.9)[a]	4.6 (2.6–6.6)	2.9 (2.5–49.7)[a]

[a]Data on file.

1. Larkin J, et al. N Engl J Med 2019:381:1535–1546.
Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019.

CheckMate 067: Tumor burden change from baseline in the mucosal population



[a]Data provided for only those patients with both baseline and ≥ 1 follow-up measurement; square, % change truncated to 100%; asterisk, responders; horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.

Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019

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CheckMate 067: Results

- Responses were durable in patients with mucosal melanoma
  - 9 patients in the NIVO+IPI group who have discontinued treatment and have not started subsequent systemic therapy (thus, were treatment-free) were still alive and being followed at 60 months, including 3 who were treated for ≤ 16 weeks
  - In the NIVO group, 4 patients were alive and being followed at 60 months, including 2 patients who remained on treatment and 1 patient who had discontinued treatment at 48 weeks and remained treatment-free
- Patients with mucosal melanoma treated with NIVO+IPI had the greatest decrease in tumor burden, with a median change of −45%

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CheckMate 067: Results

Safety

- Both the incidence of any-grade and grade 3/4 TRAEs was similar in patients in the mucosal subgroup and the ITT population (Table 3)

Subsequent therapy

- In patients with mucosal melanoma, fewer patients in the NIVO+IPI group received subsequent therapy than in the NIVO or IPI monotherapy groups, similar to that observed in the ITT population (Table 4)
- The proportion of patients who received any subsequent therapy was similar for the mucosal compared with the ITT population for both NIVO+IPI- and IPI-treated patients
  - For NIVO-treated patients, the proportion of patients with any subsequent therapy was higher in the mucosal compared with the ITT population (70% vs 59%, respectively); there was also a greater proportion of patients who received subsequent radiotherapy (39% vs 29%, respectively)
- Subsequent anti–programmed death (PD)-1 therapy or anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) therapy was received by 17% and 39% of NIVO-treated patients and 50% and 11% of IPI-treated patients, respectively
- Of patients alive and being followed at 5 years treated with NIVO+IPI, 1 of 10 have received subsequent systemic therapy and 9 of 10 were treatment-free

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CheckMate 067: Safety summary

	NIVO+IPI, n (%)		NIVO, n (%)		IPI, n (%)	
	Mucosal (n = 28)	ITT[1] (n = 313)	Mucosal (n = 23)	ITT[1] (n = 313)	Mucosal (n = 28)	ITT[1] (n = 311)
Any-grade TRAEs	27 (96)	300 (96)	19 (83)	271 (87)	22 (79)	268 (86)
Grade 3/4 TRAEs	15 (54)	186 (59)[a]	6 (26)	73 (23)[a]	7 (25)	86 (28)[a]
Increased lipase	4 (14)	34 (11)	2 (9)	18 (6)	3 (11)	12 (4)
Diarrhea	2 (7)	30 (10)	2 (9)	9 (3)	1 (4)	18 (6)
Increased amylase	2 (7)	9 (3)	0	7 (2)	2 (7)	4 (1)
Increased aspartate aminotransferase	2 (7)	19 (6)	0	3 (1)	0	2 (1)
Colitis	1 (4)	26 (8)	1 (4)	3 (1)	2 (7)	24 (8)
Fatigue	1 (4)	13 (4)	1 (4)	3 (1)	0	3 (1)
Pruritus	1 (4)	6 (2)	0	1 (< 1)	0	1 (< 1)
Rash	1 (4)	10 (3)	0	1 (< 1)	0	5 (2)
Hypophysitis	0	5 (2)	0	1 (< 1)	0	5 (2)
Increased alanine aminotransferase	0	27 (9)	0	4 (1)	1 (4)	5 (2)
Maculopapular rash	0	6 (2)	0	2 (1)	0	1 (< 1)
Nausea	0	7 (2)	0	0	0	2 (1)
Vomiting	0	7 (2)	0	1 (< 1)	0	1 (< 1)

[a]Individual grade 3/4 TRAEs are those occurring in ≥ 2% patients in the ITT population.

1. Larkin J, et al. N Engl J Med 2019:381:1535–1546.
Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019

CheckMate 067: Subsequent therapy in the mucosal and ITT populations

	NIVO+IPI, n (%)		NIVO, n (%)		IPI, n (%)	
	Mucosal (n = 28)	ITT[1] (n = 314)	Mucosal (n = 23)	ITT[1] (n = 316)	Mucosal (n = 28)	ITT[1] (n = 315)
Any subsequent therapy[a]	13 (46)	143 (46)	16 (70)	185 (59)	23 (82)	237 (75)
Subsequent systemic therapy	11 (39)	109 (35)	12 (52)	152 (48)	20 (71)	207 (66)
Subsequent immunotherapy	7 (25)	55 (18)	9 (39)	105 (33)	15 (54)	149 (47)
Anti-PD-1 agents[b]	6 (21)	39 (12)	4 (17)	49 (16)	14 (50)	144 (46)
Anti-CTLA-4 agents[b]	2 (7)	21 (7)	9 (39)	91 (29)	3 (11)	16 (5)
BRAF inhibitor[c]	0	43 (14)	1 (4)	60 (19)	2 (7)	72 (23)
MEK/NRAS inhibitor[c]	0	33 (11)	1 (4)	43 (14)	1 (4)	42 (13)
Subsequent radiotherapy	3 (11)	66 (21)	9 (39)	93 (29)	12 (43)	126 (40)
Subsequent surgery	5 (18)	65 (21)	4 (17)	72 (23)	8 (29)	94 (30)

[a]Patients may have received > 1 subsequent therapy; [b]May include patients treated with anti–PD-1+anti–CTLA-4 combination; [c]May include patients treated with BRAF+MEK inhibitor combination.

1. Larkin J, et al. N Engl J Med 2019:381:1535–1546.

Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019

CheckMate 067: Authors' conclusions

- This 5-year analysis showed that patients with mucosal melanoma in CheckMate 067 had similar safety outcomes but poorer long-term efficacy versus the ITT population
- Patients with mucosal melanoma treated with NIVO+IPI demonstrated more favorable survival outcomes than those treated with NIVO or IPI alone
  - 5-year PFS (29%, 14%, and 0, respectively)
  - 5-year OS (36%, 17%, and 7%)
- The addition of IPI to NIVO treatment in patients with mucosal melanoma appeared to increase the rate of CRs and the duration of response compared with NIVO alone
  - 9 of 28 patients in the NIVO+IPI group (32% of the total group) discontinued treatment and remained treatment-free at 60 months from randomization
- In the mucosal patient population, PFS appeared to be an appropriate surrogate for OS
- While NIVO+IPI demonstrated the highest long-term efficacy in this study, novel therapies are needed to further improve benefit in patients with mucosal melanoma

Shushtari et al., ASCO 2020, Oral Presentation, Abstract Number 10019

Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy

Ines Pires da Silva, Tasnia Ahmed, Serigne Lo, Irene LM Reijers, Alison Weppler, Allison Betof, James Randall Patrinely, Patricio Serra-bellver, Celeste Lebbe, Johanna Mangana, Khang Nguyen, Lisa Zimmer, Paolo Ascierto, Dan Stout, Megan Lyle, Olivier Klein, Camille Gerard, Christian U Blank, Alexander A Menzies, Georgina V Long

Bristol Myers Squibb

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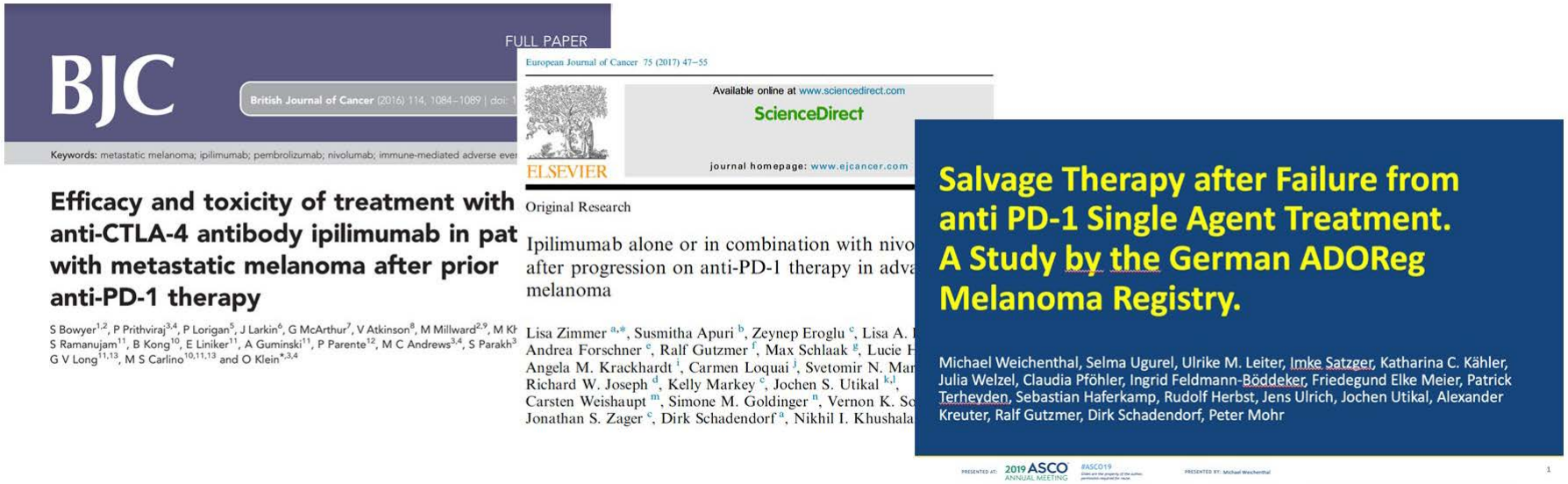
Question: Can a subset of PD1 resistant patients benefit from IPI or IPI + PD1?

1. How many patients will benefit?
2. What is the best treatment?
3. Who will benefit?



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Aims

In PD1 monotherapy progressors:

1. Determine the response rate, progression-free survival, overall survival and safety with IPI monotherapy or IPI combined with PD1.
2. Identify clinical predictors of response and survival to IPI +/- PD1.

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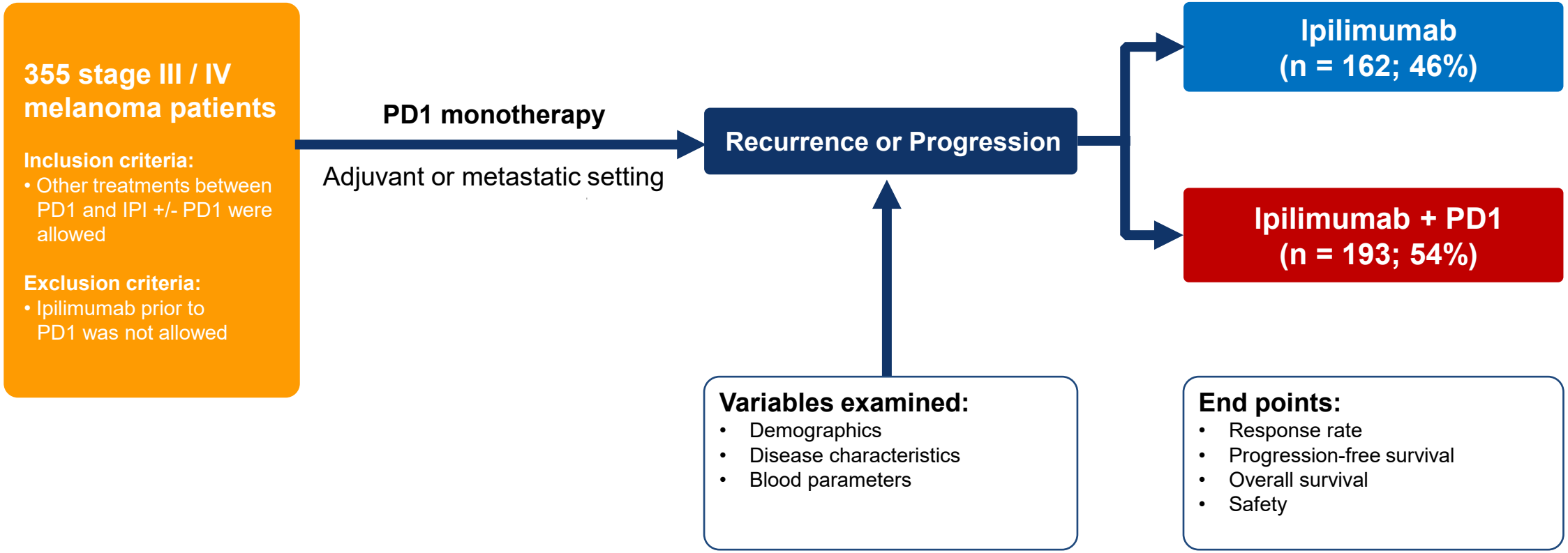
Study Design: multicenter retrospective study



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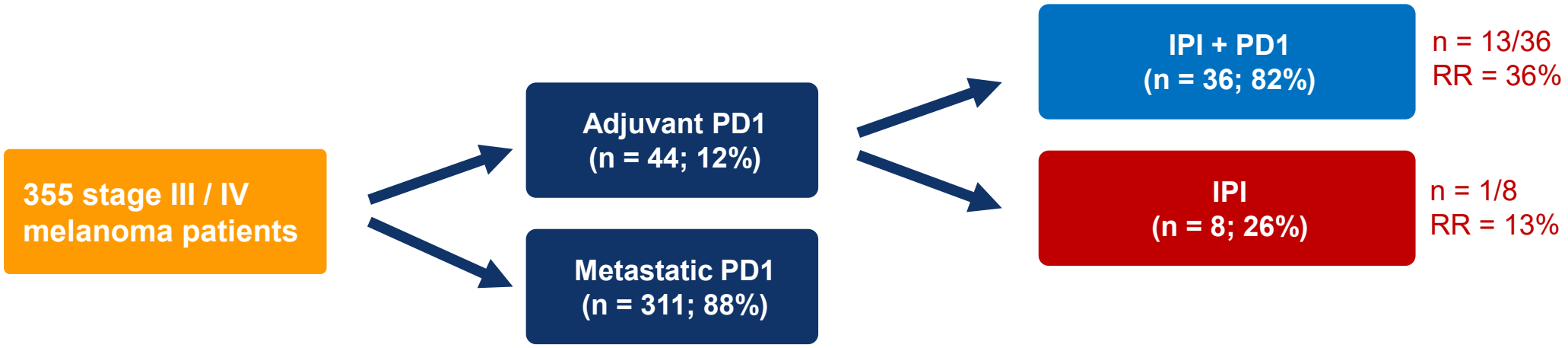
Patients who recurred after adjuvant PD-1



Neither the interval between PD1 and IPI +/- PD1 or use of other drugs affected response to IPI +/- PD1.

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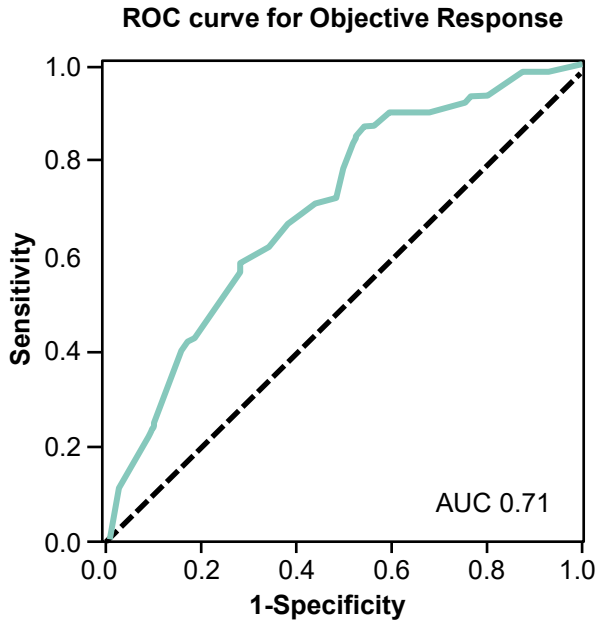
Clinical Predictors of Response with IPI +/- PD1 in PD1 resistant patients

Clinical factors	Multivariable Analysis	
	OR (95% CI)	p-value
ECOG 0 ≥ 1	1 0.56 (0.31, 1.01)	0.0529
Presence of liver mets No Yes	1 0.58 (0.30, 1.12)	0.1026
Presence of subcutaneous metastases No Yes	1 1.68 (0.96, 2.93)	0.0701
Platelets ≤ median > median	1 0.61 (0.35, 1.05)	0.0751
Treatment IPI IPI + PD1	1 2.72 (1.50, 4.93)	0.0009



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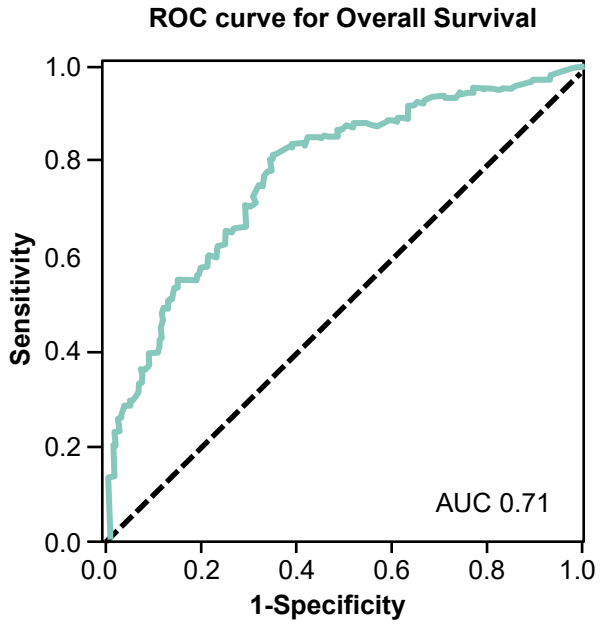
Clinical Predictors of Overall Survival with IPI +/- PD1 in PD1 resistant patients

Clinical factors	Multivariable Analysis	
	OR (95% CI)	p-value
Sex = Male	0.63 (0.46, 0.87)	0.0052
ECOG PS ≥ 1	1.78 (1.27, 2.49)	0.0009
Mutational Status		
BRAF mutant	1	0.0829
NRAS mutant	1.64 (1.04, 2.59)	
BRAF & NRAS WT	1.38 (0.96, 2.00)	
AJCC staging = M1C/M1D	1.46 (0.98, 2.22)	0.0602
Presence of bone metastases	2.72 (1.50, 4.93)	0.0009
Platelets > median	1.33 (0.98, 1.82)	0.0687
Elevated LDH	2.11 (1.54, 2.89)	0.0001
Time to progression with anti-PDI > 3 months	0.72 (0.53, 0-99)	0.0450
Treatment		
IPI	1	0.0054
IPI + PD1	0.61 (0.43, 0.86)	



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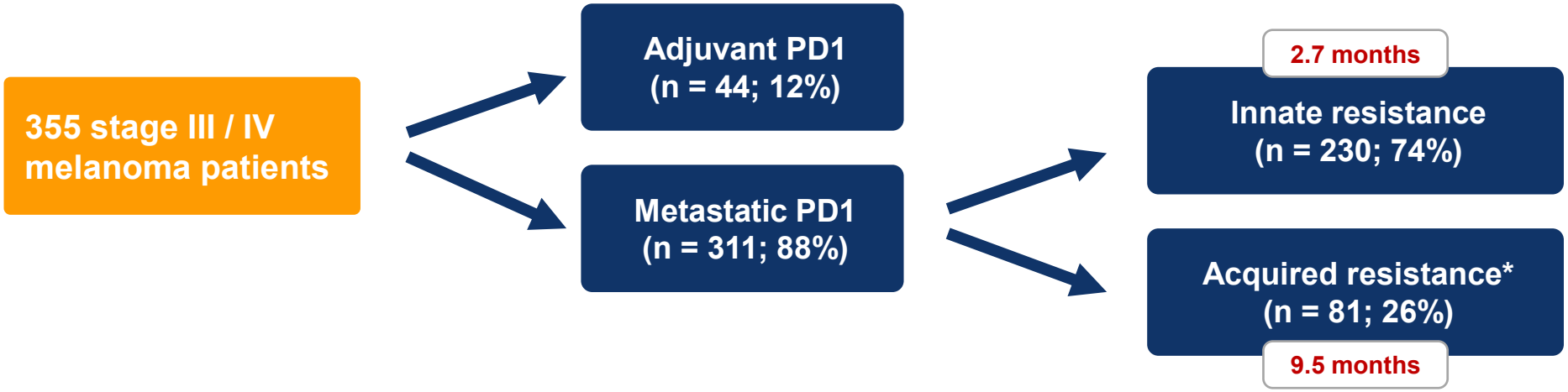
Cohort of PD1 resistant metastatic melanoma patients



Median time to PD1 progression 3 months (0.5 – 42.3)

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*Acquired resistance: disease progression after initial CR, PR or SO 2 ≥ 6 months

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Patient characteristics at start of IPI +/- PD1

	IPI + PD1 (n = 193)	IPI (n = 162)	*p-value*
Age, median (range)	61.0 (22.0, 91.0)	67.0 (21.0, 85.0)	0.0003
Sex, male (%)	124 (64.2%)	103 (63.6%)	0.8961
Geography			
Australia	93 (48.2%)	22 (13.6%)	<0.0001
Europe	55 (28.5%)	113 (69.8%)	
USA	45 (23.3%)	27 (16.7%)	
Mutational status			
BRAF mutant	70 (36.3%)	34 (21.0%)	0.0002
NRAS mutant	43 (22.3%)	26 (16.0%)	
BRAF & NRAS WT	80 (41.5%)	102 (63.0%)	
ECOG PS ≥ 1 (%)	58 (30.9%)	95 (59.7%)	<0.0001
Staging (M1C/M1D)	134 (69.4%)	121 (74.7%)	0.2723
Presence of liver metastases	56 (29.0%)	55 (34.0%)	0.3178
Presence of brain metastases	71 (36.8%)	43 (26.5%)	0.0395
LDH, > UNL (%)	67 (41.9%)	57 (37.5%)	0.4299

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Response rate

	IPI + PD1 (n = 193)	IPI (n = 162)	*p-value*
Objective Response Rate (%)	61 (32%)	21 (13%)	**0.0021**
Response			**0.0076**
Complete response (%)	21 (11%)	3 (2%)	
Partial response (%)	40 (21%)	18 (11%)	
Stable disease (%)	17 (9%)	23 (14%)	
Progressive disease (%)	115 (59%)	118 (73%)	
Rate of Disease Control (%)	78 (41%)	44 (27%)	
Responsive Duration (95% CI) - months	11.6 (9.4 – 15.5)	9.0 (4.4 – 13.7)	**0.0467**

Median follow-up from start of IPI+/-PD1 of 22.2 months (18.4 – 25.6)

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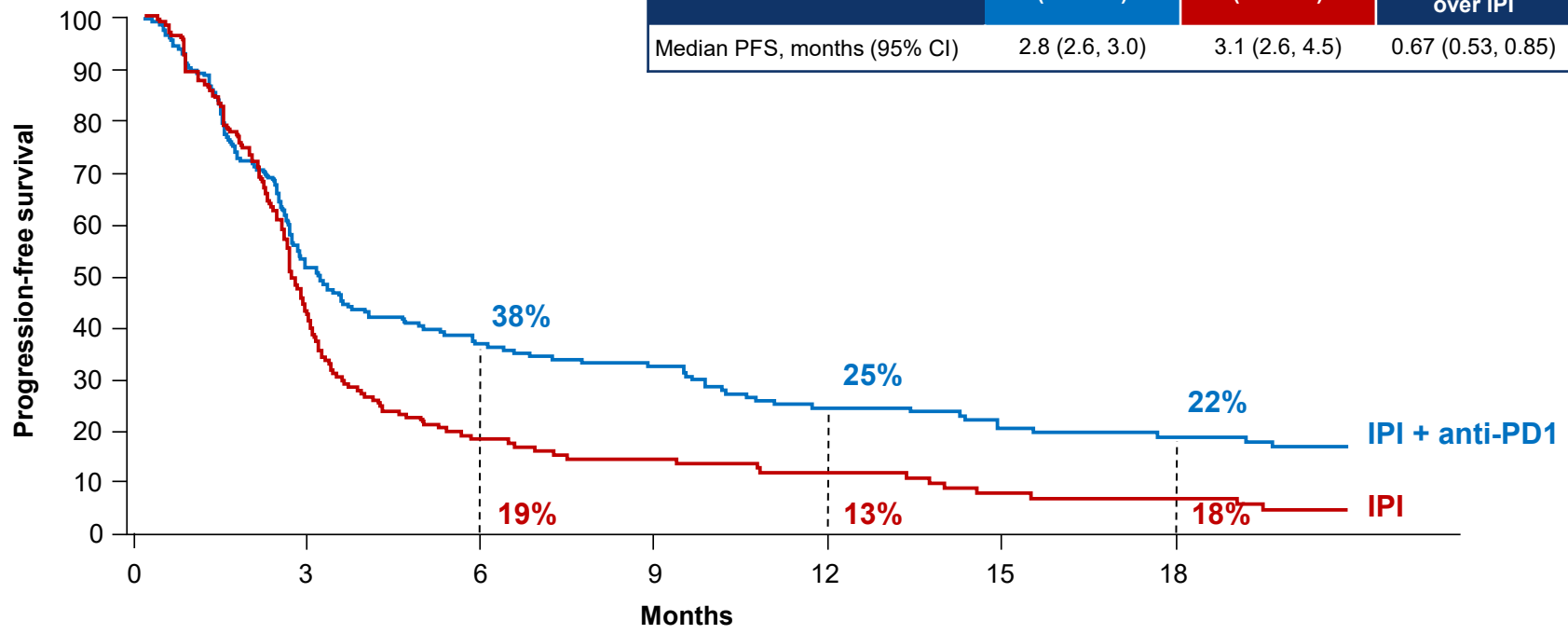
Progression-free survival

	IPI + anti-PD1 (n = 193)	IPI (n = 162)	HR (95% CI) IPI + anti-PD1 over IPI	*p-value*
Median PFS, months (95% CI)	2.8 (2.6, 3.0)	3.1 (2.6, 4.5)	0.67 (0.53, 0.85)	0.0005



No. at risk							
IPI	162	60	25	20	13	9	7
IPI + anti-PD1	193	97	63	52	35	27	24

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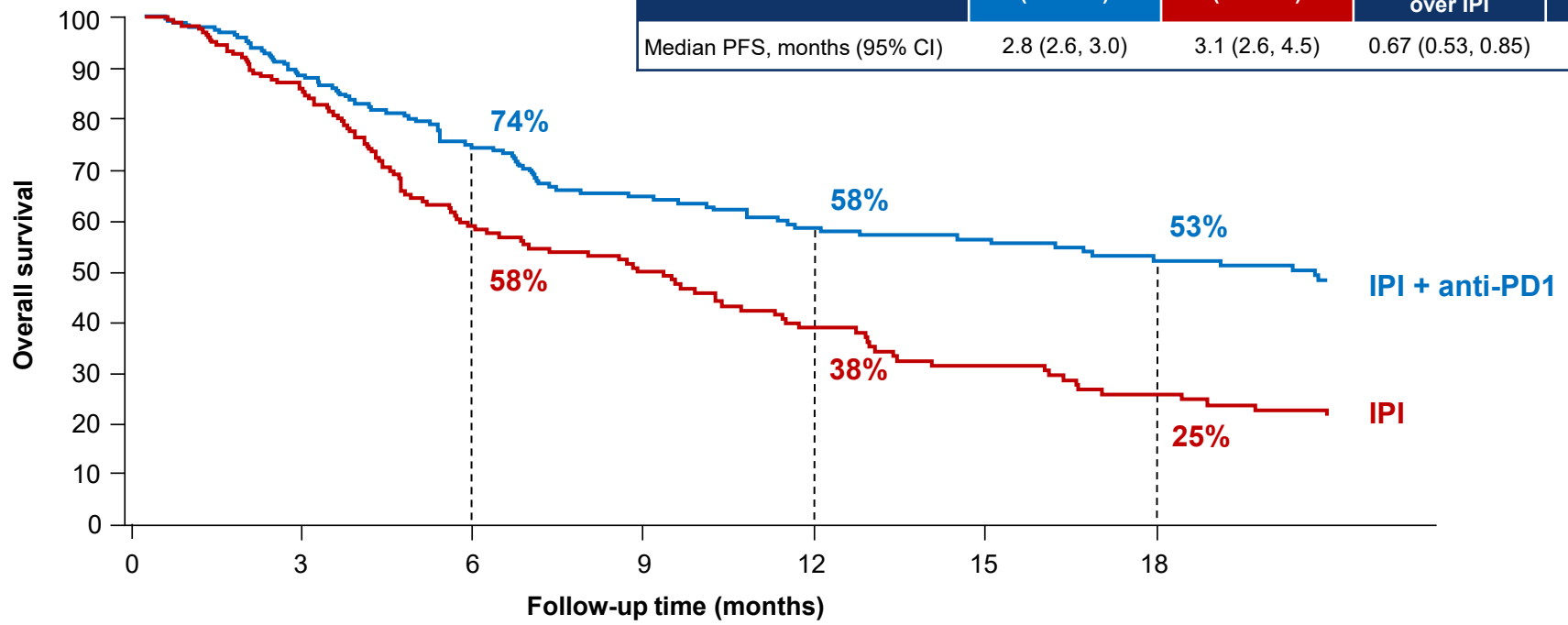
Overall survival

	IPI + anti-PD1 (n = 193)	IPI (n = 162)	HR (95% CI) IPI + anti-PD1 over IPI	*p-value*
Median PFS, months (95% CI)	2.8 (2.6, 3.0)	3.1 (2.6, 4.5)	0.67 (0.53, 0.85)	0.0005



No. at risk							
IPI	162	131	79	63	43	33	26
IPI + anti-PD1	193	165	125	98	80	69	56

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Safety

High Grade Adverse Events ≥ G3	IPI + PD1 (n = 193)	IPI (n = 162)	*p-value*
Total	59 (31%)	54 (33%)	0.6474
Rash	3 (2%)	2 (1%)	0.9999
Diarrhoea / colitis	23 (12%)	33 (20%)	0.0401
Increased ALT / AST level	24 (12%)	15 (9%)	0.3960
Dyspnea / pneumonitis	2 (1%)	1 (1%)	0.9999
Nephritis	-	1 (1%)	0.4579
Endocrinopathies	3 (2%)	2 (1%)	0.9999
Others	9 (5%)	5 (3%)	0.5869

High grade (≥ G3) toxicity was not associated with response.

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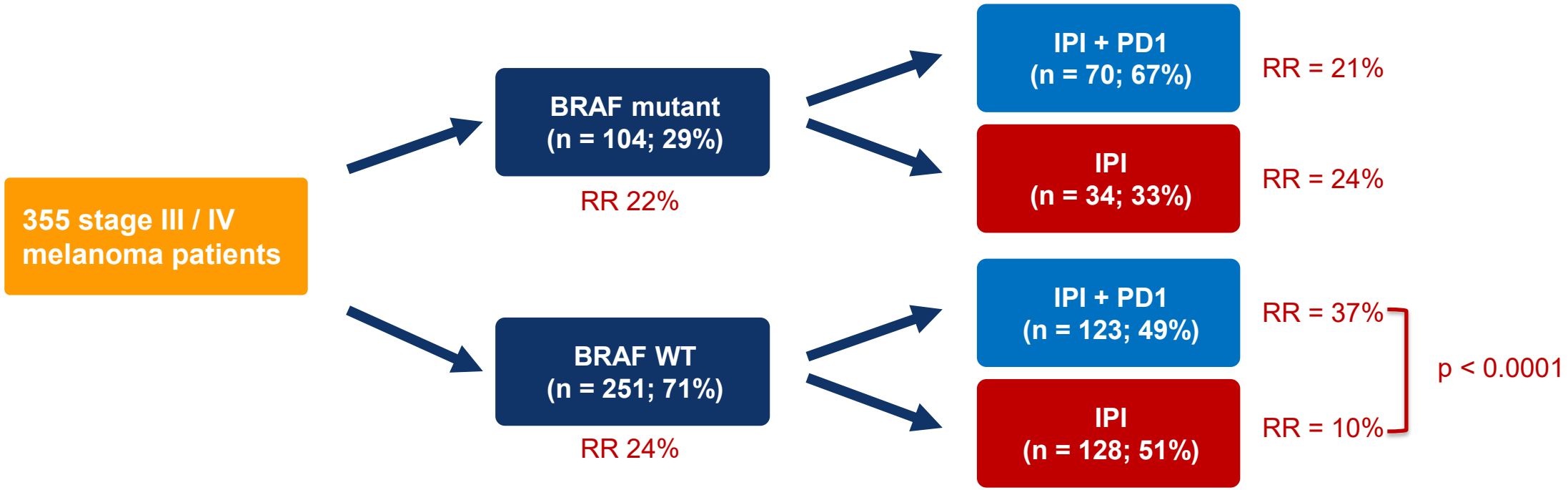
BRAF mutant vs BRAF WT



Prior BRAFi RR 13% vs No prior BRAFi RR 22%, p>0.05%

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Conclusion

1. In patients resistant to PD1, IPI combined with PD1 has a higher response rate (32%) and longer PFS (25% at 12 months) and OS (58% at 12 months), yet similar high grade toxicity than IPI alone.
2. Predictive models of response and survival will help forecast patient outcomes when treated with IPI +/- PD1 after progressing on PD1 monotherapy.

Da Silva et al., ASCO 2020, Oral Presentation

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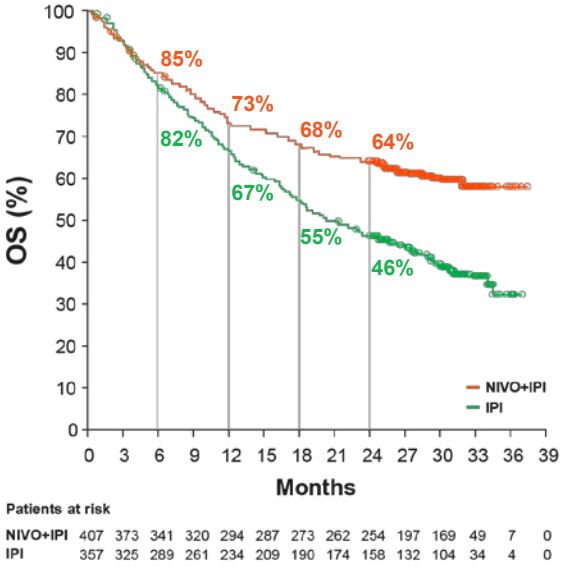
Management of Gastrointestinal Toxicity: OS in all patients and patients with select GI irAEs including those treated with CS

All Treated Patients

	NIVO+IPI	IPI
Event, n/N	**162/407**	**217/357**
Median OS, mo (95% CI)	NR	20.21 (17.68–25.72)
HR (95% CI) vs IPI	0.58 (0.47–0.71)[a]	–

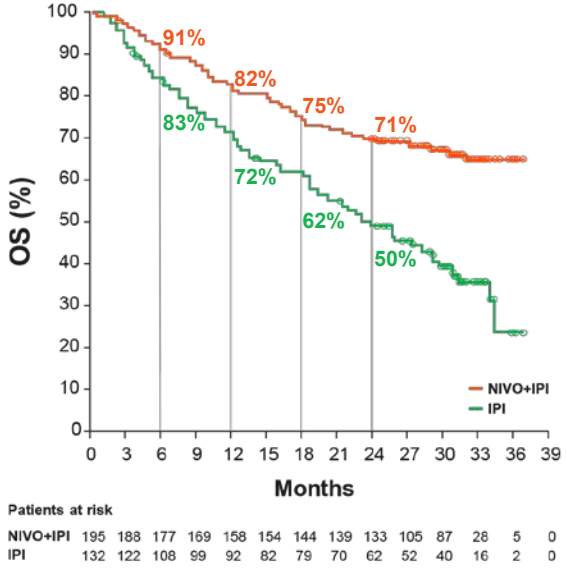


Patients at risk

NIVO+IPI	407	373	341	320	294	287	273	262	254	197	169	49	7	0
IPI	357	325	289	261	234	209	190	174	158	132	104	34	4	0

Patients With Select GI irAEs

	NIVO+IPI	IPI
Event, n/N	**64/195**	**81/132**
Median OS, mo (95% CI)	NR	23.20 (18.56–29.40)
HR (95% CI) vs IPI	0.44 (0.32–0.61)[a]	–

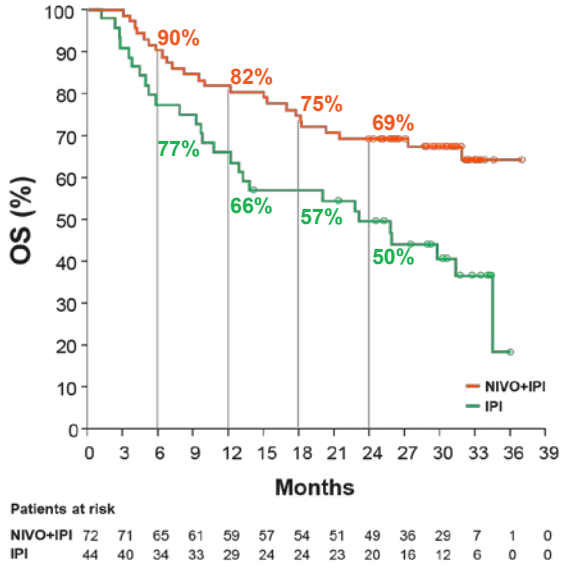


Patients at risk

NIVO+IPI	195	188	177	169	158	154	144	139	133	105	87	28	5	0
IPI	132	122	108	99	92	82	79	70	62	52	40	16	2	0

High-dose CS

	NIVO+IPI	IPI
Event, n/N	**24/72**	**27/44**
Median OS, mo (95% CI)	NR	23.03 (10.71–34.43)
HR (95% CI) vs IPI	0.44 (0.26–0.77)[b]	–



Patients at risk

NIVO+IPI	72	71	65	61	59	57	54	51	49	36	29	7	1	0
IPI	44	40	34	33	29	24	24	23	20	16	12	6	0	0

- NIVO+IPI or IPI alone is associated with a high incidence of GI select AEs, but most are effectively managed by IMMs, which do not appear to inhibit tumor response

a $P < 0.0001$; b $P = 0.0031$
Database lock: February 2016, minimum follow-up 24 months (CheckMate 069), and September 2016, minimum follow-up 28 months (CheckMate 067)
CI = confidence interval; CS = corticosteroids; HR = hazard ratio; NR = not reached

Weber et al. ASCO, 2017; Poster #9523, poster presentation

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Melanom

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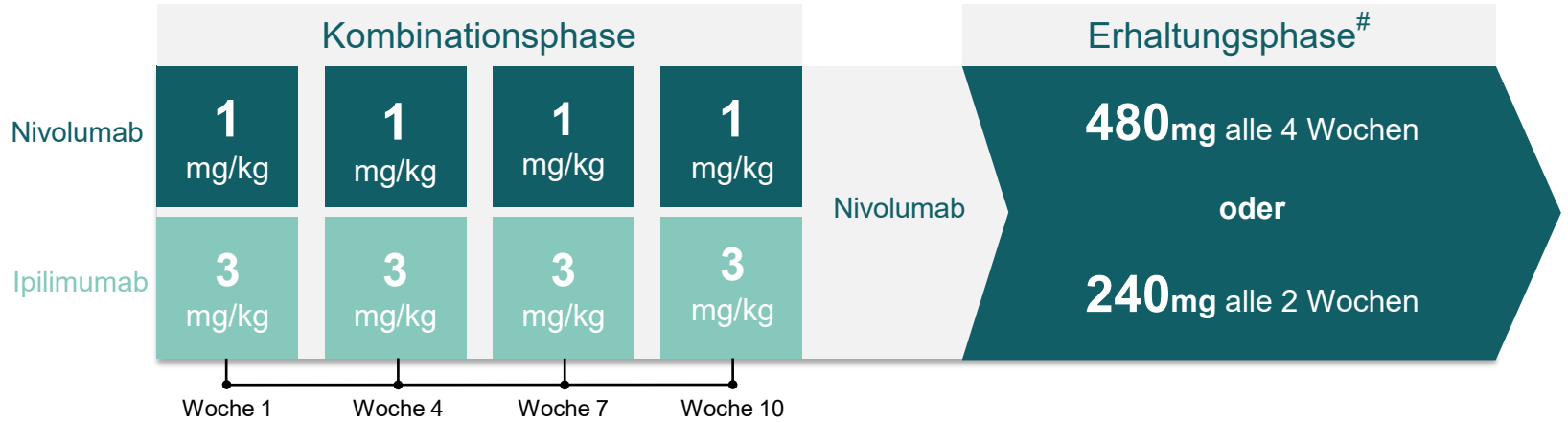
Immunonkologie

Nivolumab + Ipilimumab beim fortgeschrittenen Melanom
Dosierungs- und Verabreichungsschema*,[1, 2]

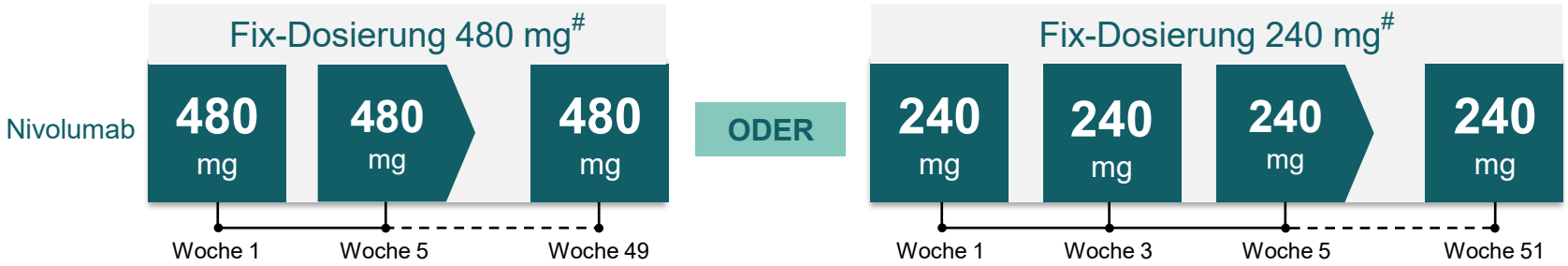


Nivolumab + Ipilimumab alle 3 Wochen für 4 Zyklen

- **Erste Fix-Dosis 480 mg q4w: 6 Wochen nach der letzten Dosis der Kombination von Nivolumab + Ipilimumab**
- **Erste Fix-Dosis 240 mg q2w: 3 Wochen nach der letzten Dosis der Kombination von Nivolumab + Ipilimumab**

* Nivolumab/Ipilimumab ist in Kombination mit Ipilimumab/Nivolumab bei Erwachsenen für die Behandlung des fortgeschrittenen (nicht resezierbaren oder metastasierten) Melanoms indiziert[1, 2]
# Nivolumab kann bei fortgeschrittenem Melanom als Monotherapie und in der Erhaltungsphase der Kombinationstherapie wahlweise in einer Dosierung von 240 mg Nivolumab alle 2 Wochen oder 480 mg Nivolumab alle 4 Wochen gegeben werden. Weitere Details siehe Nivolumab-Fachinformation.
1. Nivolumab-Fachinformation, aktueller Stand 2. Ipilimumab-Fachinformation, aktueller Stand

Nivolumab Adjuvant
Dosierungs- und Verabreichungsschema*,[1]



→ Therapiedauer: 1 Jahr

Bei Umstellung von 480 mg q4w auf 240 mg q2w: erste 240 mg-Dosis 4 Wochen nach der letzten 480 mg-Dosis

Bei Umstellung von 240 mg q2w auf 480 mg q4w: erste 480 mg-Dosis 2 Wochen nach der letzten 240 mg-Dosis

* Nivolumab ist als Monotherapie zur adjuvanten Behandlung des Melanoms mit Lymphknotenbeteiligung oder Metastasierung nach vollständiger Resektion bei Erwachsenen indiziert.
# Nivolumab Monotherapie kann für die adjuvante Therapie des Melanoms im Stadium III und IV wahlweise in der Fix-Dosierung 240 mg alle 2 Wochen als 30-minütige Infusion oder in der Fix-Dosierung 480 mg als 60-minütige Infusion alle 4 Wochen verabreicht werden. Weitere Details siehe Nivolumab-Fachinformation.
1. Nivolumab-Fachinformation, aktueller Stand

Basistext OPDIVO®

OPDIVO® 10 mg/ml Konzentrat z. Herst. e. Infusionslösung. Wirkstoff: Nivolumab. Sonst. Bestandteile: Natriumcitratdihydrat, Natriumchlorid, Mannitol, Pentetsäure, Polysorbat 80, Natriumhydroxid, Salzsäure u. Wasser f. Injektionszwecke.

Anw.:
Als Monother. b. Erw. f. d. Behandl. d. fortgeschritt. (nicht resezierb. od. met.) Melanoms.

Als Monother. b. Erw. zur adjuv. Behandl. d. Melanoms mit Lymphknotenbeteilig. od. Metastasierg. nach vollst. Resektion.

Als Monother. zur Behandl. d. lokal fortgeschritt. od. met. NSCLC nach vorheriger CTx b. Erw..

Als Monother. b. Erw. zur Behandl. d. fortgeschritt. RCC nach Vorther..

Als Monother. zur Behandl. d. rezidiv. od. refrakt. cHL b. Erw. nach ASCT u. Behandl. m. Brentuximab Vedotin.

Als Monother. zur Behandl. d. rezidiv. od. met. Plattenepithelkarzinoms d. Kopf-Hals-Bereichs b. Erw. mit Progress. während od. nach Pt-basierter Ther..

Als Monother. zur Behandl. d. lokal fortgeschritt. nicht resezierb. od. met. Urothelkarzinoms b. Erw. nach Versagen vorheriger Pt-haltiger Ther..

Als Monother. zur adjuv. Behandl. d. MIUC mit Tumorzell-PD-L1-Expression ≥ 1 % b. Erw. mit hohem Rezidivrisiko nach radikaler Resekt. d. MIUC

Als Monother. zur Behandl. d. nicht resezierb. fortgeschritt., rezidiv. od. met. Plattenepithelkarzinoms d. Ösophagus b. Erw. nach vorheriger fluoropyrimidin- u. Pt-basierter Komb.-CTx.

Als Monother. zur adjuv. Behandl. d. Karzinome d. Ösophagus od. d. gastroösophag. Übergangs b. Erw. mit patholog. Resterkr. nach vorheriger neoadjuv. Chemoradiother..

Gegenanz.: Überempf.-keit gg. d. Wirkstoff od. sonst. Bestandt..

Nebenwirk.:
Sehr häufig: Infekt. d. oberen Atemwege; Lymphopenie; Anämie; Leukopenie; Neutropenie; Thrombozytopenie; vermind. Appetit; Hyperglykämie; Hypoglykämie; Kopfschm.; Dyspnoe; Husten; Diarrhö; Erbr.; Übelk.; Bauchschm.; Obstipation; Hautausschl.; Pruritus; Muskel- u. Skelettschm.; Arthralgie; Fatigue; Pyrexie; Ödeme; Anstieg AST; Hyponatriämie; Hypoalbuminämie; Anstieg alkal. Phosphatase, Kreatinin, ALT, Lipase; Hyperkaliämie; Anstieg Amylase; Hypokalziämie; Hypomagnesiämie; Hypokaliämie; Hyperkalziämie.
Häufig: Pneumonie; Bronchitis; Infusionsbed. Reakt.; Hypersensib. (einschl. anaphylakt. Reakt.); Hypothyreose; Hyperthyreose; Thyroiditis; Dehydr.; Gew.-Verlust; periph. Neuropathie; Schwindelgef.; verschwomm. Sehen; trock. Augen; Tachykard.; Vorhofflimm.; Hypertonie; Pneumonitis; Pleuraerguss; Kolitis; Stomatitis; trock. Mund; Vitiligo; trock. Haut; Erythem; Alopezie; Urtikaria; Arthritis; Nierenvers. (einschl. akutem N.); Schm.; Schm. in d. Brust; Anstieg Gesamtbilirubin; Hypermagnesiämie; Hypernatriämie.
Gelegentl.: Sarkoidose; Nebenniereninsuff.; Hypophyseninsuff.; Hypophysitis; Diabetes mell.; metabol. Azidose; Polyneuropathie; autoimm. Neuropathie (einschl. Gesichtsnerv- u. Abduzensparese); Uveitis; Myokarditis; perikard. Erk.; Arrhythmie (einschl. ventrik. A.); Lungeninfiltr.; Pankreatitis; Gastritis; Hepatitis; Cholestase; Erythema multiforme; Psoriasis; Rosazea; rheumat. Polymyalgie.
Selten: Asept. Meningitis; Histiozytär nekrotisier. Lymphadenitis (Kikuchi-L.); Eosinophilie; diab. Ketoazidose; Hypoparathyreoidismus; GuillainBarré-Syndr.; Demyelinisier.; myasthenes Syndr.; Enzephalitis; Vaskulitis; Zwölffingerdarmgeschw.; tox. epiderm. Nekrolyse; Stevens-Johnson-Syndr.; Sjögren-Syndr.; Myopathie; Myositis (einschl. Polym.); Rhabdomyolyse; nicht-infektiöse Zystitis; tubulointerstit. Nephritis.
Nicht bekannt: Hämophagozyt. Lymphohistiozytose; Abstoß. solides Organtransplantat; Tumorlyse-Syndr.; Vogt-Koyanagi-Harada-Syndr.; Lichen sclerosus; and. Lichenerkrank..

Weitere Hinweise siehe Fachinformation. Verschreibungspflichtig. Pharmazeutischer Unternehmer: BristolMyers Squibb Pharma EEIG; Plaza 254; Blanchardstown Corporate Park 2; Dublin 15; D15 T867; Irland. Stand: v26.

Basistext YERVOY®

YERVOY® 5 mg/ml Konzentrat z. Herst. e. Infusionslösung. **Wirkstoff**: Ipilimumab. **Sonst**. **Bestandteile**: Trometamolhydrochlorid, Natriumchlorid, Mannitol, Pentetsäure, Polysorbat 80, Natriumhydroxid, Salzsäure u. Wasser f. Injektionszwecke.

Anw.:

Als Monother. z. Behandl. d. fortgeschritt. (nicht resezierbar. od. met.) Melanoms bei Erw. u. Jugendl. ab 12 Jahre.

Gegenanz.: Überempf.-keit gg. d. Wirkstoff od. sonst. Bestandt..

Nebenwirk.:

Sehr häufig: vermind. Appetit; Diarrhö; Erbr.; Übelk.; Ausschlag; Pruritus; Fatigue; Reakt. an d. Injektionsstelle; Pyrexie.

Häufig: Tumorschm.; Anämie; Lymphopenie; Hypopituitarismus (einschl. Hypophysitis); Hypothyreose; Dehydr.; Hypokaliämie; Gew.-Verlust; Verwirrth.; periph. sensor. Neuropathie; Schwindel; Kopfschm.; Lethargie; verschwom. Sehen; Augenschm.; Hypotonie; Hautröt.; Hitzewall.; Dyspnoe; Husten; gastrointest. Hämorrhagie; Kolitis; Verstopf.; gastroösophageale Refluxkrank.; Bauchschm.; Schleimhautentzünd.; Leberfunktionsstör.; Dermatitis; Erythem; Vitiligo; Urtikaria; Ekzem; Alopezie; Nachtschweiß; trock. Haut; Arthralgie; Myalgie; Muskel- u. Skelettschm.; Muskelspasmus; Schüttelfrost; Asthenie; Ödeme; Schm.; grippeähn. Erkrank.; Anstieg Alanin-Aminotransferase, Aspartat-Aminotransferase, alkal. Phosphatase, Bilirubinwerte.

Gelegentlich: Sepsis; sept. Schock; Harnweginfekt.; Infek. d. Atemwege; Pneumonie; paraneoplast. Syndr.; hämolyt. Anämie; Thrombozytopenie; Eosinophilie; Neutropenie; Hypersensitivität; Nebenniereninsuff.; sek. Nebenniereninsuff.; Hyperthyreose; Hypogonadismus; Hyponatriämie; Alkalose; Hypophosphatämie; Tumorlysesyndr.; Hypokalziämie; Veränd. d. psych. Verfassung; Depression; vermind. Libido; Guillain-Barré-Syndr.; Meningitis (asept.); zent. autoimm. Neuropathie (Enzephalitis); Synkope; kraniale Neuropathie; Gehirnödeme; periphere Neuropathie; Ataxie; Tremor; Myoklonie; Dysarthrie; Uveitis; Glaskörperblut.; Iritis; Augenödem; Blepharitis; vermind. Sehschärfe; Fremdkörpergef. i. d. Augen; Konjunktivitis; Arrhythmie; Vorhofflimm.; Vaskulitis; Angiopathie; periph. Ischämie; orthostat. Hypotonie; respirator. Insuff.; akut. respirator. Distress-Syndr.; Lungeninfiltr.; Lungenödeme; Pneumonitis; allerg. Rhinitis; gastrointest. Perfor.; Dickdarmperfor.; intest. Perfor.; Peritonitis; Gastroenteritis; Divertikulitis; Pankreatitis; Enterokolitis; Magengeschw.; Dickdarmgeschw.; Stomatitis; Ösophagitis; Ileus; Lebervers.; Hepatitis; Hepatomegalie; Gelbsucht; tox. epiderm. Nekrolyse; leukozytoklast. Vaskulitis; Hautabschälung; Veränder. d. Haarfarbe; rheumat. Polymyalgie; Myositis; Arthritis; Muskelschwäche; Nierenvers.; Glomerulonephritis; autoimm. Nephritis; Nierentubulusazidose; Hämaturie; Amenorrhö; multi. Organvers.; system. inflammator. Response-Syndr.; infusionsbed. Reak.; Anstieg Gamma-Glutamyltransferase, Kreatininwerte, thyreotropen Hormon i. Blut; Vermind. Cortisolspiegel, Corticotropinspiegel; Anstieg Lipasewerte, Amylase; pos. antinukleäre Antikörper; Vermind. Testosteronspiegel; nicht-infektiöse Zystitis.

Selten: Autoimm. Thyroiditis; Thyroiditis; Typ-1-Diabetes mell.; Myasthenia gravis; Vogt-Koyanagi-Harada-Syndr.; seröse Netzhautablös.; Arteriitis temporalis; Proktitis; Erythema multiforme; Psoriasis; Arzneimittelexanthem m. Eosinophilie u. system. Symptomen (DRESS); Polymyositis; Proteinurie; Vermind. thyreotropen Hormon i. Blut, Thyroxinspiegel; anomaler Prolaktinspiegel i. Blut.

Sehr selten: Anaphylakt. Reak..

Nicht bekannt: Hämophagozyt. Lymphohistiozytose; Abstoß. solides Organtransplantat; Myelitis; Pemphigoid.

Weitere Hinweise siehe Fachinformation. Verschreibungspflichtig. Pharmazeutischer Unternehmer: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irland. Stand: v18.

Basistext OPDIVO® + YERVOY®

OPDIVO® 10 mg/ml Konzentrat z. Herst. e. Infusionslösung. **Wirkstoff:** Nivolumab. **Sonst. Bestandteile:** Natriumcitratdihydrat; Natriumchlorid; Mannitol; Pentetsäure; Polysorbat 80; Natriumhydroxid; Salzsäure u. Wasser f. Injektionszwecke.
YERVOY® 5 mg/ml Konzentrat z. Herst. e. Infusionslösung. **Wirkstoff:** Ipilimumab. **Sonst. Bestandteile:** Trometamolhydrochlorid; Natriumchlorid; Mannitol; Pentetsäure; Polysorbat 80; Natriumhydroxid; Salzsäure u. Wasser f. Injektionszwecke.

Anw. OPDIVO®/ YERVOY® in Komb. mit Ipilimumab/Nivolumab:
- Behandl. d. fortgeschritt. (nicht resezierb. oder met.) Melanoms b. Erw.. Im Vergl. z. Nivolumab Monother. wurde in der Komb. Nivolumab mit Ipilimumab nur b. Patienten mit niedr. Tumor PD-L1-Expression ein Anstieg d. PFS u. OS gezeigt.
- Erstlinienther. d. fortgeschritt. RCC b. Erw. mit intermediärem/ungünstigem Risikoprofil.
- Mit 2 Zyklen Pt basierter CTx. f. die Erstlinienther. d. met. NSCLC b. Erw., deren Tumoren keine sensitivierende EGFR-Mutation od. ALK-Translokation aufweisen.
- Erstlinienther. d. nicht-resezierb. malignen Pleuramesothelioms bei Erw.
- Behandl. d. met. dMMR- oder MSI-H-CRC bei Erw. nach vorheriger fluoropyrimidinbasierter Kombinations-CTx.
- Erstlinienbehandl. d. nicht resezierb. fortgeschritt., rezidiv. od. met. Plattenepithelkarzinoms des Ösophagus mit Tumorzell-PD-L1-Expression ≥ 1 % bei Erw..

OPDIVO® in Komb. mit Chemotherapie: In Komb. mit fluoropyrimidin- u. Pt-basierter Kombinations-CTx für die Erstlinienbehandl. d. HER2-negat. fortgeschritt. od. met. Adenokarzinome d. Magens, d. gastroösophagealen Übergangs od. d. Ösophagus b. Erw., deren Tumoren PD-L1 (CPS ≥ 5) exprimieren.
In Komb. fluoropyrimidin- u. Pt-basierter Kombinations-CTx für die Erstlinienbehandl. d. nicht resezierb. fortgeschritt., rezidiv. od. met. Plattenepithelkarzinoms des Ösophagus mit Tumorzell-PD-L1-Expression ≥ 1 % bei Erw..

OPDIVO® in Komb. mit Cabozantinib: Erstlinienther. d. fortgeschritt. RCC b. Erw.

Gegenanz.: Überempf.-keit gg. d. Wirkstoff od. sonst. Bestandt.

Nebenwirk.:

Komb. Nivolumab mit Ipilimumab und/oder Chemotherapie:

Sehr häufig: Infekt. d. oberen Atemwege; Pneumonie; Lymphopenie; Leukopenie; Neutropenie; Thrombozytopenie; Anämie; Hypothyreose; Hyperthyreose; vermind. Appetit; Hyperglykämie; Hypoglykämie; Hypoalbuminämie, Kopfschm.; Schwindelgef.; periph. Neuropathie; Hypertonie; Dyspnoe; Husten; Kolitis; Diarrhö; Erbr.; Übelk.; Bauchschm.; Obstipation; Stomatitis; Hautausschl.; Pruritus; trock. Haut; Arthralgie; Muskel- u. Skelettschm.; Fatigue; Pyrexie; Ödeme (einschl. periph. Ö.); Anstieg AST, ALT, Gesamtbilirubin, alkal. Phosphatase, Lipase, Amylase, Kreatinin; Hyperkalziämie, Hypokalziämie; Hyperkaliämie; Hypokaliämie; Hypomagnesiämie; Hyponatriämie; Hypernatriämie, Transaminasen erhöht.
Häufig: Bronchitis; Konjunktivitis; Eosinophilie; febrile Neutropenie; Infusionsbed. Reakt.; Hypersensib.; Nebenniereninsuff.; Hypophyseninsuff.; Hypophysitis; Hyperthyreose, Thyroiditis; Diabetes mell.; Dehydr.; Gewichtverl.; Hypophosphatämie; Parästhesie; Uveitis; verschwom. Sehen; trock. Augen; Tachykardie; Thrombose; Pneumonitis; Lungenembolie; Pleuraerguss; Pankreatitis; trock. Mund; Gastritis; Hepatitis; Palmar-plant. Erythrodysästhesiesyndr.; Hauthyperpigmentier.; Vitiligo; Erythem; Alopezie; Urtikaria; Arthritis; Muskelspasmen; musk. Schwäche; Nierenvers. (einschl. akutes N.); Schm.; Schm. in d. Brust; Schüttelfrost; Hypermagnesiämie; Anstieg TSH.
Gelegentl.: Asept. Meningitis; Sarkoidose; diab. Ketoazidose; Hypoparathyreoidismus; metabol. Azidose; Guillain-Barré-Syndr.; Polyneuropathie; Neuritis; Peroneuslähm.; autoimm. Neuropathie (einschl. Gesichtsnerv- u. Abduzensparese); Enzephalitis; Myasthenia gravis; Episkleritis; Arrhythmie (einschl. ventrik. A.); Vorhofflimm.; Myokarditis; Bradykardie; Darmperfor.; Duodenitis; Psoriasis; Stevens-Johnson-Syndr.; Erythema multiforme; Spondyloarthropathie; Sjögren-Syndr.; Myopathie; Myositis (einschl. Polym.); Rhabdomyolyse; Polymyalgia rheumatica; tubulointerstit. Nephritis; Nephritis; nicht-infektiöse Zystitis; Anstieg Gammaglutamyltransferase.
Selten: Tox. epiderm. Nekrolyse.
Nicht bekannt: Hämophagozyt. Lymphohistiozytose; Abstoß. solides Organtransplantat; Tumorlyse-Syndr.; Vogt-Koyanagi-Harada-Syndr.; perikard. Erkrank.; Lichen sclerosus; and. Lichenerkank..

Komb. Nivolumab mit Cabozantinib:

Sehr häufig: Infekt. d. oberen Atemwege; Anämie; Thrombozytopenie; Leukopenie; Lymphopenie; Neutropenie; Hypothyreose; Hyperthyreose; vermind. Appetit; Hypoglykämie; Hyperglykämie; Gew.-Verlust; Dysgeusie; Schwindelgef.; Kopfschm.; Hypertonie; Dysphonie; Dyspnoe; Husten; Diarrhö; Erbr.; Übelk.; Obstipation; Stomatitis; Bauchschm.; Dyspepsie; Palmar-plant. Erythrodysästhesiesyndr.; Hautausschl.; Pruritus; Muskel- u. Skelettschm.; Arthralgie; Muskelspasmen; Proteinurie; Fatigue; Pyrexie; Ödeme; Anstieg alkal. Phosphatase, ALT, AST, Gesamtbilirubin, Kreatinin, Amylase, Lipase; Hypokaliämie; Hypomagnesiämie; Hyponatriämie; Hypokalziämie; Hyperkalziämie; Hypophosphatämie; Hyperkaliämie; Hypermagnesiämie; Hypernatriämie.
Häufig: Pneumonie; Eosinophilie; Hypersensib. (einschl. anaphylaktische Reakt.); Nebenniereninsuff.; Dehydr.; periph. Neuropathie; Tinnitus; trock. Augen; verschwom. Sehen; Vorhofflimm.; Tachykard.; Thrombose; Pneumonitis; Lungenembolie; Pleuraerguss; Epistaxis; Kolitis; Gastritis; Mundschm.; trock. Mund; Hämorrhoiden; Hepatitis; Alopezie; trock. Haut; Erythem; Änd. d. Haarfarbe; Arthritis; Nierenvers.; akute Nierenschädig.; Schm.; Schm. in d. Brust; Anstieg Cholesterin im Blut; Hypertriglyzeridämie.
Gelegentl.: Infusionsbed. Überempfindl.-reakt.; Hypophysitis; Thyroiditis; autoimm. Enzephalitis; Guillain-Barré-Syndr.; myasthenes Syndr.; Uveitis; Myokarditis; Pankreatitis; Dünndarmperfor.; Glossodynie; Psoriasis; Urtikaria; Myopathie; Osteonekrose d. Kiefers; Fistel; Nephritis.
Selten: Nicht-infektiöse Zystitis.
Nicht bekannt: Lichen sclerosus; and. Lichenerkrank..

Weitere Hinweise siehe jeweilige Fachinformation. Verschreibungspflichtig. Pharmazeutischer Unternehmer: Bristol-Myers Squibb Pharma EEIG; Plaza 254; Blanchardstown Corporate Park 2; Dublin 15; D15 T867; Irland. Stand d. Textes: v14.