SUPPLEMENTARY INFORMATION

Supplement to: 'Real-world outcomes with ipilimumab and nivolumab in advanced melanoma: a multicentre retrospective study'

Inhoud Page

Suppl. Table 1. Therapy details

	All patients (n= 697)		Treatment-naïve patients (n=516)				Previously treated patients (n=181)			
			No brain metastases (n=334)		Brain metastases (n=138)		No brain metastases (n=123)		Brain metastases (n=102)	
Number of cycles ipilimumab plus nivolumab (median, IQR)	3	(2-4)	3	(2-4)	2	(2-4)	2	(1-3)	2	(1-3)
Completed 4 cycles ipilimumab plus nivolumab	228	(32.7)	121	(36.2)	42	(30.4)	43	(35.0)	22	(21.6)
Nivolumab maintenance	253	(36.3)	137	(41.0)	51	(37.0)	41	(33.3)	24	(23.5)
Number of cycles nivolumab maintenance (median, IQR)*	8	(3-19)	10	(3-20)	10	(2-21)	7	(3-14)	5	(1-15)

*Due to missing data, this is reported for 234 patients and not all patients who received nivolumab maintenance.
IQR: interquartile range.

Suppl. Table 2. Central nervous system metastases

	All patients (n=239)		Treatment-naïve patients (n=138)		Previously treated patients (n=101)	
Number of brain metastases						
0*	3	(1.3)	0		3	(3.0)
1	64	(26.7)	48	(34.8)	16	(15.8)
2	37	(15.4)	22	(15.9)	15	(14.9)
3 or more	135	(56.5)	68	(49.3)	67	(66.3)
Leptomeningeal melanomatosis	22	(9.2)	8	(5.8)	14	(13.9)
Local treatment CNS metastases						
None	135	(56.5)	74	(53.6)	61	(60.4)
Surgery	25	(10.5)	19	(13.8)	6	(5.9)
SRS	47	(19.7)	18	(13.0)	29	(28.7)
WBRT	17	(7.1)	13	(9.4)	4	(4.0)
Surgery + SRS	15	(6.3)	14	(10.1)	1	(1.0)
Symptoms[#]	77	(32.4)	45	(32.6)	32	(31.7)
Steroids^	81	(33.9)	46	(33.3)	35	(34.7)
Best overall response CNS[+]						
Complete response	30	(12.5)	26	(18.8)	4	(4.0)
Partial response	66	(27.6)	42	(30.4)	24	(23.8)
Stable disease	28	(11.7)	19	(13.8)	9	(8.9)
Progressive disease	105	(43.9)	41	(29.7)	64	(63.4)
Missing	10	(4.2)	10	(7.2)	0	

*leptomeningeal metastases only.
[#]reported for 238 patients due to missing data.
^reported for 237 patients due to missing data.

Suppl. Table 3. Response rates per primary melanoma type

	All patients		Treatment-naïve patients (n=472)				Previously treated patients (n=225)			
			No brain metastases		Brain metastases		No brain metastases		Brain metastases	
Cutaneous	**(n=487)**		**(n=216)**		**(n=88)**		**(n=104)**		**(n=79)**	
Best overall response										
Complete response	89	(18.3)	59	(27.3)	12	(13.6)	17	(16.3)	1	(1.3)
Partial response	158	(32.4)	77	(35.6)	40	(45.5)	26	(25.0)	15	(19.0)
Stable disease	42	(8.6)	18	(8.3)	7	(8.0)	10	(9.6)	7	(8.9)
Progressive disease	198	(40.7)	62	(28.7)	29	(33.0)	51	(49.0)	56	(70.9)
Overall response rate	247	(50.7)	136	(63.0)	52	(59.1)	43	(41.3)	16	(20.3)
Disease control rate	289	(59.3)	154	(71.3)	59	(67.0)	53	(51.0)	23	(29.1)
Unknown primary	**(n=133)**		**(n=63)**		**(n=39)**		**(n=12)**		**(n=19)**	
Best overall response										
Complete response	16	(12.0)	10	(15.9)	5	(12.8)	0		1	(5.3)
Partial response	54	(40.6)	29	(46.0)	15	(38.5)	6	(50.0)	4	(21.1)
Stable disease	14	(10.5)	5	(7.9)	3	(7.7)	3	(25.0)	3	(15.8)
Progressive disease	49	(36.8)	19	(30.2)	16	(41.0)	3	(25.0)	11	(57.9)
Overall response rate	70	(52.6)	39	(61.9)	20	(51.3)	6	(50.0)	5	(26.3)
Disease control rate	84	(63.2)	44	(69.8)	23	(59.0)	9	(75.0)	8	(42.1)
Mucosal	**(n=39)**		**(n=33)**		**(n=3)**		**(n=2)**		**(n=1)**	
Best overall response										
Complete response	3	(7.7)	3	(9.1)	0		0		0	
Partial response	8	(20.5)	8	(24.2)	0		0		0	
Stable disease	3	(7.7)	2	(6.1)	1	(33.3)	0		0	
Progressive disease	25	(64.1)	20	(60.6)	2	(66.7)	2	(100.0)	1	(100.0)
Overall response rate	11	(28.2)	11	(33.3)	0		0		0	
Disease control rate	14	(35.9)	13	(39.4)	1	(33.3)	0		0	

Acral	**(n=21)**		**(n=9)**		**(n=7)**		**(n=3)**		**(n=2)**	
Best overall response										
Complete response	4	(19.0)	1	(11.1)	2	(28.6)	1	(33.3)	0	
Partial response	5	(23.8)	2	(22.2)	3	(42.9)	0		0	
Stable disease	4	(19.0)	3	(33.3)	0		1	(33.3)	0	
Progressive disease	8	(38.1)	3	(33.3)	2	(28.6)	1	(33.3)	2	(100.0)
Overall response rate	9	(42.9)	3	(33.3)	5	(71.4)	1	(33.3)	0	
Disease control rate	13	(61.9)	6	(66.7)	5	(71.4)	2	(66.7)	0	
Uveal	**(n=17)**		**(n=13)**		**(n=1)**		**(n=2)**		**(n=1)**	
Best overall response										
Complete response	0		0		0		0		0	
Partial response	1	(5.9)	0		0		1	(50.0)	0	
Stable disease	3	(17.6)	2	(15.4)	0		0		1	(100.0)
Progressive disease	13	(76.5)	11	(84.6)	1	(100.0)	1	(50.0)	0	
Overall response rate	1	(5.9)	0		0		1	(50.0)	0	
Disease control rate	4	(23.5)	2	(15.4)	0		1	(50.0)	1	(100.0)

Suppl. Table 4. Prognostic clinical factors for PFS and OS in univariable analysis

Variable name	Description	PFS		OS	
		p value	Hazard ratio	p value	Hazard ratio
Age	continuous	0.362	0.997	0.150	1.006
Sex	male vs female	0.099	1.178	0.123	1.253
Stage at start treatment					
	M1a vs IIIC-D	0.295	0.784	0.866	1.052
	M1b vs IIIC-D	0.109	0.788	0.561	0.836
	M1c vs IIIC-D	0.268	1.373	0.032	1.767
	M1d vs IIIC-D	0.295	1.258	0.071	1.642
BRAF status	mutant vs wild-type	0.015	1.271	0.999	0.999
ECOG performance status					
	1 vs 0	<0.001	1.740	<0.001	2.598
	2-3 vs 0	<0.001	2.827	<0.001	5.564
Tumour type					
	unknown vs cutaneous	0.643	1.062	0.046	1.341
	mucosal vs cutaneous	0.001	1.907	0.0015	1.997
	acral vs cutaneous	0.570	1.168	0.076	1.701
	uveal vs cutaneous	<0.001	2.562	0.004	2.372
Prior treatment					
	targeted therapy vs none	<0.001	2.126	<0.001	2.478
	immunotherapy vs. none	0.120	1.328	0.235	1.302
	immuno- + targeted therapy vs. none	0.006	1.931	0.305	1.421
	other vs none	0.196	1.550	0.538	0.698
Liver metastases	yes vs no	<0.001	1.820	<0.001	1.938
Brain metastases	yes vs no	<0.001	1.468	<0.001	1.791
Extra CNS metastases	yes vs no	0.280	0.771	0.690	0.885

Number of extra CNS metastases					
	0 vs 1	0.003	1.962	0.029	1.910
	2 vs 1	0.067	1.296	0.155	1.301
	3 vs 1	0.002	1.655	<0.001	2.318
	≥3 vs 1	<0.001	2.259	<0.001	2.639
Number of CNS metastatic sites					
	0 vs 1	0.795	1.049	0.530	1.164
	2 vs 1	0.126	1.525	0.027	2.071
	≥2 vs 1	0.003	1.820	<0.001	2.709
LDH					
	LDH >ULN2x ULN vs LDH<ULN	<0.001	1.712	<0.001	2.322
	LDH>2xULN vs LDH<ULN	<0.001	2.474	<0.001	3.535

Suppl. Table 5. Prognostic clinical factors for PFS and OS

	Treatment-naïve patients		Previously treated patients	
	No BRAF mutation (n=288)	**BRAF mutation (n=175)**	**BRAF-targeted therapy (n=141)**	**Other previous therapies (n=67)**
Median PFS (95% CI)	12.9 (8.6-23.7)	12.5 (8.6-26.5)	3.0 (2.6-4.1)	5.9 (3.3-14.4)
Multivariable hazard ratio PFS	1	1.5	2.26	1.06
Multivariable p value PFS	NA	0.004	<0.001	0.010
Median OS (95% CI)	41.7 (28.4-NA)	53.7 (53.7-NA)	10.5 (8.3-16.1)	NA (12.9-NA)
Multivariable hazard ratio OS	1	0.82	2.02	1.46
Multivariable p value OS	NA	0.270	<0.001	0.080

For both PFS and OS treatment-naïve patients without BRAF mutation were taken as reference group, p values reported are comparisons of the groups versus reference.

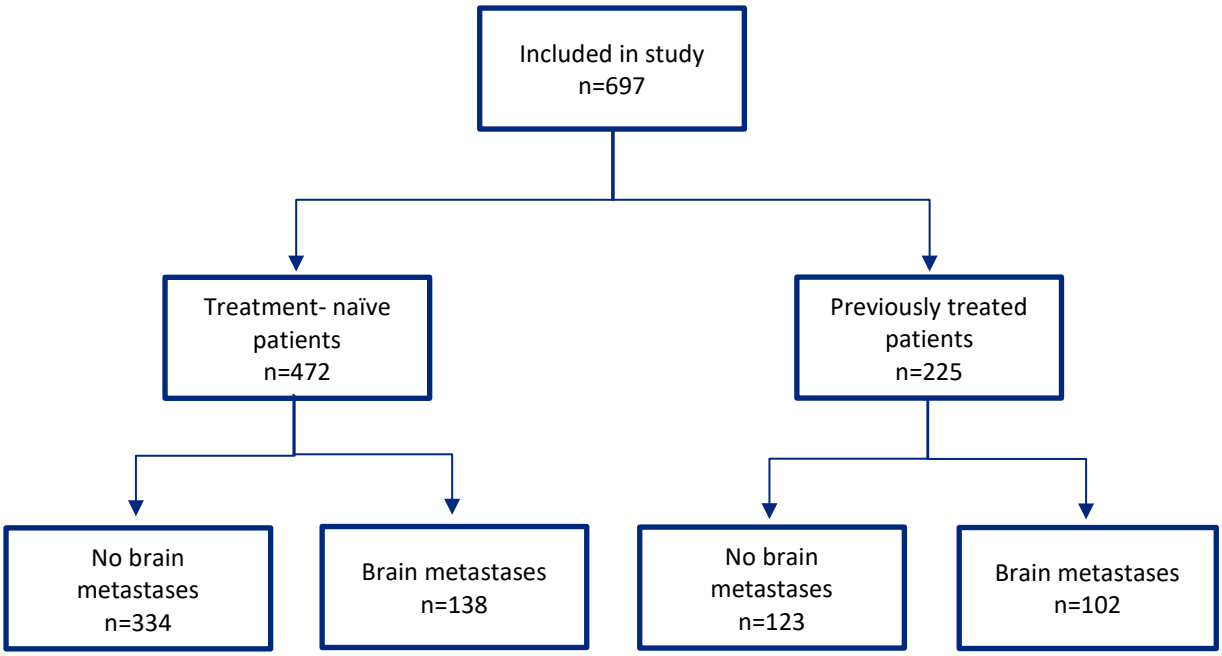
Suppl. Table 6. Subgroup analysis on number of cycles combination therapy in patients receiving nivolumab maintenance

	<4 cycles combination therapy (n=69)		4 cycles combination therapy (n=139)		p value
Age (median, IQR)	57	(46-69)	56	(48-67)	0.700
Sex					0.967
Male	40	(58.0)	81	(58.3)	
Female	29	(42.0)	58	(41.7)	
Geographic region					**0.013**
Australia	1	(1.4)	12	(8.6)	
Europe	50	(72.5)	109	(78.4)	
United States of America	18	(26.1)	18	(12.9)	
Tumour type					0.282
Cutaneous	43	(62.3)	103	(74.1)	
Unknown primary	17	(24.6)	26	(18.7)	
Mucosal	5	(7.2)	3	(2.2)	
Acral	3	(4.3)	6	(4.3)	
Uveal	1	(1.4)	1	(0.7)	
Stage at start treatment					0.319
IIIC/D	1	(1.4)	12	(8.6)	
M1a	13	(18.8)	23	(16.5)	
M1b	15	(21.7)	24	(17.3)	
M1c	22	(31.9)	40	(28.8)	
M1d	18	(26.1)	40	(28.8)	
Number of metastatic sites					0.486
0	0	(0.0)	1	(0.7)	
1	25	(36.2)	35	(25.2)	
2	20	(29.0)	46	(33.1)	
3	11	(15.9)	30	(21.6)	
4 or more	13	(18.8)	27	(19.4)	
Liver metastases	12	(17.4)	31	(22.3)	0.410
ECOG performance status					0.215
0-1	67	(97.1)	138	(99.3)	
2-3	2	(2.9)	1	(0.7)	
Baseline LDH level					0.916
<ULN	47	(68.1)	95	(68.3)	
>ULN	22	(31.9)	43	(30.9)	
Missing	0	(0.0)	1	(0.7)	
BRAF status					0.256
Mutant	28	(40.6)	68	(48.9)	
Wild-type	41	(59.4)	71	(51.1)	
First-line treatment	59	(85.5)	100	(71.9)	**0.030**
Prior treatment					0.184
Targeted therapy	7	(10.1)	20	(14.4)	
Checkpoint inhibitors	2	(2.9)	11	(7.9)	
Both	1	(1.4)	3	(2.2)	
Other	0	(0.0)	5	(3.6)	

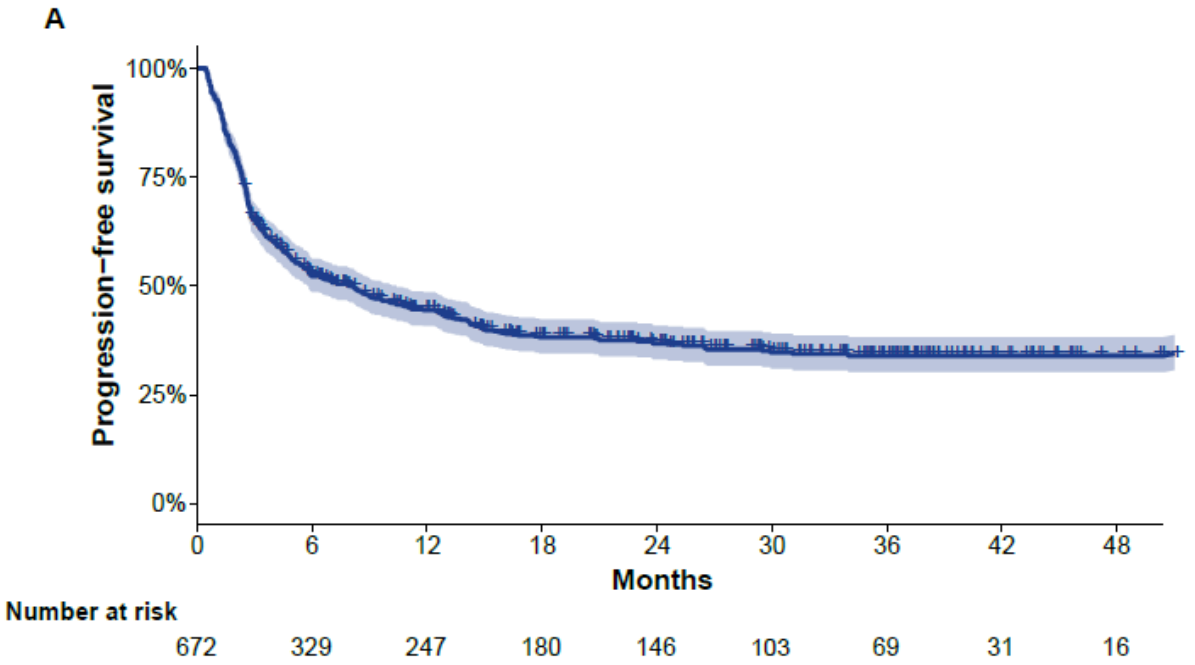
Prior treatment setting					0.360
Adjuvant	1	(10.0)	9	(23.1)	
Metastatic	9	(90.0)	30	(76.9)	
Best overall response					0.224
Complete response	16	(23.2)	37	(26.6)	
Partial response	37	(53.6)	83	(59.7)	
Stable disease	16	(23.2)	19	(13.7)	
Overall response rate	53	(76.8)	120	(86.3)	0.084
All grade adverse events	67	(97.1)	114	(82.0)	**0.002**
Grade 3-4 adverse events	43	(62.3)	29	(20.9)	**<0.001**
Treatment of adverse events[+]					
Steroids	60	(89.6)	67	(58.8)	**<0.001**
Infliximab	12	(17.9)	7	(6.1)	0.011
Mycophenolate mofetil	7	(10.4)	5	(4.4)	0.107
Admission due to adverse events+	36	(53.7)	27	(23.7)	**<0.001**
Length admission in days (median, IQR)	7	(4-11)	5	(3-9)	0.174
Resolution adverse events[+]	58	(86.6)	73	(64.0)	**0.001**

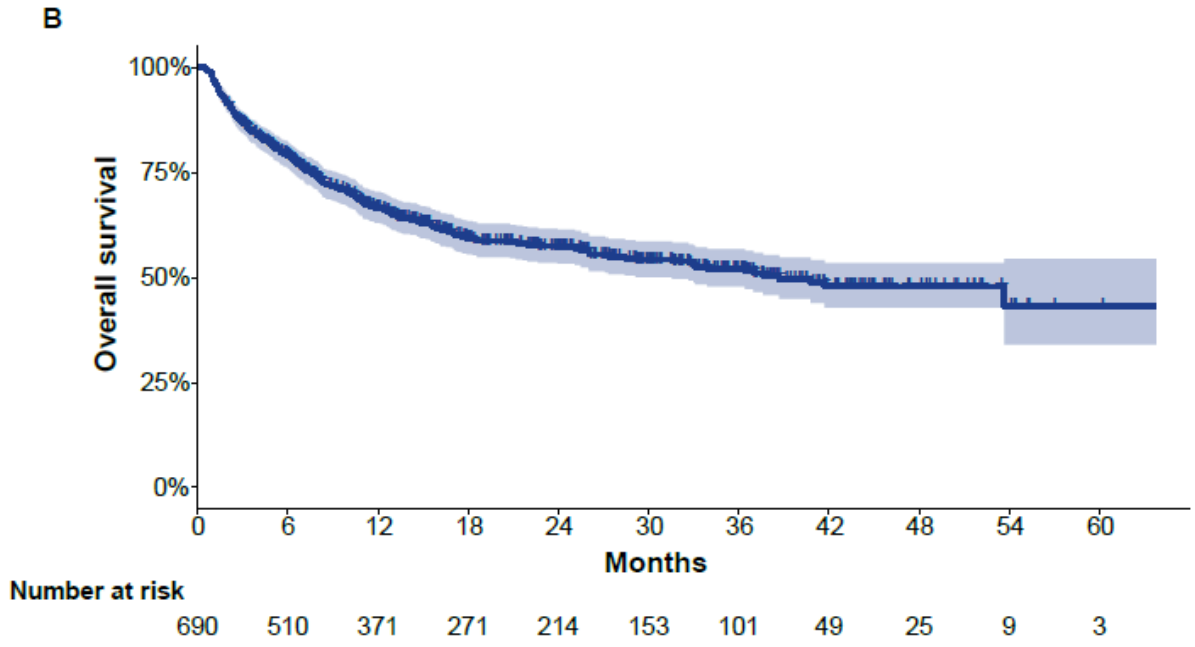
[+]reported as percentage of patients with adverse events.

Suppl. Figure 1. Flow diagram of patients included



Suppl. Figure 2. PFS and OS whole patient population

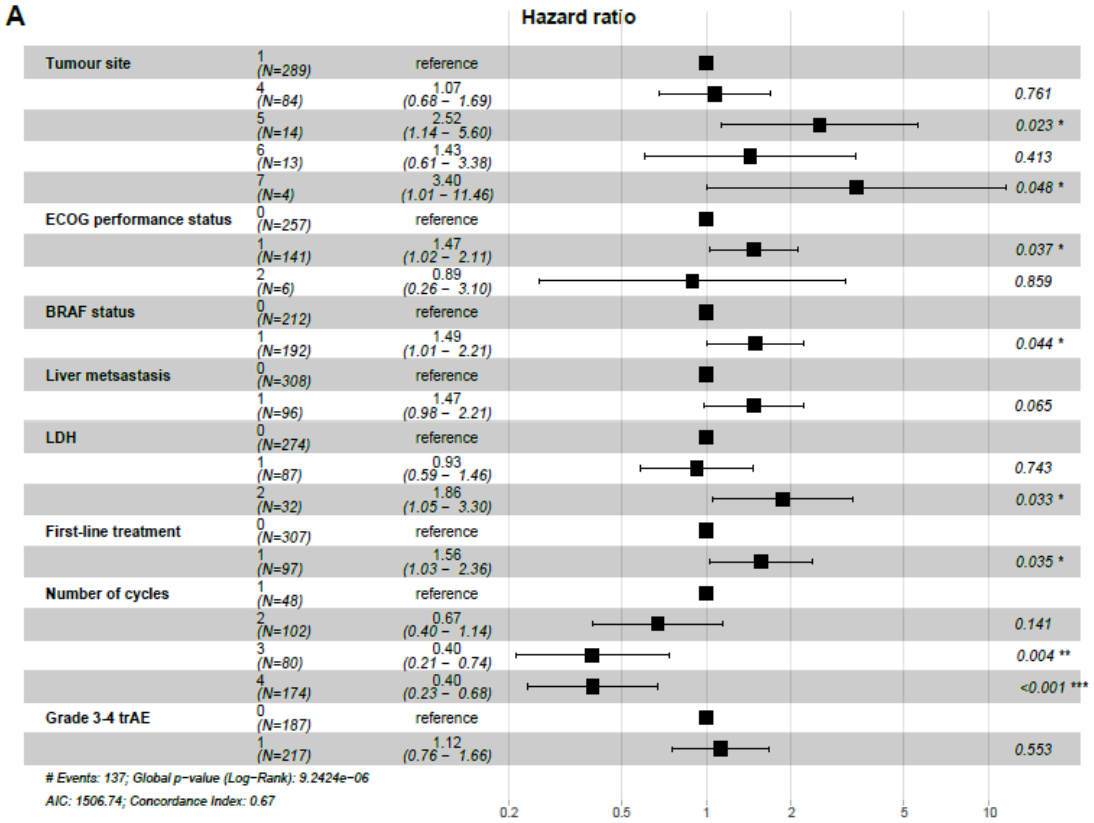




A. Progression-free survival of all patients treated with ipilimumab and nivolumab.

B. Overall survival all patients treated with ipilimumab and nivolumab.

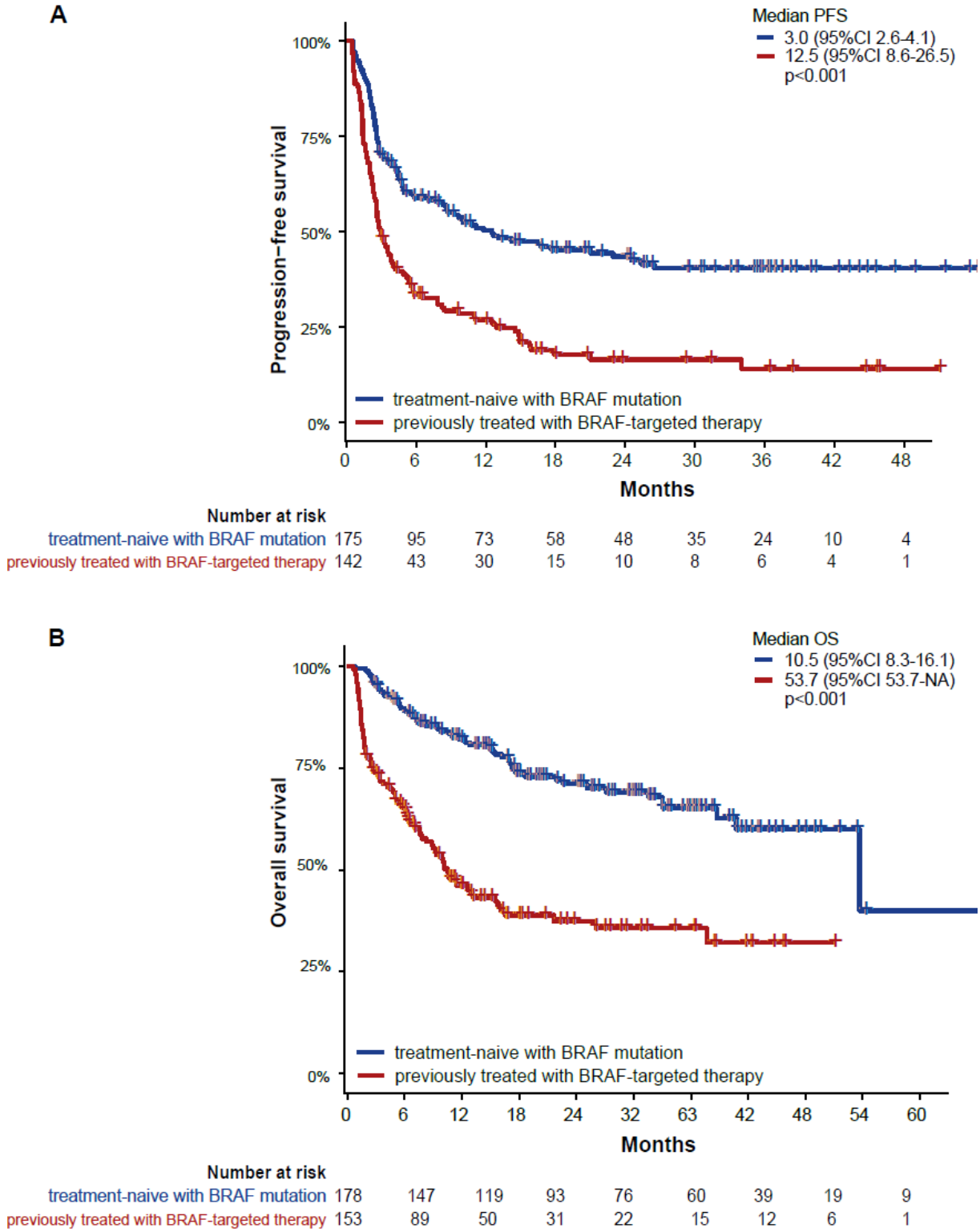
Suppl. Figure 3. Subgroup analysis on impact of steroids in patients with brain metastases



A. Multivariable subgroup analysis on progression-free survival on impact of steroids in patients with brain metastases.

B. Multivariable subgroup analysis on overall survival on impact of steroids in patients with brain metastases.

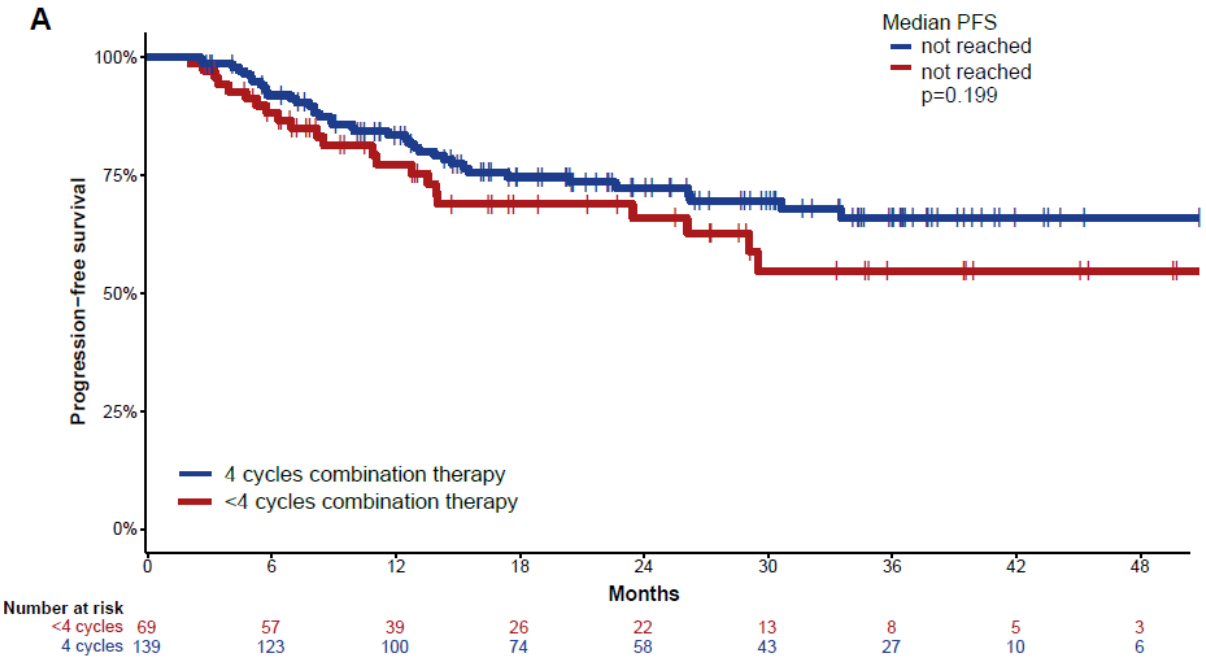
Suppl. Figure 4. Exploratory analysis on impact of BRAF-targeted therapy

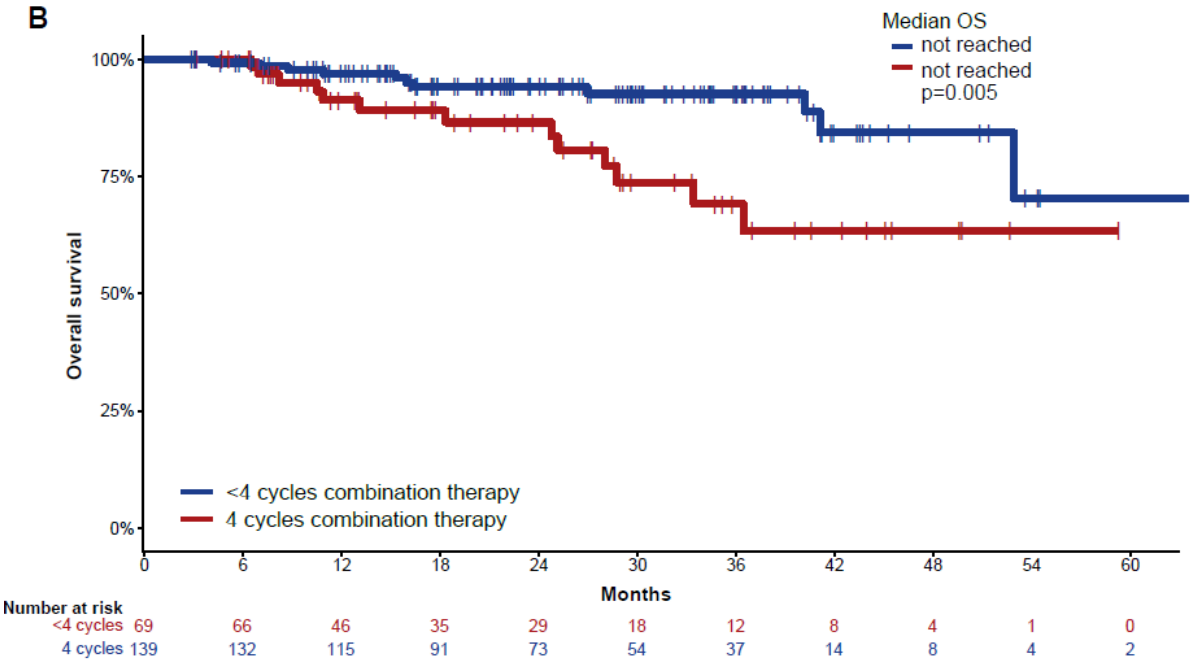


A. Progression-free survival reported for treatment-naïve patients with BRAF mutation and patients who have received previous BRAF-targeted therapy.

B. Overall survival all patients reported for treatment-naïve patients with BRAF mutation and patients who have received previous BRAF-targeted therapy.

Suppl. Figure 5. Subgroup analysis on number of cycles combination therapy in patients receiving nivolumab maintenance





A. Progression-free survival of treatment-naïve patients, compared for patients with and without brain metastases.

B. Progression-free survival of previously treated patients, compared for patients with and without brain metastases.