Supplementary files

Table S1: Analysis of patients' characteristics (n= 310) considering treatment with local therapy (STR/surgery) at any time point.

Patients' characteristics	STR/surgery [1]	No STR/surgery	*p* value[+]
	N (%)		
Gender			
Male	132 (60)	59 (65.6)	0.361
Female	88 (40)	31 (34.4)	
Age at the time of CombiIT			
<54y	90 (40.9)	30 (33.3)	0.095
54y-64y	63 (28.6)	21 (23.3)	
>64y	67 (30.5)	39 (43.3)	
BRAF status			
BRAF wild-type	82 (37.3)	32 (35.6)	0.776
BRAF mutant	138 (62.7)	58 (64.4)	
LDH level*			
Normal	120 (57.1)	39 (44.3)	0.124
Elevated	68 (32.4)	38 (43.2)	
2x >ULN	22 (10.5)	11 (12.5)	
S100 level*			
Normal	77 (41)	17 (20)	**0.003**
Elevated	76 (40.4)	49 (57.6)	
10x >ULN	35 (18.6)	19 (22.4)	
Number of MBM at the time of Combi IT*			
1 to 3	118 (57.3)	41 (47.1)	0.111
>3	88 (42.7)	46 (52.9)	
ECOG PS*			

0	147 (67.4)	62 (70.5)	0.821
1	52 (23.9)	20 (22.7)	
>1	19 (8.7)	6 (6.8)	
Presence of symptoms*			
No	68 (63.6)	42 (84)	**0.009**
Yes	39 (36.4)	8 (16)	

N= number of patients in each subgroup; CombiIT= ipilimumab plus nivolumab; ULN = upper level normal; MBM = melanoma brain metastases; ECOG PS = Eastern Cooperative Oncology Group performance status. Bold values indicate statistically significant results. Patients treated with whole brain radiotherapy were excluded from this analysis. [1] Ten patients (4.5%) of the STR/surgery group (n=220) received only surgery. Four patients receiving STR/surgery before combined immunotherapy and two patients receiving STR/surgery after combined immunotherapy were treated with the two technics within an interval of two weeks. *Denotes variables for which the missing/unknown values were excluded from the analysis. [+]Pearson chi-square test.

Table S2: Analysis of patients' characteristics (n= 220) considering the timing of local therapy: before combined immunotherapy (STR/surgery upfront) or after combined immunotherapy (STR/surgery later))

Patients' characteristics	STR/surgery upfront	STR/surgery later	*p* value[+]
	N (%)		
Gender			
Male	93 (57.1)	39 (68.4)	0.132
Female	70 (42.9)	18 (31.6)	
Age at the time of CombiIT			
<54y	62 (38)	28 (49.1)	0.252
54y-64y	47 (28.8)	16 (28.1)	
>64y	54 (33.1)	13 (22.8)	
BRAF status			
BRAF wild-type	66 (40.5)	16 (28.1)	0.095
BRAF mutant	97 (59.5)	41 (71.9)	
LDH level*			
Normal	83 (53.5)	37 (67.3)	0.141

Elevated	56 (36.2)	12 (21.8)	
2x >ULN	16 (10.3)	6 (10.9)	
S100 level*			
Normal	56 (40.3)	21 (42.9)	0.884
Elevated	56 (40.3)	20 (40.1)	
10x >ULN	27 (19.4)	8 (16.3)	
Number of MBM at the time of CombiIT*			
1 to 3	83 (55)	35 (63.6)	0.266
>3	68 (45)	20 (36.4)	
ECOG PS*			
0	103 (64)	44 (77.2)	0.125
1	41 (25.5)	11 (19.3)	
>1	17 (10.5)	2 (3.5)	
Presence of symptoms*			
No	46 (62.2)	22 (66.7)	0.655
Yes	28 (37.9)	11 (33.3)	

N= number of patients in each subgroup; CombiIT= ipilimumab plus nivolumab; ULN = upper level normal; MBM = melanoma brain metastases; ECOG PS = Eastern Cooperative Oncology Group performance status. * Denotes variables for which the missing/unknown values were excluded from the analysis. [+] Pearson chi-square test.

Table S3: Analysis of patients with BRAFV600 mutated melanoma (n= 221) considering the type of first line therapy.

	First-line BRAFi/MEKi	First-line CombiIT	*p* value[+]
Gender	N (%)		
Male	51 (61.4)	96 (69.6)	0.215
Female	32 (38.6)	42 (30.4)	
Age at the time of CombiIT			
<54y	43 (51.8)	60 (43.5)	0.126
54y-64y	25 (30.1)	36 (18.1)	

>64y	15 (18.1)	42 (30.4)	
LDH level*			
Normal	33 (41.3)	70 (52.2)	0.298
Elevated	36 (45)	49 (36.6)	
2x >ULN	11 (13.8)	15 (11.2)	
S100 level*			
Normal	28 (38.4)	38 (30.6)	0.147
Elevated	36 (49.3)	57 (46)	
10x >ULN	9 (12.3)	29 (23.4)	
Number of MBM at the time of CombiIT*			
1 to 3	21 (26.9)	64 (49.2)	**0.002**
>3	57 (73.1)	66 (50.8)	
ECOG PS*			
0	55 (67.1)	102 (74.5)	0.387
1	17 (20.7)	25 (12.3)	
>1	10 (12.2)	10 (7.3)	
Presence of symptoms*			
No	25 (67.6)	55 (70.5)	0.748
Yes	12 (32.4)	23 (29.5)	

Patients that received first-line PD-1 monotherapy (n=19) or chemotherapy (n=2) were excluded in this table. N= number of patients in each subgroup; CombiIT= nivolumab plus ipilimumab; ULN = upper level normal; MBM = melanoma brain metastases; ECOG PS = Eastern Cooperative Oncology Group performance status. Bold values indicate statistically significant results (p<0.05). *Denotes variables for which the missing/unknown values were excluded from the analysis. [+] Pearson chi-square test.

Table S4: Impact of baseline patient and disease characteristics on overall survival - univariate and multivariate Cox regression analysis. In this multivariate Cox regression analysis age, LDH level and S100B level were analyzed as numerical variables.
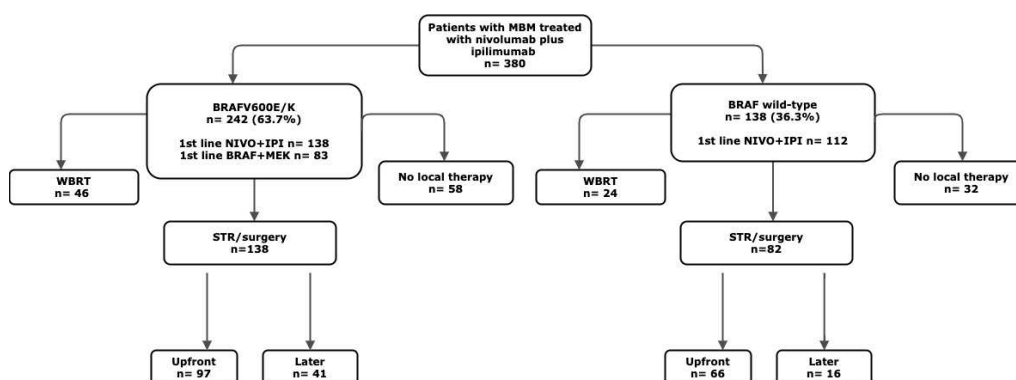
	Total	**Univariate analysis**		**Multivariate analysis**	

	N (%)	HR (death) (95% CI)	*p* value	HR (death) (95% CI	*p* value
Gender					
Male	240 (63.2)	1		1	
Female	140 (36.8)	0.94 (0.69-1.27)	0.682	1.06 (0.70-1.60)	0.79
Age at the time of CombiIT					
<54y	153 (40.3)	1	0.616	1.02 (0.99-1.02)	0.421
54y-64y	105 (27.6)	1.13 (0.78-1.62)			
>64y	122 (32.1)	1.19 (0.83-1.70)			
BRAF status					
BRAF wild-type	138 (36.3)	1	0.962	1	
BRAF mutant	242 (63.7)	0.99 (0.72-1.37)		1.01 (0.65-1.58)	0.95
LDH level*					
Normal	189 (51.4)	1	**<0.0001**	1.001 (1.00-1.001)	**0.001**
Elevated	133 (36.1)	1.24 (0.88-1.74)			
2x >ULN	46 (12.5)	2.53 (1.67-3.83)			
S100B level*				1.002 (1.001-1.003)	**0.001**
Normal	109 (32.8)	1	0.099		
Elevated	156 (47)	1.35 (0.92-2.00)			
10x >ULN	67 (20.2)	1.61 (1.02-2.54)			
Number of MBM at the time of CombiIT*					
1 to 3	167 (46.8)	1	**0.001**	1	**0.017**
>3	190 (53.2)	1.74 (1.26-2.40)		1.67 (1.09-2.55)	
ECOG PS*					
0	249 (66.4)	1	**0.001**	1	**0.041**
1	87 (23.2)	1.3 (0.91-1.87)		1.06 (0.63-1.76)	0.832

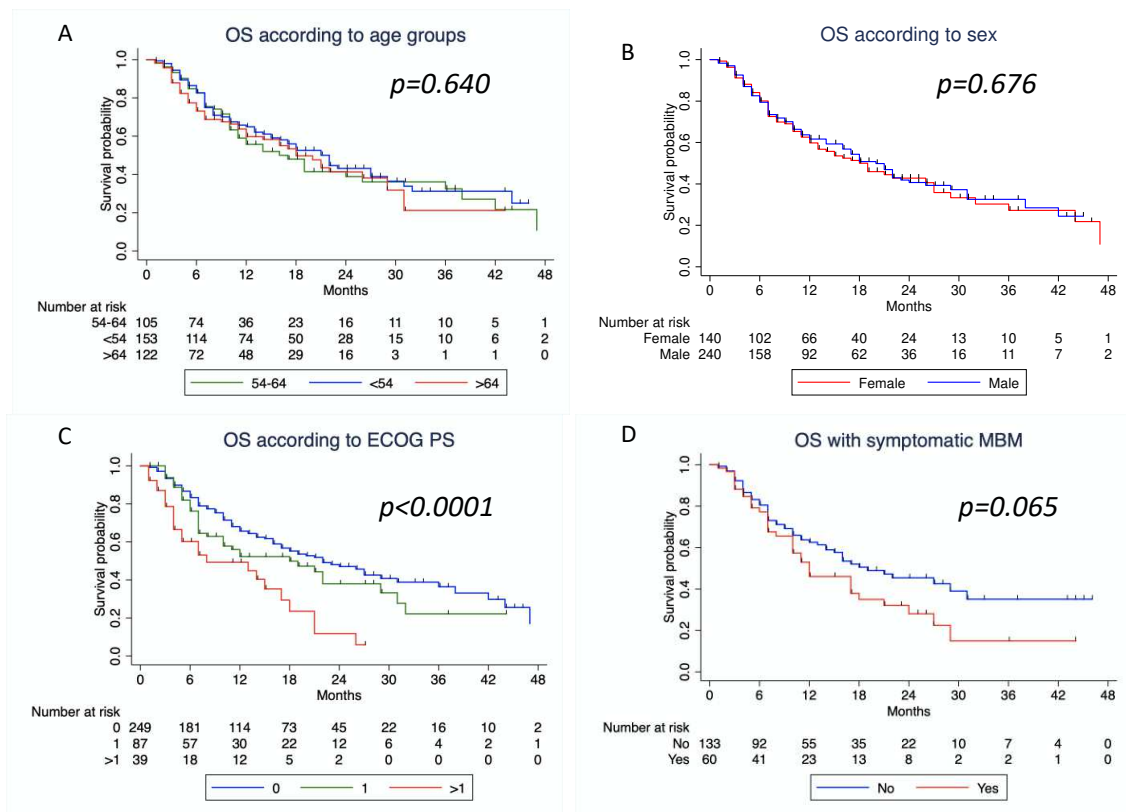| >1 | 39 (10.4) | 2.58 (1.66-4.00) | | 2.13 (1.18-3.84) | **0.012** |
Presence of symptoms*					
No	133 (69)	1			
Yes	60 (31)	1.46 (0.96-2.23)	0.078	N/A	

N= number of patients in each subgroup; CombiIT= ipilimumab plus nivolumab; ULN = upper level normal; MBM = melanoma brain metastases; ECOG PS = Eastern Cooperative Oncology Group performance status; N/A: not evaluated, since this information was available for only 50% of the patients. Bold values indicate statistically significant results. *Denotes variables for which the missing/unknown values were excluded from the analysis.

Figure S1

Supplementary figure S1 (Figure S1): flow chart illustrating the number of patients considering BRAF mutation status, the type of first-line of systemic therapy and also the type of local therapy received. STR/surgery upfront means STR/surgery before combined immunotherapy with nivolumab plus ipilimumab, and STR/surgery later means STR/surgery after combined immunotherapy with nivolumab plus ipilimumab. MBM = melanoma brain metastases; NIVO + IPI = nivolumab plus ipilimumab; STR = stereotactic radiotherapy; WBRT = whole brain radiotherapy.

Figure S2

Supplementary figure 2 (Figure S2): Kaplan-Meier curves for overall survival considering: 2-A) age groups; 2-B) sex; 2-C) ECOG performance status; and 2-D) presence of symptoms at the time of combined immunotherapy