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Original Research

Real-life data for first-line combination immune-checkpoint inhibition and targeted therapy in patients with melanoma brain metastases

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Abstract ***Background:*** Melanoma brain metastases (MBM) have a poor prognosis. Systemic treatments that have improved outcomes in advanced melanoma have been shown to have an intracranial (IC) effect. We studied the efficacy and outcomes of combined immune checkpoint inhibitor ipilimumab/nivolumab (Combi-ICI) or targeted therapy (Combi-TT) as first-line treatment in MBM.

Methods: MBM patients treated with Combi-ICI or Combi-TT within 3 months after MBM diagnosis. Endpoints were progression-free survival (PFS) and overall survival (OS).

Results: 53 patients received Combi-ICI, 32% had symptomatic MBM and 33.9% elevated LDH. 71.7% required local treatment. The disease control rate was 60.3%. IC response rate (RR) was 43.8% at 3-months with durable responses at 6- (46.5%) and 12-months (53.1%). Extracranial (EC) RR was 44.7% at 3-months and 50% at 12-months. Median PFS was 9.6 months (95% CI 3.6-NR) and median overall survival (mOS) 44.8 months (95% CI; 26.2-NR).

63 patients received Combi-TT, 55.6% of patients had symptomatic MBM, 57.2% of patients had elevated LDH and 68.3% of patients required local treatment. The disease control rate was 60.4%. ICRR was 50% at 3-months, but dropped at 6-months (20.9%). ECRR was

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69.2% at 3-months and 17.6% at 12-months. Median PFS was 5.8 months (95% CI 4.2–7.6) and mOS 14.2 months (95% CI 8.99–26.8).

In *BRAFV600* patients, 26.7% of patients received Combi-ICI and 73.3% Combi-TT with OS (p = 0.0053) and mPFS (p = 0.03) in favour to Combi-ICI.

Conclusion: Combi-ICI showed prolonged mOS with sustainable IC and EC responses. Despite the initially increased efficacy, Combi-TT responses at 12 months were low. Combi-ICI appeared superior to Combi-TT for OS and PFS in *BRAFV600* patients. Other clinical factors are determinants for first-line treatment choice.

1. Introduction

Melanoma is one of the most frequent cancers to metastasize to the brain [1]. Approximately 50% of patients with stage IV melanoma will eventually develop brain metastases (MBM), and this proportion increases up to 75% in autopsy reports [2,3]. Before the advent of effective systemic therapy, patients with MBM have historically had a poor prognosis and median overall survival (mOS) in unselected patients with active MBM ranged between 4 and 6 months [4–7].

Modern systemic therapies have revolutionized melanoma treatment. The increased efficacy of immune-checkpoint inhibitors with anti-CTLA4 and anti-PD1 in advanced melanoma [8], as well as the introduction of BRAF/MEK inhibitors that selectively inhibit tumour growth in melanoma patients that harbour a *BRAF* mutation, which is found in approximately 40% of melanomas [9], have been shown to have a substantial intracranial effect, as well [10]. Most recent data evaluating the efficacy of BRAF/MEK inhibitors in asymptomatic patients with MBM have shown response rates (RRs) of 58% but the duration of response is short and most patients progress within 6 months [11]. In contrast, immunotherapy provides durable survival in patients who respond with a 46% intracranial (IC) RR in asymptomatic patients treated with combined immune checkpoint inhibitor ipilimumab/nivolumab (Combi-ICI), such that these drugs are now used for most patients with MBM [12,13].

Nevertheless, data investigating the efficacy of contemporary systemic therapies in patients with the intracranial disease remain scarce mostly because of the fact that patients with poor prognostic factors, that is, elevated LDH, reduced performance status at baseline and symptomatic brain metastases, as well as previous local treatments, such as stereotactic radiotherapy and surgery, have been largely excluded from clinical trials until recently [10,12–15]. In the present study, we sought to explore the efficacy and outcome of patients treated with combined ipilimumab/nivolumab (Combi-ICI) or targeted therapy (Combi-TT) administered as first-line treatments in patients with MBM treated outside of clinical trials.

2. Patients and methods

2.1. Study design

We retrospectively assessed a total of 116 melanoma patients with MBM treated with Combi-ICI (n = 53) or Combi-TT (n = 63) as first-line treatment within 3 months of MBM diagnosis from four academic centres in Europe and Australia. Disease characteristics, clinical and radiologic data were retrospectively evaluated using electronic health records and local melanoma databases [16]. Extracranial (EC) and IC treatment response including best overall response were assessed in accordance with modified response evaluation criteria in solid tumors (RECIST v1.1 [17]) using magnetic resonance imaging and computed tomography or evaluated as metabolic response using positron emission tomography in accordance with each institution's protocols. IC response in patients who received local treatment was evaluated in those who continued to have RECIST measurable disease intracranially. Overall response rate (ORR) was defined as the percentage of the patients with complete response (CR) and partial response and disease control rate (DCR), including CR, partial response and stable disease. IC and EC RRs were calculated accordingly. Grading of immune-related adverse events (irAEs) was based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The data cut-off date was November 2020.

2.2. Statistics

Baseline characteristics were reported using descriptive statistics. Continuous variables were tested with the Wilcoxon rank test for significance. Categorical variables were tested with the Fisher exact test for significance. Cox regression was used to calculate hazard ratios of covariates for overall survival (OS) and progression-free survival (PFS). A p-value <0.05 was considered statistically significant. OS and follow-up (FU) were calculated from treatment initiation to last patient contact or death. PFS was assessed from treatment initiation to disease progression. OS and PFS are presented graphically using Kaplan–Meier curves. Cox

regression results are presented using forest plots. For ICRR and ECRR, patients were censored if they had no measurable disease, switched or stopped therapy or were lost to FU. Statistical analyses were conducted using R (version 3.6.1).

2.3. Ethics

Written informed consent for the use and collection of data and available tissue for use in the retrospective analysis was approved by the local ethics committee (MelProg Project KEK-ZH 2014-0193, KEK 2017-00494, Ethics Committee of Vaud 2019-00448).

3. Results

3.1. Patient characteristics

A total of 116 patients with MBM, 53 patients (45.7%) treated with Combi-ICI and 63 patients (54.3%) treated with Combi-TT were included for analysis. Baseline characteristics are summarized in Table 1. Most of patients were male (65.5%), and the median age at diagnosis of MBM was 55.9 years (range 23–93). Median FU for survival was 32.3 months (range 3.44–79.4 months). At diagnosis of brain metastases, 90.5% of patients had ECOG performance status (PS) 0–1, 61.2% of patients had 1-3 brain metastases, whereas 16.4% of patients had more than 3 brain metastases. The maximum diameter of MBM at treatment start was >3 cm in 16.4% of patients. 76.8% of patients had *BRAF* positive melanoma. At treatment initiation, EC metastases included >2 organs in 45.7% of patients, and 46.5% and 37.9% of patients had elevated LDH and s100 above the upper limit of normal (ULN), respectively. 44.8% of patients had symptomatic brain metastases at the time of diagnosis, and 26.7% required steroids at treatment start and during treatment. 60% of patients were treated with solely systemic drug therapy, whereas in 40% systemic treatment was combined with local treatment for MBM.

3.2. Combined immunotherapy cohort (Combi-ICI)

Fifty-three patients with a median age of 56.2 years (range 23–82) were treated with combination anti-PD1/anti-CTLA4 as a first-line treatment. At diagnosis of MBM, 92.5% of patients had ECOG PS 0–1, 62.3% of patients had 1-3 brain metastases, and a maximum diameter of MBM at treatment start was >3 cm in 3.8% of patients. At treatment initiation, EC metastases included >2 organs in 35.8% of patients, and 34% and 39.6% of patients had elevated LDH and s100 above ULN, respectively. 32% of patients had symptomatic brain metastases at the time of diagnosis, and 24.5% of patients required steroids at treatment start. Most of patients (71.7%) required local treatment, including surgery (9.4%), SRS (20.8%) or both (24.5%) (Table 2). Six patients (11.3%) received whole brain radiotherapy (WBRT), and in three patients (5.7%), WBRT was combined with surgery. The median treatment duration was 1.39 months (range 0–24.4), and the median number of total infusions received was 3 (1–34). Reasons for treatment discontinuation included treatment-related toxicities in 60.4%, while only 14 patients (26.4%) stopped the treatment due to progressive disease (PD). Thirty-two patients (60.4%) experienced severe, grade 3–4 CTCAEv4 irAEs, and there was one treatment-related death in a patient with endocrine irAE. After treatment discontinuation, 29 patients (54.7%) required subsequent systemic treatment, which mostly included BRAF/MEK inhibitors (25%) or anti-PD1 monotherapy (21%) (Fig. 1).

DCR was achieved in 60.3% of patients (Table 2). ORR was 45.3% with 24.5% CR. Median PFS was 9.6 months (95% CI 3.6-NR) and mOS 44.8 months (95% CI 26.2-NR). In landmark PFS analysis, 49.1% (95% CI 37.3–64.5) and 40.6% (95% CI 29.2–56.6) of patients remained progression-free at 12- and 24-months, respectively. OS analysis at 12-months was 79% (95% CI 68.6–90.8) with maintained efficacy at 24-months (64.1%, 95% CI 52.0–79.0). ICRR was achieved in 43.8% of patients at 3-months, with durable responses at 6- (46.5%) and 12-months (53.1%). Similarly, ECRR was achieved in 44.7% of patients at 3-months, 56.8% at 6-months and 50% at 12-months. ICRR was numerically higher in patients with symptomatic MBM than the asymptomatic, and a similar pattern was also observed in landmark PFS analysis, which might be attributed to the number of patients, that received local treatment (all symptomatic patients versus 52% for asymptomatic). Nevertheless, OS rates were similar for both groups.

In the univariate Cox regression analysis for OS, patients with LDH above ULN showed lower PFS (HR 2.3, $p = 0.049$) (Fig. 2). ECOG-PS was not favouring patients with ECOG ≥2 but any statistical conclusion would be misleading because this group was comparted by only 2 patients. Nevertheless, a non-significant trend towards a reduced risk of progression in patients with local treatment was observed (SRS and operation) ($p = 0.072$, HR 0.38).

3.3. Combi-TT cohort

Sixty-three patients with a median age of 54.9 years (range 26–93) received first-line BRAF/MEK inhibitors, including both dabrafenib/trametinib (87.3%) and vemurafenib/cobimetinib (12.7%). At diagnosis of MBM, 88.9% of patients had ECOG PS 0–1, 60.3% of patients had 1-3 brain metastases with maximum

Table 1
Baseline patient characteristics of the general population (n = 116) and patients treated with combined immune checkpoint inhibitor (Combi-ICI group, n = 53) and targeted therapy (Combi-TT group, n = 63).

Baseline characteristics	Total	Combi-ICI	Combi-TT
Median age at MBM diagnosis (years, range)	55.9 (23–93)	56.2 (23–82)	54.9 (26–93)
Sex (n, %)			
Female	40 (34.5%)	19 (35.8%)	21 (33.3%)
Male	76 (65.5%)	34 (64.2%)	42 (66.7%)
Melanoma subtype (n, %)			
Cutaneous	68 (50%)	23 (43.4%)	35 (55.5%)
Melanoma of unknown primary	24 (20.7%)	10 (18.9%)	14 (22.2%)
Mucosal	1 (0.9%)	2 (3.8%)	–
Not reported	32 (27.6%)	18 (34.0%)	14 (22.2%)
Mutational Status (n, %)			
BRAF V600	83 (71.6%)	23 (43.4%)	60 (95.2%)
BRAF Non-V600	3 (2.6%)	2 (3.8%)	1 (1.6%)
BRAF wild type	13 (11.2%)	13 (24.5%)	–
NRAS	11 (9.5%)	11 (20.8%)	–
Other	2 (1.7%)	2 (3.8%)	–
Not reported	4 (3.4%)	2 (3.8%)	2 (3.2%)
S100 at treatment start (n, %)			
Normal	7 (6.0%)	6 (11.3%)	1 (1.6%)
>ULN	11 (9.5%)	6 (11.3%)	5 (7.9%)
>2 ULN	33 (28.4%)	15 (28.3%)	18 (28.6%)
Not reported	65 (56.0%)	26 (49.1%)	39 (61.9%)
LDH at treatment start (n, %)			
Normal	41 (35.3%)	24 (45.3%)	17 (27.0%)
>ULN	41 (35.3%)	14 (26.4%)	27 (42.9%)
>2 ULN	13 (11.2%)	4 (7.5%)	9 (14.3%)
Not reported	21 (18.1%)	11 (20.8%)	10 (15.9%)
ECOG at treatment start (n, %)			
0–1	105 (90.5%)	49 (92.5%)	56 (88.9%)
2	3 (2.6%)	1 (1.9%)	2 (3.2%)
3	2 (1.7%)	1 (1.9%)	1 (1.6%)
Not reported	6 (5.2%)	2 (3.8%)	4 (6.3%)
Adjuvant treatment before treatment initiation (n, %)			
None	110 (94.8%)	50 (94.3%)	60 (95.2%)
Anti-PD1	4 (3.4%)	3 (5.7%)	1 (1.6%)
Anti-CTLA4	1 (0.9%)	–	1 (1.6%)
IFN-γ	1 (0.9%)	–	1 (1.6%)
Extracranial sites of metastasis at treatment start (n, %)			
≤2 extracranial sites	63 (54.3%)	34 (64.2%)	29 (46.0%)
>2 extracranial sites	53 (45.7%)	19 (35.8%)	34 (54.0%)
Number of MBM at treatment start (n, %)			
Solitary lesion	48 (41.4%)	23 (43.4%)	25 (39.7%)
2–3 lesions	23 (19.8%)	10 (18.9%)	13 (20.6%)
>3 lesions	45 (38.8%)	20 (37.7%)	25 (39.7%)
Maximum diameter of MBM at treatment start (n, %)			
<1 cm	19 (16.4%)	11 (20.8%)	8 (12.7%)
1–3 cm	37 (31.9%)	21 (39.6%)	16 (25.4%)
>3 cm	19 (16.4%)	2 (3.8%)	17 (27.0%)
Not reported	41 (35.3%)	19 (35.8%)	22 (34.9%)
Neurologic symptoms at treatment start (n, %)			
Yes	52 (44.8%)	17 (32.0%)	35 (55.6%)
No	57 (49.1%)	29 (54.7%)	28 (44.4%)
Not reported	7 (6.0%)	7 (13.2%)	–
Steroid use at treatment start (n, %)			
Yes	31 (26.7%)	13 (24.5%)	18 (28.6%)
No	84 (72.4%)	39 (73.6%)	45 (71.4%)
Not reported	1 (0.9%)	1 (1.9%)	–

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MBM, melanoma brain metastases; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Table 2
Treatment characteristics and response of the patients treated with combined immune checkpoint inhibitor (Combi-ICI group, n = 53).

Treatment characteristics	Total		
Median treatment duration (months, range)	1.39 (0–24.4)		
Number of total infusions received, n (%)	3 (1–34)		
Local treatment of MBM, n (%)			
	Overall population *(n = 53)*	***Symptomatic MBM*** *(n = 17)*	***Asymptomatic MBM*** *(n = 29)*
Surgery	5 (9.4%)	2 (12%)	2 (6.9%)
SRS	11 (20.8%)	3 (18%)	6 (21%)
WBRT	6 (11.3%)	1 (5.9%)	3 (10%)
Surgery & SRS	13 (24.5%)	10 (59%)	3 (10%)
Surgery & WBRT	3 (5.7%)	1 (5.9%)	1 (3.4%)
None	15 (28.3%)	–	14 (48%)
Reason for treatment discontinuation, n (%)			
PD	14 (26.4%)		
Toxicity (irAE)	32 (60.4%)		
Treatment completed	5 (9.4%)		
Other	1 (1.9%)		
Not reported	1 (1.9%)		
Second-line systemic therapy after treatment discontinuation, n (%)	29 (55%)		
Type of second-line systemic therapy, n (%)			
Anti-PD1	11 (21%)		
Anti-PD1 + T-VEC	1 (1.9%)		
Anti-PD1 + BRAF/MEK inhibitors	1 (1.9%)		
Chemotherapy	2 (3.8%)		
Anti-PD1 + Anti-CTLA4	1 (1.9%)		
BRAF/MEK inhibitors	13 (25%)		
Treatment-related toxicities (irAEs), grade 3–4, n (%)			
Any	32 (60.4%)		
Gastrointestinal	19 (35.8%)		
Endocrine	9 (17.0%)		
Lung	4 (7.5%)		
Skin	3 (5.7%)		
Nervous System	2 (3.8%)		
Cardiovascular	2 (3.8%)		
Musculoskeletal	1 (1.9%)		
Renal	1 (1.9%)		
Treatment-related toxicities (irAEs), grade 5, n (%)			
None	52 (98.1%)		
Endocrine	1 (1.9%)		
Best overall response, n (%)			
CR	13 (24.5%)		
PR	11 (20.8%)		
SD	4 (7.5%)		
MR	4 (7.5%)		
PD	20 (37.7%)		
Not reported	1 (1.9%)		
Intracranial response, n (%)			
	Overall population *(n = 53)*	***Symptomatic MBM*** *(n = 17)*	***Asymptomatic MBM*** *(n = 29)*
ICRR at 3 months	21 (43.8%)	9 (53%)	10 (34%)
ICRR at 6 months	20 (46.5%)	9 (53%)	9 (31%)
ICRR at 12 months	17 (53.1%)	7 (41%)	8 (28%)
ICDCR at 3 months	29 (60.4%)	9 (53%)	15 (52%)
ICDCR at 6 months	24 (55.8%)	9 (53%)	11 (38%)
ICDCR at 12 months	21 (65.6%)	9 (53%)	8 (28%)
Extracranial response			
	Overall population *(n = 53)*		
ECRR at 3 months	21 (44.7%)		
ECRR at 6 months	25 (56.8%)		

(*continued on next page*)

Table 2 (*continued*)

Treatment characteristics	Total		
ECRR at 12 months	16 (50%)		
ECDCR at 3 months	24 (51.1%)		
ECDCR at 6 months	30 (68.2%)		
ECDCR at 12 months	18 (56.2%)		
Progression-free survival			
	Overall population *(n = 53)*	***Symptomatic MBM*** *(n = 17)*	***Asymptomatic MBM*** *(n = 29)*
Median duration, months (95% CI)	9.6 months (3.60-NR)	NR	5.55 months (3.01-NR)
At 6 months (95% CI)	52.8% (41–68.1)	53% (34–83)	45% (30–67)
At 12 months (95% CI)	49.1% (37.3–64.5)	53% (34–83)	41% (27–64)
At 24 months (95% CI)	40.6% (29.2–56.6)	53% (34–83)	34% (21–57)
Overall survival			
	Overall population *(n = 53)*	***Symptomatic MBM*** *(n = 17)*	***Asymptomatic MBM*** *(n = 29)*
Median duration, months (95% CI)	44.8 months (26.2–NR)	NR	35.5 months (22.3-NR)
At 6 months (95% CI)	84.8% (75.6–95.1)	76% (59–100)	86% (74–100)
At 12 months (95% CI)	79% (68.6–90.8)	76% (59–100)	75% (61–93)
At 24 months (95% CI)	64.1% (52.0–79.0)	65% (46–92)	62% (45–84)

Abbreviations: CR, complete response; ECDCR, extracranial disease control rate; ECRR, extracranial response rate; ICRR, intracranial response rate; ICDCR, intracranial disease control rate; irAE, immune-related adverse event; MBM, melanoma brain metastases; MR, mixted response; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

diameter >3 cm in 27% of patients and symptomatic brain metastases in 55.6% of patients, thus requiring steroids (28.6%) (Table 1). At treatment initiation, EC metastases included >2 organs in 54% of patients, and 57.2% and 36.5% of patients had elevated LDH and s100 above ULN, respectively. 68.3% of patients required local treatment including surgery (15.9%), SRS (19%) or both (11.1%). Fourteen patients (22.2%) received WBRT

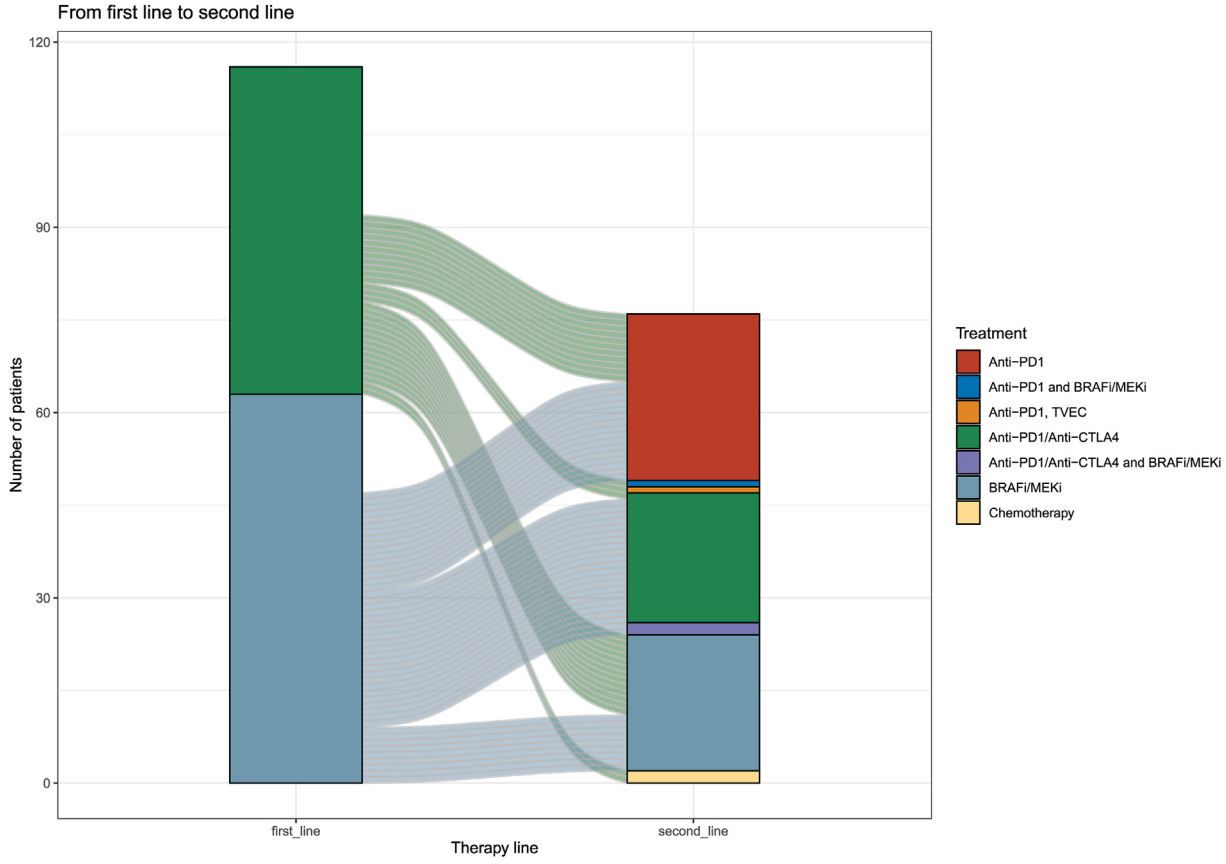
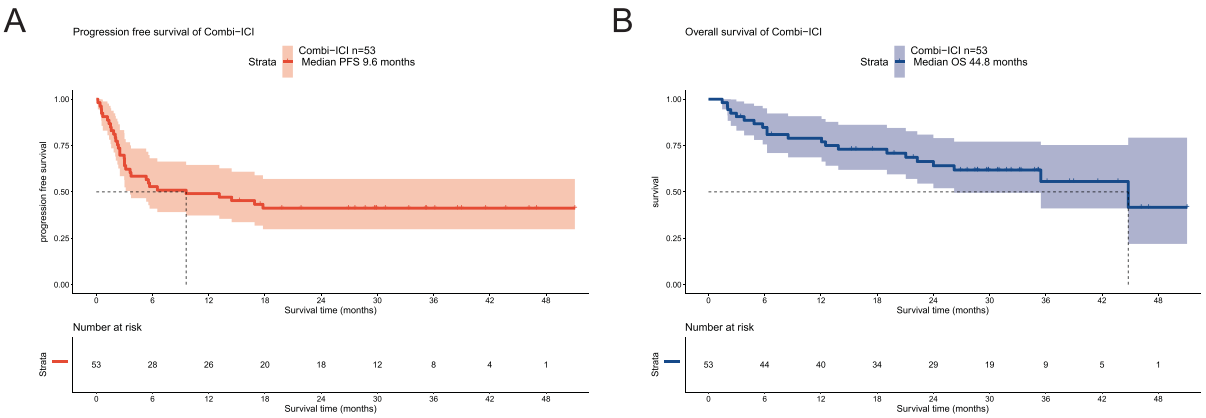
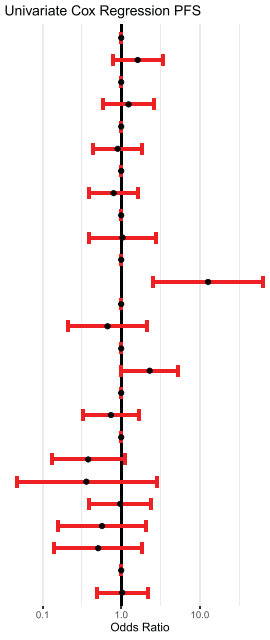


Fig. 1. First-line and subsequent second-line treatment after disease progression in the study population.



C

Immunotherapy covariates	mPFS	HR	n	p value
Age < 65	16.1	1	38	
Age => 65	3.6	1.62	15	0.2
Sex − female	16.9	1	19	
Sex − male	6	1.24	34	0.57
BRAF mutant	6.5	1	23	
BRAF wild−type	16.9	0.9	28	0.77
Brain metastases 1−2	6.1	1	28	
Brain metastases =>3	16.9	0.8	25	0.53
Brain metastases diameter < 1 cm	9.6	1	11	
Brain metastases diameter => 1 cm	17.8	1.04	23	0.94
ECOG 0−1	13.1	1	49	
ECOG => 2	1	12.72	2	0.002
S100 normal	4.3	1	6	
S100 elevated	17.8	0.67	21	0.49
LDH normal		1	24	
LDH elevated	3.9	2.3	18	0.049
Symptomatic − No	5.6	1	29	
Symptomatic − Yes		0.74	17	0.48
Local therapy − none	5.3	1	15	
Local therapy − Surgery + SRS		0.38	13	0.077
Local therapy − Surgery + WBRT		0.36	3	0.33
Local therapy − SRS	3.6	0.97	11	0.95
Local therapy − Surgery	14.4	0.57	5	0.38
Local therapy − WBRT	17.8	0.51	6	0.3
Extracranial metastases <= 2	9.8	1	34	
Extracranial metastases > 2	9.6	1.03	19	0.93



D

Immunotherapy covariates	mOS	HR	n	p value
Age < 65		1	38	
Age => 65	44.8	1.47	15	0.4
Sex − female	44.8	1	19	
Sex − male		0.99	34	0.98
BRAF mutant		1	23	
BRAF wild−type	44.8	1.33	28	0.54
Brain metastases 1−2		1	28	
Brain metastases =>3	44.8	1.2	25	0.68
Brain metastases diameter < 1 cm		1	11	
Brain metastases diameter => 1 cm	44.8	1.38	23	0.64
ECOG 0−1	44.8	1	49	
ECOG => 2	11.3	5.46	2	0.025
S100 normal		1	6	
S100 elevated		1.8	21	0.58
LDH normal		1	24	
LDH elevated	35.5	2.15	18	0.15
Symptomatic − No	35.5	1	29	
Symptomatic − Yes		0.89	17	0.81
Local therapy − none		1	15	
Local therapy − Surgery + SRS		0.42	13	0.22
Local therapy − Surgery + WBRT		0.68	3	0.73
Local therapy − SRS	44.8	1.01	11	0.99
Local therapy − Surgery		0.71	5	0.67
Local therapy − WBRT	24	1.02	6	0.98
Extracranial metastases <= 2	44.8	1	34	
Extracranial metastases > 2		0.81	19	0.66

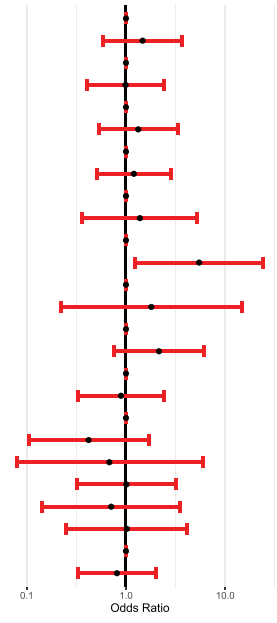


Fig. 2. Kaplan−Meier curve for progression-free survival (PFS) (A) and overall survival (OS) (B) in patients treated with combined immunotherapy (Combi-ICI). Univariate Cox regression analysis for PFS (C) and OS (D) of covariates in patients with Combi-ICI. HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; n, number of patients; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy.

with/without surgery (Table 3). The median treatment duration was 5.45 months (range 0.66–54.5). Reasons for treatment discontinuation included PD in 79.4% of patients. Notably, 17.5% discontinued the systemic treatment due to treatment-related toxicities. After treatment discontinuation, 47 patients (74.6%) required subsequent systemic treatment, which included anti-PD1/anti-CTLA4 (32%) or anti-PD1 monotherapy (25%) in the vast majority of patients. Notably, 2 patients (3.2%) commenced combined immunotherapy and targeted therapy as concomitant treatment (Fig. 1).

DCR was achieved in 60.4% of patients. ORR was 44.5% with 3.2% CR. Median PFS was 5.8 months (95% CI 4.2–7.6) and mOS 14.2 months (95% CI 8.99–26.8). In landmark PFS analysis, 48.7% (95% CI 37.6–63.1) of patients remained progression-free at 6 months, which significantly decreased at 12- and 24-months, with PFS 19.1% (95% CI 11.3–32.5) and 5.2% (95% CI 1.7–15.7), respectively. A similar pattern was observed in OS analysis at 6- (84.1%, 95% CI 75.6–93.7), 12- (51.3%, 95% CI 40.2–65.5) and 24-months (35.9%, 95% CI 25.6–50.4). ICRR was achieved in 50% of patients at 3-months, with a significant reduction at 6- (20.9%) and 12-months (13.9%). Similarly, ECRR was achieved in 69.2% of patients at 3-months, 48.6% at 6-months and 17.6% at 12-months. ICRR, PFS and OS were similar in symptomatic and asymptomatic patients.

In the univariate Cox regression analysis, the presence of IC metastases $\geq$3 was independently associated with decreased efficacy, including both PFS (HR 1.72, p = 0.047) and OS (HR 2.05, p = 0.016) (Fig. 3). Although no significant PFS difference was observed for patients with >2 EC metastases, this was a negative prognostic factor in the OS analysis (HR 1.88, p = 0.037). Similar to the Combi-ICI group, ECOG $\geq$2 was associated with decreased PFS and OS rates; nevertheless, the small patient population precludes any statistical conclusion.

3.4. Subgroup analysis of *BRAF*-mutated patients

In the subgroup analysis of *BRAFV600* patients (n = 86), 23 (26.7%) patients received Combi-ICI and 63 (73.3%) patients received Combi-TT first line. For patients in the Combi-TT group, several prognostic factors were numerically favouring worse prognosis, including LDH above ULN (57.1% versus 47.8%, p = 0.5), number of EC metastases (>2 organs, 54% versus 39.1%, p = 0.3), number of IC metastases ($\geq$3 lesions, 47.6% versus 39.1%, p = 0.6), steroid use at treatment start (29% vs 8.7%, p = 0.053) and the presence of neurologic symptoms at treatment start (55.5% vs 26%, p = 0.12) (Table 4).

Treatment with Combi-ICI was associated with significantly prolonged OS (p = 0.0053) and mPFS (0.03) compared to Combi-TT; mOS in the Combi-ICI group was not reached, whereas, in the Combi-TT group, mOS was 14.2 months (Fig. 4). After disease progression, nine patients with Combi-ICI received BRAF/MEK, and 36 patients with Combi-TT switched to combined immunotherapy and mPFS in second-line therapy was 14.7 and 3.1 months, respectively (Fig. 5). Univariate Cox regression analysis for the clinical features showed that systemic treatment with Combi-TT (HR 2.12, p = 0.014) and age $\geq$65 (HR 1.93, p = 0.02) negatively influenced PFS significantly, whereas Combi-TT (HR 2.8, p = 0.0076), number of EC (>2) (HR 1.78, p = 0.037) and IC ($\geq$3) metastases (HR 1.95, p = 0.015) were negatively influenced OS significantly. Multivariate analysis for PFS and OS confirmed that systemic treatment with Combi-TT was significant for PFS (HR 1.87, p = 0.047) and OS (HR 2.46, p = 0.021) and ECOG $\geq$2 for OS (HR 5.24, p = 0.018) (Supplementary Fig. s1 and s2, available online).

4. Discussion

In this multicenter, retrospective study of MBM patients, first-line combined immunotherapy resulted in prolonged mOS with sustainable IC and EC responses. Clinicians seemed to prefer initiating combined targeted therapy for patients with dismal disease characteristics, such as LDH above ULN, multiple sites of IC and EC metastases and symptomatic MBM at treatment start in the first-line setting. Despite the initial increased ICRR and ECRR, sustainable responses at 12 months were achieved only in 12.7% of patients in the Combi-TT cohort.

BRAFV600 patients with symptomatic MBM that required corticosteroids and thus excluded from clinical trials were more likely to receive Combi-TT in the real-life setting. Despite the initial higher ICRR and ECRR favouring Combi-TT, Combi-ICI eventually superseded targeted therapy and resulted in long-term survival benefit, with significantly prolonged mOS (p = 0.0053). Even though the difference in mPFS was small (6.5 months for Combi-ICI versus 6 months for Combi-TT), 95% of the patients in Combi-TT had progressed at 24 months, whereas 40% of Combi-ICI remained progression-free. These results are in line with an exploratory analysis of survival data from clinical trials in the metastatic setting, showing that BRAF/MEK inhibitors have superior PFS and OS within the first 12 months, later changing to the superiority of immunotherapy, with 3-year OS 41.3% for BRAF/MEK inhibition and 58.4% Ipilimumab/Nivolumab [18]. In the Combi-ICI cohort, there were no significant predictive factors for efficacy besides high LDH, whereas, in the Combi-TT cohort, the number of MBM $\geq$3 was independently associated with decreased efficacy for both PFS and OS and EC metastases >2 with decreased OS.

Currently, there are several clinical trials underway investigating the optimal front-line treatment in patients with *BRAF* mutant melanoma (NCT02968303,

Table 3
Treatment characteristics and response of the patients treated with targeted therapy (Combi-TT group, n = 63).

Treatment characteristics	Total		
Median treatment duration (months, range)	5.45 (0.7–54.5)		
Local treatment of MBM, n (%)			
	Overall population *(n = 63)*	***Symptomatic MBM*** *(n = 35)*	***Asymptomatic MBM*** *(n = 28)*
Surgery	10 (15.9%)	1 (3.6%)	9 (26%)
SRS	12 (19.0%)	8 (29%)	4 (11%)
WBRT	10 (15.9%)	4 (14%)	6 (17%)
Surgery & SRS	7 (11.1%)	3 (11%)	4 (11%)
Surgery & WBRT	4 (6.3%)	–	4 (11%)
None	20 (31.7%)	12 (43%)	8 (23%)
Reason for treatment discontinuation, n (%)			
PD	50 (79.4%)		
Toxicity (irAE)	11 (17.5%)		
Second-line systemic therapy after treatment discontinuation, n (%)	47 (75%)		
Type of second-line systemic therapy, n (%)			
Anti-PD1	16 (25%)		
Anti-PD1 + Anti-CTLA4	20 (32%)		
BRAF/MEK inhibitors	9 (14%)		
Anti-PD1 + Anti-CTLA4 + BRAF/MEK inhibitors	2 (3.2%)		
Treatment-related toxicities, grade 3–4, n (%)			
Any	5 (7.9%)		
Gastrointestinal	1 (1.6%)		
Skin	1 (5.7%)		
Hematologic	1 (1.6%)		
Fever	1 (1.6%)		
CK elevation	1 (1.6%)		
Treatment-related toxicities, grade 5, n (%)			
None	63 (100%)		
Best overall response, n (%)			
CR	2 (3.2%)		
PR	26 (41.3%)		
SD	10 (15.9%)		
MR	2 (3.2%)		
PD	20 (31.7%)		
Not reported	3 (4.8%)		
Intracranial response, n (%)			
	Overall population *(n = 63)*	***Symptomatic MBM*** *(n = 35)*	***Asymptomatic MBM*** *(n = 28)*
ICRR at 3 months	27 (50.0%)	13 (37%)	14 (50%)
ICRR at 6 months	9 (20.9%)	3 (8.6%)	6 (21%)
ICRR at 12 months	5 (13.9%)	3 (8.6%)	2 (7.1%)
ICDCR at 3 months	36 (66.7%)	20 (57%)	16 (57%)
ICDCR at 6 months	16 (37.2%)	7 (20%)	9 (32%)
ICDCR at 12 months	9 (25%)	6 (17%)	3 (11%)
Extracranial response, n (%)			
	Overall population *(n = 63)*		
ECRR at 3 months	36 (69.2%)		
ECRR at 6 months	18 (48.6%)		
ECRR at 12 months	6 (17.6%)		
ECDCR at 3 months	43 (82.7%)		
ECDCR at 6 months	21 (56.8%)		
ECDCR at 12 months	8 (23.5%)		
Progression-free survival			
	Overall population *(n = 63)*	***Symptomatic MBM*** *(n = 35)*	***Asymptomatic MBM*** *(n = 28)*
Median duration, months (95% CI)	5.8 months (4.2–7.6)	4.6 months (3.2–8.3)	6.3 months (4.5–11.5)
At 6 months (95% CI)	48.7% (37.6–63.1)	46% (32–66%)	57% (41–79%)
At 12 months (95% CI)	19.1% (11.3–32.5)	23% (12–42%)	21% (11–44%)

(*continued on next page*)

Table 3 (*continued*)

Treatment characteristics	Total		
At 24 months (95% CI)	5.2% (1.7–15.7)	11% (4.5–29%)	7.1% (1.9–27%)
Overall survival			
	Overall population *(n = 63)*	***Symptomatic MBM*** *(n = 35)*	***Asymptomatic MBM*** *(n = 28)*
Median duration, months (95% CI)	14.2 months (8.99–26.8)	16.9 months (8.66–41.9)	10.9 months (8.66–33.0)
At 6 months (95% CI)	84.1% (75.6–93.7)	80% (68–94%)	89% (79–100%)
At 12 months (95% CI)	51.3% (40.2–65.5)	53% (39–73%)	48% (33–71%)
At 24 months (95% CI)	35.9% (25.6–50.4)	38% (24–58%)	33% (20–57%)

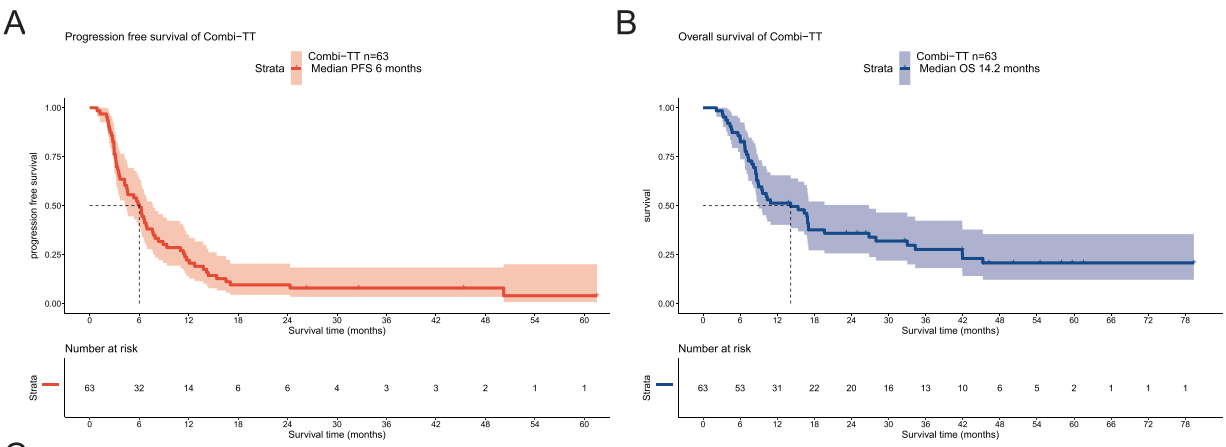
Abbreviations: CR, complete response; ECDCR, extracranial disease control rate; ECRR, extracranial response rate; ICDCR, intracranial disease control rate; ICRR, intracranial response rate; irAE, immune-related adverse event; MBM, melanoma brain metastases; MR, mixted response; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

NCT02224781, NCT02631447). Although there are no head-to-head prospective data comparing immunotherapy and targeted therapy in patients with active MBM, increasing evidence for unresectable, stage IV disease suggests that BRAF/MEK inhibitors show a low rate of primary resistance with rapid tumour eradication and thus superior short-term outcomes [19], whereas immunotherapy shows higher rates of primary resistance, but has more durable responses [20]. Our study suggests significant survival benefits with higher and durable IC and EC responses with first-line Combi-ICI. These results are consistent with prior retrospective studies suggesting a significant survival benefit for *BRAF-mutant* patients with MBM treated with Combi-ICI compared to Combi-TT ($p < 0.001$) [21]. A similar trend in favour of ICI is seen in a recent observational study, which evaluated first-line TT and anti-PD−1 monotherapy in *BRAFV600* mutant patients using propensity matching [22]. On the other hand, in a subgroup analysis of the DECOG study, no significant difference in OS was demonstrated between first-line immunotherapy versus targeted therapy in patients with MBM, although patients in the targeted therapy group showed slightly higher 1-, 2- and 3-year OS rates [23].

Of note, 74.6% of *BRAF* mutant patients in our study required subsequent systemic therapy upon progression, which eventually included immunotherapy alone or combined with targeted therapy in 60.2% of the cases. Second-line combined immunotherapy after BRAF/MEK inhibitor failure resulted in poor efficacy with mPFS 3.1 months in the second-line treatment. A recent study showed equivalent modest efficacy to second-line immunotherapy treatment after resistance to targeted therapy in patients with active MBM with ICRR <5% and mPFS of 5.5 months [24]. Furthermore, clinical data highlighting the optimal treatment sequence in BRAF mutant patients with longer FU are needed.

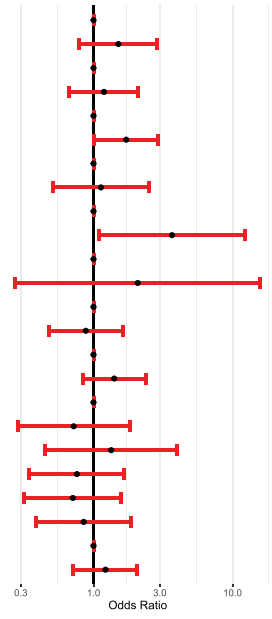
Symptomatic brain metastases at baseline were described in 32% of patients in the Combi-ICI group and 55.6% of patients in the Combi-TT group, and systemic therapy was combined with SRS and/or surgery in 45.3% of patients in the Combi-ICI group and 30.1% of patients in the Combi-TT group, which might be attributed to the small number of MBM <3 cm, which was more frequent in the former treatment cohort. We observed a non-significant survival benefit only in Combi-ICI patients treated additionally with SRS and/or surgery, as well as numerically higher ICRR and PFS in symptomatic patients than asymptomatic (in which systemic treatment was frequently combined with local therapy), but these results should be interpreted with caution because of a low number of patients and the retrospective non-randomized setting. Nevertheless, there was no significant difference in OS between the groups. Clinical and pre-clinical data support a synergistic effect between immunotherapy and radiotherapy in both irradiated and non-irradiated lesions [25–27]; yet, prospective, randomized data investigating the survival outcome of patients with combined local and systemic treatment for MBM are currently lacking. Local treatment with surgery or radiotherapy can increase local disease control, but the optimal management and combination still represents a clinical complexity and should be evaluated prospectively [6,7].

The retrospective nature, as well as potential bias due to patient selection, are limitations of the present study. Approximately 70% of the patients were *BRAF* mutated, which might be explained by the availability of treatment options that are not included in the present study (e.g. anti-PD1 alone), as well as clinical trials and patients' eligibility (45% symptomatic at baseline). Furthermore, we were unable to analyse smaller subgroups, due to the small proportion of patients in each treatment group. The presence of symptomatic MBM at treatment initiation was based on the patients' medical records, which might be a limitation in the retrospective symptom assessment. A head-to-head comparison of patients treated with first-line Combi-ICI or Combi-TT is due to the heterogeneity of both groups not feasible.



C

Targeted therapy covariates	mPFS	HR	n	p value
Age < 65	5.9	1	48	
Age => 65	6.3	1.51	15	0.22
Sex − female	6.3	1	21	
Sex − male	4.6	1.19	42	0.56
Brain metastases 1−2	6.6	1	33	
Brain metastases =>3	4.6	1.72	30	0.047
Brain metastases diameter < 1 cm	5.3	1	8	
Brain metastases diameter => 1 cm	4.3	1.13	33	0.76
ECOG 0−1	6.2	1	56	
ECOG => 2	2.5	3.67	3	0.034
S100 normal	15.4	1	1	
S100 elevated	4.6	2.08	23	0.48
LDH normal	5.7	1	17	
LDH elevated	6.3	0.88	36	0.69
Symptomatic − No	6.3	1	28	
Symptomatic − Yes	4.6	1.41	35	0.2
Local therapy − none	5.4	1	20	
Local therapy − Surgery + SRS	6.2	0.72	7	0.5
Local therapy − Surgery + WBRT	4.4	1.34	4	0.6
Local therapy − SRS	6.3	0.76	12	0.49
Local therapy − Surgery	6.6	0.71	10	0.4
Local therapy − WBRT	5	0.85	10	0.69
Extracranial metastases <= 2	6.8	1	29	
Extracranial metastases > 2	4	1.22	34	0.47



D

Targeted therapy covariates	mOS	HR	n	p value
Age < 65	12.5	1	48	
Age => 65	16.9	1.08	15	0.84
Sex − female	17	1	21	
Sex − male	10.9	1.46	42	0.25
Brain metastases 1−2	26.8	1	33	
Brain metastases =>3	8.5	2.05	30	0.016
Brain metastases diameter < 1 cm	8.9	1	8	
Brain metastases diameter => 1 cm	10.4	1.17	33	0.75
ECOG 0−1	16.4	1	56	
ECOG => 2	4.6	5.09	3	0.035
S100 normal	26.8	1	1	
S100 elevated	8.7	1.52	23	0.69
LDH normal	10.2	1	17	
LDH elevated	16.9	0.83	36	0.59
Symptomatic − No	10.9	1	28	
Symptomatic − Yes	16.9	0.94	35	0.85
Local therapy − none	8.7	1	20	
Local therapy − Surgery + SRS	17	0.52	7	0.21
Local therapy − Surgery + WBRT	6.4	1.1	4	0.88
Local therapy − SRS	18	0.74	12	0.49
Local therapy − Surgery	15.6	0.67	10	0.35
Local therapy − WBRT	17.1	0.59	10	0.27
Extracranial metastases <= 2	26.8	1	29	
Extracranial metastases > 2	8.5	1.88	34	0.037

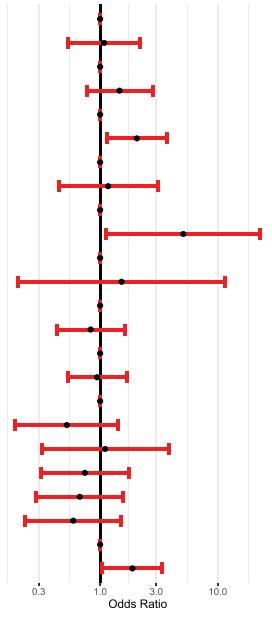


Fig. 3. Kaplan−Meier curve for progression-free survival (PFS) (A) and overall survival (OS) (B) in patients treated with combined targeted therapy (Combi-TT). Univariate Cox regression analysis for PFS (C) and OS (D) for covariates in patients with Combi-TT. HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; n, number of patients; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy.

Table 4
Comparison of baseline characteristics of patients receiving targeted therapy (n = 63) or combined immune checkpoint inhibitor (n = 23) as a first-line treatment in *BRAF* mutated patients.

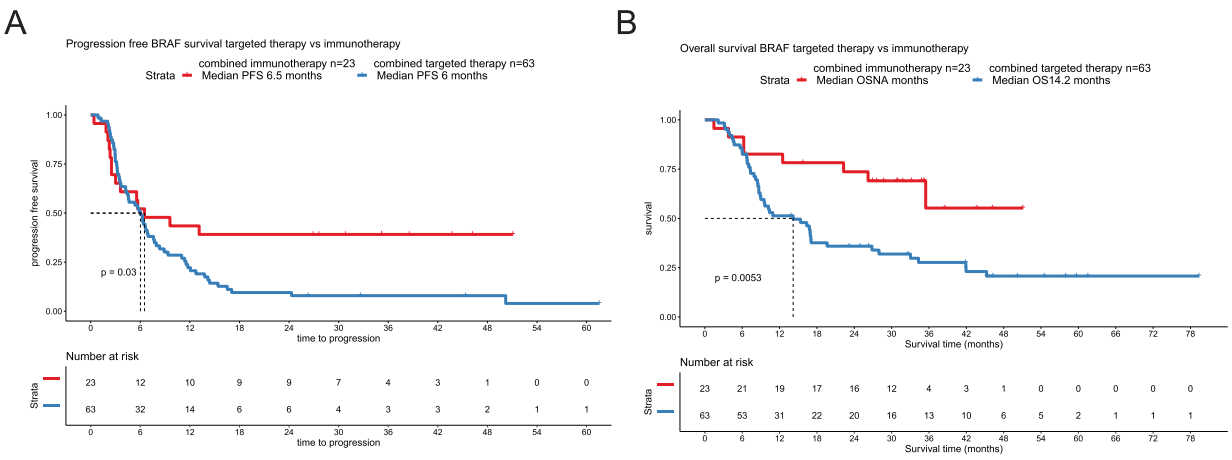
Baseline & treatment characteristics	$Total_{BRAF}$	$Combi\text{-}ICI_{BRAF}$	Combi-TT	p-value[a]
Median age at MBM diagnosis (years, range)	55 (26–93)	55 (29–77)	55 (26–93)	>0.9
Sex (n, %)				0.8
Female	30 (35%)	9 (39%)	21 (33%)	
Male	56 (65%)	14 (61%)	42 (67%)	
S100 at treatment start (n, %)				0.6
Normal	3 (3.5%)	2 (8.7%)	1 (1.6%)	
>ULN	37 (43%)	14 (60.9%)	23 (36.5%)	
Not reported	46 (53.5%)	7 (30.4%)	39 (61.9%)	
LDH at treatment start (n, %)				0.5
Normal	26 (30.2%)	9 (39.1%)	17 (27%)	
>ULN	47 (54.7%)	11 (47.8%)	36 (57.1%)	
Not reported	13 (15.1%)	3 (13%)	10 (16%)	
ECOG at treatment start (n, %)				>0.9
0–1	77 (89.5%)	21 (91.3%)	56 (88.9%)	
≥2	4 (4.7%)	1 (4.3%)	3 (4.8%)	
Not reported	5 (5.8%)	1 (4.3%)	4 (6.4%)	
Extracranial sites of metastasis at treatment start (n, %)				0.3
≤2 extracranial sites	43 (50%)	14 (60.9%)	29 (46%)	
>2 extracranial sites	43 (50%)	9 (39.1%)	34 (54%)	
Number of MBM at treatment start (n, %)				0.6
1–2 lesions	47 (54.7%)	14 (60.9%)	33 (52.4%)	
≥3 lesions	39 (45.3%)	9 (39.1%)	30 (47.6%)	
Neurologic symptoms at treatment start (n, %)				
Yes	41 (47.7%)	6 (26%)	35 (55.6%)	0.12
No	41 (47.7%)	13 (56.5%)	28 (44.4%)	
Not reported	4 (4.7%)	4 (17.4%)	–	
Steroid use at treatment start (n, %)	20 (23%)	2 (8.7%)	18 (29%)	0.053
Steroid use during treatment (n, %)	19 (25%)	4 (17%)	15 (28%)	0.3
Best overall response, n (%)				0.014
CR	8 (9.3%)	6 (26%)	2 (3.2%)	
PR	3 (3.5%)	1 (4.3%)	2 (3.2%)	
SD	29 (33.7%)	9 (39.1%)	20 (31.7%)	
MR	30 (34.9%)	4 (17.4%)	26 (41.3%)	
PD	13 (15.1%)	3 (13%)	10 (15.9%)	
Not reported	3 (3.5%)	–	3 (4.8%)	
Intracranial response, n (%)				
ICRR at 3 months	35 (40.7%)	8 (34.8%)	27 (42.9%)	0.7
ICRR at 6 months	15 (17.4%)	6 (26%)	9 (14.3%)	0.2
ICRR at 12 months	11 (12.8%)	6 (26%)	5 (7.9%)	0.061
ICDCR at 3 months	48 (55.8%)	12 (52.2%)	36 (57.1%)	0.9
ICDCR at 6 months	24 (27.9%)	8 (34.8%)	16 (25.4%)	0.6
ICDCR at 12 months	16 (18.6%)	7 (30.4%)	9 (14.3%)	0.12
Extracranial response, n (%)				
ECRR at 3 months	46 (53.5%)	10 (43.5%)	36 (57.1%)	0.4
ECRR at 6 months	29 (33.7%)	11 (47.8%)	18 (28.6%)	0.2
ECRR at 12 months	11 (12.8%)	5 (21.7%)	6 (9.5%)	0.2
ECDCR at 3 months	54 (62.8%)	11 (47.8%)	43 (68.3%)	0.14
ECDCR at 6 months	37 (43%)	16 (69.6%)	21 (33.3%)	0.006
ECDCR at 12 months	14 (16.3%)	6 (26%)	8 (12.7%)	0.2

Abbreviations: CR, complete response; ECDCR, extracranial disease control rate; ECOG, Eastern Cooperative Oncology Group; ECRR, extracranial response rate; ICDCR, intracranial disease control rate; ICRR, intracranial response rate; LDH, lactate dehydrogenase; MBM, melanoma brain metastases; MR, mixed response; PD, progressive disease; PR, partial response; SD, stable disease..

[a] Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test.

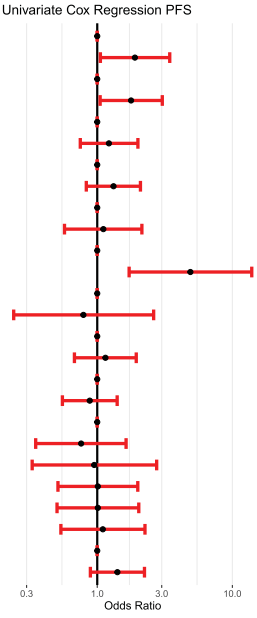
Finally, a significant proportion of patients (62.3%) received local treatment with SRS or WBRT in accordance with each institution's guidelines, wherein the absence of an international standardized radiotherapy protocol might indicate possible differences in local treatment.

Overall, this study shows that both combined immunotherapy and targeted therapy resulted in increased IC and EC efficacy and prolonged survival also in patients with unfavourable prognostic factors. In *BRAF* mutated patients, Combi-ICI outperforms Combi-TT in the first-line setting; however, patients with dismal disease



C

Covariate	mPFS	HR	n	p value
Combined Immunotherapy	6.5	1	23	
Combined Targeted therapy	6	1.9	63	0.033
Age < 65	6.3	1	65	
Age => 65	5.7	1.78	21	0.032
Sex − female	6.3	1	30	
Sex − male	5.6	1.22	56	0.42
Brain metastases 1−2	6.6	1	47	
Brain metastases =>3	4.6	1.32	39	0.24
Brain metastases diameter < 1 cm	6.4	1	14	
Brain metastases diameter => 1 cm	5.6	1.11	39	0.76
ECOG 0−1	6.3	1	77	
ECOG => 2	2.4	4.89	4	0.0029
S100 normal	5.6	1	3	
S100 elevated	6.3	0.79	37	0.7
LDH normal	6.3	1	26	
LDH elevated	6	1.15	47	0.61
Symptomatic − No	5.9	1	41	
Symptomatic − Yes	5.7	0.88	41	0.59
Local therapy − none	5.8	1	28	
Local therapy − Surgery + SRS	6.2	0.76	13	0.48
Local therapy − Surgery + WBRT	4.6	0.95	5	0.93
Local therapy − SRS	6.3	1.01	15	0.98
Local therapy − Surgery	6.6	1.01	13	0.97
Local therapy − WBRT	5	1.1	12	0.79
Extracranial metastases <= 2	6.8	1	43	
Extracranial metastases > 2	4.2	1.41	43	0.14



D

Covariate	mOS	HR	n	p value
Combined Immunotherapy		1	23	
Combined Targeted therapy	14.2	2.8	63	0.0076
Age < 65	17.1	1	65	
Age => 65	16.9	1.23	21	0.53
Sex − female	26.2	1	30	
Sex − male	16.8	1.36	56	0.3
Brain metastases 1−2	34.3	1	47	
Brain metastases =>3	9.6	1.95	39	0.015
Brain metastases diameter < 1 cm	22.3	1	14	
Brain metastases diameter => 1 cm	16.8	1.44	39	0.4
ECOG 0−1	19.6	1	77	
ECOG => 2	4.5	8.1	4	0.0011
S100 normal	24.6	1	3	
S100 elevated	17	1.11	37	0.88
LDH normal	22.3	1	26	
LDH elevated	17	1.11	47	0.74
Symptomatic − No	16.8	1	41	
Symptomatic − Yes	17	0.98	41	0.94
Local therapy − none	10.9	1	28	
Local therapy − Surgery + SRS	34.3	0.6	13	0.25
Local therapy − Surgery + WBRT	6.8	0.88	5	0.84
Local therapy − SRS	19.6	1.01	15	0.97
Local therapy − Surgery	26.2	0.79	13	0.57
Local therapy − WBRT	17.1	0.82	12	0.65
Extracranial metastases <= 2	33	1	43	
Extracranial metastases > 2	8.7	1.78	43	0.037

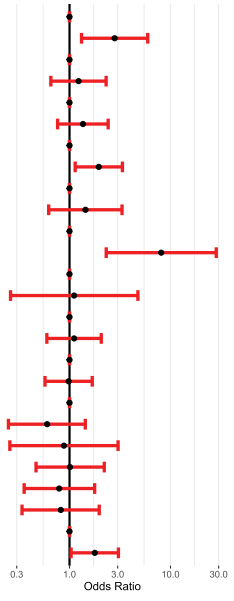


Fig. 4. Kaplan−Meier curve for progression-free survival (PFS) (A) and overall survival (OS) (B) in *BRAF*-mutant patients treated with combined immunotherapy compared to targeted therapy. Univariate Cox regression analysis for PFS (C) and OS (D) for covariates in the abovementioned study population. HR, hazard ratio; mOS, median overall survival; mPFS median progression-free survival; n, number of patients; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy.

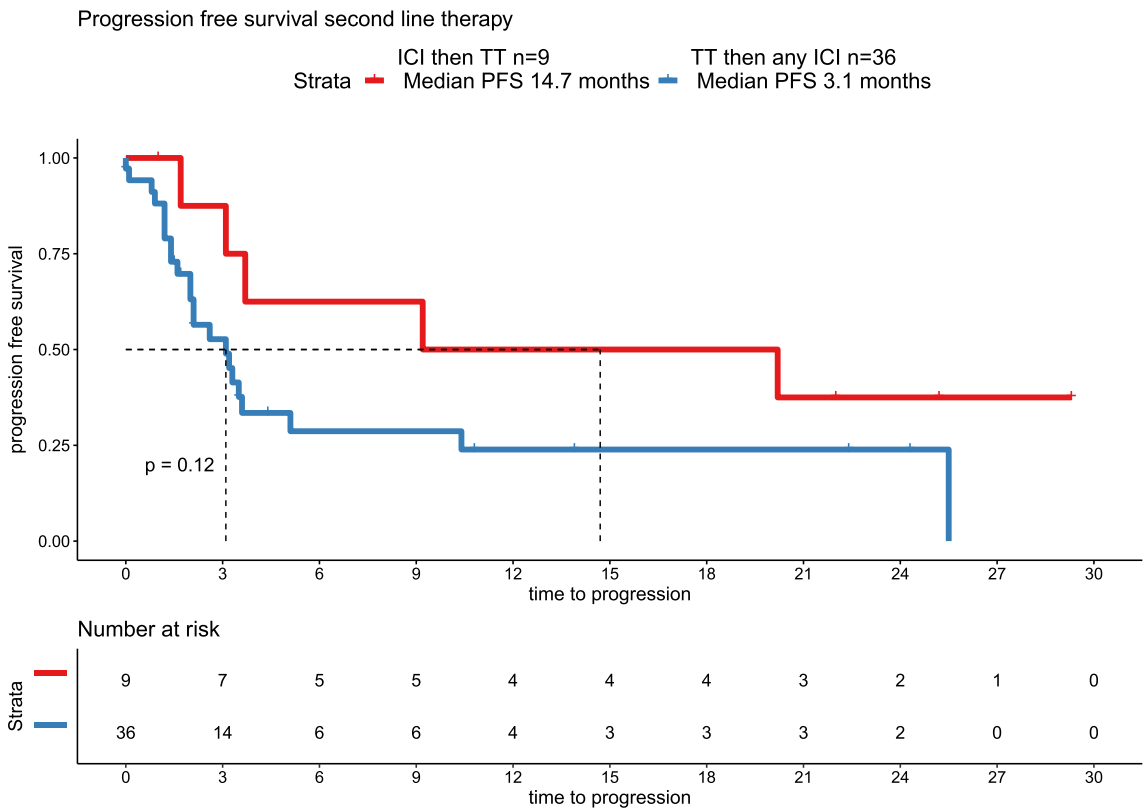


Fig. 5. Progression-free survival (PFS) in second-line treatment in *BRAF*-mutant patients after progression to first-line treatment agent. ICI, immunotherapy; TT, targeted therapy.

characteristics, such as symptomatic MBM or LDH > ULN, were more likely to receive Combi-TT as first-line treatment. Other clinical factors and disease characteristics may guide first-line treatment in these patients. Predictive models of response and further clinical trials investigating systemic and local treatment sequences will help identify the best responders and direct our therapeutic decisions.

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Conflict of interest statement

RD has intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre outside the submitted work.

JM has intermittent project focused consultant or advisory relationships with Merck/Pfizer, Merck Sharp & Dohme, Amgen, Novartis and Pierre Fabre and has received travel support from Ultrasun, L' oreal, Merck Sharp & Dohme, Bristol Myers and Squibb und Pierre Fabre outside of the submitted work.

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Appendix A. Supplementary data

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