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Discontinuation of combo immunotherapy and outcome of patients with melanoma brain metastases

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ABSTRACT

Background Nivolumab plus ipilimumab (COMBO) is the standard treatment for asymptomatic melanoma brain metastases (MBM), but current guidelines do not provide specific recommendations for treatment discontinuation in responding patients. This study aimed to evaluate outcomes after COMBO discontinuation within 24 months and the role of continuing treatment beyond 24 months.

Methods Patients with MBM treated with COMBO who discontinued treatment within 24 months for reasons other than disease progression or continued beyond this time point were retrieved. Overall survival (OS), objective response, progression-free survival (PFS) and toxicities were analyzed.

Results 465 patients were included: 392 discontinued COMBO within 24 months, while 73 continued beyond 24 months. Treatment was discontinued due to complete response (CR, n=47), partial response (PR, n=45), stable disease (SD, n=12), toxicity after SD (n=59), toxicity after CR (n=99), or toxicity after PR (n=130). At multivariable analysis, the line of treatment (>first vs first: HR 2.65 (1.62–4.32)), the immune-related adverse events (irrespective of anti-tumor necrosis factor-alpha) (HR 0.18 (0.07–0.42)); COMBO discontinuation after CR (HR 0.15 (0.05–0.40)), or PR (HR 0.08 (0.03–0.26)), as well as stopping due to toxicity after CR (HR 0.14 (0.07–0.27)) or PR (HR 0.51 (0.32–0.82)), were associated with OS. Notably, at a median follow-up of 51 months (IQR 31–70), patients with CR/PR who discontinued COMBO within 24 months had PFS and OS comparable to those who continued treatment beyond this time point. 4-year OS exceeded 83% in patients discontinuing COMBO after CR, PR, or toxicity following CR, compared with 66.4% in those discontinuing due to toxicity after PR; median PFS was not reached in the former groups but was 18.6 months in the toxicity after PR group.

Conclusion Discontinuation of COMBO within 24 months appears safe in patients with CR and in selected cases of PR, with no survival disadvantage versus prolonged therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The optimal duration of immune checkpoint inhibitor therapy in melanoma brain metastases remains unclear.

WHAT THIS STUDY ADDS

⇒ Discontinuation of nivolumab plus ipilimumab within 24 months after response is associated with survival outcomes comparable to continued treatment, and discontinuation after complete response—including due to toxicity—can result in durable disease control. Immune-related adverse events are associated with improved overall survival, independent of anti-tumor necrosis factor-alpha use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support treatment discontinuation after response in selected patients with melanoma brain metastases and provide a rationale for prospective studies to define optimal immunotherapy duration.

INTRODUCTION

The prognosis of patients with melanoma brain metastases (MBM) has been dramatically improved with the introduction of newer melanoma therapeutics.[1 2] Immune checkpoint inhibitors have demonstrated durable intracranial activity with single-agent ipilimumab and single-agent anti-programmed cell death protein-1 (anti-PD-1) treatments, although with modest response rates. Targeted therapy with dabrafenib plus trametinib in patients with BRAF-mutant MBM demonstrated clinically significant, but less durable, intracranial activity.[1–5]

The anti-PD-1 Brain Collaboration (ABC) randomized phase 2 study was the first trial to demonstrate activity of combination nivolumab plus ipilimumab (COMBO) in MBM, showing significant improvement in terms of objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) compared with anti-PD-1 alone.[2 3] Importantly, long-term follow-up with a median of over 7 years confirmed durable benefit: at 7 years, intracranial PFS was approximately 42% with COMBO versus 15% with nivolumab alone, and OS was 48% vs 26% respectively, with even higher survival (~51%) in drug-naïve patients treated in the first-line setting, underscoring the long-term impact of upfront COMBO in active, asymptomatic MBM.[3] CheckMate 204 confirmed the activity of the COMBO in patients with asymptomatic MBM, with intracranial activity in more than 50% of patients. In addition, more than 85% of responses were durable, with both median PFS and OS not reached at a median follow-up of 20.6 months.[1] Furthermore, in a 27-patient cohort, the NIBIT-M2 trial (ClinicalTrials.gov. Identifier: NCT02460068; European Union Drug Regulating Authorities Clinical Trials, number 2012–004301-27) also demonstrated similar efficacy of COMBO with a median OS of 29.2 months.[4] Based on these trials, and a meta-analysis,[5] COMBO is widely considered one of the standards of care for patients with asymptomatic MBM who are candidates for COMBO immunotherapy[1–6] as well as a first-line treatment for patients without brain metastases, as shown in the CheckMate 067 trial.[7] While there is growing evidence supporting the discontinuation of immunotherapy in patients with metastatic melanoma who achieve a response in extracranial metastases, data regarding discontinuation in the context of MBM remain limited.

Outside clinical trials, the average duration of immune checkpoint inhibitors in advanced unresectable melanoma is typically 2 years if no progression or severe toxicities are documented.[8] The tumor microenvironment of brain metastases poses unique challenges, including differential immune infiltration and the hypothetical impact of the blood–brain barrier, which may influence the robustness and longevity of immune responses compared with extracranial sites.[9 10]

Current European Society for Medical Oncology (ESMO) consensus guidelines, European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), and the European Organization of Research and Treatment of Cancer (EORTC) consensus, and American Society of Clinical Oncology (ASCO) guidelines acknowledge the efficacy of checkpoint inhibitors in brain metastases but do not provide specific recommendations for treatment discontinuation in this challenging subgroup.[8 11–13] Consequently, clinicians may remain cautious about stopping therapy in patients with MBM within 2 years of treatment and in several centers even after 2 years.

Durable responses in patients with MBM, after elective discontinuation of anti-PD1-based immunotherapy due to complete response (CR), have been reported in small retrospective studies (20 patients overall),[14–16] suggesting that treatment discontinuation may be considered in patients with a good response.

ABC trial[2 3] and CheckMate 204 study[1] set up, per study protocol, the duration of COMBO for 2 years but findings on discontinuation within 2 years and data on patients who discontinued treatment at 2 years compared with those who did not, are not available. Based on the lack of available data, and most importantly, considering that ESMO consensus and guidelines,[8 11] or EADO/EDF/EORTC consensus,[12] as well as ASCO recommendations[13] do not suggest the optimal duration of treatment in patients with MBM, our study aimed to investigate the outcome of patients with MBM, who discontinued COMBO treatment within 2 years for reasons other than progressive disease and to investigate whether continuing treatment beyond 2 years yields benefit.

METHODS

Patients with MBM who received COMBO between January 2012 and April 2025, and discontinued treatment for reasons other than progression of disease, were identified from a dedicated collected dataset. All patients were treated and followed up in 27 referral melanoma centers (*detailed in* online supplemental methods). The following parameters were retrieved: brain metastasis, presence of extracranial disease, date of last follow-up, surgery, timing of stereotactic radiosurgery, number and size of brain metastases, steroid therapy given at baseline due to central nervous system (CNS)-symptoms (defined as neurologic signs or symptoms related to CNS metastases that were clinically significant and/or required therapeutic intervention including corticosteroid and antiepileptic therapy, as well as locoregional treatments such as surgical resection or radiotherapy) or later for toxicity management, immune-related adverse events (irAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03[17] and associated immunosuppressive treatments, reasons for treatment discontinuation, COMBO duration, best overall response, date of progression and date of death. Reasons for treatment discontinuation were extracted and classified as follows: (1) Medical judgment—as per standard based on clinical trials[1–4]—or patient decision because of CR, partial response (PR) or stable disease (SD);

treatment-limiting toxicity. Patients who interrupted treatment due to disease progression, ocular and mucosal melanoma, or those who did not receive COMBO were excluded from this analysis.

Outcome

The primary endpoint was OS-discontinuation, defined as the time from discontinuing COMBO to death due to any cause. PFS-discontinuation was calculated as the time between immunotherapy discontinuation and tumor progression or death; both survival times were censored at the last follow-up. For the landmark analysis, the time point was set at 24 months, and accordingly PFS and OS were compared between patients with CR/PR who did or did not discontinue before 24 months. The study design and methodology were approved by the institutional review boards or ethical committee of each participating institution. The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice.

Statistical analysis

Patients characteristics were categorized based on variable types. Categorical factors were presented as absolute frequencies and percentages while quantitative variables were represented by their median and IQR. Survival times were analyzed using the Kaplan-Meier method and the median survival time was reported along with its corresponding 95% CIs. Survival rates at different time points were also derived from the Kaplan-Meier curve. To estimate HRs and their 95% CIs, a proportional hazard model was employed. Factors with a statistically significant p value at univariate analysis were considered in the multivariable model. This model was built through a stepwise forward selection based on Wald statistics, aiming to identify independent variables associated with survival times. The significance level was set to 0.05. Missing data frequency was reported in each table and no missing imputation was done. Statistical analysis was conducted using the IBM-SPSS V.28.0 statistical software and R V.4.1.0.

RESULTS

Patients

465 patients with MBM, who received COMBO between January 2012 and April 2025 and who discontinued treatment for reasons other than progressive disease, were retrieved (figure 1S shows a flowchart of the study population and baseline characteristics). Overall, 392 (84.3%) patients discontinued treatment within 24 months from starting COMBO, and 73 (15.7%) continued beyond 24 months.

The median age was 62 years, 308 (66.2%) were males, 212 (45.6%) were BRAFV600-mutated. Baseline lactate dehydrogenase level was below the upper normal limit in 237 patients (51.0%). Overall, 406 (87.3%) received COMBO as first-line treatment and the majority of patients (393, (84.5%)) had extracranial disease. In our cohort, only 59 (12.7%) patients received the COMBO in the second-line setting. First-line treatment consisted of targeted therapy in 32 (54.2%) patients, primarily selected to achieve rapid disease control due to symptomatic brain metastases. The remaining 27 (45.8%) patients received other treatments, mainly anti-PD-1 monotherapy. The

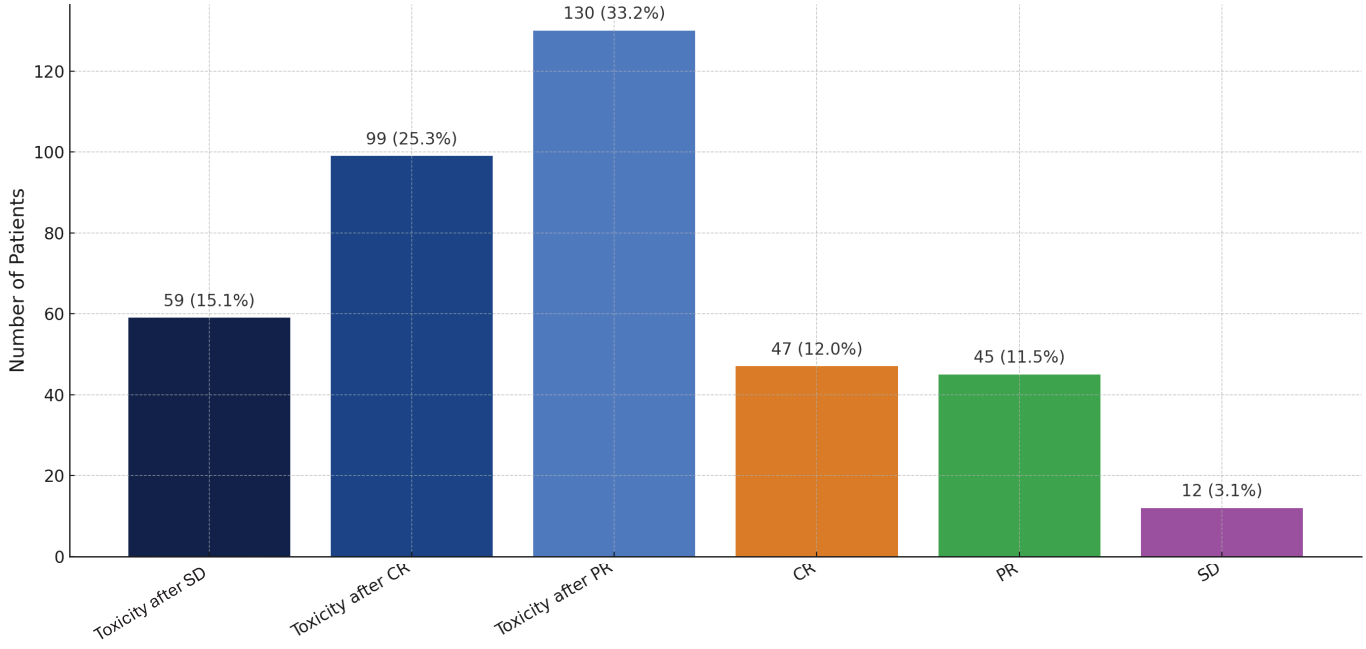

Figure 1 Histogram showing the distribution for immunotherapy discontinuation within 24 months according to the cause of treatment interruption. CR, complete response; PR, partial response; SD, stable disease.

median duration of prior treatment before switching to the combination therapy was 6 months (IQR 2–15).

The baseline Eastern Cooperative Oncology Group performance status (ECOG PS) was 0 in 228 patients (58.2%) who discontinued COMBO within 24 months, and in 53 patients (72.6%) among those who continued treatment beyond 24 months.

Overall, 406 patients (87.3%) received COMBO as first-line treatment, while surgery and radiotherapy to MBM were administered at comparable rates in the two groups: 114 patients (29.1%) who discontinued within 24 months and 9 patients (12.3%) who continued treatment beyond 24 months underwent surgery, while radiotherapy was delivered to 223 patients (56.9%) and 48 patients (65.8%), respectively. Specifically, in the discontinuation group stereotactic radiosurgery (SRS) was performed in 203 patients (91.0%), WBRT in 17 patients (7.6%), whereas in the discontinuation group, SRS was used in 42 patients (87.5%) and Whole Brain Radiotherapy (WBRT) in 6 patients (12.5%) (p=0.28). Baseline characteristics of patients who continued treatment within or after 24 months are reported in online supplemental table 1).

Among the overall cohort, 232 patients (49.9%) required corticosteroids during COMBO; 125 (53.8%) due to CNS-related symptoms and 65 (28.0%) to manage radiotherapy-related complications.

In addition, 404 patients (86.8%) experienced immune-related toxicities, among them 357 (76.7%) required immunosuppressive therapy and 113 (24.3%) an anti-tumor necrosis factor-alpha (anti-TNF-α) drug, while 244 (52.4%) received other immunosuppressive agents. The online supplemental table 2 summarizes the grading of toxicity across the different patient groups, as well as the number of patients who discontinued treatment due to irAEs and the corresponding toxicity grade leading to treatment discontinuation.

Among the 392 patients who discontinued treatment within 24 months, overall response was one of the main reasons for discontinuation: 47 (12.0%) patients with CR, 45 (11.5%) with PR, while only 12 (3.1%) patients discontinued with SD Furthermore 59 (15.1%) patients discontinued COMBO due to toxicity without any response and without evidence of disease progression prior to treatment discontinuation, 99 (25.3%) due to toxicity after CR and 130 (33.2%) after PR (figure 1 illustrates the reasons for treatment discontinuation).

Treatment duration differed depending on the reason for discontinuation, with median duration ranging from 1.2 months in patients discontinuing due to toxicity, to 2.5 months in those who discontinued because of toxicity after achieving CR, and up to 22 months in patients who stopped after achieving CR (figure 2S).

Outcome

At a median follow-up of 51 months (IQR 31–70), patients who discontinued COMBO within 24 months due to toxicity (without PR/CR) had the shortest PFS (median 4.1 months), whereas median PFS was not reached in those who stopped due to response (CR/PR) or because of toxicity occurring after CR. Among patients with PR who discontinued for toxicity, median PFS was 18.6 months (figure 2A). 4-year PFS rates ranged from 16.2% in the toxicity group without CR or PR to 78.5% and 73.9% in patients who stopped treatment in CR or for toxicity after achieving a CR, respectively. The 1-year, 2-year, 3-year, 4-year time points outcomes for the different subgroups are reported in table 1 (full version is provided in the online supplemental material). At univariate analysis (table 2), a worse PFS was associated with ECOG PS 2–3 (HR 1.80 (1.00–3.24)), radiotherapy to brain metastases (HR 2.01 (1.46–2.78)), and second–third line COMBO versus first line (HR 1.92 (1.29–2.86)). Best response correlated with outcomes; PFS was longer in patients achieving CR/PR versus SD (HR 0.24 (0.17–0.33)). The reason for treatment discontinuation remained a key determinant of PFS. Compared

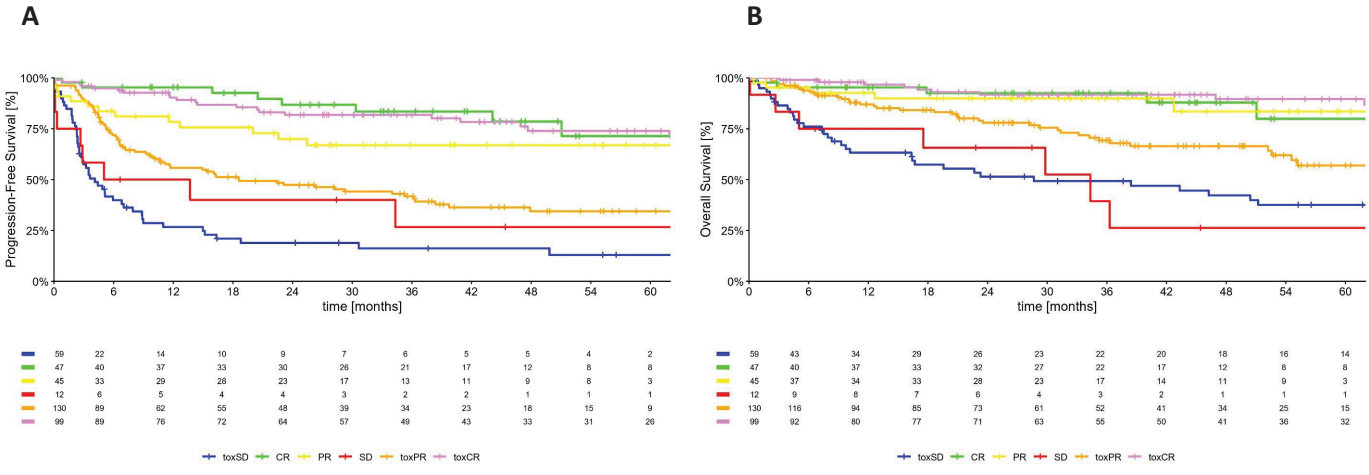

Figure 2 Kaplan-Meier survival curves show PFS (A) and OS (B) in patients who discontinued combination therapy within 24 months, according to the reason for treatment discontinuation. CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 1 OS and PFS according to the reason of COMBO discontinuation in patients with MBM

Reasons for discontinuation within 24 months	Median PFS	2-year PFS	3-year PFS	4-year PFS	Median OS	2-year OS	3-year OS	4-year OS
Toxicity without CR or PR	4.1 (2.1–6.1)	18.9%	16.2%	16.2%	28.6 (0–58.1)	51.4%	49.3%	42.2%
CR achievement	Not yet reached	86.8%	83.4%	78.5%	Not yet reached	92.5%	92.5%	87.9%
Toxicity after achieving CR	Not yet reached	81.8%	81.8%	73.9%	Not yet reached	91.7%	91.7%	89.6%
PR achievement	Not yet reached	69.9%	66.9%	66.9%	Not yet reached	89.9%	89.9%	83.5%
Toxicity after achieving PR	18.6 (5.0–32.2)	47.4%	41.8%	34.4%	Not yet reached	77.9%	69.3%	66.4%
SD achievement	5.0 (0–21.7)	40.0%	26.7%	26.7%	34.3 (13.4–55.3)	65.6%	39.4%	26.3%

The full version of the table is provided in the online supplemental materials.
COMBO, nivolumab plus ipilimumab; CR, complete response; MBM, melanoma brain metastasis; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

with discontinuation due to toxicity (without CR/PR), stopping treatment in CR (HR 0.10 (0.05–0.21)) or PR (HR 0.20 (0.11–0.37)), as well as discontinuation due to toxicity after achieving CR (HR 0.13 (0.08–0.21)) or PR (HR 0.43 (0.30–0.62)), was associated with significantly improved PFS. In contrast, discontinuation due to SD was not associated with a significant PFS benefit (HR 0.66 (0.31–1.39)).

At multivariate analysis, second–third line treatment (vs first line, HR 1.76 (1.16–2.69)), and radiotherapy to brain metastases (HR 1.55 (1.11–2.17)) were independently associated with a worse PFS, while discontinuation for CR (HR 0.10 (0.05–0.22)), PR (HR 0.14 (0.06–0.29)), for toxicity after achieving a CR (HR 0.13 (0.08–0.21)) or PR (HR 0.48 (0.33–0.70)) were independently associated with a longer PFS.

The development of irAEs, regardless of the administration of anti-TNF-a (administered in patients with grade 3/4 toxicity or in those who were refractory to corticosteroid therapy) was associated with a longer PFS (irAEs not treated with anti-TNF-α vs no irAEs HR 0.35 (0.18–0.69) and irAEs treated with anti-TNF-α vs no irAEs HR 0.42 (0.20–0.87)).

Regarding OS, outcome varied according to the reason for treatment discontinuation and median OS was reached only in patients discontinuing due to toxicity without achieving CR or PR (28.6 months) and in those stopping after SD (34.3 months), while it was not yet reached in all other groups (figure 2B). Additionally, 2-year OS was 92.5% in patients discontinuing in CR, 89.9% in those stopping in PR, and 91.7% in those discontinuing due to toxicity after a CR. Notably, patients discontinuing COMBO due to toxicity after achieving PR had inferior outcomes, with a 2-year OS rate of 77.9% (table 1).

Among the 229 patients who discontinued treatment for toxicity after achieving CR/PR, 95 (41.5%) had received at least two doses of combination immunotherapy, whereas 134 (58.5%) had completed the induction phase. The 4-year OS was 75.2% and 77.7%, respectively. Of the 59 patients who discontinued treatment due to toxicity without achieving a response, 41 (69.5%) had received only two doses, while 18 (30.5%) had completed the induction phase. The median treatment duration in this group was 1.2 months (IQR 0.7–2.1). The 4-year OS was 42.7% in the former group (<2 months of treatment) and 40.3% in the latter (>2 months).

In the overall population, at univariate analysis, an inferior OS was associated with male sex (HR 1.64 (1.06–2.55)), lack of irAEs (HR 2.07 (1.13–3.80)), and second or third line therapies (vs first line, HR 2.65 (1.65–4.25)). Achieving a CR or PR remained strongly associated with improved OS (HR 0.27 (0.18–0.41)). Likewise, compared with discontinuation due to toxicity, treatment interruption on CR (HR 0.17 (0.07–0.44)) or PR (HR 0.19 (0.07–0.49)), as well as discontinuation due to toxicity after PR (HR 0.49 (0.31–0.78)) or CR (HR 0.16 (0.08–0.31)), were associated with significantly longer OS. In contrast, discontinuation in SD was not associated with an OS benefit (table 3).

At multivariate analysis, male sex (HR 1.73 (1.11–2.70)), second–third line (vs first line, HR 2.65 (1.62–4.32)) remained independently associated with worse OS. Discontinuation in CR (HR 0.15 (0.05–0.40)), in PR (HR 0.08 (0.03–0.26)), and interruption due to toxicity after CR (HR 0.14 (0.07–0.27)) or PR (HR 0.51 (0.32–0.82)) continued to be associated with OS. In addition, the development of irAEs, regardless of anti-TNFα administration, was associated with a longer OS. Specifically, irAEs not treated with anti-TNFα versus no irAEs showed an HR of 0.18 (0.07–0.42), while irAEs treated with anti-TNFα versus no irAEs showed an HR of 0.27 (0.11–0.67). When comparing patients who achieved a CR/PR and discontinued COMBO within 24 months with those who continued treatment beyond 24 months, by using a landmark analysis fixed at 24 months for both groups, no differences were observed in either PFS or OS (figure 3A,B). In both subgroups of patients median PFS and median OS were not reached, the 4-year PFS was 78.6% in the discontinuation group and 69.0% in the group who continued, while the 4-year OS was 88.2% and 80.8%, respectively. Baseline characteristics of these patients are reported in online supplemental table 1.

Table 2 PFS in patients with MBM: univariate and multivariate analysis

	Univariate HR (95% CI)	Multivariate HR (95% CI)
Gender	p=0.18	--
M	1.24 (0.91 to 1.71)	
F	Ref.	
Age	p=0.72	--
<62 years	Ref.	
≥62 years	1.06 (0.76 to 1.48)	
ECOG PS	p=0.050	p=0.65
0–1	Ref.	
2–3	1.80 (1.00 to 3.24)	
LDH	p=0.39	--
<ULN	Ref.	
>ULN	1.14 (0.84 to 1.55)	
B-RAF status	p=0.77	--
wt	Ref.	
mut	1.04 (0.78 to 1.41)	
Extracranial disease	p=0.36	--
No	Ref.	
Yes	0.83 (0.56 to 1.24)	
irAEs	p=0.42	--
No	1.24 (0.73 to 2.11)	
Yes	Ref.	
ANTI-TNF	p=0.03	p=0.007
No	0.70 (0.41 to 1.21)	0.35 (0.18 to 0.69)
Yes	1.06 (0.60 to 1.88)	0.42 (0.20 to 0.87)
No irAEs	Ref.	Ref.
Radiotherapy	p<0.001	p=0.010
No	Ref.	Ref.
Yes	2.01 (1.46 to 2.78)	1.55 (1.11 to 2.17)
Line of therapy	p=0.001	p=0.009
1 line	Ref.	Ref.
2–3 line	1.92 (1.29 to 2.86)	1.76 (1.16 to 2.69)
Best response to combo	p<0.001	p=0.16
CR-PR	0.24 (0.17 to 0.33)	
SD	Ref.	
Reason for Discontinuation	p<0.001	p<0.001
Toxicity	Ref.	Ref.
CR	0.10 (0.05 to 0.21)	0.10 (0.05 to 0.21)
PR	0.20 (0.11 to 0.37)	0.14 (0.06 to 0.29)
SD	0.66 (0.31 to 1.39)	0.43 (0.19 to 0.97)
Toxicity in PR	0.43 (0.30 to 0.62)	0.48 (0.33 to 0.70)
Toxicity in CR	0.13 (0.08 to 0.21)	0.13 (0.08 to 0.21)

Anti-TNF, anti-tumor necrosis factor therapy; BRAF, B-rapidly accelerated fibrosarcoma gene; COMBO, nivolumab plus ipilimumab; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; F, female; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; M, male; MBM, melanoma brain metastases; mut, mutated; PFS, progression-free survival; PR, partial response; SD, stable disease; ULN, upper limit of normal; wt, wild-type.

Table 3 OS in patients with MBM: univariate and multivariate analysis

	Univariate HR (95% CI)	Multivariate HR (95% CI)
Gender	p=0.03	p=0.016
M	1.64 (1.06 to 2.55)	1.73 (1.11 to 2.70)
F	Ref.	Ref.
Age	p=0.58	--
<62 years	Ref.	
≥62 years	1.14 (0.72 to 1.78)	
ECOG PS	p=0.96	--
0–1	Ref.	
2–3	0.97 (0.40 to 2.40)	
LDH	p=0.22	--
<ULN	Ref.	
>ULN	1.28 (0.86 to 1.92)	
B-RAF status	p=0.31	--
wt	Ref.	
mut	0.81 (0.55 to 1.21)	
Extracranial disease	p=0.39	--
No	Ref.	
Yes	0.80 (0.48 to 1.33)	
irAEs	p=0.018	p=0.99
No	2.07 (1.13 to 3.80)	
Yes	Ref.	
ANTI-TNF	p=0.002	p<0.001
No	0.18 (0.07 to 0.42)	0.18 (0.07 to 0.42)
Yes	0.18 (0.07 to 0.42)	0.18 (0.07 to 0.42)
No irAEs	Ref.	Ref.
Radiotherapy	p=0.06	p=0.83
No	Ref.	
Yes	1.49 (0.99 to 2.24)	
Line of therapy	p<0.001	p<0.001
1 line	Ref.	Ref.
2–3 line	2.65 (1.65 to 4.25)	2.65 (1.62 to 4.32)
Best response to Combo	p<0.001	p=0.53
CR-PR	0.27 (0.18 to 0.41)	
SD	Ref.	
Reason for Discontinuation	p<0.001	p<0.001
Toxicity	Ref.	Ref.
CR	0.17 (0.07 to 0.44)	0.15 (0.05 to 0.40)
PR	0.19 (0.07 to 0.49)	0.08 (0.03 to 0.26)
SD	1.21 (0.53 to 2.75)	0.60 (0.22 to 1.64)
Toxicity in PR	0.49 (0.31 to 0.78)	0.51 (0.32 to 0.82)
Toxicity in CR	0.16 (0.08 to 0.31)	0.14 (0.07 to 0.27)

anti-TNF, anti-tumor necrosis factor therapy; BRAF, B-rapidly accelerated fibrosarcoma gene; COMBO, nivolumab plus ipilimumab; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; F, female; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; M, male; MBM, melanoma brain metastases; mut, mutated; OS, overall survival; PR, partial response; SD, stable disease; ULN, upper limit of normal; wt, wild-typ.

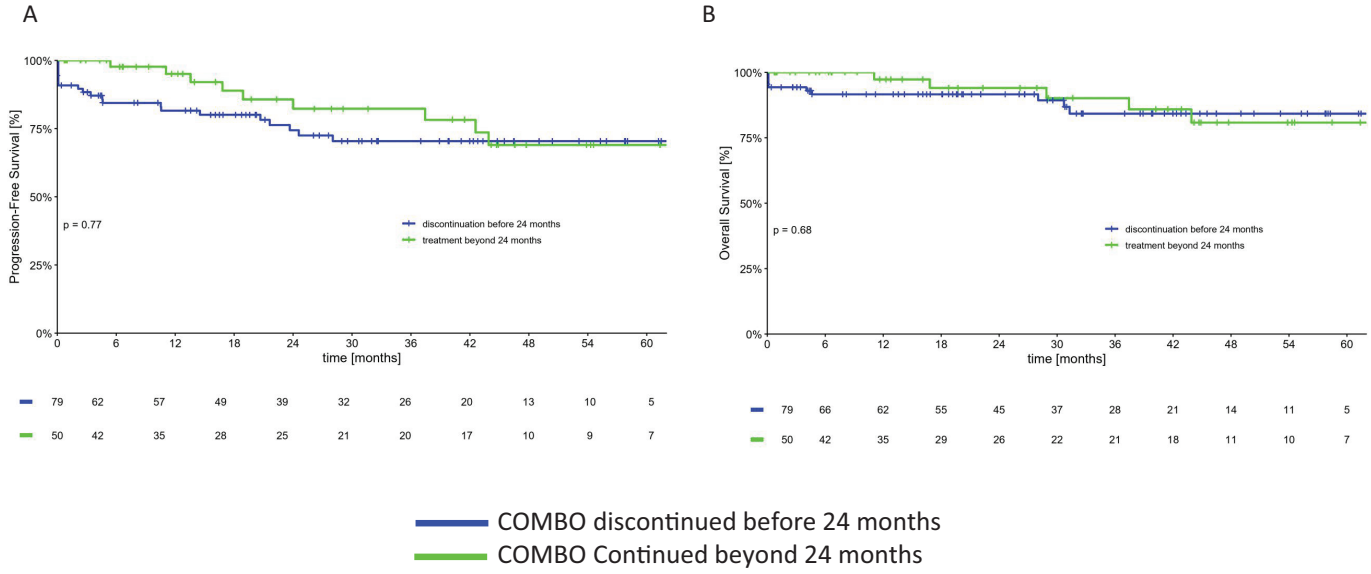

Figure 3 (A) PFS, and (B) OS at 24 months landmark. No statistically significant differences were observed between the two groups. COMBO, combination immunotherapy; OS, overall survival; PFS, progression-free survival.

Additionally, among the 146 patients achieving CR, 95 had a treatment duration <12 months and 51>12 months. In the <12-month group, the 4-year PFS from treatment discontinuation was 74.0%, compared with 78.9% in the >12-month group (p=0.86), while the 4-year OS was 89.2%, compared with 88.8% in the >12-month group, with no statistically significant difference (p=0.41).

Interestingly, among the 394 (84.7%) patients with CR/PR, 198 (42.6%) received baseline steroids (for symptomatic brain metastases) and 194 (41.7%) did not (data were missing for 2 patients). We observed no significant differences in long-term outcomes between the two groups: specifically, the 5-year PFS was 55.5% in patients without baseline steroids and 61.5% in those receiving steroids (p=0.39), while the 5-year OS was 74.7% and 75.5%, respectively (p=0.65).

Online supplemental table 3 summarizes the outcomes of patients with CNS-symptoms who discontinued COMBO within 24 months, with discontinuation mainly driven by toxicity (median PFS 3.2 months, range 0.0–6.6). Patients achieving a CR had a 4-year PFS of 100%, while those experiencing toxicity after CR showed a 4-year PFS of 80.7%. 4-year PFS was 75.0% in patients with PR and 58.4% in those discontinuing due to toxicity after PR. The 1-year, 2-year, 3-year, and 4-year time points PFS rates for the different subgroups are reported in online supplemental table S3. In the CNS symptomatic subgroup (n=115), median OS was not reached. Patients who discontinued for toxicity without response had a 4-year OS of 40.0%. Patients achieving a CR showed a 4-year OS of 100%, while it was 86.6% for those who developed toxicity after CR. In patients with PR, a 4-year OS was 100%, whereas it was 72.1% for those discontinuing due to toxicity after PR. Detailed 1-year, 2-year, 3-year, and 4-year OS time points rates across the different categories are reported in the online supplemental table 3.

DISCUSSION

The most relevant findings of the present study are the following: (1) at a rather long median follow-up of 51 months, median PFS was not reached in patients who, within 24 months, stopped COMBO due to objective response (CR/PR) or because of toxicity occurring after CR; (2) 4-year OS was 87.9% in patients discontinuing in CR, 83.5% in those with PR, and 89.6% in those discontinuing due to toxicity after a CR, (3) PFS and OS were similar in patients with CR/PR who discontinued COMBO within 24 months compared with those, who, after achieving CR/PR, continued treatment beyond 24 months, (4) the development of irAEs, regardless of anti-TNFα administration, was associated with a longer OS.

Our data have potential clinical implications for several reasons. The duration of immune checkpoint inhibitors in advanced melanoma, with extracranial disease only, is well established according to the current guidelines.[11–13] Specifically, patients with a CR that persists at the following radiological evaluation (at least 4 weeks after treatment), and who have received at least 6 months of anti-PD-1-based treatment, can be considered for stopping therapy.[16] In patients with MBM three independent prospective trials,[1–4] a real-world study[14] and a meta-analysis[15] support the use of COMBO in patients with brain metastases. Current ESMO consensus and guidelines, EADO/EDF/EORTC consensus and ASCO guidelines acknowledge the efficacy of COMBO in brain metastases but do not provide specific recommendations for treatment discontinuation in this subgroup of patients.[8 11–13] Consequently, clinicians may be reluctant to stop therapy in patients with MBM either before or after 2 years of treatment. For this reason, clinicians may opt for extended treatment duration to ensure sustained disease control.

The main clinical concern is driven by the uncertainty of the durability of responses after treatment discontinuation within 24 months, which is not well established, and because data regarding discontinuation in the context of brain metastases remain scarce. Furthermore, it is unclear if continuing COMBO after CR/PR provides a benefit compared to treatment discontinuation.

The ABC trial[2 3] and CheckMate 204 study[1] set up the duration of COMBO at 2 years. Nevertheless, data on discontinuation within 2 years and data on patients who discontinued treatment at 2 years compared with those who did not discontinue treatment are not available. Hence our findings extend our knowledge providing potentially useful information to clinicians for patient management.

Outside clinical trials, durable responses in MBM, after elective discontinuation of anti-PD1-based immunotherapy due to CR, have been reported in a small retrospective study on only 20 patients overall,[14–16] suggesting that treatment discontinuation may be considered in patients achieving response. Our study, which included patients outside clinical trials, provides strong results and supports discontinuation of treatment within 24 months in patients who achieved CR or PR. Remarkably, the median duration of treatment in patients developing irAEs after CR was only 2 months, suggesting that the induction phase during COMBO might be enough to maintain long-term control of the disease in these patients. The impact of severe irAEs seems to be different in patients with CR versus those in PR. The outcome in terms of PFS and OS was similar in patients who achieved CR with or without irAEs, which led to treatment discontinuation after CR. Interestingly the outcome in terms of PFS and OS in patients with a PR, was worse in those who developed severe irAEs leading to treatment discontinuation versus those who did not. Whether the tumor control in patients with irAEs and PR can be impaired by subsequent immunosuppressive treatment should be further evaluated.

In our study, the development of irAEs, regardless of anti-TNFα administration was associated with a longer OS. We can hypothesize that the development of irAEs could be a signal that an immune reaction has been activated. The lack of an obvious effect of infliximab on response in our study is consistent with the results of recent pooled analyses of data from the CheckMate 069 and CheckMate 067 trials.[18 19] In these analyses, OS outcomes were similar between patients with irAEs, who received corticosteroids, with or without infliximab, and those who had immune-related gastrointestinal AEs but did not receive immunosuppressive agents.

Interestingly, in our study the long-term outcome was similar in patients with CR/PR who discontinued COMBO within 24 months compared with those, who, after achieving CR/PR, continued treatment beyond 24 months. Hence, our study does not support continuing treatment in patients achieving CR/PR. These patients could stop treatment at 24 months, this strategy could spare useless treatment, reduce potential long-term irAEs in our patients as well as financial toxicity.

Patients with CNS-related symptoms show a worse PFS and OS than those who were asymptomatic.[1–3] However, in our series a subgroup of patients with CNS-related symptoms (3.7%) achieved a CR/PR, which in turn, was associated with a durable response, even after discontinuation of treatment. Notably, in a post hoc analysis among patients achieving CR/PR, long-term outcomes were comparable regardless of baseline steroid use, with similar PFS and OS observed in patients receiving steroids and those not receiving steroids, suggesting that steroid use did not compromise outcomes in responding patients.

Nevertheless, to improve prognosis, new treatments are needed.

Our study has several strengths, including (1) the largest cohort of patients evaluated to address the impact of COMBO discontinuation in patients with MBM outside clinical trials; (2) comprehensive data collection from specific databases including information on diagnosis, radiotherapy, surgical, systemic therapies and outcomes; (3) long-term follow-up allowing for the examination of mature data on PFS and OS and investigating the outcome of patients continuing treatment versus those who discontinue after achieving CR/PR. Moreover, data was retrieved from centers with expertise in melanoma management.

Nevertheless, we are also aware of some limitations, including the retrospective nature of our analysis with potential enrollment bias and the inability to use a target trial emulation approach. Furthermore, in patients who do not achieve a CR, the effect of SRS should be investigated in prospective studies such as the ABC-X study[20] (NCT03340129).

In conclusion, our study supports discontinuation of COMBO at 24 months in patients with CR and PR. Our study does not support continuing treatment beyond 24 months in patients who have achieved an objective response, since outcomes were similar between patients who continued COMBO and those who discontinued treatment. Strategies to optimize treatment should be pursued in patients who develop irAE after PR, since the long-term control seems to be suboptimal in this subgroup of patients compared with those in CR. Whether a locoregional treatment could be a strategy in this context should be tested in prospective clinical studies.

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