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Combined immunotherapy in melanoma patients with brain metastases: A multicenter international study

Mario Mandalà [a,1,*], Paul Lorigan [b,1], Maria Chiara Sergi [c], Naima Benannoune [d], Patricio Serra [b], Maria Grazia Vitale [e], Diana Giannarelli [f], Ana Maria Arance [g], Eva Munoz Couselo [h], Bart Neyns [i], Marco Tucci [c], Michele Guida [j], Francesco Spagnolo [k], Ernesto Rossi [l], Marcella Occelli [m], Paola Queirolo [n], Pietro Quaglino [o], Roberta Depenni [p], Barbara Merelli [q], Joanna Placzke [r], Anna Maria Di Giacomo [s], Michele del Vecchio [t], Alice Indini [t], Ines Pires da Silva [u], Alexander M. Menzies [v], Georgina V. Long [v], Caroline Robert [w], Piotr Rutkowski [r,2], Paolo A. Ascierto [e,2]

[a] Unit of Medical Oncology, University of Perugia, Perugia, Italy
[b] The University of Manchester, Oxford Rd, Manchester M13 9PL, UK
[c] Medical Oncology Unit, Azienda Ospedaliero Universitaria Policlinico di Bari, Bari, Italy
[d] Gustave Roussy Cancer Campus, Villejuif, France
[e] Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, I.N.T. IRCCS Fondazione "G. Pascale" Napoli, Naples, Italy
[f] Epidemiology and Biostatistics, Fondazione Policlinico Universitario, A. Gemelli IRCCS, Rome, Italy
[g] Hospital Clínic Barcelona, 08036 Barcelona, Spain
[h] Department of Medical Oncology. Vall d'Hebron Hospital, Barcelona, Spain & Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[i] Department of Medical Oncology, UZ Brussel, Brussels, Belgium
[j] Rare Tumors and Melanoma Unit, IRCCS Istituto dei Tumori "Giovanni Paolo II," Bari, Italy
[k] IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy
[l] Medical Oncology, Fondazione Policlinico Universitario, A. Gemelli IRCCS, Rome, Italy
[m] Medical Oncology, AO S.Croce e Carle, Cuneo, Italy
[n] IEO European Institute of Oncology, IRCCS, Milan, Italy
[o] Department of Dermatology, University of Turin, Turin, Italy
[p] University of Modena and Reggio Emilia, Department of Oncology, Hematology, Modena, Emilia-Romagna, Italy
[q] Oncology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy
[r] Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[s] Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy
[t] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[u] Melanoma Institute Australia, University of Sydney, and Blacktown Hospital, Sydney, New South Wales, Australia
[v] Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, New South Wales, Australia
[w] Gustave Roussy and Paris-Saclay University, Villejuif, France

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ABSTRACT

Background: Ipilimumab plus nivolumab (COMBO) is the standard treatment in asymptomatic patients with melanoma brain metastases (MBM). We report a retrospective study aiming to assess the outcome of patients with MBM treated with COMBO outside clinical trials.
Methods: Consecutive patients treated with COMBO have been included. Demographics, steroid treatment, Central Nervous System (CNS)-related symptoms, *BRAF* status, radiotherapy or surgery, response rate (RR), progression-free (PFS) and overall survival (OS) have been analyzed.
Results: 376 patients were included: 262 received COMBO as first-line and 114 as a subsequent line of therapy, respectively. In multivariate analysis, Eastern Cooperative Oncology Group (ECOG) (≥1 vs 0) [HR 1.97 (1.46–2.66)], extracerebral metastases [HR 1.92 (1.09–3.40)], steroid use at the start of COMBO [HR 1.59

* Correspondence to: Unit of Medical Oncology, University of Perugia, 06123 Perugia, Italy.
E-mail address: mario.mandala@unipg.it (M. Mandalà).
[1] Equally contributed first name.
[2] Equally senior contribution.

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(1.08–2.38)], CNS-related symptoms [HR 1.59 (1.08–2.34)], SRS (Stereotactic radiosurgery) [HR 0.63 (0.45–0.88)] and surgery [HR 0.63 (0.43–0.91)] were associated with OS. At a median follow-up of 30 months, the median OS (mOS) in the overall population was 21.3 months (18.1–24.5), whilst OS was not yet reached in treatment-naive patients, steroid-free at baseline. In patients receiving COMBO after BRAF/MEK inhibitors(i) PFS at 1-year was 15.7%. The dose of steroids (dexamethasone $<$ vs $\geq$ 4 mg/day) was not prognostic. SRS alongside COMBO vs COMBO alone in asymptomatic patients prolonged survival. ($p = 0.013$). Toxicities were consistent with previous studies. An independent validation cohort ($n = 51$) confirmed the findings.

Conclusions: Our results demonstrate remarkable long-term survival in treatment-naïve, asymptomatic, steroid-free patients, as well as in those receiving SRS plus COMBO. PFS and OS were poor in patients receiving COMBO after progressing to BRAF/MEKi.

1. Introduction

Melanoma is characterized by a high incidence of brain metastases [1,2]. Melanoma brain metastases (MBM) are not only frequent but are one of the leading causes of death from this disease. The presence of symptomatic brain metastases, a poor ECOG performance status (PS), and a leptomeningeal involvement have been consistently associated with shorter survival [3]. Immune checkpoint inhibitors with single-agent ipilimumab [4] and anti-PD-1 (nivolumab and pembrolizumab) have shown some activity in asymptomatic MBM patients but with low response rate (RR) (20–25%) [5,6]. BRAF/MEKi demonstrated higher RR (50%) but with short-term intracranial response duration (PFS 6 months) [7,8]. Three independent prospective studies [6,9,10] and a systematic review and meta-analysis support the use of COMBO in patients with MBMs [7]. These trials have shown an objective response rate (ORR) of ~50–55% in asymptomatic MBM patients with over 80% of these responses being durable. Based on these results, COMBO has become the recognized standard of care for patients with asymptomatic MBM. However, patients with CNS-related symptoms, including those requiring corticosteroids at the outset, have shown only modest responses, reinforcing the notion that treating these patients remains a significant challenge [6,9]. It is essential to acknowledge that patients enrolled in clinical studies represent a highly selected population and their outcomes may not be directly applicable to routine clinical practice. Unfortunately, the effectiveness of COMBO outside of the clinical trial setting is much less clear. Moreover, clinical studies have included only a small number of patients with CNS-related symptoms receiving steroids and there is also a scarcity of data regarding the long-term efficacy of COMBO in this population of patients outside clinical trials. Additionally, the clinical outcome after exposure to BRAF/MEKi has been explored only in a very limited cohort of patients [6]. Importantly, the prognostic impact of locoregional treatment remains uncertain. In a large retrospective study, no difference in survival outcomes was found among patients with MBM, who received different first-line therapies in addition to various types of radiotherapy [11]. A prospective clinical trial exploring the benefit of stereotactic radiotherapy (SRS) alongside COMBO in asymptomatic patients is still ongoing (ABC -X trial NCT03340129).

The aim of this study was to assess, in a retrospectively collected multicenter real-world patient cohort, the clinical impact of COMBO in patients with MBM, and to explore areas worthy of further investigation in future clinical trials.

2. Materials and methods

Patients with MBM treated with COMBO, between January 2015 and January 2023, were identified from the multicenter skin cancer registries of 17 centers (*detailed in* Supplementary Methods). The following parameters were retrieved: CNS-related symptoms before starting COMBO, use and dose of steroids during COMBO, concomitant extracranial disease, previous exposure to BRAF/MEKi, modalities and radiotherapy timing (concomitant if radiotherapy was performed within two weeks of starting or ending immunotherapy, and sequential radiotherapy in other cases), ORR, PFS, and OS as well as toxicity. Symptomatic brain disease was defined as either headache with or without nausea or vomiting, seizures, dizziness, or focal neurologic symptoms.

Ocular melanoma, patients without brain metastasis or those who didn't receive COMBO were excluded from this analysis.

2.1. Outcome

The primary end-point was OS, defined as the time from starting drug therapy upon diagnosis of brain metastases and death due to any cause. *Secondary endpoints and clinical assessment are included in* Supplementary Methods. The study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice.

2.2. Statistical analysis

In the initial step, patient characteristics were categorized based on variable types. Categorical factors were presented as absolute frequencies and percentages while quantitative variables were represented by their median, inter-quartile range and minimum and maximum values. Survival times were analyzed using the Kaplan-Meier method and the median survival time was reported along with its corresponding 95% confidence intervals. Survival rates at different time points were also derived from the Kaplan-Meier curve. To estimate Hazard Ratios (HR) and their 95% confidence intervals, a proportional hazard model was employed. Factors with a 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. Statistical analysis was conducted using the iBM-SPSS v.28.0 statistical software and R v.4.1.0.

3. Results

Three hundred seventy-six patients with MBM receiving COMBO were included in the analysis (Fig. 1). Overall, 247 patients (65.7%) were males and the median age at the time of MBM diagnosis was 57.4 years (IQR 45.9–68.5). The majority of melanomas [201 (53.5%)] harbored a $BRAF^{V600}$ mutation. 262 (69.7%) patients received COMBO as first-line, 109 (64.9%) as second-line treatment [102 (27%) after BRAF-MEKi failure]. 147 (39.1%) patients were symptomatic at MBM diagnosis, and 209 (55.6%) received steroids during COMBO (due to oedema, concomitant radiotherapy, or CNS-related symptoms). Of these, 160 (76.6%) received $\geq$ 4 mg of dexamethasone, 44 (21.4%) $<$ 4 mg per day. 86 (23%) patients underwent surgery of MBM, 163 (43.3%) received SRS: 102 (27%) concomitant SRS and 58 (15.4%) sequential SRS before or after COMBO treatment. Other demographic characteristics are detailed in Table S1. The median follow-up for the whole population was 30 months.

3.1. Overall response rate, progression-free survival, and overall survival in first-line patients

Regarding patients who received COMBO as first-line, the ORR was 52%; 45 (17%) had a complete response (CR), 92 (35%) partial response (PR), 15 (6%) stable disease (SD), and 92 (35%) progressive disease (PD). For 18 pts the ORR was not available. The median PFS (mPFS) was 5.2 months (95% CI: 3.5–6.9).

In asymptomatic patients, PFS at 1-year, 2-year and 3-year was 47.4%, 40.4% and 39.1% respectively, whilst in symptomatic patients was 22.9%, 18.3% and 16.0%. The mPFS of subgroups of patients is reported in Table S2.

In patients without CNS-related symptoms and steroids at start of immunotherapy, the mPFS was 13.9 months (n = 120, 95%CI: 1.1–26.6), while in those with CNS-related symptoms or steroids the mPFS was 3.5 months (n = 51, 95%CI 2.2–4.9), in those with CNS-related symptoms and steroids the mPFS was 2.9 months (n = 91, 95% CI 2.3–3.4) ($p < 0.001$).

In a multivariate analysis, ECOG PS (≥ 1 vs 0) [HR 1.58 (95% CI 1.16–2.16)], steroids during COMBO [HR 1.64 (1.09–2.47)] and the presence of CNS-related symptoms before starting COMBO [HR 1.55 (1.04–2.31)] were independently associated with a worse PFS.

Regarding survival, median OS (mOS) was not yet reached in asymptomatic patients, who did not receive steroids, while in patients who either had CNS-related symptoms or received steroids mOS was 18.2 months (95% CI: 12.9–23.5). In symptomatic patients, who received steroids, mOS was 6.1 months (95% CI: 4.0–8.2) ($p < 0.0001$) (Fig. 2A).

Moreover, in asymptomatic patients, the OS at 5-year was 52%, while in patients who didn't receive steroids was 58,4%. The mOS of subgroups of patients is detailed in Table S2.

Considering the dose of steroids (dexamethasone < 4 mg vs ≥4 mg) during COMBO, 2-year OS was not different. (Fig. S1A and Table S2).

In a multivariate ECOG status (≥1 vs 0) [HR 1.97(1.46–2.66)], extracerebral metastases [HR 1.92 (1.09–3.40)], steroid use at start of COMBO [HR 1.59 (1.08–2.38)], CNS-related symptoms [HR 1.59 (1.08–2.34)] negatively affected patient outcome, whilst SRS (Stereotactic radiosurgery) [HR 0.63 (0.45–0.88)] and surgery [HR 0.63 (0.43–0.91)] were positively associated with OS (Table 1).

In terms of intracranial response and its impact on patient outcome, the OS at 5-year was 0% in patients with PD, 33.6% with SD, 54.7% with PR, and 93.9% with CR ($p < 0.001$) (Fig. 2B) (Table S2).

3.2. Progression-free survival, overall response rate, and overall survival in subsequent lines patients

In patients who received COMBO as a second-line treatment, the ORR was 19% (21/109): 4 (3.6%) had a CR, 17 (15.5%) PR, 18 (16.5%) SD and 67 (61.4%) had PD. For 3 pts the ORR was not available. One hundred two (27%) received COMBO after BRAF/MEKi, among them 66 received steroids during COMBO. Patients receiving COMBO in the second-line after BRAF/MEKi failure experienced poor outcomes regardless of CNS-related symptoms and steroid use ($p = 0.67$). Specifically, the mPFS was 3.1 (2.1–4.1) months in those who received steroids vs 2.3 months (1.8–2.8) in those who didn't. The mOS after BRAF/MEKi progression was 21.9 months (Fig. S1B).

With regards to the whole pretreated population, the mPFS was 2.2 (n = 45, CI: 1.7–2.7) months in patients with both CNS-related symptoms and steroids, 2.5 (n = 19, CI: 1.6–3.4) months in those with CNS-related symptoms or steroids, and 2.6 (n = 37, CI:1.4–3.7) months in those without CNS-related symptoms and steroids, respectively.

Finally, 6 patients received COMBO as third-line treatment and the mPFS was 1.5 months (95% CI 0.7–2.3).

In asymptomatic patients, who did not receive steroids, mOS was 25.7 months, (n = 41, 95% CI: 17.3–34.1) in those who either had CNS-related symptoms or received steroids mOS was 22.3 months (n = 25, 95% CI: 16.2–28.4), while in symptomatic patients who received steroids, mOS was 21.2 months (n = 48; 95% CI: 17.6–24.8) respectively (Fig. 2C).

In asymptomatic patients, the OS at 3-year, 4-year, and 5-year was 33.1%, 24.9%, 19.3%, respectively, while in patients who didn't receive steroids was 34.8%, 30.1%, 21.5% (Table S2).

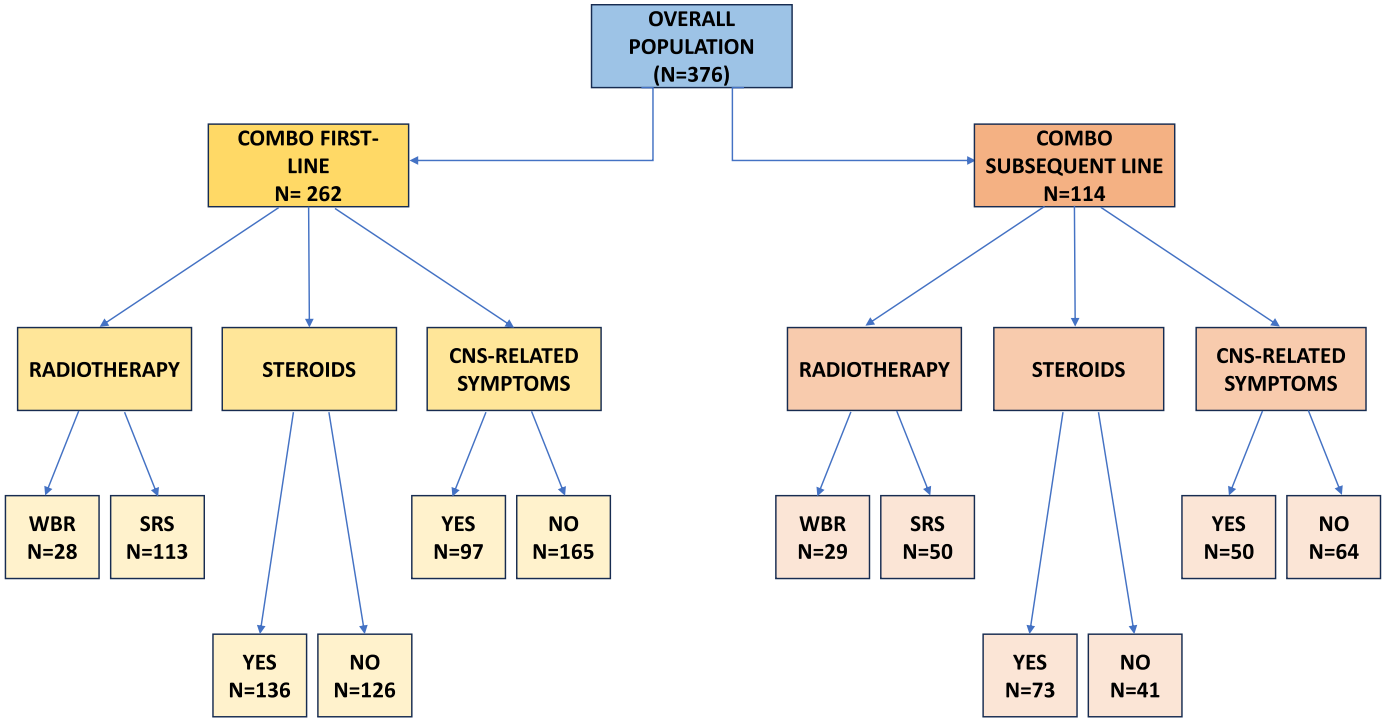

Fig. 1. Consort diagram: population who received COMBO as first-line or subsequent line, radiotherapy, with or without CNS-related symptoms and use of steroids. CNS: Central Nervous System. SRS: Stereotactic radiosurgery. WBR: Whole Brain Radiotherapy.

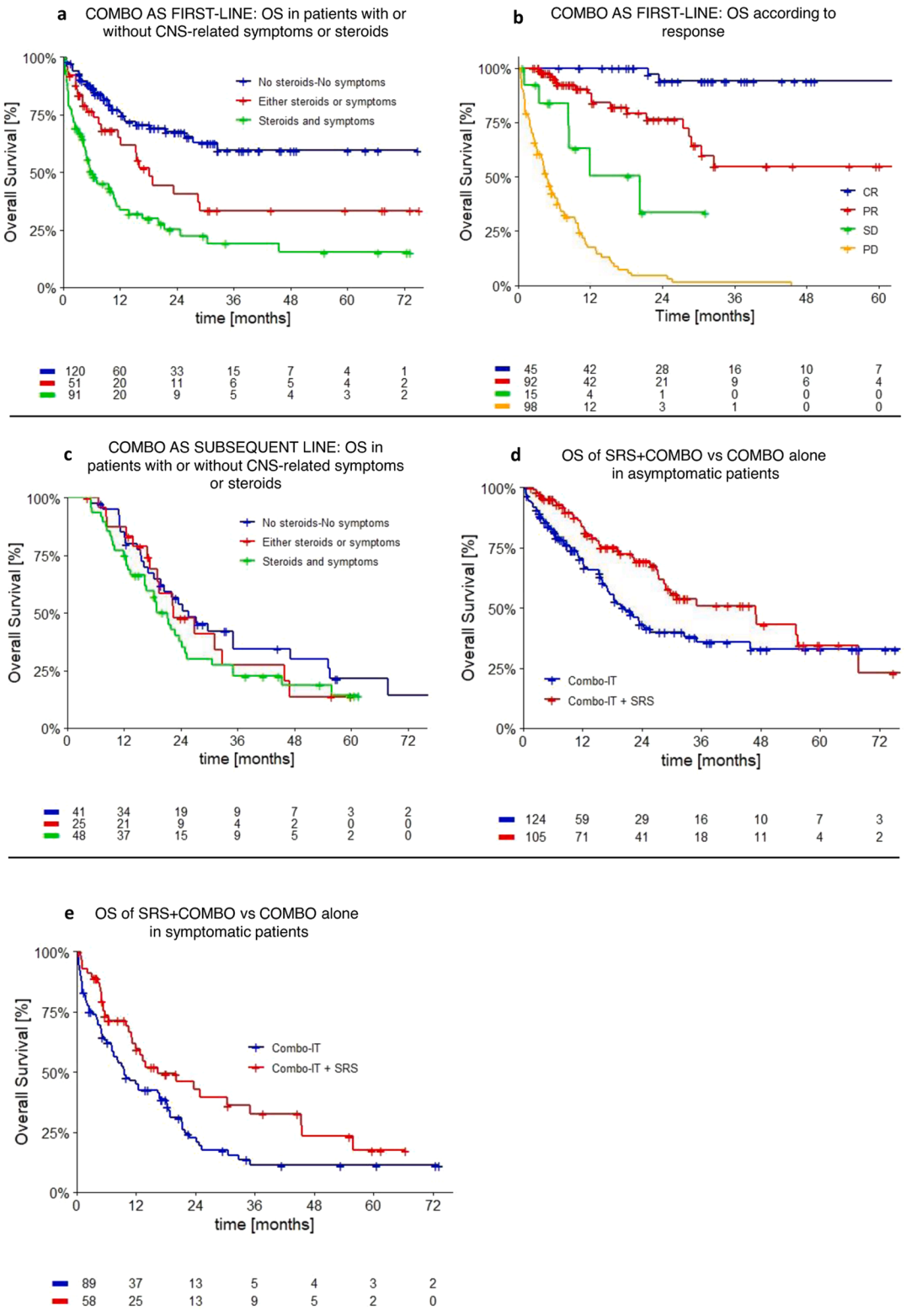

Fig. 2. A: OS in asymptomatic patients didn't receive steroids (n = 120), either had CNS-related symptoms or received steroids (n = 51), and symptomatic + received steroids (n = 91) in first-line with COMBO. B: OS in the first-line COMBO according to the response (CR=45, PR=92, SD=15, PD=98). C: OS in asymptomatic patients didn't receive steroids (n = 41), either had CNS-related symptoms or received steroids (n = 25), and symptomatic + received steroids (n = 48) in subsequent line with COMBO. D: OS in asymptomatic patients receiving SRS+ COMBO (n = 105) vs combo alone (n = 124). E: OS in symptomatic patients receiving SRS+ COMBO (n = 58) vs combo alone (n = 89). COMBO: Ipilimumab plus Nivolumab. CNS: Central Nervous System. CR: complete response. OS: Overall Survival. PD: Progressive disease. PR: Partial response. SD: Stable disease. SRS: Stereotactic radiosurgery.

Table 1
Univariate and Multivariable analysis for OS.

	Univariate Analysis for OSHR (95% CI)	Multivariable Analysis for OSHR (95% CI)
SEX		
Male	Ref.	
Female	1.08 (0.81-1.44)	
AGE in years	1.00 (0.99-1.01)	
ECOG PS		
0	**Ref.**	**Ref.**
> =1	**2.34 (1.77-3.11)**	**1.97 (1.46-2.66)**
LDH		
Normal	**Ref.**	—
Elevated	**1.34 (1.01-1.79)**	
BRAF STATUS		
Wt	Ref.	
Mutated	1.01 (0.76-1.34)	
EXTRA SITE		
No	**Ref.**	**Ref.**
Yes	**1.68 (1.00-2.85)**	**1.92 (1.09-3.40)**
TIME TO BRAIN METASTASES		
Synchronous	Ref.	
< 24 months	1.06 (0.67-1.69)	
≥ 24 months	0.93 (0.60-1.46)	
STEROIDS DURING IMMUNOTHERAPY		
No	**Ref.**	**Ref.**
Yes	**2.07 (1.54-2.79)**	**1.59 (1.08-2.38)**
FIRST-LINE THERAPY		
COMBO	Ref.	
Targeted	0.94 (0.71-1.26)	
COMBO		
First-line	Ref.	
Subsequent line	0.94 (0.71-1.25)	
CNS-related SYMPTOMS		
No	**Ref.**	**Ref.**
Yes	**2.15 (1.62-2.84)**	**1.59 (1.08-2.34)**
RADIOTHERAPY		
No	Ref.	Ref.
WBR	1.35 (0.93-1.96)	0.90 (0.60-1.34)
SRS	**0.64 (0.46-0.88)**	**0.63 (0.45-0.88)**
SURGERY		
No	**Ref.**	**Ref.**
Yes	**0.64 (0.46-0.92)**	**0.63 (0.43-0.91)**

CNS: Central Nervous System. COMBO: ipilimumab and nivolumab. ECOG: Eastern Cooperative Oncology Group Performance status. LDH: Lactate dehydrogenase. OS: Overall Survival. SRS: stereotactic radiosurgery. WBR: Whole Brain Radiotherapy.

Fig. S1C and D show OS in asymptomatic patients and in those who didn't receive steroids during COMBO as first or subsequent lines of therapy.

Finally, among patients receiving dexamethasone at dose < 4 mg/day the 2-year OS was 61.9%, while in those receiving dexamethasone ≥ 4 mg, the 2-year OS was 35.5% (Fig. S1E). The mOS is reported in Table S2.

3.3. Treatment with COMBO and radiotherapy: ORR, PFS and OS

Overall, 57 patients (15.1%) received Whole Brain Radiotherapy (WBR) and 163 (43.3%) received SRS. Among patients receiving SRS, 102 (62.5%) received concomitant SRS and 58 (35.5%) received SRS before or after COMBO treatment. Timing for 3 patients was not available. Patients who received COMBO and SRS (concomitant or sequential) showed a better OS compared to those receiving WBR: mOS was 30.5 months (15.8–20.5) and 18.2 months (23.6–37.4), respectively ($p < 0.0001$). Moreover, we evaluated SRS and COMBO vs COMBO alone: in asymptomatic patients receiving SRS and COMBO vs COMBO alone the mOS was 47.0 (28.0–65.0) vs 20.5 months (14.7–26.3) [$p = 0.013$], while mOS in symptomatic patients was 16.4 (5.2–27.5) vs 9.6 months (5.7–13.4)[$p = 0.016$], respectively, in patients receiving SRS and COMBO vs COMBO alone (Fig. 2D,E).

The ORR, in patients who received sequential or concomitant SRS, was 55.9% vs 60.5% [$p = 0.62$], respectively. The mPFS and mOS were 6.9 months (3.8–9.9) and 30.5 months (22.3–38.7), respectively, in patients who received concomitant SRS, while mPFS was 4.9 months (1.5–8.3) and mOS 35.0 months (12.8–57.2) in those who received sequential SRS.

3.4. Discontinuation of COMBO and long-term response

Among 376 patients, 75 (20%) and 11 (3%) discontinued treatment for toxicity or clinical choice in patients with a CR. Among patients who discontinued treatment due to CR, the median duration of treatment was 23.8 months, the median follow-up after discontinuation of immunotherapy was 15 months and 100% of patients were alive at the last follow-up (median follow-up: 32.5 months). Furthermore, 75 patients (20%) discontinued treatment due to toxicity. The median duration of treatment for this cohort was 1.2 months and the median follow-up after discontinuation of immunotherapy was 7 months. In these patients the landmark survival at 6 and 12 months was respectively 76.6% and 57.0%.

3.5. Safety

In our study, 274 (73%) patients were reported to have at least one immune-related adverse event (irAE). Grade 3 or 4 treatment-related adverse events occurred in 139 (37%) patients treated with COMBO. All treatment-related adverse events are listed in Table S3. Treatment-related deaths occurred in 4 (1.5%) patients; pneumonitis was the most common cause of death (2 patients).

3.6. Validation cohort

An independent, validation cohort from Institute Gustave Roussy was retrieved and analyzed. Overall, 51 patients were included, among them 32 pts (62.7%) received COMBO in first-line, and 19 (37.3%) in subsequent lines. The mOS in patients with steroids was 24.9 months, while in those without steroids was not yet reached [$p = 0.031$] after a median follow-up time of 38 months.

OS was also evaluated in different subgroups of patients, based on CNS-related symptoms and the use of steroids (Fig. S2A, B, C).

mOS according to the response to COMBO was as follows: 8.5 months for PD, 24.9 months for SD, 14.7 for PR and not yet reached for CR. (Fig. S2D).

Overall, 17 patients (33%) discontinued treatment due to toxicity. The median duration of treatment for this cohort was 1.4 months and the median follow-up after discontinuation of immunotherapy was 12 months. In these patients the landmark survival at 6, and 12 months was 87.1% and 62.5%. In patients who received concomitant radiotherapy ($n = 5$) OS at 12 months was 75%, while in patients who received sequential radiotherapy ($n = 9$) was 53.3%.

4. Discussion

Our study yields several findings of clinical value in patients treated with COMBO outside of clinical trials: 1) remarkable long-term survival outcomes were achieved in asymptomatic MBM patients without steroids and in those achieving a complete (13%) and partial (28%) response; 2) patients receiving COMBO after BRAF/MEKi failure exhibited a poor prognosis, regardless of steroids use and CNS-related symptoms; 3) the dosage of steroids (dexamethasone < or ≥ 4 mg) during COMBO did not impact prognosis; 4) SRS, given sequentially or concomitantly with COMBO, was associated with improved survival compared to no SRS or WBRT; 5) in a subgroup of patients, durable responses was maintained after immunotherapy interruption.

In this study, we collected data from both academic institutions and

general hospitals. Although high quality evidence is generally conveyed through randomized clinical trials, studies that produce real-world evidence provide some advantages over conventional clinical trials [12] including: i) patients are not selected with stringent inclusion or exclusion criteria, ii) real-world studies typically involve larger dataset that encompasses a broader and more representative cross-section of the patient population under investigation, iii) results obtained from real-world evidence can enhance the generalizability of the findings obtained from clinical trials.

In this context, our results show that COMBO is effective in MBM, with durable responses in most patients who were treatment-naive. These results align well with those reported by prospective clinical trials [6,9,10].

The long-term efficacy differs between patients receiving COMBO at first-line versus subsequent lines. Specifically, OS at 5-year was 19.3% in asymptomatic patients and 21.5% in those without steroids receiving COMBO in subsequent lines, while, it was 52% and 58.4%, at first-line, in these subgroup of patients, respectively. This underscores the benefit of initiating COMBO as a first-line strategy, as its effectiveness decreases when considered in subsequent lines. Furthermore, we observed that, regardless of steroids and CNS-related symptoms, the PFS and OS outcomes were poor after progression on combined BRAF/MEKi. These results match well with translational studies demonstrating the development of an immune-resistance tumor microenvironment upon BRAF/MEKi progression [13,14]. Furthermore, considering the short PFS and OS with BRAF/MEKi in patients with $BRAF^{V600E}$-mutated asymptomatic untreated MBM [8], our data strongly suggests that first-line treatment for patients with asymptomatic MBM should be the COMBO rather than BRAF/MEKi. Our results are in line and extend, outside clinical trials, findings reported by the ABC study [6].

Unsurprisingly, patients with symptomatic MBM, with or without corticosteroid use, had worse OS compared with those who were asymptomatic and steroid-free. In patients without CNS-related symptoms or steroids, the mPFS was 13.9 months, in those with CNS-related symptoms and steroids the mPFS was 2.9 months ($p < 0.001$). However, a few patients with CNS-related symptoms exhibited durable responses, suggesting that the COMBO may be active in a subset of these patients, with steroids potentially negatively impacting survival. We did not identify a specific threshold for steroids-related detrimental effects; patients receiving dexamethasone < 4 mg or ≥ 4 mg showed similar outcomes. Strategies, for example, SRS/surgery to dominant brain metastases in non-eloquent areas, to enable patients to discontinue corticosteroids are needed to overcome the immune suppressive effects of corticosteroids. Considering that patients pretreated with BRAF/MEKi have poor outcomes regardless of steroids and CNS-related symptoms, alternative strategies are warranted. Ongoing approaches include: I) anti-angiogenic drugs agents that impact cerebral and peritumoral oedema (trials NCT02681549 and NCT04955743), ii) initial stereotactic radiotherapy (ABC-X study [NCT03340129]), or iii) new less toxic checkpoint inhibitors in combination with BRAF/MEKi.

Findings from our study reveal a possible positive impact of SRS on the outcome of patients with MBM. Patients with SRS showed a longer median survival and SRS was an independent prognostic factor for OS in multivariate analysis. An improved survival with SRS had also been detected in a recent study by Franklin et al. [11], who evaluated various systemic therapies and in contrast to our results found a positive effect with conventional radiotherapy. Furthermore, Amaral et al. found a positive impact of SRS in MBM patients treated with COMBO in univariate analysis, but the type of treatment and addition of radiotherapy were not included in multivariate to adjust for confounding parameters [15]. However, major selection bias likely impacts results, hence a trial is required.

Whether SRS given concomitantly or in sequence, before or after initiation of systemic therapy, is more beneficial is still unclear. It is supposed that SRS may synergize with immunotherapy by eradicating T regulatory cells that, in turn, dampen the immune response [16–20], NCT03340129].

An individual patient meta-analysis showed improved OS of patients treated with ICIs and concomitant ($\pm$ 1 month before or after therapy start) SRS when compared with ICIs and non-concomitant SRS [21].

We did not find any significant impact on OS for patients who received sequential vs concomitant SRS during COMBO. Our findings are in agreement with the results reported by Franklin et al. [11].

Recently several studies reported that long-lasting responses can be maintained after anti-PD1 interruption. In the majority of the studies, patients with MBM were excluded [22,23]. Sustainable responses in metastatic melanoma patients, with and without brain metastases, after elective discontinuation of anti-PD1-based immunotherapy due to CR, have been reported in a small retrospective study [24]. In the challenging context of MBM, our study extends these results and suggests that treatment discontinuation may be considered in patients achieving a CR.

Our study boasts several strengths, including i) a very large cohort of patients to address the impact of COMBO in patients with MBM outside clinical trials; ii) comprehensive data collection from specific databases including information on diagnosis, radiotherapy, surgical, systemic therapies and outcomes; iii) long-term follow-up allowing for the examination of mature data on PFS and OS. Moreover, data was collected from referral centers with expertise in melanoma management, providing a consistent approach. Finally, our results were confirmed by an independent validation cohort.

Nonetheless, we are also aware of some limitations, including the retrospective nature of our analysis with potential enrollment bias. Additionally, we did not consider the number and the size of brain metastases, which may have prognostic significance in patients with MBM. Indeed, in asymptomatic patients treated with first-line COMBO, the OS across 3 studies [6,9,10] differed based on the median size and number of BM at baseline: 48% in NIBIT-M2 trial (43% of patients had >4 BM), 57% in ABC trial (40% of patients had >4 BM and medium size of 19 mm) and 72% in Checkmate 204 (33% of patients had >3 BM and medium size of 15 mm). Finally, the effect of SRS should be investigated in prospective studies such as ABC-X study [NCT03340129].

In conclusion, our study supports COMBO as a first-line treatment in asymptomatic patients treated outside of clinical trials. Our results underscore the need for innovative strategies in patients progressing after BRAF/MEKi and advocate for studies investigating SRS in combination with COMBO. Furthermore, treatment discontinuation may be considered for patients achieving a CR to COMBO treatment.

Ethics approval and consent to participate

The study protocol and all amendments were approved by the independent ethics committee of each participating institution. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent prior to study enrollment.

CRediT authorship contribution statement

Mario Mandalà and Paolo A. Ascierto conceived, designed the study and wrote first manuscript draft. Piotr Rutkowski and Paul Lorigan contributed to the design of the study as well. Maria Chiara Sergi collected, assembled data and wrote first manuscript draft. Diana Giannarelli performed the statistics and wrote first manuscript draft. All authors provided the data patients, revised and agreed to the published version of the manuscript.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113542.

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