



Combined immunotherapy with nivolumab and ipilimumab with and without sequential or concomitant stereotactic radiotherapy in patients with melanoma brain metastasis: An international retrospective study

Mario Mandalà^{a,*}, Teresa Amaral^{b,1}, Piotr Rutkowski^{c,1}, Maria Chiara Sergi^d, Marie-Lena Rasch^b, Naima Benannoune^e, Patricio Serra^f, Maria Grazia Vitale^g, Diana Giannarelli^h, Ana Maria Aranceⁱ, Eva Munoz Couselo^j, Bart Neyns^k, Iris Dirven^l, Marco Tucci^m, Michele Guidaⁿ, Francesco Spagnolo^o, Ernesto Rossi^p, Paola Queirolo^q, Pietro Quaglino^r, Roberta Depenni^s, Joanna Placzke^c, Anna Maria Di Giacomo^t, Michele Del Vecchio^u, Alice Indini^u, Ines Pires da Silva^v, Alexander M. Menzies^w, Angela Hong^{x,y}, Paul Lorigan^f, Georgina V. Long^{w,2}, Caroline Robert^{z,2}, Paolo A. Ascierto^{g,2}

^a Unit of Medical Oncology, University of Perugia, Perugia, Italy

^b Skin Cancer Clinical Trials Center, Department of Dermatology, Eberhard Karls University, Tuebingen, Germany

^c Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

^d Unit of Medical Oncology, "Mons. A.R. Dimiccoli" Hospital, Asl BT, Viale Ippocrate, 15, Barletta, BT 70051, Italy

^e Gustave Roussy Cancer Campus, Villejuif, France

^f The University of Manchester, Oxford Rd, Manchester M13 9PL, UK

^g Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, I.N.T. IRCCS Fondazione "G. Pascale" Napoli, Naples, Italy

^h Epidemiology and Biostatistics, Fondazione Policlinico Universitario, A. Gemelli IRCCS, Rome, Italy

ⁱ Hospital Clínic Barcelona and IDIBAPS, Barcelona 08036, Spain

^j Department of medical oncology, Vall d'Hebron Hospital, Barcelona, Spain & Vall d'Hebron Institute of oncology (VHIO), Barcelona, Spain

^k Department of Medical Oncology, UZ Brussel, Brussels, Belgium

^l Department of medical oncology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

^m Medical Oncology Unit, University of Bari Aldo Moro, Policlinico Hospital of Bari, Bari 70124, Italy

ⁿ Rare Tumors and Melanoma Unit, IRCCS Istituto dei Tumori "Giovanni Paolo II", Bari, Italy

^o IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy

^p Medical Oncology, Fondazione Policlinico Universitario, A. Gemelli IRCCS, Rome, Italy

^q IEO European Institute of Oncology, IRCCS, Milan, Italy

^r Department of Dermatology, University of Turin, Turin, Italy

^s University of Modena and Reggio Emilia, Department of Oncology, Hematology, Modena, Emilia-Romagna, Italy

^t Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy

^u Unit of Melanoma Medical Oncology, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

^v Melanoma Institute Australia, University of Sydney, and Blacktown Hospital, Sydney, New South Wales, Australia

^w Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, New South Wales, Australia

^x Department of Radiation Oncology, Chris O'Brien Lifehouse, Camperdown, New South Wales 2050, Australia

^y Faculty of Medicine and Health, Sydney Medical School, The University of Sydney, Australia

^z Gustave Roussy and Paris-Saclay University, Villejuif, France

ARTICLE INFO

Keywords:
Melanoma brain metastases
Sequential radiotherapy

ABSTRACT

Background: Ipilimumab plus nivolumab (COMBO) is the standard treatment in patients with asymptomatic melanoma brain metastases (MBM). We report a retrospective study aiming to assess the outcome of patients with MBM treated with COMBO with or without sequential/concomitant stereotactic radiotherapy (SRT).

* Corresponding author.

E-mail address: mario.mandala@unipg.it (M. Mandalà).

¹ Equally first author contribution

² Equally senior contribution

<https://doi.org/10.1016/j.ejca.2025.115567>

Received 8 April 2025; Received in revised form 29 May 2025; Accepted 3 June 2025

Available online 9 June 2025

0959-8049/© 2025 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Concomitant radiotherapy
Combioimmunotherapy

Methods: MBM patients treated with COMBO with or without SRT have been retrieved: demographics, steroid treatment, Central Nervous System [CNS]-related symptoms, *BRAF* status, radiotherapy (yes/no and timing) or surgery, number of MBM, maximum diameter of metastasis, overall response rate (ORR), progression-free (PFS) and overall survival (OS) have been analyzed.

Results: 453 patients were included: 190 received COMBO alone, 107 received COMBO and concomitant SRT, 156 COMBO and sequential SRT, respectively. At multivariable analysis the line of treatment [> 1 st vs 1 st: HR 2.60 (1.93–3.50)], sequential SRT vs no radiotherapy [HR 0.45 (0.32–0.64)], concomitant SRT vs no radiotherapy [HR 0.48 (0.33–0.69)], steroids [HR 1.56 (1.17–2.08)], age [HR 1.01 (1.00–1.02)] and number of MBM [≥ 3 vs 1 HR 1.55 (1.11–2.17)], 2 vs 1 HR 1.53 (1.02–2.31)] at baseline were associated with OS.

There was no significant difference between patients who received concomitant vs sequential SRT. At a median follow-up of 29 months, the median-OS in the overall population was 17.8 months while in those who received SRT was 27.3 (15.3–39.4) for patients receiving sequential radiotherapy and 22.2 (12.7–31.7) for those receiving radiotherapy concomitantly to COMBO. The incidence of radionecrosis was 10.3 %. Toxicities were consistent with previous studies.

Conclusions: Our results suggest a better OS in patients who receive SRT plus COMBO, regardless of timing of SRT. Prospective studies are needed to validate our findings.

1. Introduction

Brain metastasis is common in advanced melanoma and one of the leading causes of death from this disease [1,2]. The number and size of brain metastases, symptoms at diagnosis, the use of steroids, a poor ECOG performance status (PS), and a leptomeningeal involvement have been consistently reported as associated with a poor outcome [3]. In patients with melanoma brain metastases (MBM), immune checkpoint inhibitors (ICI) given as monotherapy have shown low ORR (20–25 %) [4–6] while *BRAF*/MEKi demonstrated high ORR (50 %) but the median PFS is only 6 months [7,8]. Three independent prospective studies [6,9,10], a real-life experience [11] and a systematic review and meta-analysis support the use of combined ipilimumab with nivolumab (COMBO) standard of care for asymptomatic patients with MBM [7]. Stereotactic radiotherapy (SRT) is a modality that can be used for MBM, while whole brain radiation therapy (WBRT) is usually confined to selected patients who have widespread, symptomatic MBM, and it is given with a palliative purpose without a survival benefit [12–14]. In a large retrospective study, adding radiotherapy to systemic therapy improves the outcome in patients with MBM, although no difference was observed according to different types of systemic therapies [15]. Two prospective clinical trials exploring the benefit of SRT alongside COMBO in asymptomatic patients are ongoing (ABC -X trial NCT03340129, ETOP-19–21 USZ-Strike, 16). Moreover, a recent update of the Melanoma Graded Prognostic Assessment (Melanoma-GPA), based on a large contemporary cohort of patients with MBM ($n = 1796$) [17], has significantly enhanced the accuracy of survival prediction in this population. This revised tool integrates key prognostic factors—Karnofsky Performance Status, number of brain metastases, presence of extracranial metastases, serum LDH levels, and prior exposure to immunotherapy—to reflect outcomes in the modern therapeutic era, characterized by widespread use of immune checkpoint inhibitors and targeted therapies. Although treatment modality was not included in the prognostic model, the improved survival outcomes observed are likely influenced by advances in both systemic therapies and local treatments such as SRS, which has become a key component in the multidisciplinary management of MBM [17]. Considering that the indication, the clinical impact and the best timing of SRT in patients with MBM receiving COMBO remains uncertain, the aim of this study was to assess the outcome of patients with MBM treated with COMBO outside clinical trials with or without sequential or concomitant SRT.

2. Materials and methods

Patients with MBM treated with COMBO (Ipilimumab 3 mg/Kg plus Nivolumab 1 mg/Kg) with or without SRT, between January 2012 and April 2024, were identified from the multicenter skin cancer registries of 18 centers (detailed in [Supplementary Methods](#)), regardless of the

adjuvant treatment received. The following parameters were retrieved: CNS-related symptoms and/or steroids before starting COMBO, number of brain metastases, maximum size of brain metastasis, SRT exposure and timing (concomitant if radiotherapy was performed within two weeks of starting or ending immunotherapy, and sequential radiotherapy in other cases), ORR, PFS, and overall 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 did not receive COMBO were excluded from this analysis. For patients who received SRT, Magnetic Resonance Imaging (MRI) acquisition and a planning CT scan were performed before SRT and during follow up. Selection of dosimetry parameters (maximum dose, marginal isodose and number of isocenters) was carried out based on size, number, shape, localization of MBM in order to spare critical structures. Radionecrosis, a complication of radiotherapy characterized by necrosis and inflammation, was diagnosed according to the previous literature [18,19] based on radiological features as a ring-enhancing lesion that indicates a disruption in the blood-brain barrier (BBB) on T1-weighted imaging and surrounding vasogenic edema on T2/FLAIR signal. Radionecrosis was monitored through longitudinal MRI and clinical follow-up, and treatment decisions were guided by radiological findings and clinical improvement [20].

2.1. Outcome

The primary endpoint was OS, defined as the time from starting COMBO upon diagnosis of brain metastases to the death due to any cause. *Secondary endpoints and clinical assessment are included in [Supplementary Methods](#)*. The study design and methodology were approved by the institutional review boards of each participating institution. The study was carried out 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 timepoints 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

Four hundred fifty-three patients with brain metastases were included: 190 (42.0 %) received COMBO alone, 107 (23.6 %) received COMBO plus concomitant SRT, 156 (34.4 %) COMBO plus sequential SRT. Median age for the entire group was 60 years, 63.6 % of them were males. About half (49.9 %) were *BRAF*-mutated, 69.8 % received COMBO in a first line metastatic setting, median time to brain metastases diagnosis from melanoma detection was 28.6 months and the majority of patients (89.8 %) had also extracranial disease.

Baseline characteristics of patients treated with concomitant/sequencing SRT or COMBO alone are reported in [Supplementary Table 1](#). Overall, 64 (60 %), 110 (70 %), 105 (55 %) of patients treated with concomitant SRT, sequential SRT, or COMBO alone respectively had ECOG PS 0. LDH level was high in 48 % of patients treated with COMBO alone vs 34 % and 38 % of those treated with sequential and concomitant SRT, respectively. The median diameter of the largest brain metastasis was 14 mm in the overall population, specifically in COMBO alone 10 mm, in sequential SRT 14 mm, and in concomitant SRT 15 mm ([Supplementary Table 1](#)).

Among patients treated with COMBO alone, 38 patients (8.4 %) received dexamethasone > 4 mg for symptom management and among these, 30 (78.9 %) had more than three BM.

COMBO was a first line treatment in 75 % of patients receiving concomitant SRT cohort, 61 % in the sequential SRT cohort and 74 % in the COMBO-alone cohort.

3.1. Outcomes

At a median follow-up of 29 months, 245 (54.1 %) patients died, with a one-year OS of 58.7 %, two-year OS of 43.6 % and three-year of 35.6 %. In patients who received COMBO alone, the one-year, two-year, three-year landmark OS was 47.3 %, 32.7 % and 29.6 %, respectively; in those receiving concomitant SRT plus COMBO the one-year, two-year,

three-year landmark OS was 68.1 %, 48.1 % and 35.5 %, respectively; while, in patients receiving COMBO plus sequential SRT group, one-year OS was 66.8 %, two-year OS was 53.2 %, and three-year OS was 42.7 %.

The median OS in the entire population was 17.8 months (95 % CI: 13.3–22.2). Median OS was 9.4 months (3.9–15.0) for patients not receiving radiotherapy, 27.3 (15.3–39.4) for patients receiving sequential radiotherapy and 22.2 (12.7–31.7) for those receiving radiotherapy concomitantly to COMBO ($p < 0.001$) [[Figure 1](#)].

In patients undergoing concomitant SRT, 90 (84.1 %) started RT within 3 months from the beginning of COMBO with an OS at 3 years of 38.0 % and the remaining 17 (15.9 %) later that 3 months with an OS at 3 years of 28.6 % ($p = 0.19$).

Patients receiving RT within 2 months from the diagnosis of brain metastasis had a median OS of 27.5 (95 % CI: 16.3–38.7) while those receiving RT later had a median OS of 26.1 months (95 % CI: 15.3–37.0) ($p = 0.76$).

Factors associated with OS are summarized in [Table 1](#). At univariate analysis, the line of treatment [> 1 st vs 1st; HR 2.02 (1.56–2.62)], LDH levels [elevated vs normal; HR 1.59 (1.23–2.06)], number of brain metastases [2 vs 1: HR 1.47 (0.99–2.20); ≥ 3 vs 1: HR 1.77 (1.29–2.44)], type of radiotherapy [sequential vs no; HR 0.58 (0.43–0.77); concomitant vs no; HR 0.59 (0.43–0.82)], surgery [HR 0.69 (0.52–0.91)], use of steroids [HR 1.43 (1.11–1.84)] and symptoms [HR 1.29 (1.00–1.66)] impacted on OS. At multivariate analysis, line of treatment (> 1 st vs 1st) [HR 2.60 (1.93–3.50)], SRT (sequential vs no radiotherapy) [HR 0.45 (0.32–0.64)], SRT (concomitant vs no radiotherapy) [HR 0.48 (0.33–0.69)], and steroids [HR 1.56 (1.17–2.08)], age [HR 1.01 (1.00–1.02)] and number of MBM [≥ 3 vs 1 HR 1.55 (1.11–2.17)], 2 vs 1 HR 1.53 (1.02–2.31)] were associated with OS. No significant impact of surgery was observed at multivariate analysis. There was no significant difference between patients who received concomitant vs sequential SRT [[Table 1](#)].

[Supplementary Table 2](#) summarizes PFS univariate and multivariate analysis. At univariate analysis the line of treatment [> 1 st vs 1st; 2.11 (1.67–2.65)], LDH levels [elevated vs normal; HR 1.25 (0.99–1.57)], number of brain metastases [2 vs 1; HR 1.19 (0.88–1.60), ≥ 3 vs 1; HR 1.53 (1.16–2.01)], use of steroids [HR 1.77 (1.41–2.23)] and symptoms [HR 1.32 (1.05–1.64)] were associated with a worse PFS.

At multivariate analysis, line of COMBO [> 1 st vs 1st; 2.00

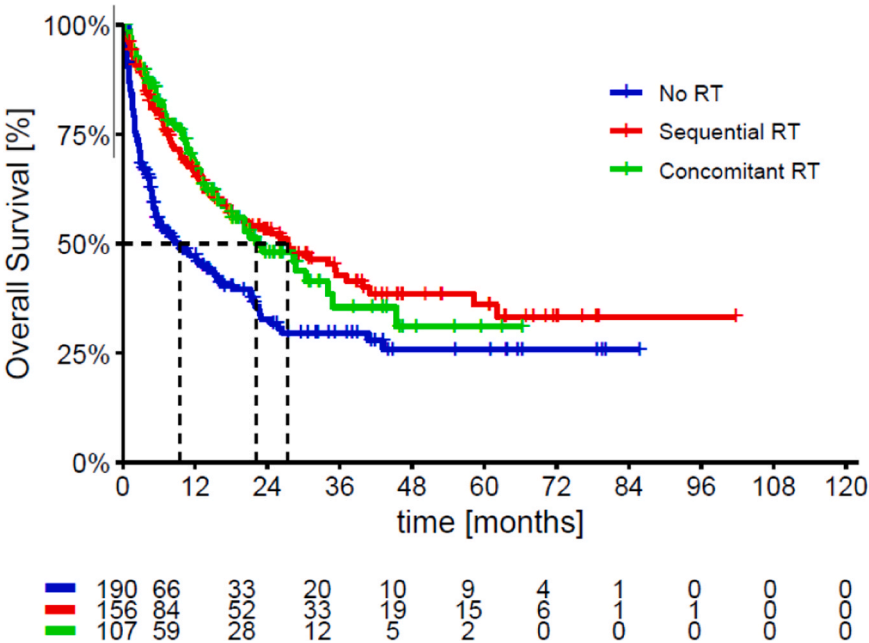


Fig. 1. OS of NO SRT, sequential RT and concomitant RT cohorts. Os of patients not receiving radiotherapy (n = 190), receiving sequential radiotherapy (n = 156) and radiotherapy concomitantly (n = 107) to COMBO. Combo: ipilimumab plus nivolumab, OS: overall survival, SRT: stereotactic radiotherapy.

Table 1
Univariate and multivariate analysis for OS from start of COMBO-IT.

	UNIVARIATE HR (95 % CI)	MULTIVARIABLEHR (95 % CI)
Gender		Not considered
MF	1.09 (0.84–1.42) p = 0.52Ref.	
AGE in years	1.01 (0.99–1.02) p = 0.076	1.01 (1.00–1.02) p = 0.033
TIME FROM DIAGNOSIS TO BRAIN METS in months	1.00 (0.99–1.00) p = 0.10	Not considered
COMBO-IT SETTING		P < 0.001
1st line2nd /3rd line	P < 0.001Ref.2.02 (1.56–2.62)	Ref.2.60 (1.93–3.50)
NUMBER OF BRAIN METS		P = 0.025
12 > =3	P = 0.002Ref.1.47 (0.99–2.20)1.77 (1.29–2.44)	Ref.1.53 (1.02–2.31)1.55 (1.11–2.17)
LARGEST LESION in mm	1.01 (1.00–1.02) p = 0.25	Not considered
LDH		—
NormalElevated	P < 0.001Ref.1.59 (1.23–2.06)	
TYPE OF RT		P < 0.001Ref.0.45
No SequentialConcomitant	P < 0.001Ref.0.58 (0.43–0.77) 0.59 (0.43–0.82)	(0.32–0.64)0.48 (0.33–0.69)
STEROIDS		P = 0.003Ref.1.56
NoYes	P = 0.006Ref.1.43 (1.11–1.84)	(1.17–2.08)
CNS-SYMPTOMS		—
NoYes	P = 0.049Ref.1.29 (1.00–1.66)	
SURGERY		—
NoYes	P = 0.010Ref.0.69 (0.52–0.91)	

CNS: Central nervous system, COMBO-IT: combo-immunotherapy, RT: radiotherapy,

(1.56–2.55)], type of RT [sequential SRT vs no radiotherapy, HR 0.74 (0.1.84 (1.45–2.34)57–0.97) and concomitant SRT vs no radiotherapy, HR 0.63 (0.46–0.85)], and use of steroids [HR 1.84 (1.45–2.34)] were associated with a shorter PFS.

The incidence of radionecrosis was 10.3 %, without any difference between sequential (10.9 %) and concomitant (9.3 %) SRT. All these patients were managed conservatively with high-dose steroids, and none required surgical intervention.

ORR with COMBO was 188/453 (41.5 %), and a significantly higher ORR was observed in patients who received SRT 125/263 (47.5 %) compared to those who did not (63/190, 33.2 %, p = 0.002). The response rate was numerically higher in patients who received concomitant (58/107, 54.2 %) vs sequential (67/156, 42.9 %) SRT (p = 0.073). Moreover, 46 %, 60 %, 50 % of patients receiving COMBO alone, concomitant or sequential SRT and received steroids, achieved a complete or a partial response, respectively (p = 0.087). Hence, SRT was associated with a numerically higher response rate in this subgroup of patients (Supplementary Table 1).

In our study, 63 patients (33.5 %) who didn't receive SRT, achieved CR or PR and 127 (47.9 %) achieved SD and PD. Among patients who responded, the 5-year overall survival (OS) rate was 68.6 %, while in non-responders, the 5-year OS was 2.9 %. Of the 156 patients who underwent sequential SRT, 65 (41.6 %) received SRT as salvage therapy for progressive brain disease or in case of a suboptimal response, such as stable disease, while 91 (58.4 %) underwent SRT prior to COMBO for symptom control.

Data on immune related adverse events (irAEs) were consistent with previous studies. Specifically, any grade irAEs occurred in 49.3 % of patients, ranging from 40.1 % in patients who did not receive radiotherapy, 53.9 % and 58.9 % in those who received sequential and concomitant radiotherapy, respectively. The G3-G4 irAEs rates for the

three groups were 21.4 %, 25.3 % and 30.8 %, respectively.

4. Discussion

The results of this retrospective study suggest that SRT plus COMBO therapy may significantly increase OS compared to COMBO alone. Although the median OS was 27.3 months in patients receiving sequential SRT, 22.2 months for with concomitant SRT, and 9.4 months in patients who received COMBO alone, selection bias may account for this difference. The impact of SRT treatment from prospective studies on COMBO in patients with MBM is partially reported. In the last update of the ABC trial [6], the landmark 7-year OS was 51 % for patients who received COMBO as a first-line treatment. Further insights are expected from the ABC-X trial, a randomized study evaluating the efficacy of SRT combined with COMBO versus COMBO alone (NCT03340129). Our study findings match well with those reported from a recent meta-analysis [21], which reported a potential benefit from the combination of SRT and immunotherapy. In this meta-analysis of 126 studies, which included a variety of systemic treatments (targeted therapy, anti-PD1, and anti-CTLA4 +anti-PD1), the addition of SRT to immunotherapy resulted in a median OS of 22 months. Despite the limitations of retrospective data collection and heterogeneity in outcomes across the included studies, the meta-analysis suggests that the addition of SRT to immunotherapy may reduce the risk of death by approximately 30 %. Similarly, a Bayesian meta-analysis by Cong Li [22] examined seven different treatment approaches for MBM and confirmed that SRT combined with immunotherapy provides the best benefit in terms of intracranial PFS and OS.

However, Cong Li' study [22] also suggested a potential higher incidence of radiation necrosis with the combined approach.

Interestingly, our study found that only 10 % of patients developed radionecrosis across different combined treatment groups, although the true incidence of radionecrosis may have been underestimated given the retrospective nature of this study. A key secondary outcome in the prospective ABC-X study is the rate of radionecrosis in those who receive SRT + COMBO.

Our findings underscore the importance of SRT combined with COMBO, regardless of radiotherapy timing. No significant difference in OS was observed between sequential and concomitant administration. This benefit was also reported in a study by the German group [23], where median OS for RT+ ICI was 21 months, consistent with our data. Rauschenberg et al. suggested that the timing of ICI and RT administration does not significantly impact OS, in line with findings by Qian et al. (2016) [24], which suggested a benefit of ICI within 4 weeks of SRT but no impact on OS. Although these studies primarily evaluated single-agent immunotherapy, their data support our findings.

Our results are partially in disagreement with other studies. In DECOG study [25], no significant difference was found in OS between first line and later-line COMBO, whereas our study suggests an OS benefit with first-line treatment. This discrepancy may be due to patient characteristics and the number of brain metastases. On the other hand, in the DECOG study [25], locoregional therapy with RT or surgery improved OS, similarly to our study. OS was significantly influenced by intracranial disease response, with 2-year OS rates ranging from 63 % to 86 % in patients with stable disease, partial response, or complete response, while those with progressive disease had a 2-year OS rate of 20 %. Notably, in the DECOG study, patients who did not receive RT or local therapy had a median OS of 16 months, whereas in our study, it was 9.4 months. This difference could be attributed to included patients, as the proportion of symptomatic patients was 30 % in DECOG's study and 50 % in the present study. Additionally, the German study had 50 % missing data regarding symptoms. Timing analysis in the DECOG study favored upfront SRT, with an OS of 26 months, whereas delayed locoregional therapy reduced OS to 16 months. Furthermore, previous studies evaluating single-agent immunotherapy in combination with SRT showed no impact on outcome. A retrospective study of 54 patients

treated with ipilimumab within 4 months of SRT versus SRT alone [26] found no significant differences in 1-year local control (71.4 % vs. 92.3 %, $P = 0.40$) or intracranial control (12.7 % vs. 29.1 %, $P = 0.59$) between the two groups. Patients who received ipilimumab within 14 days of SRT had higher 1-year and 2-year OS (42.9 %) than those receiving it after 14 days (33.8 % and 16.9 %) or SRT alone (38.5 % and 25.7 %), though these differences were not statistically significant.

We are aware of some limitations of our studies: 1) the retrospective data collection brings inherent biases and confounding factors that cannot be entirely excluded; 2) potential treatment bias: the decision to administer radiotherapy and its timing may have been influenced by unmeasured clinical factors, such as treatment availability, the patient's clinical status, or physicians' preferences; 3) rate of radionecrosis could be underestimated considering the retrospective analysis and the challenges in clinical diagnosis [18–20]; 4) lack of data on quality of life and neurological symptoms, 5) we assessed intracranial response using RECIST 1.1 criteria: although RANO-BM criteria are specifically designed to assess intracranial response in patients with brain metastases, their application is more commonly limited to prospective clinical trials due to the need for standardized, detailed imaging protocols and comprehensive clinical data, including corticosteroid use and neurological assessments. In the context of a real-world, retrospective study, RECIST 1.1 criteria were adopted as they are routinely used in clinical practice, more easily applicable to existing imaging reports, and allow for consistent and reproducible evaluation of treatment response across heterogeneous datasets [27].

Our study has several strengths: 1) this is the largest series so far reported 2) data derived from melanoma referral centers with experience in treating patients with MBM, 3) all patients were treated with COMBO; 4) were able to retrieve data on timing of SRT for all patients, 5) we adjusted our results for number and size of brain metastases, which, in turn, are associated with outcome. Hence, regardless of the number of brain metastases, patients may benefit from radiotherapy if SRT is technically feasible, in order to optimize intracranial response. Indeed, in the COMBO alone group, 8 % of patients receiving steroids for symptom management did not undergo SRT or surgery, due to the burden of intracranial disease. Therefore, despite the presence of symptoms requiring steroids, the high burden of brain metastases in these patients precluded locoregional interventions.

In our study, sequential SRT was limited to patients who did not achieve a deep response to COMBO. Interestingly, we did not observe any difference in terms of outcome between concomitant and sequential SRT. Hence, it's reasonable to consider SRT in patients without complete or partial response to COMBO, to consolidate the intracranial tumour control and potentially reduce the risk of toxicity, although we found no difference in the overall incidence of adverse events between the two subgroups, in line with previous studies. [28]

In summary our study suggests a long-term benefit of SRT plus COMBO regardless of their timing and the number of brain metastases. Prospective, randomized trials, such as the ABC-X study and ETOP 19–21 USZ-STRIKE study [16], are warranted to validate these findings and optimize treatment protocols.

CRediT authorship contribution statement

Diana Giannarelli: Writing – review & editing, Data curation. **Paolo A. Ascierto:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Maria Grazia Vitale:** Writing – review & editing, Data curation. **Caroline Robert:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Eva Munoz Couso:** Writing – review & editing, Data curation. **Ana Maria Arance:** Writing – review & editing, Data curation. **Iris Dirven:** Writing – review & editing, Data curation. **Bart Neyns:** Writing – review & editing, Data curation. **Michele Guida:** Writing – review & editing, Data curation. **Marco Tucci:** Writing – review & editing, Data curation. **Ernesto Rossi:** Writing – review & editing, Data curation. **Francesco Spagnolo:**

Writing – review & editing, Data curation. **Georgina V. Long:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Paul Lorigan:** Writing – review & editing, Data curation. **Roberta Depenni:** Writing – review & editing, Data curation. **Pietro Quagliano:** Writing – review & editing, Data curation. **Anna Maria Di Giacomo:** Writing – review & editing, Data curation. **Joanna Placzke:** Writing – review & editing, Data curation. **Alice Indini:** Writing – review & editing, Data curation. **Teresa Amaral:** Writing – review & editing, Supervision, Data curation. **Michele Del Vecchio:** Writing – review & editing, Data curation. **MANDALA' MARIO:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Alexander M. Menzies:** Writing – review & editing, Data curation. **Maria Chiara Sergi:** Writing – review & editing, Writing – original draft, Data curation. **Ines Pires da Silva:** Writing – review & editing, Data curation. **Piotr Rutkowski:** Writing – review & editing, Supervision, Data curation. **Naima Benannoune:** Writing – review & editing, Data curation. **Marie-Lena Rasch:** Writing – review & editing, Data curation. **Angela Hong:** Writing – review & editing, Data curation. **Patricio Serra:** Writing – review & editing, Data curation. **Paola Queirolo:** Writing – review & editing, Data curation.

Funding

None.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mario Mandalà: consulting fees for Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi, Merck, Sun Pharma. Payment or honoraria for lectures, presentations: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi, Merck, Sun Pharma. Participation on a Data Safety/Advisory board for Merck Sharp & Dohme.

Teresa Amaral: Advisory board membership from Delcath and Philogen; personal fees as an invited speaker from Bristol Myers Squibb (BMS), Medscape, Neracare, Novartis and Pierre Fabre; personal fees for a writing engagement from CeCaVa and Medtrix; institutional fees as local principal investigator (PI) from Agenus Inc., AstraZeneca, BioNTech, BMS, HUYA Bioscience, Immunocore, IO Biotech, MSD, Pfizer, Philogen, Regeneron, Roche and University Hospital Essen; institutional fees as coordinating PI from Unicancer; institutional research grants from iFIT and Novartis; institutional funding from MNI - Naturwissenschaftliches und Medizinisches Institut, Neracare, Novartis, Pascoe, Sanofi and Skyline-Dx; non-remunerated membership of the American Society of Clinical Oncology (ASCO) and the Portuguese Society for Medical Oncology; a role as clinical expert in the area of medical oncology for Infarmed, and a role as an expert for SGA Oncology at EMA

Marie-Lena Rasch: No conflicts of interest

Piotr Rutkowski: Honoraria: Bristol Myers Squibb, MSD, Novartis, Roche, Pfizer, Pierre Fabre, Sanofi, Merck. Consulting or Advisory Role: Novartis, Blueprint Medicines, Bristol Myers Squibb, Pierre Fabre, MSD, Amgen. Speaker's Bureau: Pfizer, Novartis, Pierre Fabre. Research Funding: Novartis (Inst), Roche (Inst), Bristol Myers Squibb (Inst). Travel Accommodations, Expenses: Orphan Europe, Pierre Fabre.

Maria Chiara Sergi: No conflicts of interest

Naima Benannoune: No conflicts of interest

Patricio Serra: No conflicts of interest

Maria Grazia Vitale: No conflicts of interest

Diana Giannarelli: No conflicts of interest.

Ana Maria Arance: Consulting or advisory board for BMS, Roche, Novartis, Pierre Fabre, MSD, Merck, Sanofi. Speakers' Bureau for Pierre Fabre, Novartis, MSD, BMS, Roche, Merck, Sanofi. Travel, Accommodations, Expenses: BMS, MSD, Novartis, Pierre Fabre. Research Funding: Pierre Fabre, Novartis, Roche, BMS, MSD, Merck, Sanofi.

Eva Munoz Couselo: Advisory board for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi. Honoraria for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche. Clinical trial participation (principal investigator): Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi.

Bart Neyns: Speakers bureaus, consulting or advisory board from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and AstraZeneca.

Iris Dirven: No conflicts of interest

Marco Tucci: Honoraria for Bristol Meyer Squibb, Novartis.

Michele Guida: No conflicts of interest

Francesco Spagnolo: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Novartis, MSD, BMS, Pierre Fabre, Merck, Sanofi, Sun Pharma, IGEA, Philogen. Consulting fees: Novartis, MSD, Sun Pharma, Pierre Fabre.

Ernesto Rossi: Consultant for Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Immunocore and Pfizer.

Paola Queirolo: Consulting or Advisory Role: Roche/Genentech, Novartis, MSD, Bristol Myers Squibb, Pierre Fabre, Sanofi, Sun Pharma Advanced Research Company, Merck Serono. Travel, Accommodations, Expenses: MSD Oncology, Sanofi/Regeneron.

Pietro Quaglino: Advisory board and speaker fees from BMS, MSD, Novartis, Pierre-Fabre

Roberta Depenni: advisory board and speaker fees from BMS, MSD, Novartis, Pierre-Fabre, Sanofi.

Joanna Placzke: Travel grants from MSD and BMS.

Anna Maria Di Giacomo: consultant and/or advisor to Incyte, Pierre Fabre, Glaxo Smith Kline, Bristol-Myers Squibb, Merck Sharp Dohme, Sunpharma, Immunocore and Sanofi and has received compensated educational activities from Bristol Myers Squibb, Merck Sharp Dohme, Pierre Fabre and Sanofi.

Michele Del Vecchio: Advisor and Consultant for BMS, MSD, Novartis, Pierre Fabre, Immunocore.

Alice Indini: Advisory board: MSD. Honoraria for lectures: BMS, MSD, Novartis, Pierre-Fabre, Sanofi, AstraZeneca. Consultant: Need, Inc.

Paul Lorigan: Honoraria: Novartis, Pierre Fabre, Merck, BMS, MSD, NeraCare GmbH, Amgen, Roche, Oncology Education, Nektar. Consulting or Advisory Role: Merck Sharp & Dohme, Bristol Myers Squibb, Amgen, Pierre Fabre, Novartis, Nektar. Speaker's Bureau: Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, Pierre Fabre, BMS. Travel Accommodations, Expenses: Merck Sharp & Dohme, Bristol Myers Squibb.

Ines Pires da Silva: travel support by BMS and MSD, speaker fee by Pierre Fabre, Roche, BMS and MSD, and has served as consultant on advisory boards from MSD

Alexander M. Menzies: consultant advisor to BMS, MSD, Novartis, Roche, Pierre-Fabre and QBiotech.

Angela Hong: has received compensation from OncoBeta for participation in Advisory Boards

Georgina V. Long: consultant advisor for Agenus, Amgen, Array BioPharma, AstraZeneca, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, Hexal AG (Sandoz Company), Highlight Therapeutics S.L., Immunocore, Inovvent Biologics USA, Merck Sharpe & Dohme, Novartis, PHMR Ltd, Pierre Fabre, Provectus, Qbiotics, Regeneron

Caroline Robert: Consulting or Advisory Role from Bristol Myers Squibb, Roche, Novartis, Pierre Fabre, MSD, Sanofi, AstraZeneca, Pfizer.

Paolo A. Ascierto: Stock and Other Ownership Interests: PrimeVax. Consulting or Advisory Role: Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Array BioPharma, Merck Serono, Pierre Fabre, Incyte, MedImmune, AstraZeneca, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore, 4SC, Alkermes, Italfarmaco, Nektar, Boehringer Ingelheim, Eisai, Regeneron, Daiichi Sankyo, Pfizer, OncoSec, Nouscom, Takis Biotech, Lunaphore Technologies, Seattle Genetics, ITEos Therapeutics. Research Funding: Bristol Myers Squibb

(Inst), Roche/Genentech (Inst), Array BioPharma (Inst), Sanofi (Inst). Travel Accommodations, Expenses: Merck Sharp & Dohme

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115567.

References

- [1] Cagney DN, Martin AM, Catalano PJ, Redig AJ, Lin NU, Lee EQ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *NeuroOncol* 2017;19:1511–21. <https://doi.org/10.1093/neuonc/nox077>.
- [2] Tawbi HA, Boutros C, Kok D, Robert C, McArthur G. New era in the management of melanoma brain metastases. *Am Soc Clin Oncol Educ Book* 2018;741–50. <https://doi.org/10.1200/EDBK.200819>.
- [3] Tan X-L, Le A, Scherrer E, Tang H, Kiehl N, Han J, et al. Systematic literature review and meta-analysis of clinical outcomes and prognostic factors for melanoma brain metastases. *Front Oncol* 2022;12:1025664. <https://doi.org/10.3389/fonc.2022.1025664>.
- [4] Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012;13:459–65. [https://doi.org/10.1016/S1470-2045\(12\)70090-6](https://doi.org/10.1016/S1470-2045(12)70090-6).
- [5] Kluger HM, Chiang V, Mahajan A, Zito CR, Szol M, Tran T, et al. Long-Term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *JCO* 2019;37:52–60. <https://doi.org/10.1200/JCO.18.00204>.
- [6] Long GV, Atkinson V, Lo SN, Guminski AD, Sandhu SK, Brown MP, et al. Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study. *Lancet Oncol* 2025;26:320–30. [https://doi.org/10.1016/S1470-2045\(24\)00735-6](https://doi.org/10.1016/S1470-2045(24)00735-6).
- [7] Rulli E, Legramandi L, Salvati L, Mandalà M. The impact of targeted therapies and immunotherapy in melanoma brain metastases: a systematic review and meta-analysis. *Cancer* 2019;125:3776–89. <https://doi.org/10.1002/cncr.32375>.
- [8] Davies MA, Saiag P, Robert C, Grob J-J, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017;18:863–73. [https://doi.org/10.1016/S1470-2045\(17\)30429-1](https://doi.org/10.1016/S1470-2045(17)30429-1).
- [9] Tawbi HA, Forsyth PA, Hodi FS, Algazi AP, Hamid O, Lao CD, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol* 2021;22:1692–704. [https://doi.org/10.1016/S1470-2045\(21\)00545-3](https://doi.org/10.1016/S1470-2045(21)00545-3).
- [10] Di Giacomo AM, Chiarion-Sileni V, Del Vecchio M, Ferrucci PF, Guida M, Quaglino P, et al. Primary analysis and 4-Year Follow-Up of the phase III NIBIT-M2 trial in melanoma patients with brain metastases. *Clin Cancer Res* 2021;27:4737–45. <https://doi.org/10.1158/1078-0432.CCR-21-1046>.
- [11] Mandalà M, Lorigan P, Sergi MC, Benannoun N, Serra P, Vitale MG, et al. Combined immunotherapy in melanoma patients with brain metastases: a multicenter international study. *Eur J Cancer* 2024;199:113542. <https://doi.org/10.1016/j.ejca.2024.113542>.
- [12] Yamamoto M, Higuchi Y, Sato Y, Aiyama H, Kasuya H, Barfod BE. Stereotactic radiosurgery for patients with 10 or more brain metastases. In: Niranjan A, Lunsford LD, Kano H, editors. *Progress in Neurological Surgery*, 34. S. Karger AG; 2019. p. 110–24. <https://doi.org/10.1159/000493056>.
- [13] Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387–95. [https://doi.org/10.1016/S1470-2045\(14\)70061-0](https://doi.org/10.1016/S1470-2045(14)70061-0).
- [14] Hong AM, Fogarty GB, Dolven-Jacobsen K, Burmeister BH, Lo SN, Haydu LE, et al. Adjuvant Whole-Brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. *JCO* 2019;37:3132–41. <https://doi.org/10.1200/JCO.19.01414>.
- [15] Franklin C, Mohr P, Bluhm L, Grimmelmann I, Gutzmer R, Meier F, et al. Impact of radiotherapy and sequencing of systemic therapy on survival outcomes in melanoma patients with previously untreated brain metastasis: a multicenter DeCOG study on 450 patients from the prospective skin cancer registry ADORREG. *J Immunother Cancer* 2022;10:e004509. <https://doi.org/10.1136/jitc-2022-004509>.
- [16] Weller M, Le Rhun E, Tsamtsouri L, Dummer R, Guckenberger M, Ribí K, et al. Immunotherapy or targeted therapy with or without stereotactic radiosurgery for patients with brain metastases from melanoma or non-small cell lung cancer - the ETOP 19-21 USZ-STRIKE study. *Lung Cancer* 2025;199:108069. <https://doi.org/10.1016/j.lungcan.2024.108069>.
- [17] Sperduto PW, Marquee KE, Chang E, Li J, Davies MA, Ebner DK, et al. Improved survival and prognostication in melanoma patients with brain metastases: an update of the melanoma graded prognostic assessment. *JCO* 2025;JCO-24-01351. <https://doi.org/10.1200/JCO-24-01351>.
- [18] Kohutek ZA, Yamada Y, Chan TA, Brennan CW, Tabar V, Gutin PH, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain

- metastases. *J Neurooncol* 2015;125:149–56. <https://doi.org/10.1007/s11060-015-1881-3>.
- [19] Pires da Silva I, Glitza IC, Haydu LE, Johnpulle R, Banks PD, Grass GD, et al. Incidence, features and management of radionecrosis in melanoma patients treated with cerebral radiotherapy and anti-PD-1 antibodies. *Pigment Cell Melanoma Res* 2019;32:553–63. <https://doi.org/10.1111/pcmr.12775>.
- [20.] Mayo ZS, Billena C, Suh JH, Lo SS, Chao ST. The dilemma of radiation necrosis from diagnosis to treatment in the management of brain metastases. *NeuroOncol* 2024;26:S56–65. <https://doi.org/10.1093/neuonc/noad188>.
- [21] Williams GJ, Hong AM, Thompson JF. Treatment of melanoma brain metastases with radiation and immunotherapy or targeted therapy: a systematic review with meta-analysis. *Crit Rev Oncol/Hematol* 2024;202:104462. <https://doi.org/10.1016/j.critrevonc.2024.104462>.
- [22] Li C, Li K, Zhong S, Tang M, Shi X, Bao Y. Which is the best treatment for melanoma brain metastases? A Bayesian network meta-analysis and systematic review. *Crit Rev Oncol/Hematol* 2024;194:104227. <https://doi.org/10.1016/j.critrevonc.2023.104227>.
- [23] Rauschenberg R, Bruns J, Brütting J, Daubner D, Lohaus F, Zimmer L, et al. Impact of radiation, systemic therapy and treatment sequencing on survival of patients with melanoma brain metastases. *Eur J Cancer* 2019;110:11–20. <https://doi.org/10.1016/j.ejca.2018.12.023>.
- [24] Qian JM, Yu JB, Kluger HM, Chiang VLS. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* 2016;122:3051–8. <https://doi.org/10.1002/cncr.30138>.
- [25] Amaral T, Kiecker F, Schaefer S, Stege H, Kaehler K, Terheyden P, et al. Combined immunotherapy with nivolumab and ipilimumab with and without local therapy in patients with melanoma brain metastasis: a DeCOG* study in 380 patients. *J Immunother Cancer* 2020;8:e000333. <https://doi.org/10.1136/jitc-2019-000333>.
- [26] Patel KR, Shoukat S, Oliver DE, Chowdhary M, Rizzo M, Lawson DH, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. *Am J Clin Oncol* 2017;40:444–50. <https://doi.org/10.1097/COC.000000000000199>.
- [27.] Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol* 2015;16:e270–8. [https://doi.org/10.1016/S1470-2045\(15\)70057-4](https://doi.org/10.1016/S1470-2045(15)70057-4).
- [28] Elyan N, Schwenkenbecher P, Grote-Levi L, Becker J-N, Merten R, Christiansen H, et al. Radiotherapy in patients with brain metastases with and without concomitant immunotherapy: comparison of patient outcome and neurotoxicity. *Discov Onc* 2024;15:656. <https://doi.org/10.1007/s12672-024-01560-6>.