



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

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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).

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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

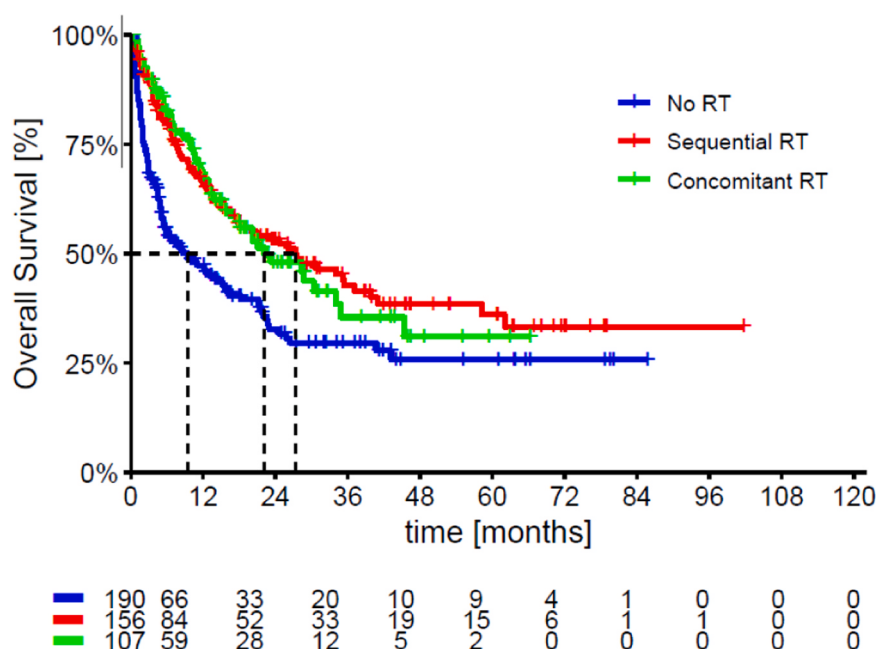


Fig. 1. OS of NO SRT, sequential RT and concomitant RT cohorts. OS of patients not receiving radiotherapy ($n = 190$), receiving sequential radiotherapy ($n = 156$) and radiotherapy concomitantly ($n = 107$) to COMBO. Combo: ipilimumab plus nivolumab, OS: overall survival, SRT: stereotactic radiotherapy.

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.

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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.

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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

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

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Appendix A. Supporting information

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