



# Clinical outcomes of melanoma brain metastases treated with nivolumab and ipilimumab alone versus nivolumab and ipilimumab with stereotactic radiosurgery

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## Abstract

**Purpose** Upfront dual checkpoint blockade with immune checkpoint inhibitors (ICI) has demonstrated efficacy for treating melanoma brain metastases (MBM) in asymptomatic patients. Whether the combination of stereotactic radiosurgery (SRS) with dual checkpoint blockade improves outcomes over dual-checkpoint blockade alone is unknown. We evaluated clinical outcomes of patients with MBM receiving ICI with nivolumab and ipilimumab, with and without SRS.

**Methods** 49 patients with 158 MBM receiving nivolumab and ipilimumab for untreated MBM between 2015 and 2022 were identified at our institution. Patient and tumor characteristics including age, Karnofsky Performance Status (KPS), presence of symptoms, cancer history, MBM burden, and therapy course were recorded. Outcomes measured from initiation of MBM-directed therapy included overall survival (OS), local control (LC), and distant intracranial control (DIC). Time-to-event analysis was conducted with the Kaplan–Meier method.

**Results** 25 patients with 74 MBM received ICI alone, and 24 patients with 84 MBM received concurrent SRS. Median follow-up was 24 months. No differences in age ( $p=0.96$ ), KPS ( $p=0.85$ ), presence of symptoms ( $p=0.79$ ), prior MBM ( $p=0.68$ ), prior MBM-directed surgery ( $p=0.96$ ) or SRS ( $p=0.68$ ), MBM size ( $p=0.67$ ), or MBM number ( $p=0.94$ ) were seen. There was a higher rate of nivolumab and ipilimumab course completion in the SRS group (54% vs. 24%;  $p=0.029$ ). The SRS group received prior immunotherapy more often than the ICI alone group (54% vs. 8.0%;  $p<0.001$ ). There was no significant difference in 1-year OS (72% vs. 71%,  $p=0.20$ ) and DIC (63% v 51%,  $p=0.26$ ) between groups. The SRS group had higher 1-year LC (92% vs. 64%;  $p=0.002$ ). On multivariate analysis, LC was improved with combination therapy (AHR 0.38,  $p=0.01$ ).

**Conclusion** In our analysis, patients who received SRS with nivolumab and ipilimumab had superior LC without increased risk of toxicity or compromised immunotherapy treatment completion despite the SRS cohort having higher rates of prior immunotherapy. Further prospective study of combination nivolumab and ipilimumab with SRS is warranted.

**Keywords** Brain metastasis · Stereotactic radiosurgery · Melanoma · Prognosis

## Introduction

Melanoma is the fifth most common cancer diagnosis in the United States excluding nonmelanoma skin cancers [1]. An estimated 97,610 Americans will be newly diagnosed with melanoma and 7990 will pass due to melanoma in 2023

[2]. Up to 40–50% of patients with advanced disease will develop melanoma brain metastases (MBMs) which are highly associated with increased morbidity and mortality [3]. Historically, stereotactic radiosurgery (SRS) and neurosurgical resection were the cornerstone of MBM management, offering local control, symptom relief, and survival benefit, though their effectiveness was mostly limited to oligometastatic disease [4]. Whole brain radiotherapy (WBRT) and traditional chemotherapy drugs remained options but were ultimately less therapeutic due to high toxicity and poor CNS penetrance [5–7]. Therefore, strategies to prevent the

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development of new MBM were few and prognosis remained grim, ranging on average from 4 to 13 months with very few patients surviving over 5 years [3, 8–10].

Improvements in imaging techniques, neurosurgical, and radiotherapeutic techniques have steadily increased survival for patients with MBM over the years. Concurrently, development of contemporary systemic therapies has revolutionized MBM treatment. Single agent immune checkpoint inhibitors (ICI), such as ipilimumab (anti CTLA-4) or pembrolizumab (anti PD-1), and BRAF/MEK inhibitors have demonstrated durable intracranial activity in clinical trials [11–13]. Double agent immunotherapies have been shown to yield even greater response, extending progression-free survival and overall survival more than single agent or targeted therapies [14]. Recently, Checkmate-204, a phase II clinical trial, has suggested viability of first-line ipilimumab and nivolumab for active asymptomatic MBM, deferring local therapies until event of progression [15].

Current treatment strategies for MBM management often involve surgery, radiation, and systemic therapy either sequentially or concurrently at the discretion of multidisciplinary review or tumor boards. However, clinical practice guidelines regarding radiation are inconsistent and based on low-level evidence or consensus opinion [16]. Furthermore, no prospective clinical trials combining ICI with SRS/surgery for MBM have been completed [17]. Questions remain unanswered regarding outcomes, optimal timing, sequencing of therapy, and potential toxicities of combined approaches. Thus, we conducted a single-institution retrospective study comparing clinical outcomes of active MBM treated with ipilimumab and nivolumab only, versus ipilimumab and nivolumab with SRS.

## Materials and methods

We identified 49 patients with untreated-MBM who received nivolumab and ipilimumab from August 2015 to October 2022, from a prospectively maintained database of patients receiving nivolumab and ipilimumab. Of those patients, 24 received additional SRS as part of their original treatment plan within 6 weeks of ICI, including single-fraction SRS and fractionated stereotactic radiation (FSRT), delivered to intact brain metastases. Decision on whether to treat with SRS or nivolumab and ipilimumab alone was left up to the multi-disciplinary team. Patients were stratified into 2 groups by intended therapy: ICI alone, or ICI with SRS. The study was approved by the Moffitt Cancer Center Institutional Review Board (Protocol No: 21960).

## Systemic therapy

Patients received nivolumab 1 mg/kg and ipilimumab 3 mg/kg intravenously once every 3 weeks over 12 weeks (total 4 doses), followed by nivolumab 3 mg/kg intravenously every 2 weeks over 24 months or until progression or unacceptable toxicity.

## Stereotactic radiation technique

Magnetic resonance imaging (MRI, Siemens Sonata, Siemens Medical Systems, Erlangen, Germany) with 1 mm slices was completed prior to the delivery of radiation for treatment planning purposes. The MRI was co-registered and fused with computed tomography (CT) simulation imaging (General Electric Medical System, Milwaukee, WI). Patient immobilization was achieved by using a head mask fixation system (BrainlabAG, Feldkirchen, Germany).

The gross tumor volume (GTV) was expanded uniformly by 1–2 mm to create the planning target volume (PTV). Doses were prescribed to ensure that the prescription dose covered at least 95% of the PTV. Treatments were delivered using multiple dynamic conformal arcs or intensity modulated radiotherapy (IMRT). Image guidance was provided with the BrainLab ExacTrac positioning system.

## Follow-Up

Each patient was followed with physical examination with full neurologic assessment and MRI of the brain at 2–3 month intervals with the treating radiation oncologist, neurosurgeon, and/or medical oncologist. Local brain metastasis failure was defined by RANO-BM criteria in which there was a  $\geq 20\%$  increase that remained consistent or demonstrated continued progression on subsequent imaging, while local brain metastasis control (LC) included all treated lesions not meeting these criteria [18]. Distant intracranial failure was defined as the development of new brain metastasis or leptomeningeal disease (LMD) outside the previously treated field. Cases were deemed radionecrosis (RN) either after pathological confirmation or following a multidisciplinary review including neuro-radiology, radiation oncology, and neurosurgery. Patient and tumor characteristics and outcomes including age, gender, Karnofsky Performance Status (KPS), presence of symptoms, cancer history, MBM burden, toleration of therapy, and salvage therapy were recorded via retrospective chart review.

## Statistical analysis

Patient, tumor, and treatment characteristics were compared between the 2 groups via the Wilcoxon signed rank test and Chi-square test as appropriate. The Kaplan–Meier (KM) method was used to calculate overall survival (OS), local control (LC), and distant intracranial control (DIC) from start date of therapy, with log-rank testing used to assess differences between groups. The Cox proportional hazards model was used for univariable analysis (UVA) and multivariable analysis (MVA). Only variables found to be statistically significant ( $p < 0.05$ ) upon UVA were included for multivariable analysis (MVA). Statistical analyses were performed using JMP 13 (SAS Institute Inc, Cary, NC, USA).

## Results

### Patient and treatment characteristics

A total of 49 patients with 158 untreated MBM received nivolumab and ipilimumab (Table 1). 25 patients with 74 MBM received ICI only, while 24 patients with 84 MBM received ICI and SRS. The median interval between SRS/FSRT and ICI was 8 days (range: 1–41 days). Eighteen patients received SRS or FSRT prior to ICI, while 6 patients received ICI prior to SRS or FSRT. The two groups were balanced in terms of gender ( $p = 0.40$ ), age ( $p = 0.96$ ), KPS ( $p = 0.85$ ), active extracranial disease ( $p = 0.48$ ), presence of symptoms ( $p = 0.79$ ), current MBM size ( $p = 0.67$ ), and number of active MBM ( $p = 0.94$ ). Both groups also had similar rates of prior MBM ( $p = 0.68$ ), prior MBM-directed surgery ( $p = 0.96$ ), and prior MBM-directed SRS ( $p = 0.68$ ). The SRS group more often received prior immunotherapy compared to the nivolumab and ipilimumab only group (54% vs. 8%,  $p < 0.001$ ).

### Toxicity

In the entire cohort, 43% of patients experienced grade 3 acute toxicity, and 4% experienced grade 4 acute toxicity (Supplemental Table 1). The most common toxicities experienced included rash, fatigue, headache, hypothyroidism, colitis, and elevated transaminases. The SRS group completed the current course of nivolumab and ipilimumab more often (54% vs. 24%,  $p = 0.029$ , Table 1) and less commonly experienced toxicity requiring discontinuation of the ipilimumab and nivolumab (12.0% vs. 48.0%,  $p = 0.022$ ). The majority of patients who discontinued ipilimumab and nivolumab completed either 1 cycle (39%) or 2 cycles (42%). The SRS group had a lower rate of grade 3+ acute toxicity, though this did not reach statistical significance (33.3% vs.

52.0%,  $p = 0.185$ ). The SRS group experienced more intracranial acute grade 1–2 (37.5% vs. 4.0%,  $p = 0.002$ ) and grade 3 (12.5% vs. 0%,  $p = 0.034$ ) toxicities, though there were no cases of acute grade 4 intracranial toxicity (Table 2).

Of the 84 MBM treated with SRS/FSRT, there were 5 cases (6.0%) of symptomatic radiation necrosis (RN). The 1- and 2-year rates of symptomatic RN were 1.6 and 1.6%, respectively.

### Clinical outcomes

The median follow-up by reverse KM was 24.0 months (range 0.7–96.2 months). For the entire cohort, the 1-year OS (Fig. 1a), DIC (Fig. 1b), and LC (Fig. 1c) were 71.2, 57.1, and 77.8%, respectively. There was no significant difference in OS (1-year OS 71.8% vs. 70.8%,  $p = 0.2$ , Fig. 2a) or DIC (1-year DIC 63.0% vs. 50.7%,  $p = 0.26$ , Fig. 2b) between groups. The SRS group had superior LC (1-year LC 92.1% vs. 63.9%,  $p = 0.002$ , Fig. 2c).

On UVA, only KPS ( $p = 0.027$ ) and the receipt of ICI with SRS significantly predicted improved LC compared to ICI only ( $p = 0.004$ ; HR 0.34, Table 3). Upon MVA, only receipt of ICI with SRS remained significant ((adjusted hazard ratio (AHR) 0.38, 95% CI 0.18–0.79,  $p = 0.01$ )). There were no significant predictors for OS or DIC upon UVA.

## Discussion

To our knowledge, this retrospective, single-institution study is the first series to date comparing outcomes in active and untreated MBM managed with upfront nivolumab and ipilimumab alone or with SRS. Our analysis suggests the following: (i) combination therapy with SRS and nivolumab with ipilimumab was well tolerated with no increased toxicity over nivolumab and ipilimumab alone to compromise systemic therapy course completion, and (ii) inclusion of SRS was associated with improved LC.

Current joint ASCO-SNO-ASTRO guidelines recommend upfront ipilimumab and nivolumab for asymptomatic MBM, reserving local therapy for progression [19]. Data supporting this guideline primarily stems from several clinical trials. Margolin et al. investigated asymptomatic and symptomatic MBM treated with ipilimumab (NCT00623766) in an open label trial, and found disease control rates of 24 and 10%, respectively [12]. Long et al. conducted the only randomized phase 2 clinical trial (NCT02374242), comparing efficacy and safety of nivolumab versus ipilimumab and nivolumab for MBM showed 46% response rate in MBM treated with dual-agent versus 20% in single-agent therapy [20]. Checkmate204 (NCT02320058), also an open-label trial studying nivolumab and ipilimumab in asymptomatic MBM reported an intracranial response rate of 55% with a 6-month

**Table 1** Patient and Tumor Characteristics

Variable	Total Cohort		Ipi/Nivo		Ipi/Nivo + SRS		p value
	n	%	n	%	n	%	
No. of Patients	49		25	51.0%	24	49.0%	
No. of Lesions	158		74	46.8%	84	53.2%	
Age at time of Treatment							0.961
Median (range)	64 (23–78)		64 (28–78)		65 (23–78)		
Gender							0.402
Male	34	69.4%	16	64.0%	18	75.0%	
Female	15	30.6%	9	36.0%	6	25.0%	
Histology							0.077
Superficial Spreading	12	24.5%	6	24.0%	6	25.0%	
Nodular	7	14.3%	4	16.0%	3	12.5%	
Acral Lentiginous	3	6.1%	0	0.0%	3	12.5%	
Desmoplastic	2	4.1%	2	8.0%	0	0.0%	
Mucosal	2	4.1%	0	0.0%	2	8.3%	
Ocular	1	2.0%	1	4.0%	0	0.0%	
Unknown	22	44.9%	12	48.0%	10	41.7%	
KPS							0.845
90–100	32	65.3%	16	64.0%	16	66.7%	
70–80	17	34.7%	9	36.0%	8	33.3%	
Prior Diagnosis of BM	13	26.5%	6	24.0%	7	29.2%	0.682
Prior MBM Treatment							
Prior surgery	6	12.2%	3	12.0%	3	12.5%	0.957
Prior SRS/FSRT	13	26.5%	6	24.0%	7	29.2%	0.682
Prior Immunotherapy	15	30.6%	2	8.0%	13	54.2%	<b>0.0003</b>
Symptomatic	11	22.4%	6	24.0%	5	20.8%	0.790
Active Extracranial Disease	41	83.7%	20	80.0%	21	87.5%	0.475
BM Size (mm)	8 (1–37)		7 (1–30)		8 (2.8–37)		0.673
Number of BMs at Current DX	3 (1–20)		3 (1–20)		3 (1–9)		0.935
Radiation							
SRS					76	90.5%	
FSRT					8	9.5%	
SRS Dose (Gy)							
Median (range)					24 (15–24)		
FSRT Dose (Gy)							
Median (range)					27 (27–27)		
Completed Full Ipi/Nivo Course	19	38.8%	6	24.0%	13	54.2%	<b>0.029</b>
Nivo/Ipi DC d/t Toxicity	22	44.9%	16	64.0%	6	25.0%	<b>0.005</b>
Nivo/Ipi DC d/t Intracranial Progression	13	26.5%	7	28.0%	6	25.0%	0.812
Nivo/Ipi DC d/t Extracranial Progression	10	20.4%	5	20.0%	5	20.8%	0.942
Grade 3 + Treatment Toxicity	21	42.9%	13	52.0%	8	33.3%	0.185
Salvage Systemic Therapy	15	30.6%	8	32.0%	7	29.2%	0.811
Salvage Local Therapy							0.503
SRS/FSRT	10	20.4%	5	20.0%	5	20.8%	
WBRT	3	6.1%	2	8.0%	1	4.2%	
Surgery + RT	12	24.5%	4	16.0%	8	33.3%	

Bold p-values are significant (p<0.05)

*Ipi/Nivo* ipilimumab and nivolumab, *SRS* stereotactic radiosurgery, *KPS* Karnofsky Performance Status, *MBM* melanoma brain metastasis/es, *FSRT* fractionated stereotactic radiosurgery, *DC* discontinuation, *d/t* secondary to, *WBRT* whole brain radiation therapy, *RT* radiation therapy

**Table 2** Acute Intracranial Treatment Toxicity

Toxicity	Total (n=49)		Ipi/Nivo + SRS (n=24)		Ipi/Nivo (n=25)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Any	10 (20.4%)	3 (6.1%)	1 (4.0%)	0	9 (37.5%)	3 (12.5%)
Headache	7 (14.3%)	0	1 (4.0%)	0	6 (25.0%)	0
Hypophysitis	3 (6.1%)	0	0	0	3 (12.5%)	0
Vasogenic Edema	0	3 (6.1%)	0	0	0	3 (12.5%)
Blurred Vision	1 (2.0%)	0	0	0	1 (4.2%)	0
Dysarthria	1 (2.0%)	0	0	0	1 (4.2%)	0
Confusion	1 (2.0%)	0	0	0	1 (4.2%)	0
Uveitis	1 (2.0%)	0	0	0	1 (4.2%)	0

*Ipi/Nivo* ipilimumab and nivolumab, *SRS* stereotactic radiosurgery

progression free survival of 64% [21]. No clinical trial has been conducted comparing ipilimumab and nivolumab versus ipilimumab and nivolumab with SRS in active, untreated MBM head-to-head.

Notably, our study found no decreased course completion or increased toxicity with combination SRS and immunotherapy. This was noted in the context of the SRS group having been exposed to more lines of prior immunotherapy. Moreover, there was an increased rate of early systemic therapy discontinuation in the ipilimumab and nivolumab alone arm; however, this was related to increased systemic toxicity. Commonly reported neurotoxicities in SRS include fatigue, headache, and radiation necrosis [22]. Our 6% symptomatic RN rate is comparable to the reported rates in SRS (0–20%) and FSRT (1–8%) administered alone [23]. Patel et al. investigated outcomes of MBM treated with SRS and ipilimumab and versus SRS alone reported no difference in RN [24]. Ultimately, our results are consistent with the literature and indicate combination treatment of brain metastases with SRS and immunotherapy is well-tolerated, and the addition of SRS does not jeopardize completion of immunotherapy.

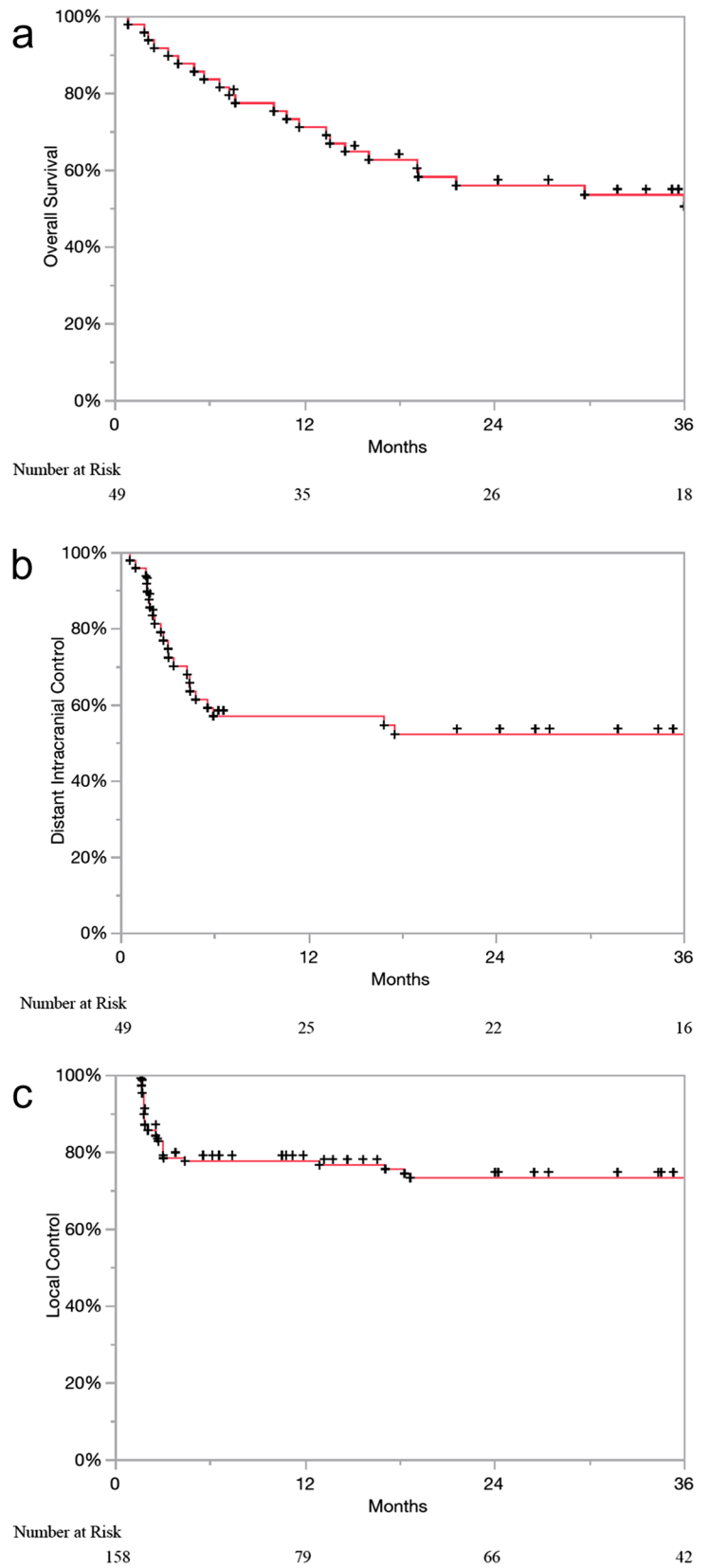
SRS was associated with LC in MBMs compared to those that only received nivolumab and ipilimumab, with 12-month LCs of 89.5 and 63.9%, respectively (Table 2, Fig. 2). Our results are consistent with those reported in literature, as SRS has been shown to provide 1-year LC rates to brain metastases of varying primary histologies ranging from 73 to 92% [25]. The previously referenced retrospective review published by Patel et al. comparing SRS with ipilimumab vs SRS alone reported similar 1-year LC rates of 92.3 and 71.4%, respectively with no significant difference

between the two cohorts [24]. Kotecha et al. found a 1-year LC rate of 93% for patients with MBM treated with SRS and PD-1/CTLA-4 agents [26]. These rates also compare with our institutional results assessing LC in 1048 MBM across multiple different systemic therapies where LC ranged between 83 and 96% at 1 year between groups [27].

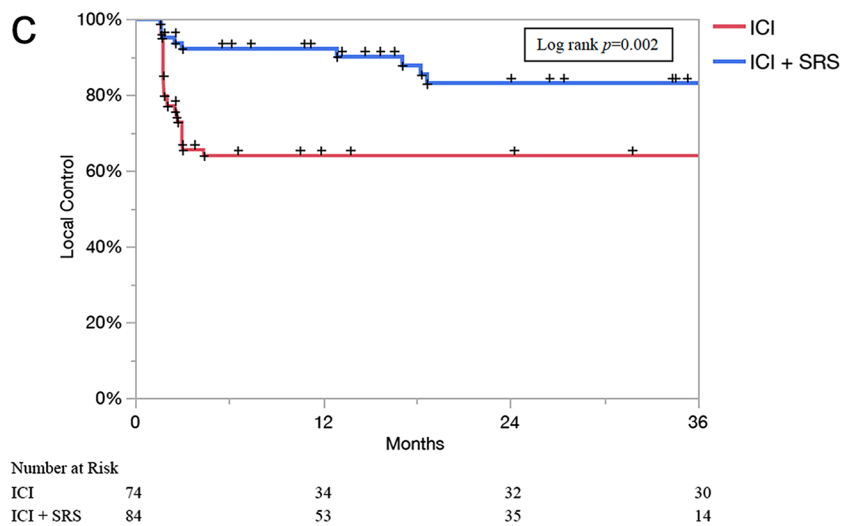
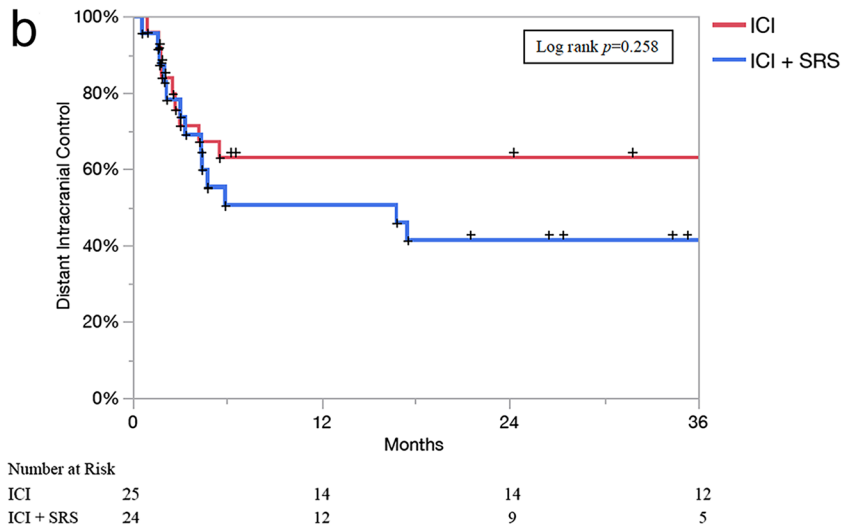
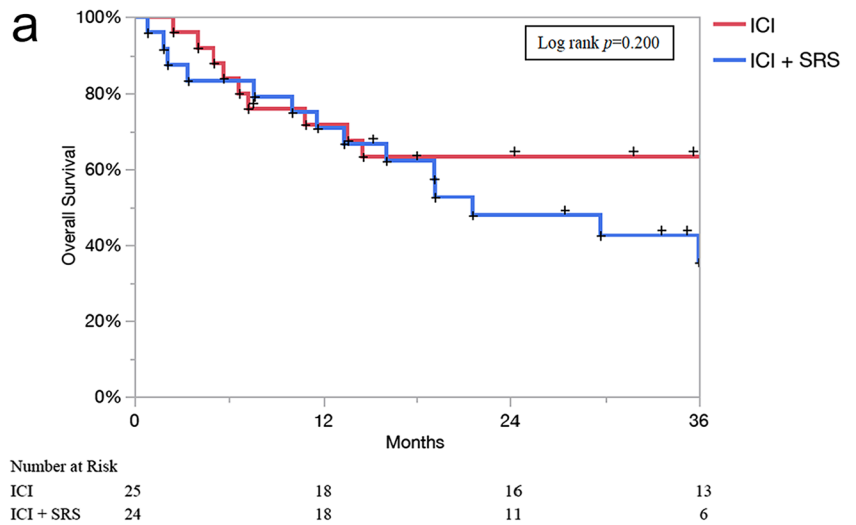
Limitations of this study include its retrospective nature without predefined endpoints, relatively small sample size, follow-up intervals, relatively small metastasis treated, and criteria for dosing of stereotactic radiation. Additionally, though our cohorts were balanced in terms of patient characteristics, symptoms, tumor burden, prior surgery, and prior radiation, our combination therapy cohort was more advanced in terms of systemic therapy, more often having prior immunotherapy. Despite its limitations, this study is one of the few investigating MBM treated with nivolumab and ipilimumab and SRS. These results require prospective validation, which may come from the currently enrolling phase II ABC-X Study, which randomizes patients with asymptomatic, untreated MBM to ipilimumab and nivolumab alone versus ipilimumab and nivolumab with stereotactic radiotherapy (NCT03340129).

In conclusion, patients with active and untreated MBM receiving nivolumab and ipilimumab may receive SRS without added toxicity or increased risk of treatment discontinuation. No differences in OS or DIC were noted; however, lesions treated with SRS had superior LC. Further prospective study of combination nivolumab and ipilimumab with SRS in MBM management is warranted to assess the potential synergy between combination therapies.

**Fig. 1** Kaplan–Meier curves depicting overall survival (A), distant intracranial control (B), and local control (C) measured from initiation of therapy



**Fig. 2** Kaplan–Meier curve depicting overall survival (A), distant intracranial control (B), and local control (C) for patients who received immune checkpoint inhibitors (ICI) alone (red) compared with those who received ICI and stereotactic radiosurgery (SRS, blue)



**Table 3** Univariate Analysis for Overall Survival, Distant Intracranial Control, and Local Control

Variable	Overall Survival		Distant Intracranial Control		Local Control	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age at Treatment	1.00 (0.97–1.03)	0.968	0.99 (0.96–1.02)	0.374	0.99 (0.97–1.01)	0.233
KPS						
90–100	1.00	-	1.00	-	1.00	-
70–80	0.95 (0.40–2.21)	0.898	1.25 (0.52–2.98)	0.616	2.10 (1.09–4.04)	<b>0.027</b>
Size of BM (mm)	1.37 (0.56–3.32)	0.492	1.29 (0.50–3.30)	0.594	1.00 (0.95–1.05)	0.905
BED <sub>12</sub> (Gy)					0.99 (0.93–1.07)	0.762
Initial Diagnosis of BM	1.16 (0.35–3.90)	0.809	1.80 (0.52–6.22)	0.350	1.66 (0.84–3.25)	0.142
Prior Immunotherapy	1.85 (0.80–4.32)	0.153	1.73 (0.74–4.05)	0.207	1.47 (0.74–2.91)	0.270
Symptomatic	1.51 (0.63–3.66)	0.357	1.40 (0.55–3.60)	0.482	1.62 (0.81–3.24)	0.176
Active Extracranial Disease	1.46 (0.44–4.91)	0.538	2.53 (0.59–10.8)	0.211	1.47 (0.57–3.79)	0.400
Number of BMs at Current Diagnosis	1.01 (0.89–1.11)	0.807	1.02 (0.90–1.12)	0.687	1.00 (0.90–1.08)	0.984
Treatment Plan						
Ipi/Nivo	1.000	-	1.00	-	1.00	-
Ipi/Nivo + SRS	1.71 (0.75–3.92)	0.205	1.63 (0.69–3.81)	0.262	0.34 (0.16–0.71)	<b>0.004</b>

Bold *p*-values are significant (*p*<0.05)

HR hazard ratio, CI=confidence interval, KPS Karnofsky performance status, BM brain metastasis, BED biologically effective dose, Ipi/Nivo ipilimumab and nivolumab, SRS stereotactic radiosurgery

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11060-023-04543-9>.

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**Data availability** Summary data supporting the results reported in this article can be requested by emailing the corresponding author.

## Declarations

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