BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases

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OBJECTIVE Recent advancements in molecular biology have identified the BRAF mutation as a common mutation in melanoma. The wide use of BRAF kinase inhibitor (BRAFi) in patients with metastatic melanoma has been established. The objective of this study was to examine the impact of BRAF mutation status and use of BRAFi in conjunction with stereotactic radiosurgery (SRS).

METHODS This was a single-center retrospective study. Patient’s charts and electronic records were reviewed for date of diagnosis of primary malignancy, BRAF mutation status, chemotherapies used, date of the diagnosis of CNS metastases, date of SRS, survival, local tumor control after SRS, and adverse events. Patients were divided into 3 groups: Group A, those with mutant BRAF without BRAFi treatment (13 patients); Group B, those with mutant BRAF with BRAFi treatment (17 patients); and Group C, those with wild-type BRAF (35 patients). Within a cohort of 65 patients with the known BRAF mutation status and treated with SRS between 2010 and 2014, 436 individual brain metastases (BMs) were identified. Kaplan-Meier methodology was then used to compare survival based on each binary parameter.

RESULTS Median survival times after the diagnosis of melanoma BM and after SRS were favorable in patients with a BRAF mutation and treated with SRS in conjunction with BRAFi (Group B) compared with the patients with wild-type BRAF (Group C) or with BRAF mutation but no BRAFi (Group A) as an adjunct treatment for BMs. Furthermore, the local control rate was improved in the patients treated with SRS in conjunction with BRAFi (Group B) compared with patients with wild-type (Group C) or with BRAF mutation but no BRAFi (Group A) as an adjunct treatment for BMs.

CONCLUSIONS BRAF mutation status appears to play an important role as a potent prognostic factor in patients harboring melanoma BM. BRAFi in conjunction with SRS may benefit this group of patients in terms of BM survival and SRS with an acceptable safety profile.

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KEY WORDS BRAF kinase inhibitor; BRAF mutation; brain metastases; melanoma; stereotactic radiosurgery; oncology

Malignant melanoma causes 75% of all skin cancer–related deaths and has been increasing in incidence since at least 2004.7 Melanoma has a high incidence of brain metastasis (BM), with nearly half of these patients developing them over the course of the disease.25 The median survival from time of diagnosis of BM in treated patients is 16–22 weeks,21,25,29 but it is less than 1 month in untreated patients.28

BM can be treated by surgery, radiation therapy, chemotherapy, immunotherapy, and stereotactic radiosurgery (SRS).28 Whole brain radiation therapy (WBRT) has limited utility, because melanomas are relatively radiore-
SRS has been widely used in the treatment of small-to-moderate sized BMs, and it is increasingly used to treat metastatic brain lesions from melanoma.\textsuperscript{15,20,25} SRS overcomes the radioresistance usually exhibited by melanoma by allowing the delivery of higher radiation doses to the tumor with a dramatically sharp radiation dose falloff, thereby minimizing the radiation to the surrounding normal tissue.\textsuperscript{28} Outcomes from SRS are equivalent to those obtained by successful surgical excision in terms of local tumor control, with a low risk of morbidity and almost no deaths.\textsuperscript{28}

Melanoma is the third most common primary tumor responsible for BM, and there is no Level 1 evidence regarding treatment once it has metastasized to the brain.\textsuperscript{21} In clinical practice, multidisciplinary treatment options are used, including immunotherapy and small molecular inhibitors. Recent advancements in molecular biology have identified the \textit{BRAF} mutation as a common mutation (approximately 50\%) in melanoma.\textsuperscript{19} \textit{BRAF} mutation kinase inhibitors (\textit{BRAFi}) have been shown to be effective in treating patients with \textit{BRAF} mutation–positive cancer cells.\textsuperscript{19} However, due to the expected short-term survival after the diagnosis of melanoma intracranial metastases, patients with melanoma BMs were generally excluded from the clinical trial of ipilimumab and \textit{BRAFi}.\textsuperscript{19,20} Hence, the impact of \textit{BRAF} mutation status and adjuvant \textit{BRAFi} on the local control of BMs treated with SRS in those patients remains elusive.

In this study, we aimed to investigate the effectiveness of this combined treatment option for patients with melanoma BM and the role of \textit{BRAF} mutation status as a prognostic factor after the development of BMs.

**Methods**

**Patient Selection**

The institutional review board approved this retrospective study. In 2011, ipilimumab and vemurafenib were approved by the US FDA for treating patients harboring metastatic melanomas. Therefore, we selected patients who had developed cutaneous melanoma BM between June of 2010 and August of 2014. The inclusion criteria were set as patients with melanoma whose \textit{BRAF} V600E mutation status of the metastatic melanoma was confirmed histologically, and who underwent SRS for their brain metastases at the University of Virginia Health System. Because of highly congruent \textit{BRAF} mutation status results in tumor samples identified with Western blot analysis, immunohistochemistry, or direct \textit{BRAF} gene sequencing,\textsuperscript{8,9} in this study we identified a total of 65 patients with a known \textit{BRAF} mutation status regardless of the specific detection method used. BMs were diagnosed based on MRI coupled with clinical characteristics. Five patients (8\%) underwent a craniotomy and tumor resection prior to Gamma Knife radiosurgery (GKRS). Five patients who were diagnosed with an ocular melanoma or who developed a second malignancy were excluded from this study. A total of 65 patients, 30 (46\%) who exhibited a \textit{BRAF} mutation and 35 (54\%) with a wild-type \textit{BRAF} melanoma were included in the study analysis. Patient charts, electronic records, and imaging were reviewed.

The patients were stratified into 3 groups on the basis of \textit{BRAF} mutation status and administration of \textit{BRAFi} for melanoma BMs. In Group A, 13 patients (20\%) exhibited a \textit{BRAF} mutation, but they either did not receive an adequate dose of \textit{BRAFi} due to the severe adverse effect after 1 dose administration (1 patient), refused to use \textit{BRAFi} due to the potential risks (2 patients), or \textit{BRAFi} was only given prior to the development of BMs (10 patients). In Group B, 17 patients (26\%) presented with a \textit{BRAF} mutation and received adequate doses of \textit{BRAFi} in conjunction with SRS for BMs. In Group C, 35 patients (54\%) exhibited wild-type \textit{BRAF}. They received no \textit{BRAFi} during the course of treatment. Patients in Group B were treated with \textit{BRAFi}, either dabrafenib or vemurafenib, at the recommended dose of 150 mg and 960 mg, respectively, orally twice daily.

The baseline clinical characteristics are detailed in Table 1. No patients’ Karnofsky Performance Scale (KPS) score was less than 70. In addition, no significant difference was detected regarding the distribution of disease-specific graded prognostic assessment (DS-GPA) between the 3 groups (\(p = 0.730\), independent sample Kruskal-Wallis test). The following patients and disease parameters of the primary malignancy were evaluated: sex, age at the time of diagnosis of primary melanoma, site of primary melanoma, Breslow thickness, Clark’s level, sentinel lymph node status, and presence of ulceration. Table 2 displays the patient characteristics with respect to the melanoma BMs.

**Radiosurgery Procedures**

SRS was performed using the Perfexion Gamma Knife and GammaPlan software (Elekta Instruments AB). SRS was used after the diagnosis of melanoma BM in this cohort of patients as an upfront or adjuvant treatment modality to progression after the previous WBRT or a boost treatment for the surgical tumor cavity. The technique of using GKRS for melanoma BM has been published previously.\textsuperscript{34,41}

A total of 65 patients harboring 436 melanoma BMs were treated with SRS in this series. The median tumor volume treated was 0.23 cm\(^3\) (range 0.02–22.44 cm\(^3\)). The median largest dimension of treated tumor was 6 mm (range 1.1–59.7 mm). The median margin radiation dose to the tumor was 20 Gy (range 13–23 Gy), and the median isodose line used was 85\% (range 50\%–98\%). The radiation dose selection was determined based on the status of previous radiation therapy, tumor volume, proximity to critical structures (e.g., the optic apparatus or brainstem), total number of brain metastases, and location.

**Follow-Up Assessment**

After SRS, patients were followed clinically and radiologically every 3 months. All MRI was evaluated by a treating neurosurgeon and a neuroradiologist at the University of Virginia. A tumor was deemed progressed if the volume increased by 15\% or greater than the volume at the time of the patient’s SRS.\textsuperscript{28} Otherwise, it was regarded as nonprogressive. Adverse radiation effect (ARE) was defined as worsening T2 or FLAIR signal around the site of a known and SRS-treated BM but no progression of the T1 postcontrast volume of that same BM.
Statistical Analysis and Definitions

The overall survival (OS) was defined as the time interval in months between the diagnosis of primary melanoma and the date of last follow-up or death. The survival after the diagnosis of BMs was referred to as BM survival, whereas the survival time after the treatment of SRS was referred to as SRS survival. The online Social Security Death Index was used to attain the survival data when necessary. All patient deaths in this study were related to melanoma.

Generally, the normality of data was tested using the Shapiro-Wilk test. For the data that were not normally distributed, nonparametric data analyses were conducted. The Student t-test was performed for parametric data with possible normal distribution, and Levene’s test for equality of variances was used if the assumption of equal variances was not met. Parametric data are presented as mean ± SD. Kaplan-Meier methodology was used in the survival analysis, and the log-rank test was used to detect the survival difference in different groups of patients. A social statistical package, SPSS (version 22, IBM Inc.), was used for all statistical analyses. All statistical studies were 2-sided, and a p value < 0.05 was deemed statistically significant.

Results

There was no statistical significance in terms of the age at the diagnosis of primary melanoma and the age at the development of BM between the mutant group \(BRAF\) and the wild-type \(BRAF\) group (\(p = 0.19\) and \(0.15\), respectively; Student t-test). The Kruskal-Wallis test did not identify any discrepancies in terms of median time intervals between the diagnosis of primary malignancy and the development of intracranial metastases between the 3 groups (\(p = 0.522\)).

Patient Survival

No patients in this series were lost to clinical follow-up. Imaging follow-up was available in 49 patients (75%). At the time of analysis, 51 patients (78%) had died, and 14
patients (22%) maintained their clinical follow-up at the University of Virginia Health System.

In this entire patient cohort, the medians for OS, BM survival, and SRS survival were 46 months, 9 months, and 6 months, respectively. Median survival times and actuarial survival rates after the diagnosis of primary melanoma, after the diagnosis of BM, and after SRS are illustrated in Table 3. Survival after the diagnosis of BM in patients with mutant BRAF and treated with SRS in conjunction with BRAFi was increased compared with survival in patients with wild-type BRAF or those who had mutant BRAF but no BRAFi treatment given after the development of BM (median survival 23 months, 8 months, and 3 months, respectively; p = 0.004, log-rank test). The Kaplan-Meier plots show patient survival in the 3 groups regarding BM survival and SRS survival (Fig. 1).

Local Tumor Control

Notably, in the analysis, those patients whose BMs responded initially to SRS but later progressed were classified into the group of progression, not into the group of regression. Therefore, local tumor control in this study was categorized as 2 groups, progression or nonprogression. Local tumor control was evaluated in 310/436 tumors (71%) available for imaging follow-up.

Six patients in Group A (mutant BRAF but no BRAFi), 15 patients in Group B (mutant BRAF and BRAFi), and 28 patients in Group C (wild-type BRAF) had the available radiological follow-up. The progression-free survival and local tumor control rate are displayed using the Kaplan-Meier plot in Fig. 2 (p = 0.042 and p = 0.022, respectively; log-rank test). At 1 year, the local tumor control rate in Groups A, B, and C was 82.4%, 92%, and 69.2%, respectively. In a total of 310 tumors available for the radiological follow-up, local tumor control was achieved in 277 tumors (89.4%) at the last follow-up with a median follow-up of 3 months (range 1–42 months).

The manifestation of tumor changes (ARE, intratumoral hemorrhage, and necrosis) after SRS with or without BRAFi are displayed in Table 4 and Fig. 3. After SRS, a total of 20 patients developed ARE (range 0.5–10.9 months), 9 patients had intratumoral hemorrhages (range 0.8–15.9 months), and 6 patients developed tumor necrosis (range 1.4–2.3 months). Following SRS, no significant difference was found with respect to the rate of intratumoral hemorrhage or tumor necrosis in the 3 groups (p = 0.487 for hemorrhage, p = 0.721 for tumor necrosis; log-rank test). The rate of ARE was significantly lower in Group B compared with that in the other 2 groups (p = 0.041, log-rank test).

Additional Treatment for Melanoma BM

New BMs were identified in 20 (41%) of 49 patients who underwent imaging follow-up. The management of BMs is considered a multidisciplinary treatment that includes focal treatments, such as radiation therapy, radiosurgery, and resection, and systemic therapies such as chemotherapy and immunotherapy. Neurosurgeons can directly deliver only resection and radiosurgery. Therefore, to account for the potentially confounding factors of non-neurosurgical treatment effects, we presented the time to distant failure after the diagnosis of BMs, and after the first SRS. The median time to distant failure was 6.5 months (95% CI 6.0–7.1 months) after the diagnosis of BM or 5.5 months (95% CI 4.8–6.1 months) after the first SRS. No difference in the number of BMs developed among groups (p = 0.12, log-rank test) was detected. Concerning the chemo- and radioresistance of melanoma, the patients in this cohort were treated promptly with SRS for any newly developed BMs where indicated. Of 65 patients, 1 patient underwent SRS 4 times, 5 patients had SRS 3 times, and 7 patients had SRS 2 times. WBRT was administered in 17 patients (26%) as either an upfront or adjuvant treatment (Table 2). WBRT was given prior to SRS in 10 patients (15%). Of the

### Table 3. Patient survival times in relation to BRAF mutation status and administration of BRAFi

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire Cohort</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>65</td>
<td>13</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Survival after diagnosis of primary melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MST in mos (95% CI)</td>
<td>46 (35.0–57.0)</td>
<td>37 (23.9–50.1)</td>
<td>49 (5.4–92.6)</td>
<td>46 (32.4–59.6)</td>
</tr>
<tr>
<td>1-yr survival %</td>
<td>94</td>
<td>77</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>3-yr survival %</td>
<td>61</td>
<td>51</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>5-yr survival %</td>
<td>40</td>
<td>26</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>Survival after diagnosis of BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MST in mos (95% CI)</td>
<td>9 (7.3–10.7)</td>
<td>3 (0–6.5)</td>
<td>23 (0–46.4)</td>
<td>8 (6.2–9.8)</td>
</tr>
<tr>
<td>0.5-yr survival %</td>
<td>69</td>
<td>39</td>
<td>94</td>
<td>65</td>
</tr>
<tr>
<td>1-yr survival %</td>
<td>38</td>
<td>39</td>
<td>58</td>
<td>30</td>
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<td>2-yr survival %</td>
<td>17</td>
<td>19</td>
<td>44</td>
<td>0.04</td>
</tr>
<tr>
<td>Survival after SRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MST in mos (95% CI)</td>
<td>6 (3.1–8.9)</td>
<td>1 (0.1–1.9)</td>
<td>13 (0–29.4)</td>
<td>5 (0.9–9.1)</td>
</tr>
<tr>
<td>0.5-yr survival %</td>
<td>50</td>
<td>31</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>1-yr survival %</td>
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<tr>
<td>2-yr survival %</td>
<td>14</td>
<td>31</td>
<td>31</td>
<td>0.1</td>
</tr>
</tbody>
</table>

CI = confidence interval; MST = median survival time.
7 patients (11%) who received WBRT after SRS, 3 were treated in a planned fashion (within 3 weeks) due to the presence of multiple tumors (Table 2). Table 5 displays the additional treatment modalities for melanoma BM other than WBRT and SRS.

### Adverse Events in Response to BRAFi

All 17 patients in Group B received BRAFi after the development of melanoma BMs (Table 6). Among them, 12 patients (71%) received vemurafenib while 5 patients received dabrafenib. One patient received dabrafenib 8 days before and again 8 days after SRS out of concern for synergistic toxicity secondary to the combination of radiation therapy and BRAFi. Four other patients received dabrafenib at a median of 4.5 months after the initial SRS (range 4–6 months). In 12 patients who received vemurafenib during the disease’s course, 2 patients had it during the SRS, while 10 other patients received it at a median of 5.5 months (range 1 week to 10 months) after SRS for...
BMs. Three patients had to discontinue vemurafenib due to the development of a severe rash.

Discussion

The typical OS of patients who develop melanoma BMs remains poor, with a median survival time between 3.4 and 10.6 months prior to 2010, when no BRAF mutation status was addressed. SRS provides effective local tumor control in patients harboring melanoma BMs. Melanoma BM is regarded as a radio- and chemoresistant malignancy. Therefore, at many centers, WBRT is less frequently performed to treat patients with melanoma BM. In contrast, SRS is playing an increasingly important role in this subset of patients. In particular, treatment of patients with multiple BMs, which was previously considered a contraindication for SRS, has led to a high rate of local tumor control. High local control rates make subsequent immunotherapy or targeted therapy more attractive.

In this series, we found a significant correlation between BRAF mutation status, the combination treatment of BM with SRS and BRAFi, and patient survival in terms of OS, BM survival, and SRS survival (Table 3). The median survival in Group B (mutant BRAF and BRAFi) was 16 months after the diagnosis of BMs. The Group B patients whose metastases were BRAF mutation-positive and underwent combination therapy with SRS and BRAFi after the diagnosis of BMs had the longest survival. The OS, BM survival, and SRS survival of the wild-type BRAF group (Group C) and the group of patients (Group A) with BRAF mutations who did not receive the BRAFi treatment were substantially lower.

BRAF Mutation Status and Ionizing Radiation

The mechanism of BRAF mutation in the tumorigenesis and differentiation has been a hot topic recently. In the Ras-Raf-MEK-ERK signaling pathway, the serine/threonine-protein kinase BRAF is a potent activator of the downstream effector mitogen-activated protein kinase (MEK). Ras phosphorylation resulting from the stimulation of extracellular growth factors or hormones leads to activation of BRAF. As a consequence, MEKs are activated by the phosphorylation of RAF, and then extracellular signal-regulated kinase stimulates the tumor proliferation and differentiation. Before the era of BRAF mutation inhibitors, the BRAF mutation was associated with a worse prognosis compared with the wild-type BRAF. Several studies have demonstrated the benefit of BRAFi in patients harboring melanoma BMs. Our research is consistent with the findings of Menzies et al., who demonstrated a statistically significant difference in 1-year survival times from the diagnosis of metastasis. In decreasing order of survival, they were patients with BRAF-mutant melanoma treated with an inhibitor (83%), patients with BRAF wild-type melanoma (37%), and those not treated with an inhibitor (29%). Of note, unlike in our study, the aforementioned study addressed the OS after the diagnosis of distant metastasis. In the present study, we found a similar survival pattern but in BM survival and SRS survival.

BRAFi only 0 10 0
BRAFi + ipilimumab 0 2 0
BRAFi + MEK inhibitor 0 5 0
Temozolomide 2 2 8
Taxol 0 0 4

1 IL-2 = interleukin-2.
* Investigational agents included MEL58, MEL51, MEL44, MK3475, and CDX-1127.
† All patients received at least SRS and/or WBRT for brain metastases.
all patients with metastatic melanoma. Dabrafenib is an inhibitor of BRAF kinase. It has been shown in Phase II clinical trials to have activity in BRAF mutation-positive melanoma as well as to have an acceptable safety profile. Dabrafenib was found to prolong survival by roughly 3 times compared with standard temozolomide therapy. Additionally, dabrafenib was effective in both patients who had not undergone previous therapy for melanoma metastasis and those who had received prior treatments. Dabrafenib performed better with an intracranial response rate of 30%–40%. 

Vemurafenib is a small-molecule kinase inhibitor that is very specific for the mutated BRAF V600E mutation, with a 70%–80% response rate for systemic disease. Anecdotal evidence of the efficacy of vemurafenib in melanoma metastatic to the brain exists, but no published trials are available that evaluate its use in this context. The use of vemurafenib with radiation therapy has not been well studied. Radiation therapy with vemurafenib could be helpful, because radiation causes transient disruption of the blood-brain barrier, allowing better penetration by vemurafenib. An ongoing Phase II clinical trial of vemurafenib is in progress. In our study, the safety profile in patients treated with vemurafenib or dabrafenib was acceptable and comparable to safety in the studies performed by Long et al. and Dummer et al. 

### Stereotactic Radiosurgery for Melanoma Brain Metastases

SRS is capable of delivering a high dose to the tumor. SRS typically results in excellent local tumor control and may prolong survival in certain groups of patients. The Pittsburgh group reported on 333 consecutive patients with melanoma treated with SRS prior to 2010. The actuarial survival rates after SRS were 47% at 6 months and 25% at 12 months after SRS, which are comparable to the counterpart in our study (Table 3). The study from Pittsburgh and our study are very similar with respect to patient survival after the diagnosis of primary melanoma, after the diagnosis of BM, and after SRS. The local tumor control rate was 94% in the Pittsburgh study and 89.4% in our study.

In the current study, 41% of patients developed new BM identified on surveillance imaging, and the 6-month survival rate was 71%. This is in close agreement with the study performed by Gaudy-Marqueste et al. who reported a 6-month survival rate of 78.8% after the first SRS for patients with melanoma BM who received adjuvant BRAFi. Interestingly, Ly and colleagues found a similar improvement in the local control rate in the patient group that received BRAFi and SRS (Group B in the current study). It further demonstrated that there might be a synergistic effect when using BRAF inhibitors and SRS for treating melanoma BMs. The potential synergistic effect of targeted chemotherapies (e.g., BRAF inhibition or immunotherapy) and SRS warrants further investigation and may be a pathway to exploit for therapeutic gain of a patient’s intracranial metastatic disease.

BM detected on subsequent follow-up MRI. Meanwhile, they could tolerate the adjuvant long-term treatment of BRAFi without any devastating adverse events. Our study suggests that under the circumstance of well-controlled intracranial metastases with SRS, and systemic treatment in particular, the BRAFi if applicable may contribute to the survival benefit in this cohort of patients. Although current scoring systems (e.g., recursive partitioning analysis, GPA, or DS-GPA) for patients with brain metastases do not take into account the genetic markers of specific cancers, evidence of the prognostic value of these factors is increasing in patients treated with SRS. Revisions to scoring systems likely need to take into account these factors in predicting survival and the eligibility for SRS.

With the burgeoning use of BRAFi and immunotherapeutics in conjunction with radiation therapy including SRS, the effectiveness of these combined treatments has not been well defined. Sequencing treatment with ipilimumab followed by BRAFi exhibits a favorable survival benefit in select patients with metastatic melanoma. Ipilimumab is a humanized monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), which reduces tolerance to tumor-associated antigens. It was FDA approved for use in metastatic melanoma in 2011. Several trials have shown that ipilimumab improved OS in patients with Stage III or IV melanoma compared with the then standard of care therapies. Ipilimumab has been shown to be synergistic with a variety of treatments, and combination trials are ongoing. Although ipilimumab works to modulate the immune response, we did not identify any survival benefit in this study (data not shown).

Targeted therapy in conjunction with SRS remains a hot topic and is well administered in the treatment of melanoma BMs. A multicenter study with a large number of patients is warranted to confirm the findings in this study.

### Limitations of the Study

This single-center, retrospective study has some intrinsic limitations. Selection and referral bias were unavoidable. In addition, this group of patients had been treated with heterogeneous treatment modalities. The small number of patients included in the study precluded us from performing further statistical analysis to adjust for the confounding factors, including DS-GPA and status of extracranial metastases control. Lactate dehydrogenases levels were not included in this study, which have been shown to be an adverse risk factor for melanoma BMs.

### Conclusions

Overall, the survival of patients with melanoma BM remains short. BRAFi in conjunction with SRS led to improved survival times after BM diagnosis or SRS. BRAFi was not associated with a greater risk of AREs after SRS. Our study suggests that under the circumstance of well-controlled intracranial metastases with SRS, and systemic treatment in particular, the BRAFi if applicable may contribute to the survival benefit in this cohort of patients. While current grading systems focus on the age, global performance status, extent of extracranial disease, and general type of underlying cancer, genetic subtypes of can-
cers such as melanoma should be taken into account when predicting a prognosis in patients with BMs treated with SRS. This is particularly true for patients undergoing targeted therapies aimed at exploiting therapeutic gains of cancer mutations.

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References


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