Commentary: BRAF V600 Mutation and BRAF Kinase Inhibitors in Conjunction with Stereotactic Radiosurgery for Intracranial Melanoma Metastases: A Multicenter Retrospective Study

In the current study, the authors present a retrospective multiinstitutional study of patients (n = 198) with melanoma brain metastases (n = 710 cerebral metastases) treated with stereotactic radiosurgery (SRS). The mean follow-up was 25.6 mo after the diagnosis of brain metastases. Patients were grouped into those with wild-type BRAF (BRAFwt) and V600 mutated BRAF (BRAFmut) in the primary tumors. The mutational status of the brain metastases was not reported as it was presumably unknown. This is of importance as it has been clearly described that the mutational status of the primary tumor, extra-central nervous system metastases, and brain metastases may vary within the same patient via a process of branched evolution. The degree to which this is present in melanoma has not been spelled out as of yet. All patients in the current study received SRS to the brain metastases. A subset of the BRAFmut patients received BRAF inhibitors (BRAFi; n = 67) while the BRAFwt (n = 108) patients did not receive BRAFi. Some patients treated with BRAFi received single agent vemurafenib while others received a combination of dabrafenib and the MEK inhibitor trametinib.

In this study, the presence of BRAF mutations in the primary tumor was associated with improved survival on multivariate analyses. This echoes our growing understanding in other histologies as well as melanoma that the molecular phenotype of the tumor influences prognosis in patients with brain metastases. While BRAFmut was prognostic, the study as designed was not able to demonstrate that BRAFmut is a predictive biomarker in patients with melanoma brain metastases. As the authors note, this is possibly secondary to the study being underpowered to do so. Additionally, there were no significant differences in local tumor control of brain metastases suggesting that the status of the patients’ systemic disease may influence survival outcomes. Further subgroup analyses demonstrated that in BRAFmut brain metastases patients treated with BRAFi a significant improvement in survival was seen in patients treated with BRAFi after SRS (n = 36, median 24 mo) as compared to prior (n = 12, median 8 mo, \( P < .001 \)) to SRS or concomitant with (n = 19, median 10.1 mo, \( P = .007 \)) SRS. Whether these findings are reflective of the importance of the timing of systemic therapies with respect to SRS or reflect differences in the biology of the disease is not addressed by the current study. It is possible that the patients who had developed brain metastases while on BRAFi have more limited systemic treatment options available to them and in turn would be expected to have a shorter overall survival. The limited number of patients and the retrospective nature of the study make it impossible to definitively state that the sequencing of therapies impacts survival outcomes in these patients. With regard to primary brain tumors, we do hold an understanding that the timing of our treatments with respect to the newly diagnosed vs the recurrent disease setting influences their efficacy.

In addition to addressing questions regarding potential efficacy it is also important to evaluate the safety of therapeutic interventions. An increased risk of radiation necrosis in patients treated with SRS and BRAFi has been previously demonstrated. Interestingly, the current study does not note the development of any radiation necrosis, likely a limitation due to both the retrospective nature of the study and the need for pathological confirmation to definitively establish a diagnosis of radiation necrosis. The authors did note that the utilization of BRAFi was not without risk. There was a significant increase in the risk of intracranial hemorrhage (ICH) in the BRAFi

**ABBREVIATIONS: ICH, intracranial hemorrhage; SRS, stereotactic radiosurgery**
treated group (10.4% vs 3%, \( P = .03 \)). It is possible that again due to the retrospective nature of the current study that this is an underreporting of the ICH risk. While it was noted the ICH did not lead to hospitalization, indicating they were likely mild in severity, it would be beneficial to have a clearer understanding of the ICH risk and hypotheses for what is driving it.

The authors provide the results of a study which is beneficial as it analyzes data from real-world clinical practice. As we further develop experience utilizing efficacious systemic therapies in conjunction with treatments with longstanding track records for efficacy in brain metastases we should be able to make a favorable impact on our patients.

Disclosure

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES