Intracranial Activity of Sotorasib in *KRAS*^{G12C}-Mutated Recurrent Glioblastoma

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Background

Glioblastoma (GBM) is the most common and aggressive malignant brain tumor in adults and accounts for about 16% of all primary brain tumors.[1] In the United States, the median age of onset is 64 years and the 5-year overall survival rate after diagnosis is <5%.[2] Only 1% of GBM cases are hereditary, making a genetic component unlikely.[1] Three main signaling pathways are implicated in this disease: the tumor protein p53 (TP53) pathway, the receptor tyrosine kinase/Ras/phosphoinositide 3-kinase signaling pathway, and the retinoblastoma pathway.[1] Changes to these signaling pathways can result in enhanced cancer cell survival as cancer cells are able to escape pathway checkpoints and grow uncontrollably.[1] Genetic markers specific to primary GBM include alterations in the epidermal growth factor receptor (*EGFR*), phosphate and tensin homolog mutations, and the loss of chromosome 10q, whereas secondary GBM might have isocitrate dehydrogenase 1 mutations, *TP53* mutations, and chromosome 19q loss.[1] GBM subtypes have been defined on the basis of the presence or absence of these mutations. Despite this, patients usually receive identical frontline treatment.[3]

Effective second-line therapy options to treat GBM are lacking, which has led to exploration of targeted therapies in the setting of recurrence or progressive disease. In GBM, however, the ability of targeted therapies to cross the blood brain barrier (BBB), the heterogeneity of the tumors, and the lack of druggable mutations have traditionally limited the use of targeted therapies among this population, especially in the frontline setting. For second-line therapies, in addition to minimally effective traditional chemotherapy options, The National Comprehensive Cancer Network guidelines recommend BRAF/MEK inhibitors dabrafenib + trametinib or vemurafenib + cobimetinib for patients with tumors harboring a *BRAF*^{V600E} mutation and TRK inhibitors larotrectinib or entrectinib for those with an *NTRK* gene fusion,[4] but otherwise recommend clinical trial enrollment. The intracranial efficacy of the BRAF/MEK inhibitors, however, was initially extrapolated from trials evaluating the response of these agents in metastatic melanoma rather than evaluation in a primary CNS tumor.[5,6] Case reports have also been published confirming their response in primary CNS malignancies.[7,8] Similarly, the use of TRK inhibitors is based on data from a post hoc analysis of a pan-tumor study evaluating the efficacy of these agents in brain metastases, but primary CNS tumors were excluded.[9,10]

Alterations in *KRAS* are the most frequently mutated oncogenes in humans; however, they are only detected in 1.92% of patients with GBM.[11,12] There was a lack of approved *KRAS* targeted therapies until May 2021 when sotorasib was approved for patients with *KRAS*^{G12C}-mutated locally advanced or metastatic non–small cell lung cancer (NSCLC).[13] Initially thought to be unable to cross the BBB in animal trials, sotorasib has demonstrated intracranial activity because of its effect on brain metastases in NSCLC.[4,14] Despite the initial lack of effect, sotorasib monotherapy in NSCLC has demonstrated the ability to shrink brain metastases, which suggests that BBB penetration likely occurs.[15] These data do not encompass patients with primary CNS tumors; however, the data show that intracranial activity is possible, which prompted our use of sotorasib in a patient with *KRAS*^{G12C}-mutated GBM. Here, we report a 49-year-old man with *KRAS*^{G12C}-mutated GBM that demonstrated prolonged disease stabilization after previous tumor progression. To our knowledge, this is the first report of successful sotorasib use in a patient with primary CNS cancer.