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Phase 1/2 trial of temsirolimus and sorafenib in the treatment of patients with recurrent glioblastoma: North Central Cancer Treatment Group Study/Alliance N0572.

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BACKGROUND: Mitogen-activated protein kinase (MAPK) activation and mammalian target of rapamycin (mTOR)-dependent signaling are hallmarks of glioblastoma. In the current study, the authors conducted a phase 1/2 study of sorafenib (an inhibitor of Raf kinase and vascular endothelial growth factor receptor 2 [VEGFR-2]) and the mTOR inhibitor temsirolimus in patients with recurrent glioblastoma.

METHODS: Patients with recurrent glioblastoma who developed disease progression after surgery or radiotherapy plus temozolomide and with ≤2 prior chemotherapy regimens were eligible. The phase 1 endpoint was the maximum tolerated dose (MTD), using a cohorts-of-3 design. The 2-stage phase 2 study included separate arms for VEGF inhibitor (VEGFi)-naive patients and patients who progressed after prior VEGFi.

RESULTS: The MTD was sorafenib at a dose of 200 mg twice daily and temsirolimus at a dose of 20 mg weekly. In the first 41 evaluable patients who were treated at the phase 2 dose, there were 7 who were free of disease progression at 6 months (progression-free survival at 6 months [PFS6]) in the VEGFi-naive group (17.1%); this finding met the prestudy threshold of success. In the prior VEGFi group, only 4 of the first 41 evaluable patients treated at the phase 2 dose achieved PFS6 (9.8%), and this did not meet the prestudy threshold for success. The median PFS for the 2 groups was 2.6 months and 1.9 months, respectively. The median overall survival for the 2 groups was 6.3 months and 3.9 months, respectively. At least 1 adverse event of grade ≥3 was observed in 75.5% of the VEGFi-naive patients and in 73.9% of the prior VEGFi patients.

CONCLUSIONS: The limited activity of sorafenib and temsirolimus at the dose and schedule used in the current study was observed with considerable toxicity of grade ≥3. Significant dose reductions that were required in this treatment combination compared with tolerated single-agent doses may have contributed to the lack of efficacy. Cancer 2018. © 2018 American Cancer Society.

KEYWORDS: clinical trial; glioblastoma; sorafenib; targeted therapy; temsirolimus

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