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Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

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Abstract

Background: Detection of the *BRAF* V600E mutation in pediatric low-grade glioma has been associated with a lower response to standard chemotherapy. In previous trials, dabrafenib (both as monotherapy and in combination with trametinib) has shown efficacy in recurrent pediatric low-grade glioma with *BRAF* V600 mutations, findings that warrant further evaluation of this combination as first-line therapy.

Methods: In this phase 2 trial, patients with pediatric low-grade glioma with *BRAF* V600 mutations who were scheduled to receive first-line therapy were randomly assigned in a 2:1 ratio to receive dabrafenib plus trametinib or standard chemotherapy (carboplatin plus vincristine). The primary outcome was the independently assessed overall response (complete or partial response) according to the Response Assessment in Neuro-Oncology criteria. Also assessed were the clinical benefit (complete or partial response or stable disease for ≥24 weeks) and progression-free survival.

Results: A total of 110 patients underwent randomization (73 to receive dabrafenib plus trametinib and 37 to receive standard chemotherapy). At a median follow-up of 18.9 months, an overall response occurred in 47% of the patients treated with dabrafenib plus trametinib and in 11% of those treated with chemotherapy (risk ratio, 4.31; 95% confidence interval [CI], 1.7 to 11.2; P<0.001). Clinical benefit was observed in 86% of the patients receiving dabrafenib plus trametinib and in 46% receiving chemotherapy (risk ratio, 1.88; 95% CI, 1.3 to 2.7). The median progression-free survival was significantly longer with dabrafenib plus trametinib than with chemotherapy (20.1 months vs. 7.4 months; hazard ratio, 0.31; 95% CI, 0.17 to 0.55; P<0.001). Grade 3 or higher adverse events occurred in 47% of the patients receiving dabrafenib plus trametinib and in 94% of those receiving chemotherapy.

Conclusions: Among pediatric patients with low-grade glioma with *BRAF* V600 mutations, dabrafenib plus trametinib resulted in significantly more responses, longer progression-free survival, and a better safety profile than standard chemotherapy as first-line therapy. (Funded by Novartis; ClinicalTrials.gov number, NCT02684058.).