Editorial Commentary

Advances in the treatment of BRAF-mutant low-grade glioma with MAPK inhibitors

Peter J. Houghton^

Department of Molecular Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Correspondence to: Peter J. Houghton, PhD. Greehey Children's Cancer Research Institute, UT Health San Antonio, 8403 Floyd Curl Drive, San Antonio, TX 78229, USA. Email: Houghtonp@uthscsa.edu.

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Brain tumors constitute about 21% of pediatric cancers, and of these low-grade tumors occur most frequently and account for 45% of tumors in the central nervous system (1) or approximately 1,400 cases diagnosed per year in the US. These are indolent tumors that are non-invasive and may be cured through complete surgical resection. For patients where complete resection is not an option or have progressed or recurred additional therapies are often necessary. With current therapies 5-year overall survival is ~95% (2), however, this statistic does not convey that many patients who receive chemotherapy may have multiple relapses or progressions and worsening functional decline (3). For older patients, intensive treatment may include chemotherapy and X-radiation. The latter modality may cause these relatively benign tumors to transform into higher grade malignancies, and can be associated with cognitive decline that can be progressive (4). Long-term adverse outcomes include blindness, hormonal imbalance, and hearing loss which occur with frequencies between 18–25%. The incidence of obesity exceeds 50%, and approximately one-third of patients have an intelligent quotient (IQ) below average. The most common cause of death is progressive disease (PD) that is resistant to chemo-radiation therapy (5).

Genomic studies have shown that in low-grade tumors (grades 1 and 2, including pilocytic astrocytoma and ganglioglioma), ~85% have a tandem duplication involving the *KIAA1549* locus and *BRAF* genes that generate constitutively active *KIAA1549::BRAF* fusions that eliminate the N-terminal regulatory domain of *BRAF* leading to constitutive activation (6,7). Some low-grade gliomas have activating mutations such as the V600E variant, although activating mutations are more frequent in higher-grade tumors such as diffuse astrocytomas and pediatric glioblastomas. The highest rate of BRAF activating mutations is found in pleomorphic xanthoastrocytoma (70%). BRAF-point mutations also occur in ganglioglioma, epithelial glioblastomas.

The characteristic of these tumors is activation of the mitogen activated protein kinase (MAPK) signal transduction pathway that stimulates tumor cell proliferation (8). First generation BRAF inhibitors are not active against tumor cells with the *KIAA1549::BRAF* fusion (9), whereas selective antitumor activity of the MEK1-2 inhibitor, selumetinib was active in a $BRAF^{V600E}$ mutant astrocytoma (10) preclinical data that led to development of the Pediatric Brain Tumor Consortium phase 1 trial (11) that showed significant antitumor activity that was largely replicated in a subsequent phase 2 clinical trial (12). These results suggested that targeting MEK in low-grade glioma may be an alternative to conventional chemo-radiation treatment. Two phase 3 trials comparing standard chemotherapy to selumetinib in newly diagnosed children with low-grade

^ ORCID: 0000-0002-2400-8184.

glioma are ongoing. However, although overall survival in this population is good, disease often recurs with a relapse rate after chemotherapy or MEK inhibitors of 50–70%. In the selumetinib clinical studies, a majority of patients with *BRAF*^{V600} mutant tumors either progressed on treatment (i.e., became drug resistant), or progressed rapidly when selumetinib was dose-reduced or terminated. Thus, single agent MEK inhibitor therapy was of clinical value, but not curative, particularly in patients harboring *BRAF*^{V600} mutations that historically have shown lower response rates to chemotherapy than unselected patients with low-grade glioma (13,14).

In patients with metastatic melanoma 'vertical targeting' of the MAPK pathway through combination of trametinib, a potent allosteric MEK1-2 inhibitor, with dabrafenib, a direct inhibitor of BRAF, extended progression-free survival (PFS) from 5.8 months for trametinib monotherapy to 9.4 months (15), reduced toxicity as shown in preclinical studies (16) and subsequently improved 5-year outcomes in patients with metastatic melanoma (17). The mechanistic basis for superior activity of this vertical targeting approach is complex. Firstly, targeting BRAF and its downstream target MEK1-2 would be anticipated to reduce the signaling flux through the MAPK pathway. However, in melanoma and other cancers inhibition of MEK1-2 alone leads to activation of other RAF isoforms, most commonly CRAF, that leads to reactivation of the MAPK pathway and maintained tumor cell proliferation or survival. Dabrafenib is equally potent as an inhibitor of BRAF and CRAF (16), thus potentially suppresses reactivation of the MAPK pathway and retards the emergence of trametinib resistance.

The recent study by Bouffet *et al.* (18), that is the focus of this commentary, focused on developing more effective targeted therapy for BRAF^{V600}-driven low-grade glioma, through vertical targeting of the MAPK pathway by combining trametinib with a BRAF inhibitor, dabrafenib, shown to be effective in metastatic melanoma. This complex, pharmacokinetically guided clinical trial (ClinicalTrials.gov identifier: NCT2124772) was sponsored by Novartis the pharmaceutical company that provided trametinib, and dabrafenib. Whereas the tolerability of dabrafenib had been established in children with *BRAF*-mutant solid tumors (19), trametinib had not been used in children. Thus the objective of part A of the study, which did not require *BRAF*^{V600} mutation, was to evaluate the tolerability of trametinib in low-grade glioma with either *BRAF*^{V600} or *KIAA1549::BRAF* fusions, *BRAF*-wild type or unknown status and a single patient with neuroblastoma. Inclusion of fusion positive low-grade glioma was based on the published efficacy of selumetinib in these patients (12). Part A explored a range of trametinib doses (0.025–0.04 mg/kg) once daily by oral administration and part B was a disease specific expansion cohort. Part C evaluated toxicity and efficacy of trametinib [0.025 mg/kg + dabrafenib 50% of the recommended phase 2 dose (RP2D), or dabrafenib 100% of the RP2D] in patients with *BRAF*^{V600} mutant low-grade glioma, or *BRAF*^{V600}-mutant Langerhans cell histiocytosis. In addition, two *BRAF*^{V600} mutant high grade glioma patients were entered. Part D was an expansion for patients only with *BRAF*^{V600} mutant disease. The study enrolled 25 patients with fusion-positive low-grade glioma to trametinib monotherapy, but efficacy for this cohort was not presented, hence it is not possible to compare the phase II efficacy of selumetinib (12) with trametinib in the current trial.

In part A, the daily dose of 0.04 mg/kg was not tolerated, but pharmacokinetic data predicted that a significant population of patients under the age of 6 years would not achieve the target exposure (10 ng/mL steady state) at the 0.025 mg/kg dose, necessitating an additional dose (0.032 mg/kg) to be evaluated. This dose had acceptable toxicity and achieved the planned drug exposure. Trametinib monotherapy was associated with grade 3 dose limiting toxicities (DLTs), mainly at the 0.04 mg/kg dose level and included mucosal inflammation (n=3), grade 4 hyponatremia and hypotension at the higher dose level. No DLTs were observed at the 0.032 mg/kg dose level or in part C (dabrafenib + trametinib). For combination studies, the age adjusted dose of trametinib determined in part A and 50% or 100% of the age adjusted RP2D for dabrafenib were used (4.5 mg/kg for patients 12 years or older and 5.35 mg/kg for patients less than 12 years old). Dabrafenib was divided into two equal doses and administered orally daily. No DLTs were observed in part C (dabrafenib + trametinib), thus reaffirming both preclinical and adult clinical results that indicated the combination was less toxic than trametinib monotherapy. However, neither monotherapy nor trametinib + dabrafenib lack toxicity. In the trametinib monotherapy cohort, 54% of patients discontinued treatment primarily because of toxicity whereas in the combination treatment group the discontinuation rate due to toxicity was 22%. For trametinib, the most frequently reported treatment related adverse event (TRAE) was paronychia (inflammation of the skin around the nail), diarrhea and dry skin. For the combination group the most frequent TRAE's were pyrexia and dry skin. Ocular, cardiac and skin-related adverse effects were usually mild and not

dose limiting for any therapy.

For parts A and B (trametinib monotherapy) 2 of 13 (15%) patients with *BRAF*^{V600} mutant low-grade glioma had objective partial responses (PRs) and 46% had stable disease (SD) for at least 12 weeks from treatment initiation. For *BRAF*^{V600} mutant low-grade glioma treated with dabrafenib + trametinib 9 of 36 (25%) had objective PRs and 23 (64%) had SD, significantly better than monotherapy. The median duration of response (DOR), which includes only responders (n=2), was not reached in the monotherapy arm as both patients had ongoing responses at the time of data cutoff. For the combination group the median DOR was 33.6 months with seven responses ongoing at data cutoff. By independent assessment, PFS was 16.4 months for the trametinib alone group and 36.9 months in the dabrafenib + trametinib cohort. Of note, patients in both the monotherapy and combination treatment cohorts remained on treatment after tumor progression, in part a consequence of the definition of PD which was defined as 25% increase in tumor area [by Response Assessment in Neuro-Oncology (RANO 2017) criteria] from the tumor nadir. Thus, for those patients that had marked tumor volume reduction early in the treatment course the assessment of PD was determined at a time when the tumor volume was still smaller than prior to starting therapy. Consequently, patients remained on treatment as they were still demonstrating benefit. Also of note, is that in both groups the earlier responses (PR <20 weeks of treatment) appeared to be associated with a trend for longer duration of treatment (130 to >200 weeks) with two exceptions. In contrast, those patients achieving PR later in their course of treatment tended to have shorter treatment history after achieving PR. Of importance is that five patients remained on combination treatment for greater than 200 weeks. In terms of best percentage change in tumor perpendicular diameters all but one patient in the monotherapy arm had SD or some reduction in tumor area, and similarly with the combination treatment only a single patient had PD without initial tumor shrinkage.

What have we learned from this trial? Firstly, in patients with BRAF^{V600} mutant low-grade glioma, combination therapy with trametinib and dabrafenib is better tolerated than trametinib monotherapy, consistent with adult data. Several patients remained on combination therapy for over 4 years without reports of excessive or cumulative toxicity. Combination therapy is effective in inducing tumor shrinkage in a subset (25%), and leads to prolonged tumor stasis, but is not curative. As noted by the authors, the response rate to combination treatment is similar to that reported for single agent BRAF inhibitors, dabrafenib and vemurafenib. Thus, although addition of dabrafenib enhances the activity of trametinib, it is unclear that trametinib adds to the efficacy of dabrafenib. Further studies comparing single agent BRAF inhibitors with combinations will be required to determine the most effective treatments. These future studies should have clear criteria for defining tumor progression. In the current study, PD was defined using RANO 2017 criteria that assessed increase in tumor area from the nadir and not relative to the pretreatment tumor dimensions. Whether this PD represents drug-resistant tumor is questionable, as assessments made by independent review and by investigator assessment (presented in Data Supplement) frequently varied. In this study, patients considered to be benefitting from each treatment at the time of data cutoff were eligible to enter a rollover trial (Clinicaltrials.gov identifier NCT03975829). Entry into the rollover trial was higher from parts C and D (44% and 77%, respectively) than from parts A and B (26% and 17% respectively) consistent with the superiority of combination treatment controlling disease progression.

An important question is how quickly, and with what frequency, does drug resistance emerge in this population treated with combination therapy versus monotherapy with BRAF inhibitors, and such studies will need uniform criteria for defining drug resistance. This trial enrolled patients <18 years with relapsed or refractory malignancies although prior treatment was not provided, except for the two high-grade glioma patients entered in part C, one of whom had prolonged SD and the other had PD. Thus, whether prior chemotherapy or radiation therapy would influence the efficacy of molecularly targeted therapies will require other clinical trials.

Treatment of patients with low-grade glioma relies on surgical resection as the primary curative modality. For those patients where complete excision is not possible traditional chemotherapy with addition of radiation treatment in older patients has been used. A report published after the current study (20) directly compared trametinib-dabrafenib combination therapy with standard of care chemotherapy (carboplatin/vincristine) in pediatric patients with low-grade *BRAF*^{V600} mutant glioma scheduled to receive first-line therapy. In this randomized trial, patients were assigned to receive targeted therapy (2:1), 73 patients received trametinib-dabrafenib and 37 received standard chemotherapy. MAPK-targeted therapy was statistically significantly better than standard chemotherapy

with respect to objective response rate (P<0.001) and PFS (P<0.001). Median follow-up was 18.9 months. In the trametinib-dabrafenib arm, the overall response rate was 47% and clinical benefit was observed in 86% of patients. The objective response rate in the chemotherapy cohort was 11% and clinical benefit was 46%. Median PFS for trametinib-dabrafenib was 20.1 months compared to 7.4 months with chemotherapy. Further the incidence of grade 3 or higher adverse events (AEs) were lower in the targeted therapy cohort compared to the chemotherapy cohort (47% versus 94%).

In part, this study answers one of the questions remaining from the study of trametinib-dabrafenib in patients at relapse. In relapse or previously treated patients the objective response was 25%, whereas in the first line setting the objective response rate was 47%, suggesting that prior therapy compromises the response rate for targeted therapies. The response rates and clinical benefit where trametinib-dabrafenib was administered in therapy-naive children definitively shows that molecularly targeted therapy directed at inhibiting MAPK signaling is now the new standard of care for low-grade $BRAF^{V600}$ mutation-driven glioma. This therapeutic approach, developed relatively rapidly following the molecular characterization of these tumors, now forms the template for building more efficacious and curative therapies for these patients. Despite significant advances in treatment of these patients through use of MAPK-targeted therapy that focuses on the oncogenic driver, challenges remain. The treatment causes tumor shrinkage but is largely cytostatic and not curative. We don't know the long-term toxicities that may be observed after years of treatment, and clearly some patients progress on the current combination treatment. Thus, the challenge remains to integrate molecular therapy with other modalities that may enhance the cure rate without returning to therapies that have devastating sequelae.

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References

1. Ostrom QT, Cioffi G, Waite K, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. Neuro Oncol 2021;23:iii1-iii105.
2. Stokland T, Liu JF, Ironside JW, et al. A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). Neuro Oncol 2010;12:1257-68.
3. Sadighi ZS, Curtis E, Zabrowksi J, et al. Neurologic impairments from pediatric low-grade glioma by tumor location and timing of diagnosis. Pediatr Blood Cancer 2018;65:e27063.
4. Merchant TE, Hodgson D, Laack NN, et al. Children's Oncology Group's 2013 blueprint for research: radiation oncology. Pediatr Blood Cancer 2013;60:1037-43.
5. Upadhyaya SA, Ghazwani Y, Wu S, et al. Mortality in children with low-grade glioma or glioneuronal tumors: A single-institution study. Pediatr Blood Cancer 2018.
6. Pfister S, Janzarik WG, Remke M, et al. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest

2008;118:1739-49.
7. Sievert AJ, Jackson EM, Gai X, et al. Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single-nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. Brain Pathol 2009;19:449-58.
8. Schreck KC, Grossman SA, Pratilas CA. BRAF Mutations and the Utility of RAF and MEK Inhibitors in Primary Brain Tumors. Cancers (Basel) 2019;11:1262.
9. Sievert AJ, Lang SS, Boucher KL, et al. Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. Proc Natl Acad Sci U S A 2013;110:5957-62.
10. Kolb EA, Gorlick R, Houghton PJ, et al. Initial testing (stage 1) of AZD6244 (ARRY-142886) by the Pediatric Preclinical Testing Program. Pediatr Blood Cancer 2010;55:668-77.
11. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. Neuro Oncol 2017;19:1135-44.
12. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. Lancet Oncol 2019;20:1011-22.
13. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 2012;30:2641-7.
14. Nobre L, Zapotocky M, Ramaswamy V, et al. Outcomes of BRAF V600E Pediatric Gliomas Treated With Targeted BRAF Inhibition. JCO Precis Oncol 2020;4:PO.19.00298.
15. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694-703.
16. King AJ, Arnone MR, Bleam MR, et al. Dabrafenib; preclinical characterization, increased efficacy when combined with trametinib, while BRAF/MEK tool combination reduced skin lesions. PLoS One 2013;8:e67583.
17. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med 2019;381:626-36.
18. Bouffet E, Geoerger B, Moertel C, et al. Efficacy and Safety of Trametinib Monotherapy or in Combination With Dabrafenib in Pediatric BRAF V600-Mutant Low-Grade Glioma. J Clin Oncol 2023;41:664-74.
19. Kieran MW, Geoerger B, Dunkel IJ, et al. A Phase I and Pharmacokinetic Study of Oral Dabrafenib in Children and Adolescent Patients with Recurrent or Refractory BRAF V600 Mutation-Positive Solid Tumors. Clin Cancer Res 2019;25:7294-302.
20. Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus Trametinib in Pediatric Glioma with BRAF V600 Mutations. N Engl J Med 2023;389:1108-20.

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