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EDITORIAL



# How will tovorafenib change our treatment of pediatric low-grade glioma?

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## 1. Background

Pediatric low-grade gliomas (pLGGs) are the most common pediatric brain tumors. The majority of pLGGs are pilocytic astrocytomas. The World Health Organization (WHO) has introduced many changes in the 2021 classification of pLGG, including a trend for increasing role of molecular markers to better characterize various entities. Despite the low-grade histology and slow-growing nature of these tumors, treatment remains challenging in many cases due to their location. pLGG most frequently arises in the cerebellum (35%), followed by the cerebral hemispheres (17%), the optic pathway and hypothalamic region (15%), and the brainstem (9%) [1,2]. Optic pathway/hypothalamic gliomas can cause long-term morbidities, including vision loss, proptosis, endocrinopathies, and hypothalamic dysfunction. Because of the unpredictable nature of the clinical course, which alternates between periods of growth and periods of quiescence, it is difficult to determine when to initiate treatment.

## 2. Existing treatment and medical need

For treating pLGG, surgical resection is the best option if it is amenable. Chemotherapy and radiotherapy have been traditionally alternative options for patients when radical surgery was not possible. The most commonly used chemotherapy protocols for pLGGs are vincristine and carboplatin, or monotherapy with vinblastine. Chemotherapy regimens achieve 5-year PFS between 30% and 40% in most series [3]. Even though tumor control appears higher in patients treated with radiation compared to chemotherapy, concerns over long-term side effects limit the use of radiation therapy. Over the last decade, our understanding of the biology and underlying molecular alterations of pLGG has improved dramatically. It has been shown that genomic alterations of BRAF, KIAA1549:BRAF fusion (50–60%), and BRAF V600E mutations (5–15%) are the most frequent oncogenic drivers in pLGGs. BRAF is a component of the MAPK and PI3K/AKT/mTOR pathways that play a crucial role in cellular proliferation, differentiation, migration, and angiogenesis. A number of RAS/MAPK pathway inhibitors have been shown to be effective against pLGGs, including vemurafenib and dabrafenib (BRAF inhibitors) and trametinib and selumetinib (MEK1/MEK2 inhibitors). A MEK1/MEK2 inhibitor is preferred over a BRAF inhibitor for patients with BRAF-fused LGG due to the possibility of paradoxical MAPK pathway activation. The majority of patients respond well to MEKi treatment; however, resistance to MEKi or PLX8394 (a RAF inhibitor) develops *via* increased RTK expression, causing activation of PI3K/mTOR pathway in BRAF fusion expressing resistant clones urging the need for new agents [4].

## 3. Scientific rationale

Tovorafenib (DAY101, TAK-580, MLN2480, or BIIB024) was initially introduced in 2017 by Sun Y et al. [5] as an investigational, oral, selective, brain-penetrant, small molecule, type II pan-RAF inhibitor. Tovorafenib is most potent against CRAF but markedly less potent against ARAF [6]. It has been shown to be effective in the treatment of BRAF-altered solid tumors, including melanoma and LGG [7,8]. In 2021, tovorafenib was granted Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients with pLGG harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options. The FDA has also granted Rare Pediatric Disease Designation to tovorafenib for the treatment of low-grade gliomas harboring an activating RAF alteration that disproportionately affect children. It has also received Orphan Drug designation from the FDA and the European Medicines Agency (EMA) for treating malignant glioma. In biochemical assays, tovorafenib demonstrated potency against V600E-mutated BRAF monomers and unlike type I BRAF inhibitors, tovorafenib does not induce paradoxical MAPK signaling [5].

## 4. Studies with tovorafenib for patients with pLGG

PNOC014 (Pacific Pediatric Neuro-Oncology Consortium) study (ClinicalTrials.gov identifier: NCT03429803) is a phase 1 study designed for patients with RAF-altered tumors.

In part A of the study [9], nine pediatric patients with recurrent/progressive low-grade glioma (LGG) were enrolled in the study, including eight patients with KIAA1549:BRAF fusion and one patient with neurofibromatosis type 1 (NF1).

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Outcomes of these nine patients based on RANO-HGG criteria were two complete response (CR), two partial response (PR), three stable disease (SD), and two, including the patient with NF1, progressive disease (PD). Results were also analyzed using RAPNO criteria, with five PR, three SD, and one PD. Considering the occurrence of progression in the patient with NF1 during this pilot study, DayOne decided to exclude NF1 patients from further early phase trials.

In Part B of this study [10], 35 patients were enrolled: 21 with KIAA1549:BRAF fusion, 9 with BRAFV600E mutation, 4 with novel RAF alterations, and 1 with an FGFR1-altered tumor. Histopathological diagnosis was LGG in 30, high-grade gliomas in 4, and soft tissue sarcoma in 1 patient. Overall, 2 patients had CR, 7 had PR, and 15 had SD. Tovorafenib was well tolerated.

FIREFLY-1 (NCT04775485) is a pivotal Phase 2, multicenter, open-label study designed to evaluate the safety and efficacy of tovorafenib in patients aged 6 months to 25 years of age with pLGG harboring a known activating BRAF (arm 1; registrational, n: 77) or RAF (arm 2; extension, n: 60) alteration. Recently, the efficacy outcomes for arm 1 and safety outcomes for arms 1 and 2 were reported [11]. Based on an independent review, according to RANO-HGG criteria, the overall response rate (ORR) of 67% met the arm 1 prespecified primary endpoint; median duration of response (DOR) was 16.6 months; and median time to response (TTR) was 3.0 months (secondary endpoints). Other select arm 1 secondary endpoints included ORR, DOR, and TTR as assessed by Response Assessment in Pediatric Neuro-Oncology Low-Grade Glioma (RAPNO) criteria and safety (assessed in all treated patients and the primary endpoint for arm 2, $n = 137$). The ORR according to RAPNO criteria (including minor responses) was 51%; median DOR was 13.8 months; and median TTR was 5.3 months. The most common treatment-related adverse events (TRAEs) were hair color changes (76%), elevated creatine phosphokinase (56%), and anemia (49%). Grade ≥ 3 TRAEs occurred in 42% of patients. Nine (7%) patients had TRAEs leading to discontinuation of tovorafenib. Intratumoral hemorrhage was reported in 15 patients and led to discontinuation of therapy in three patients. This is an important TRAE since it has never been reported before in previous clinical trials of Selumetinib, Dabrafenib, Trametinib, or with the combination of Dabrafenib and Trametinib and this definitely requires further follow-up during this ongoing study and future studies with tovorafenib.

LOGGIC/FIREFLY-2 (NCT05566795) is a phase 3, randomized, multicenter, open-label study evaluating once-weekly tovorafenib monotherapy versus standard of care (SoC) chemotherapy in pediatric patients with newly diagnosed RAF-altered low-grade glioma [12]. The primary endpoint is ORR based on RANO. Secondary endpoints include progression-free survival (PFS) by an independent review committee (IRC) per RANO-LGG, duration of response (DOR) assessed by IRC per RANO-LGG, and overall survival. This study is open and recruiting pediatric patients with RAF-altered pLGG requiring front-line systemic therapy and will likely provide important information.

## 5. Expert opinion

Results of phase 1 and 2 studies of tovorafenib in pediatric low-grade gliomas show promise. This agent has several advantages over traditional MEK and BRAF inhibitors. The long half-life of the compound allows once weekly dosing, which is important for children and families and may improve compliance. The side effects are manageable, with hair color changes as the most common adverse event (71%) and skin toxicity (maculopapular rash and acneiform dermatitis) as the most common grade 3 adverse events (<10%).

It is a brain penetrant Pan-RAF inhibitor, and this may result in improved activity. However, in the absence of direct comparison trials, it is premature to conclude that tovorafenib is superior to other MEK or BRAF inhibitors. Early reports suggested an impressive activity with an overall response rate (CR+PR) of 64% and a clinical benefit (CR+PR+SD) of 91%. The median time to response was also remarkable, with the majority of patients responding within 3 months of initiation of treatment. However, these data were based on RANO-HGG criteria and mostly related to the resolution of enhancement on post-contrast MRI scans, a common observation with the use of MEK and BRAF inhibitors. Further reports using RANO-LGG criteria demonstrated a complete plus partial response rate of 26%, a minor response rate of 26%, and a clinical benefit rate of 86%. The time to response with the RANO-LGG criteria was 5.5 months. On paper, these results are not different from previous reports in MEK and BRAF inhibitors phase 2 trials. An interesting observation is the evidence of activity in patients who had shown progression on MAPK inhibitors. Although these data are still preliminary, this suggests a role of tovorafenib in patients who have failed previous treatment or progressed on MAPK inhibitors. Another interesting observation is the occurrence of delayed responses following early progression within 3 months of initiation of treatment. In FIRELY-1, among 11 patients who showed early progression at 3 months and continued treatment, 6 eventually experienced some tumor shrinkage, including 4 PR.

Data on tovorafenib are still immature, and more follow-up is needed to have a clear idea of the response rate and long-term activity of this agent. At the 2023 ASCO meeting, the median duration of treatment in the FIREFLY-1 cohort of 77 patients was 10.8 months. It will be critical to periodically review these results and reevaluate the efficacy with longer follow-up. The majority of the patients enrolled in FIREFLY-1 had pLGG associated with BRAF fusion and only 17% of patients had BRAF-mutated pLGG in the series of 77 patients presented at the 2023 ASCO meeting. Additional information is also needed on the toxicity profile over time. The situation of patients with NF1 is still unclear. As mentioned above, patients with NF1 were excluded from FIREFLY-1 and are not eligible in FIREFLY-2. The scientific rationale for this decision is based on a single preliminary incidental finding and there have been no preclinical studies to confirm the possibility of a paradoxical activation of NF1-associated pLGG with tovorafenib.

## 6. Conclusion

Altogether, considering the critical needs of patients with pLGG, DayOne brings a novel and promising targeted agent in the field. The recently opened LOGGIC/FIREFLY-2 trial (NCT05566795) compares tovorafenib to standard chemotherapy as the first-line systemic treatment in the pLGG population. With a planned accrual of 400 patients, this trial will provide valuable data regarding the role of this promising targeted agent to the field. Retrospective analyses of biospecimens may further clarify molecular markers indicative of a subset of patients benefitting most from tovorafenib.

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## Declaration of interest

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