LOGGIC/FIREFLY-2: A phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric patients with newly diagnosed low-grade glioma harboring an activating *RAF* alteration

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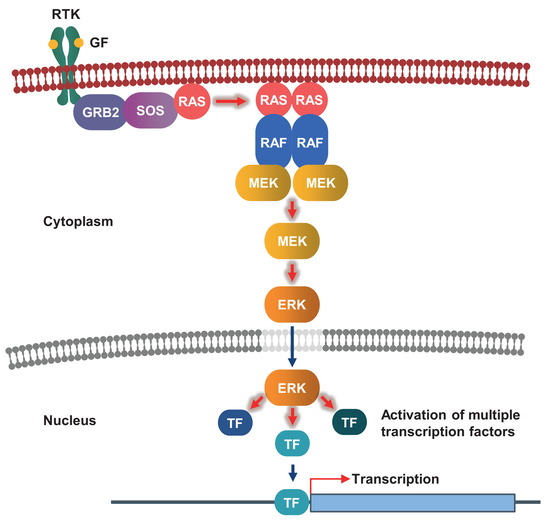
Background

- The serine/threonine RAF kinases (ARAF, BRAF and RAF1), are signaling components of the mitogen activated protein kinase/ERK (MAPK) pathway, a key regulator of cell proliferation and survival (**Figure 1**)[1,2]
- *RAF* fusions (involving either *BRAF* or *RAF1*) and BRAF V600E mutations are oncogenic drivers found on a mutually exclusive basis in most pediatric low-grade gliomas (LGGs)[3]
  - *KIAA1549-BRAF* fusions are the most commonly seen *RAF* alterations in pediatric LGG, occurring in 30–40% of all cases and up to 80% of pilocytic astrocytomas[3,4]
- Pediatric LGG may be considered a chronic disease with multiple relapses.[5] Chemotherapy remains a standard treatment for patients requiring systemic therapy[6,7]
- Tovorafenib (DAY101) is an investigational, oral, selective, CNS-penetrant, small molecule, type II pan-RAF inhibitor
  - In contrast to type I BRAF inhibitors, tovorafenib does not induce RAS-dependent paradoxical activation of the MAPK pathway
  - Tovorafenib inhibits both oncogenic RAF fusions, which signal as RAS-independent dimers and V600E-mutated BRAF, which signals as a RAS-independent monomer[8]
- An interim analysis of the registrational arm of the phase 2 FIREFLY-1 study reported an overall response rate of 64% and a clinical benefit rate of 91% per independent assessment in children with pretreated *BRAF*-altered LGG[9,10]
- The randomized phase 3 LOGGIC/FIREFLY-2 study will evaluate the efficacy, safety, and tolerability of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in children and young adults with LGG harboring an activating *RAF* alteration and requiring front-line systemic therapy

Figure 1. MAPK signaling pathway

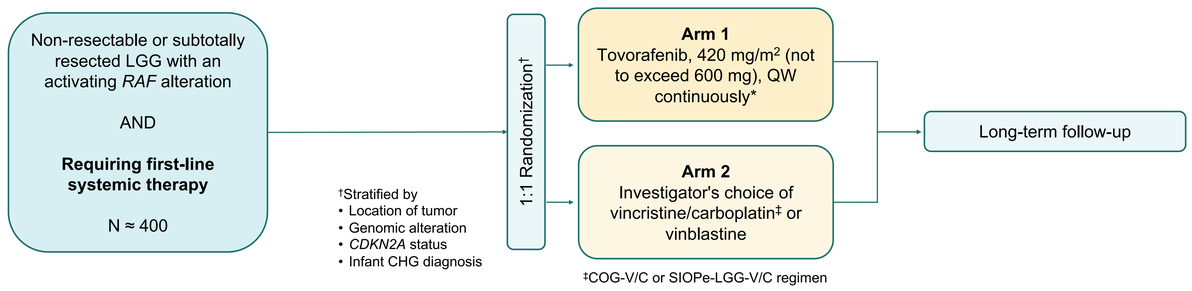


GF, growth factor; MAPK, mitogen activated protein kinase; RTK, receptor tyrosine kinase; TF, transcription factor

Study design

- LOGGIC/FIREFLY-2 (NCT05566795) is a 2-arm, randomized, open-label, multicenter, global, phase 3 trial
- Approximately 400 treatment-naïve patients with a *RAF*-altered LGG will be enrolled from ~100 sites and randomized 1:1 to either tovorafenib (arm 1) or investigator's choice of SoC chemotherapy (arm 2)
- Randomization will be stratified by:
  - Primary location of the tumor (supratentorial midline vs. other)
  - Type of genomic alteration (fusion vs. mutation)
  - *CDKN2A* status (deletion vs. wild-type/unknown)
  - Infant chiasmatic-hypothalamic glioma diagnosis (yes vs. no)

Study design



*Treatment continued until the occurrence of radiographic progression, unacceptable toxicity, withdrawal of consent, or end of study
CHG, chiasmatic-hypothalamic glioma; COG, Children's Oncology Group; QW, once weekly; LGG, low-grade glioma; SIOPe, International Society of Pediatric Oncology Europe; V/C, vincristine/carboplatin

- The study includes a screening phase, a treatment phase, an end of treatment visit, a 30-day safety follow-up visit, and a long-term follow-up period; the total length of the study (from first patient screened to end of study) is expected to be ~7 years

Key inclusion criteria

- Age <25 years with LGG harboring a documented known activating *RAF* alteration, as identified through a molecular assay performed at a CLIA or other similarly certified laboratory
- Histopathologic diagnosis of glioma or glioneuronal tumor (grade 1 or 2, according to 2021 WHO classification of tumors of the CNS)[11]
- Availability of a formalin-fixed paraffin-embedded, frozen or fresh tumor tissue sample
- At least one measurable lesion
- Indication for first-line systemic therapy

Key exclusion criteria

- Patient has any of the following tumor histological findings:
  - Schwannoma
  - Subependymal giant cell astrocytoma (tuberous sclerosis)
  - Diffuse intrinsic pontine glioma, even if histologically diagnosed as WHO grade 1–2
- Patient's tumor has additional activating molecular alterations (even if histologically low grade) including, but not limited to any of the following:
  - *IDH1/2* mutation
  - Histone H3 mutation
  - *FGFR* mutations or fusions
  - *MYBL* alterations
  - *NF1* loss of function mutation
- Known or suspected diagnosis of neurofibromatosis type 1 or 2 via genetic testing or current diagnostic clinical criteria

Treatment

- Patients will be randomized 1:1 to receive either oral tovorafenib, 420 mg/m² (not to exceed 600 mg) once weekly (tablet or liquid suspension) in 28 day-cycles (arm 1), or investigator's choice of SoC chemotherapy (arm 2)
  - SoC chemotherapy in arm 2 comprises one of the following three regimen: the Children's Oncology Group-vincristine/carboplatin (COG-V/C) regimen, the International Society for Pediatric Oncology Europe-low-grade glioma-vincristine/carboplatin (SIOPe-LGG-V/C) regimen, or vinblastine
- In arm 1, tovorafenib will be continued until the occurrence of radiographic progression (based on RANO criteria as determined by the investigator and confirmed by the independent review committee [IRC]), unacceptable toxicity, withdrawal of consent to treatment, or end of study
  - During the treatment phase, patients in arm 1 with radiographic progression may be allowed to continue tovorafenib if, in the opinion of the treating investigator, the patient is deriving clinical benefit from continuing study treatment
- In arm 2 treatment will be continued until completion of the scheduled regimen, or the occurrence of radiographic progression (based on RANO criteria as determined by the investigator and confirmed by the IRC), unacceptable toxicity, withdrawal of consent to treatment, or end of study
  - Patients in arm 2 who demonstrate radiographic progression during the treatment phase or after completion of chemotherapy may be eligible to receive tovorafenib

Assessments

- Radiographic tumor measurements will be performed using MRI of the brain and/or spine
  - Scheduled at screening and every 12 weeks throughout treatment and long-term follow-up
- Screening visual acuity testing is required for all patients
  - Patients with underlying visual function deficit related to optic pathway glioma will undergo visual acuity testing (logMAR) at every radiographic response assessment, the end-of-treatment visit, and every 6 months during long-term follow-up
  - For all other patients, symptom-directed visual acuity testing may be completed as needed
- Neurological functioning and adaptive behaviors will be assessed using the Vineland-III Adaptive Behavior Scale
- In patients ≥2 years of age, health-related quality of life will be assessed using the Pediatrics Quality of Life™-Core Module (PedsQL-Core), Pediatrics Quality of Life™-Cancer (PedsQL-Cancer), and Patient-Reported Outcomes Measurement Information System (PROMIS®) assessments
- Standard monitoring for safety will include physical examination, neurological examination, dermatology examination, ophthalmology examination, bone assessment (Tanner stage <4–5), Karnofsky/Lansky score, clinical adverse events, laboratory variables and vital signs

Endpoints

Primary endpoint

- Objective response rate (ORR) for tovorafenib monotherapy vs. SoC chemotherapy based on RANO criteria, as determined by the IRC

Secondary and exploratory endpoints

Secondary	Exploratory
Key	
• PFS by IRC per RANO	• ORR, CBR, PFS, DOR, TTR by investigator per RANO
• DOR by IRC per RANO	• Changes in body length, weight, epiphysial growth plate closure and Tanner staging
• Overall survival	• Endocrine event-free survival
Other	• Endocrine morbidity score
• Changes in neurological function	• Tumor volume (based on MRI data)
• Changes in visual acuity	• Changes from baseline in quality of life
• ORR by IRC per RAPNO	• Time to next anticancer therapy
• CBR by IRC per RANO and RAPNO	• Efficacy and safety comparisons between the SoC chemotherapy regimens
• TTR by IRC per RANO and RAPNO	• PK
• PFS by IRC per RAPNO	
• DOR by IRC per RAPNO	
• Adverse events, vital signs, laboratory parameters	

CBR, clinical benefit rate; DOR, duration of response; IRC, independent review committee; MRI, magnetic resonance imaging; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SoC, standard of care; TTR, time to response

Statistical methods

- The ORR primary analysis will include all randomized patients; patients who are non-evaluable for efficacy will be considered non-responders
  - The planned sample size of ~400 patients will provide ~85% power to detect a 15% improvement in ORR for the tovorafenib arm at a 2-tailed level of significance of 0.05, assuming 30% ORR in the control arm and dropout rate of up to 10%
  - The ORR primary analysis is expected to occur approximately after the 12 months follow-up period for the last patient randomized
- The progression-free survival (PFS) analysis will include all randomized patients
  - The planned sample size of ~400 patients will provide ~85% power to detect a hazard ratio of 0.67 for PFS at a 2-tailed level of significance of 0.05
  - The PFS interim analysis is expected to occur at the time of the ORR primary analysis, and the PFS final analysis is anticipated 2 years thereafter, approximately 36 months after the last patient randomized

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