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

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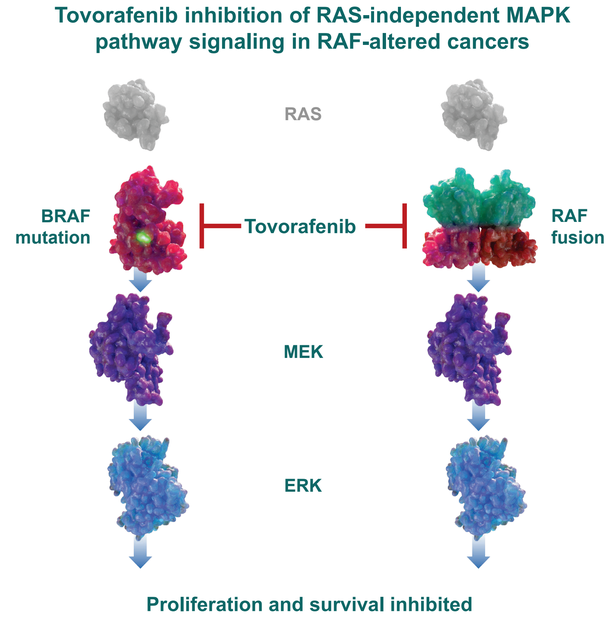
Background

- 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[1,2]
- *RAF* fusions (*BRAF* or *RAF1/CRAF*) and BRAF V600E mutations are oncogenic drivers found on a mutually exclusive basis in most pediatric low-grade gliomas (pLGGs):[3]
  - *KIAA1549-BRAF* fusions are the most commonly occurring *RAF* alterations in pLGGs, present in 30–40% of all tumors and up to 80% of pilocytic astrocytomas[3,4]
- pLGG is typically a chronic disease with multiple relapses; chemotherapy remains a standard treatment for patients requiring systemic therapy[5-7]
- Tovorafenib (DAY101) is an investigational, oral, CNS-penetrant, selective, type II pan-RAF inhibitor. Preclinical studies in murine model systems have shown:
  - 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 (**Figure 1**)[8]
- An interim analysis of the registrational arm of the phase 2 FIREFLY-1 study (NCT04775485) reported an overall response rate (RANO-HGG criteria[9]) of 64% and a clinical benefit rate of 91% (according to independent assessment) in children with pretreated *BRAF*-altered LGG[10]
- The randomized phase 3 LOGGIC/FIREFLY-2 (NCT05566795) study is evaluating the efficacy, safety, and tolerability of tovorafenib monotherapy vs. standard of care (SoC) chemotherapy in children and young adults with LGG harboring an activating *RAF* alteration and requiring first-line systemic therapy

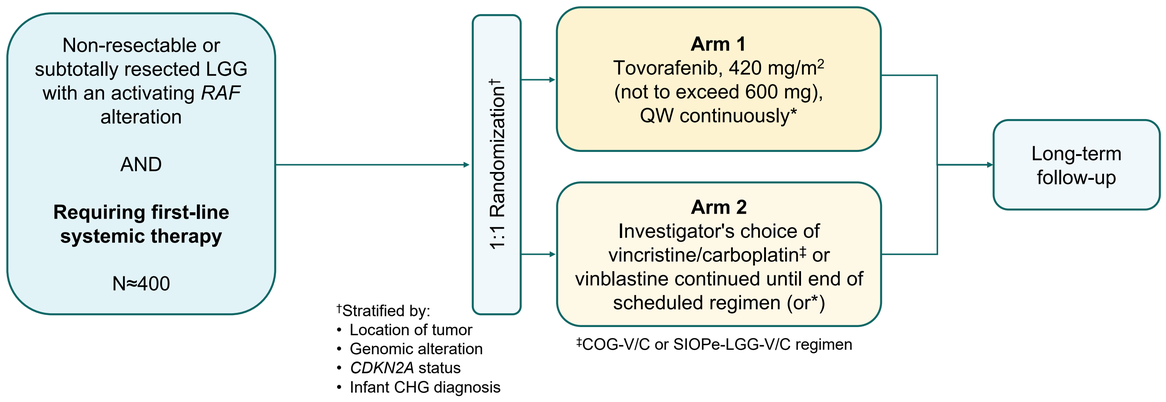
Figure 1. Tovorafenib mechanism of action



Study design

- LOGGIC/FIREFLY-2 is a 2-arm, randomized, open-label, multicenter, global, phase 3 trial (**Figure 2**)
- ~400 treatment-naïve patients with a *RAF*-altered LGG are being 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)

Figure 2. Study design



The study includes screening and treatment phases, an end of treatment visit, a 30-day safety follow-up visit, and a long-term follow-up period.
*Until the occurrence of radiographic progression (based on RANO-LGG criteria,[11] as determined by the investigator and confirmed by the IRC), unacceptable toxicity, withdrawal of consent to treatment, or end of study

CHG, chiasmatic-hypothalamic glioma; COG, Children's Oncology Group; IRC, independent review committee; LGG, low-grade glioma; QW, once weekly; RANO, Response Assessment in Neuro-Oncology; SIOPe, International Society of Pediatric Oncology Europe; V/C, vincristine and carboplatin

Key inclusion criteria

- <25 years (yrs) of age with an 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)[12]
- Availability of a formalin-fixed paraffin-embedded, frozen or fresh tumor tissue sample
- ≥1 measurable lesion
- Indication for first-line systemic therapy

Key exclusion criteria

- 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
- Tumor harbors additional activating molecular alterations (even if histologically low grade)
- 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), continuously, in 28 day-cycles (arm 1), or investigator's choice of SoC chemotherapy (arm 2; **Figure 2**):
  - SoC chemotherapy in arm 2 comprises one of the following three regimens:
    - The Children's Oncology Group-vincristine and carboplatin (COG-V/C) regimen (planned treatment period, 60 weeks)
    - The International Society for Pediatric Oncology Europe-low-grade glioma-vincristine/carboplatin (SIOPe-LGG-V/C) regimen (planned treatment period, 81 weeks)
    - Vinblastine (planned treatment period, 70 weeks)
- If patients in arm 1 experience an adverse event that is clinically or medically intolerable (or otherwise specifically defined in the protocol), tovorafenib dosing may be interrupted until resolution to grade 1 or baseline level:
  - Upon resolution, dosing may be restarted at the same dose or a lower dose, at the discretion of the local investigator
  - Patients who experience drug-related toxicity requiring a recovery period >42 days will be withdrawn from study drug administration unless there is evidence of benefit, and no alternative treatment is available
- Chemotherapy dosing for patients in arm 2 may be modified due to toxicity in accordance with protocol-defined criteria
- During the treatment phase, patients in arm 1 with radiographic progression may continue tovorafenib if, in the opinion of the treating investigator, they are deriving clinical benefit from study treatment
- Patients in arm 2 who demonstrate radiographic progression during the treatment phase or after completion of chemotherapy may be eligible to receive tovorafenib

Tests and evaluations

- 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
  - Radiographic response assessments:
    - Investigator: RANO-LGG[11]
    - Independent Review Committee (IRC): RANO-LGG,[11] RANO-HGG,[9] and RAPNO-LGG criteria[13]
- Screening visual acuity testing is required for all patients:
  - Patients with underlying visual function deficit related to optic pathway glioma:
    - Visual acuity testing (logMAR) at every radiographic response assessment, the end-of-treatment visit, and every 6 months (mos) 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 yrs of age QoL will be assessed using:
  - Pediatrics Quality of Life™-Core Module (PedsQL-Core)
  - Pediatrics Quality of Life™-Cancer Module (PedsQL-Cancer)
  - Patient-Reported Outcomes Measurement Information System (PROMIS®) assessments
- Standard monitoring for safety will include physical, neurological, dermatology, and ophthalmology examinations, bone age assessment (Tanner stage <5), Karnofsky/Lansky score, cardiac function, clinical adverse events, laboratory variables (eg, hematology and serum chemistries), and vital signs
- Prognostic and predictive molecular biomarkers, including senescence profiles for treatment outcome, response prediction, and treatment resistance, will be explored in parallel studies

Endpoints

Primary endpoint

ORR for tovorafenib monotherapy vs. SoC chemotherapy based on RANO-LGG criteria, as determined by the IRC

Secondary and exploratory endpoints

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

CBR, clinical benefit rate; DOR, duration of response; HGG, high-grade glioma; IRC, independent review committee; LGG, low-grade glioma; 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 objective response rate (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 a dropout rate of up to 10%
  - The ORR primary analysis is expected to occur approximately 12 mos after the last patient is randomized
- The progression-free survival (PFS) interim and final analyses 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
  - Interim analysis: to occur at the time of the ORR primary analysis
  - Final analysis: 2 yrs thereafter, ~36 mos after the last patient is randomized

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