FIREFLY-1 (PNOC 026): A phase 2 study to evaluate the safety and efficacy of tovorafenib (DAY101) in pediatric patients with *RAF*-altered recurrent or progressive low-grade glioma or advanced solid tumors

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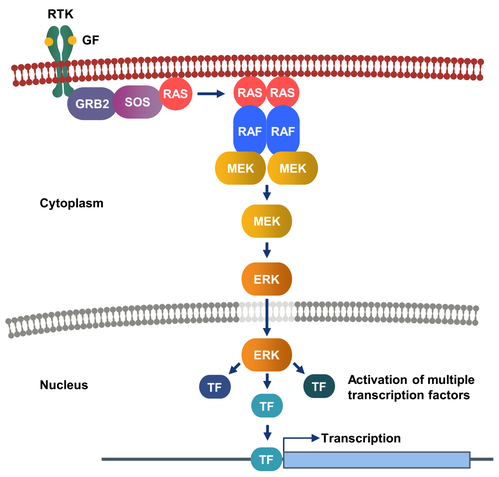
Background

- 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]
- In addition, *RAF* fusions (*BRAF* and *RAF1*) have also been identified in other pediatric tumors[5]
- Tovorafenib (DAY101) is an investigational, oral, highly 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[6]
- In the ongoing phase 1 PNOC014 study (NCT03429803) in pediatric patients with recurrent/progressive LGG, tovorafenib was well tolerated and 7/8 patients with tumors harboring *RAF* fusions derived a clinically meaningful benefit from treatment[7]
- Recently, a child with a novel *SNX8-BRAF* fusion spindle cell sarcoma demonstrated a rapid and deep response when treated with tovorafenib under a compassionate use protocol[8]
- This study was designed to explore the safety and efficacy of tovorafenib in children and young adults with tumors harboring *RAF* alterations

Figure 1. MAPK/ERK signaling pathway

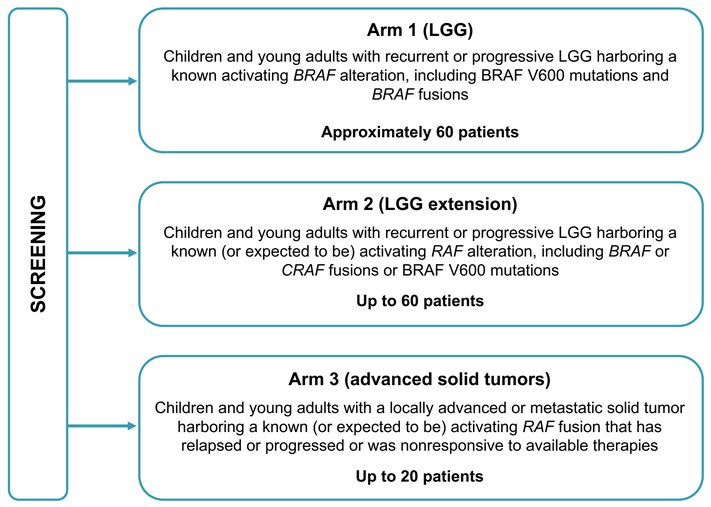


GF, growth factor; MAPK, mitogen activated protein kinase; RTK, receptor tyrosine kinase; TF, transcription factor

Study design

- FIREFLY-1 (NCT04775485) is an open-label, multicenter, phase 2 study evaluating the safety and efficacy of tovorafenib monotherapy in pediatric and young adult patients with *RAF*-altered recurrent or progressive LGG or advanced solid tumors
- The initial design included only patients with LGG with activating *BRAF* alterations (Arm 1). Two new arms have now been added (Figure 2):
  - Arm 2 will allow tovorafenib treatment for patients with LGG harboring an activating *RAF* alteration after completion of enrollment to Arm 1, and prior to tovorafenib regulatory approval
  - Arm 3 will enroll patients with advanced solid tumors harboring an activating *RAF* fusion
- Tovorafenib (available in tablet or liquid suspension formulations) will be administered at the dose of 420 mg/m^2 (not to exceed 600 mg), orally, once weekly (days 1, 8, 15, and 22 of a 28-day cycle), in the absence of disease progression or unacceptable toxicity
  - Patients will be treated for a planned period of 26 cycles, after which they may continue on tovorafenib or, at any point, opt to enter a drug holiday discontinuation period
- Clinical assessments will be conducted days (D)1 and 15 of cycle (C)1, D1 of C2–26, then every third cycle to end of study (EOS). Radiological assessments will be conducted every 3 cycles to EOS for Arms 1 and 2, and every 2 cycles for 12 months, then every 3 cycles to EOS for Arm 3
- Patients with radiographic evidence of disease progression may be allowed to continue tovorafenib if, in the opinion of the investigator, and as approved by the sponsor, they are deriving clinical benefit from continuing treatment
- A planned sample size of 60 evaluable patients in Arm 1 provides 88% power to reject the null overall response rate (ORR) of 21%, assuming that the true underlying ORR of tovorafenib is 40% based on a test at the 2-sided 0.05 level. A result of at least 20 out of 60 (0.33) will be statistically significant

Figure 2. Study design



Key inclusion criteria

- Aged 6 months to 25 years with a *RAF*-altered LGG (Arms 1/2) or advanced solid tumor (Arm 3) histopathologically verified at either original diagnosis or relapse (per criteria defined in Figure 2)
- At least one line of prior systemic therapy and documented evidence of radiographic progression
- Evaluable and/or measurable disease (imaging performed within 28 days of initiation of treatment):
  - Arm 1 (LGG): at least one measurable lesion as defined by Response Assessment in Neuro-Oncology (RANO) criteria
  - Arm 2 (LGG extension): evaluable (either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm) and/or measurable disease as defined by RANO criteria
  - Arm 3 (advanced solid tumor): at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Karnofsky (aged ≥16 years) or Lansky (aged <16 years) performance score of at least 50
- Fully recovered from any prior surgery and the acute toxic effects of prior anticancer chemotherapy, and have undergone defined washout periods
- Chronic toxicities from prior anticancer therapy must be stable
- Available archival tumor tissue sample or fresh biopsy
- Adequate organ function

Key exclusion criteria

- Additional previously known or expected to be activating molecular alteration, including histone mutation, *IDH1/2* mutation, *FGFR* mutation or fusion, *MYBL* alteration, *NF1* somatic or germline mutation
- Symptoms of clinical progression without radiographically recurrent or radiographically progressive disease
- Known or suspected diagnosis of neurofibromatosis type 1
- History of any major disease, other than the primary malignancy under study, that might interfere with safe protocol participation
- Central serous retinopathy or retinal vein occlusion, or ophthalmopathy present at baseline that would be considered a risk factor for either
- Major surgery within 14 days prior to C1D1
- Clinically significant active cardiovascular disease
- Enrolled in any other investigational treatment study
- Active systemic bacterial, viral, or fungal infection
- Nausea and vomiting ≥National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 grade 2, malabsorption requiring supplementation, or significant bowel or stomach resection that would preclude adequate absorption of tovorafenib
- Neurological instability despite adequate treatment
- Current treatment with a strong CYP2C8 inhibitor or inducer (other than those specified as allowed). Medications that are substrates of CYP2C8 are allowed but should be used with caution
- Pregnant or lactating

Objectives and endpoints

Arm 1: LGG	
Objectives	**Endpoints**
Primary	
Evaluate the efficacy of tovorafenib in patients with a relapsed or progressive LGG harboring a known activating *BRAF* alteration	ORR, as determined by an IRC, according to RANO criteria
Secondary	
Assess the safety and tolerability of tovorafenib in patients with LGG	Type, frequency, and severity of AEs and laboratory abnormalities
Determine the relationship between PK and drug effects, including efficacy and safety	PK profile of tovorafenib
Evaluate the effect of tovorafenib on the QT interval and ECG parameters	Change from baseline (Δ)QTcF; ΔPR; ΔQRS; ΔHR; ECG waveform morphology
Assess ORR based on the treating investigator's response assessment	ORR by RANO criteria
Assess ORR based on RAPNO–LGG criteria as determined by an IRC	ORR by RAPNO–LGG criteria
Evaluate the duration of PFS as determined by an IRC, based on RANO and RAPNO criteria, and by investigators, based on RANO criteria	Time following initiation of tovorafenib to progression or death in treated patients
Evaluate the DOR as determined by an IRC (RANO and RAPNO), and investigators (RANO only)	Length of response in patients with a confirmed response by RANO and RAPNO criteria
Evaluate TTR as determined by an IRC (RANO and RAPNO) and investigators (RANO only)	Time to first response by RANO and RAPNO criteria
Evaluate the clinical benefit rate as determined by an IRC (RANO and RAPNO) and investigators (RANO only)	Proportion of patients with BOR of CR, PR, or SD lasting 12 months or more, following initiation of tovorafenib
Evaluate changes in BCVA outcomes	Change from baseline in BCVA (converted as logMAR) for each eye
Evaluate the concordance of prior local laboratory *BRAF* molecular profiling with a central *BRAF* alteration assay being evaluated by the sponsor	Molecular analysis of cells obtained from archival tissue

Arm 2: LGG extension	
Objectives	**Endpoints**
Primary	
Assess the safety and tolerability of tovorafenib in patients with LGG	Type, frequency, and severity of AEs and laboratory abnormalities
Secondary	
Determine the ORR per RANO and RAPNO–LGG criteria as determined by an IRC and investigators (RANO only)	ORR by RANO and RAPNO–LGG criteria
Evaluate PFS, DOR, TTR, clinical benefit rate, the relationship between PK and drug effects, and the effect of tovorafenib on the QT interval and ECG parameters, as described for Arm 1	As described for Arm 1

Arm 3: advanced solid tumors	
Objectives	**Endpoints**
Primary	
Evaluate the preliminary efficacy of tovorafenib in patients with a relapsed or progressive advanced solid tumor harboring a known or expected to be activating *RAF* fusion	ORR, as determined by an IRC, according to RECIST v1.1
Secondary	
Assess the safety and tolerability of tovorafenib in pediatric patients with advanced solid tumors	Type, frequency, and severity of AEs and laboratory abnormalities
Evaluate the relationship between PK and drug effects, and the effect of tovorafenib on the QT interval and ECG parameters	As described for Arm 1
Determine the ORR based on investigator assessment	ORR, as assessed by investigators, according to RECIST v1.1
Evaluate PFS, DOR, TTR, and clinical benefit rate	As for Arm 1, but with response assessments based on RECIST v1.1
Evaluate the concordance of prior local laboratory *RAF* molecular profiling with a central *RAF* alteration assay being evaluated by the sponsor	Molecular analysis of cells obtained from archival tissue

AEs, adverse events; BCVA, best corrected visual acuity; BOR, best overall response; CR, complete response; DOR, duration of response; ECG, electrocardiogram; HR, heart rate; IRC, independent radiology review committee; LGG, low-grade glioma; ORR, overall response rate, PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QTcF, QT interval corrected for heart rate by Fridericia's formula; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response

Current status

- Arm 1 has fully accrued and is closed to further screening and enrollment. Arms 2 and 3 are actively recruiting patients

References

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