FIREFLY-1 (PNOC026): Phase 2 study of pan-RAF inhibitor tovorafenib in pediatric and young adult 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[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 (pLGGs)[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]
- 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[5]

Objective

- To evaluate the efficacy and safety of tovorafenib monotherapy in patients with recurrent or progressive pLGG or solid tumors harboring activating *BRAF* alterations

Methods

- FIREFLY-1 (NCT04775485) is a 3-arm, open-label, global, registrational phase 2 trial of tovorafenib monotherapy in recurrent or progressive pLGG and solid tumors (**Figure 1**)
  - Primary endpoint of registrational arm 1 is the overall response rate (ORR) based on RANO criteria, assessed by blinded independent central review (IRC)
  - Secondary endpoints include ORR by RAPNO criteria and safety
- Here we report an interim analysis of antitumor activity and safety in the first 25 patients enrolled in arm 1 (recurrent or progressive LGG) with ≥6 months follow up (data cutoff Apr 14, 2022)

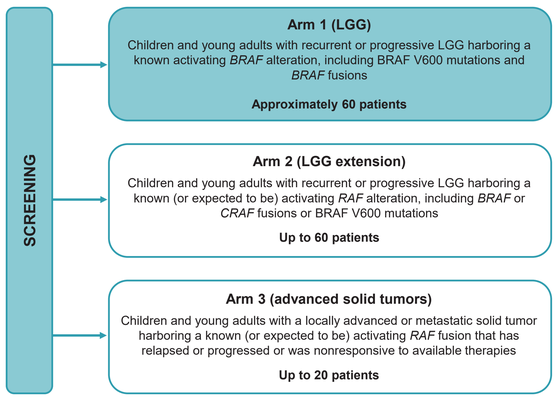
Key inclusion criteria

- Aged 6 months to 25 years with a *RAF*-altered LGG histopathologically verified at either original diagnosis or relapse (per criteria defined in **Figure 1**)
- At least one line of prior systemic therapy and documented evidence of radiographic progression
- At least one RANO-measurable lesion (imaging performed within 28 days of initiation of treatment)
- Karnofsky (aged ≥16 years) or Lansky (aged <16 years) performance score of at least 50
- Fully recovered from any prior surgery and 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
- 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
- Neurological instability despite adequate treatment
- Current treatment with a strong CYP2C8 inhibitor or inducer (other than those specified as allowed)

Figure 1. Study design

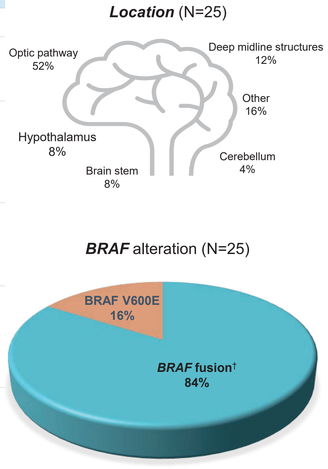


Results

- As of April 14, 2022, 25 patients were enrolled to arm 1 and had ≥6 months of follow-up (**Figure 2**)
- Per independent assessment according to RANO criteria, partial responses (1 unconfirmed) were seen in 14 (64%) of 22 evaluable patients, with 6 additional patients having stable disease, and a clinical benefit rate of 91% (**Figures 3, 4, 6**)
  - Responses were achieved in tumors with *BRAF* fusions and V600E mutations
- Per independent assessment according to RAPNO criteria in the 22 evaluable patients, the ORR was 50% and the clinical benefit rate was 100% (**Figure 5**)
- Tovorafenib was generally well tolerated (**Table 1**), with most treatment-emergent adverse events (TEAEs) being grade 1 or 2 (96%)
  - The most common grade ≥3 TEAEs were anemia (12%), vomiting, increased blood creatinine phosphokinase and maculopapular rash (8% each)
  - Seven patients (28%) required dose modification due to treatment-related adverse events (AEs); no patients discontinued tovorafenib due to AEs

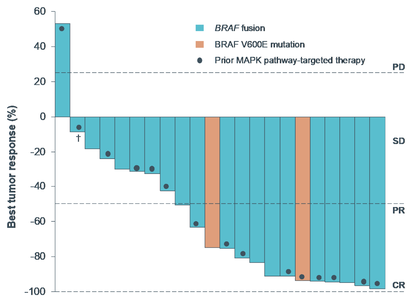
Figure 2. Baseline characteristics

Characteristic	Arm 1 (N=25)
Median age, years (range)	8 (3–18)
Sex, n (%)	
Male	13 (52)
Female	12 (48)
Race, n (%)	
Black or African American	1 (4)
Asian	2 (8)
White	15 (60)
Other[a]	7 (28)
Karnofsky/Lansky performance status, n (%)	
50-70	1 (4)
80-100	24 (96)
Number of lines of prior therapy, median (range)	3 (1–9)
1, n (%)	5 (20)
2, n (%)	6 (24)
≥3, n (%)	14 (56)
Prior MAPK pathway targeted therapy[b], n (%)	
Yes	18 (72)
No	7 (28)



[a]Includes 4 patients with race not specified. [b]Prior MAPK pathway targeted therapy indicates either prior MEK inhibitor and/or prior type I RAF inhibitor therapy. †Includes 2 patients with tumors harboring *BRAF* duplication and 1 with *BRAF* rearrangement per fluorescence in situ hybridization.
N, number of patients evaluated; n, number of patients with the specified event

Figure 3. Tumor response in patients with RANO-evaluable lesions



Response (IRC)	RANO Evaluable N=22*
ORR (95% CI)	64% (41–83)
BRAF fusion (n=20)	60%
BRAF V600E (n=2)	100%
CBR#	91%
Best overall response	
PR (13/22)	59%
uPR (1/22)	5%
SD (6/22)	27%

*3/25 patients lacked evaluable lesions per RANO criteria based on IRC evaluation. †Progressive disease due to presence of new lesions. #Patients with best overall response of CR, PR/uPR and SD
CBR, clinical benefit rate; CI, confidence interval; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response

Figure 4. Individual patient tumor change from baseline in RANO-evaluable patients

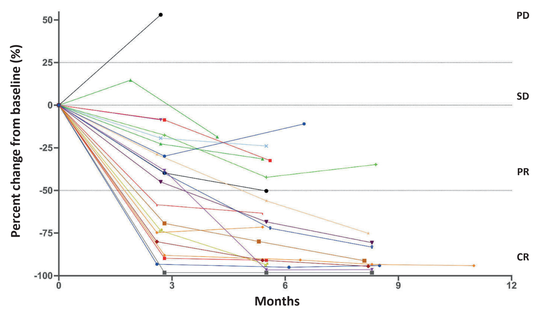
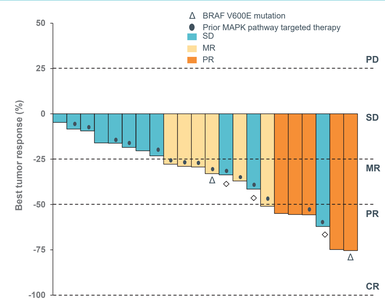


Figure 5. Tumor response according to RAPNO criteria

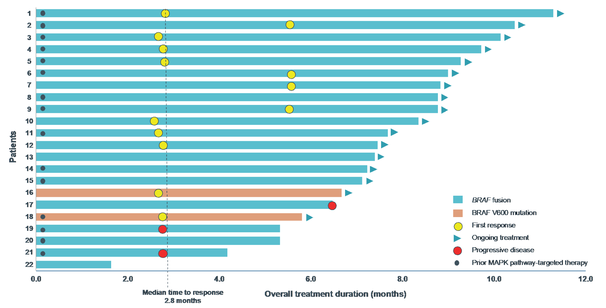


Response (IRC)	RAPNO assessed N=22
ORR* (95% CI)	50% (28–72)
CBR#	100%
Best overall response	
PR (5/22)	23%
MR* (6/22)	27%
SD (11/22)	50%

*Includes 4 unconfirmed MR

◇Response not sustained on subsequent assessment. #Patients with best overall response of CR, PR, MR/uMR and SD
MR, minor response

Figure 6. Duration of tovorafenib therapy in patients with RANO-evaluable lesions



17/22 patients remain on therapy; All responders remain on treatment

Table 1. Adverse events

Preferred term, n (%)	Treatment-emergent AEs[a] Any grade	Treatment-emergent AEs[a] Grade ≥3	Treatment-related AEs Any grade	Treatment-related AEs Grade ≥3
Blood creatine phosphokinase increased	20 (80)	2 (8)	18 (72)	2 (8)
Hair color changes	17 (68)	-	17 (68)	-
Anemia	14 (56)	3 (12)	10 (40)	2 (8)
Aspartate aminotransferase increased	14 (56)	-	12 (48)	-
Vomiting	14 (56)	2 (8)	6 (24)	1 (4)
Rash*	13 (52)	3 (12)	13 (52)	3 (12)
Blood lactate dehydrogenase increased	12 (48)	-	9 (36)	-
Headache	10 (40)	-	3 (12)	-
Dry skin	9 (36)	-	7 (28)	-
Epistaxis	9 (36)	-	4 (16)	-
Constipation	8 (32)	-	5 (20)	-
Hypocalcemia	8 (32)	-	6 (24)	-
Nausea	8 (32)	-	3 (12)	-
Alanine aminotransferase increased	7 (28)	1 (4)	4 (16)	1 (4)
Fatigue	7 (28)	-	7 (28)	-

[a]Includes all any grade TEAEs ≥25%
*Includes maculopapular and erythematous rash

Conclusions

- 56% of patients had received ≥ 3 prior lines of therapy, and 72% were previously treated with MAPK pathway-targeted agents
- Tovorafenib showed encouraging anticancer activity in pediatric patients with *BRAF*-altered recurrent or progressive LGG
  - Independent assessment (RANO) reported an ORR of 64% and CBR of 91%
  - All patients with a response by RANO demonstrated tumor shrinkage as assessed by RAPNO, with a CBR of 100%
    - Tumor shrinkage by T2/FLAIR may trend behind reduction in T1 contrast uptake in some patients
- Initial safety data suggested tovorafenib was generally well tolerated, with most adverse events being grade 1 or 2
- As of April 14, 2022, all responders remained on treatment, and no patients had discontinued due to adverse events

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