CTNI-09 Type II RAF inhibitor tovorafenib in relapsed/refractory (r/r) pediatric low-grade glioma (pLGG): Results from patients on a drug holiday (DH) in the phase 2 FIREFLY-1 trial

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Background

- At 30%, pLGGs are the most common pediatric brain tumor; *BRAF* alterations drive 70% of all pLGGs, with *KIAA1549*::*BRAF* fusions being the most common[1–5]
- Tovorafenib is an oral, selective, CNS-penetrant, type II RAF inhibitor active against monomeric (class I alterations) and dimeric (class II alterations, including fusions) forms of RAF signaling[6]
  - Dosed once-weekly (QW) and is available as tablets and a pediatric-friendly oral suspension[7]
- Results from the ongoing FIREFLY-1 (NCT04775485) phase 2 in patients with r/r *BRAF*-altered pLGG demonstrated that tovorafenib provided clinically meaningful tumor responses and had a manageable safety profile (June 5, 2023 data cutoff)[7]
  - In April 2024, the FDA granted accelerated approval for patients ≥6 months of age with r/r *BRAF*-altered pLGG[8]
- Patients in FIREFLY-1 arms 1 and 2 had the option of entering a drug-holiday (DH) period after 26 cycles (~24 months) of treatment with tovorafenib or to continue treatment until disease progression[7]

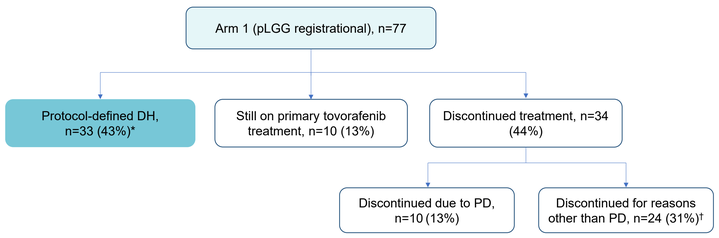
Objectives

- Assess stability of response and need for additional treatment in patients from FIREFLY-1 arm 1 who entered a DH
- Determine if patients can be rechallenged with tovorafenib upon PD when in a DH

Methods

- The trial design for FIREFLY-1 has been described previously; 77 patients were enrolled in arm 1[7]
  - Patients had routine radiographic tumor assessments every ~3 months while on treatment, during a DH, during retreatment, or if they discontinued treatment for reasons other than PD (up to start of subsequent therapy or end of study); one of the criteria used was RAPNO (Response Assessment in Pediatric Neuro-Oncology) by independent radiology review committee (IRC)
  - Those with radiographic evidence of progression could continue treatment if, in the opinion of the investigator and approved by the sponsor, they were deriving clinical benefit; assessments continued per the regular schedule
  - During a DH, tovorafenib retreatment could begin based on radiographic progression per INV RANO-HGG (investigator assessed Response Assessment in Neuro-Oncology-High Grade Glioma) and/or clinical progression
- The treatment status for patients in FIREFLY-1 arm 1 is shown in **Figure 1**; this analysis examined patients on a DH and received ≥2 years of tovorafenib (May 10, 2024 data cutoff)

Figure 1. FIREFLY-1 arm 1 Treatment status



*Includes one patient who received treatment through cycle 18, day 1 and subsequently went on a prolonged dose hold until the protocol-defined DH timepoint after completion of 27 cycles. †Reasons included patient/caregiver choice (n=9), adverse event (AE) (n=8), physician choice (n=2), death deemed unrelated to tovorafenib (n=2; 1 neurologic due to PD; other was unexplained), other (n=2), and prolonged dose hold (≥3 months) (n=1).

Results

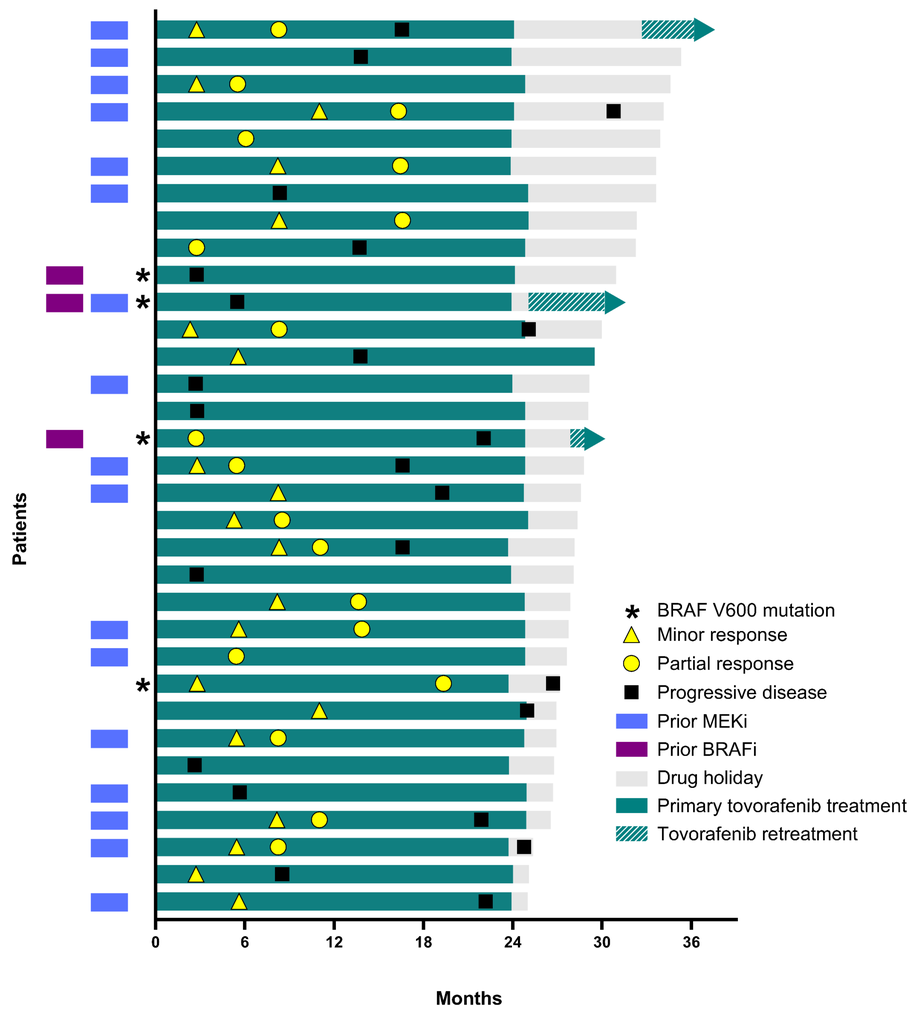
Table 1. Patient and baseline characteristics

	DH (n=33)
Median age, years (range)	8 (3–16)
Gender, n (%)	
Male	19 (58)
Female	14 (42)
***BRAF* alteration status, n (%)**	
BRAF fusion*	29 (88)
KIAA1549::*BRAF* fusion	24 (73)
Other	5 (15)
BRAF V600E mutation	4 (12)
Prior systemic therapy	
Median lines (range)	2 (1–7)
1 line, n (%)	7 (21)
2 lines, n (%)	10 (30)
≥3 lines, n (%)	16 (49)

Percentages may not add to 100% due to rounding.
*Includes 4 patients with *BRAF* duplication and 1 with *BRAF* rearrangement per fluorescence in situ hybridization or in situ hybridization.

Results

Figure 2. Duration of treatment, follow-up, and tovorafenib retreatment



As of the May 10, 2024 data cutoff
- 97% (32/33) of patients had no signs of clinical progression during a DH
- 15% (5/33) of patients experienced an additional ≥25% tumor shrinkage while on a DH

Table 2. Duration of primary tovorafenib treatment, DH, and need for retreatment

	n	DH
Median treatment duration, months (range)	33	24 (16–29)
Median follow-up since end of treatment, months (range)	32*	3.4 (0.3–10.6)
Rechallenged with tovorafenib, n (%)	33	3 (9)

Percentages may not add to 100% due to rounding. *Data for duration of DH not available for one patient as the data cutoff was prior to 30 days after last dose.

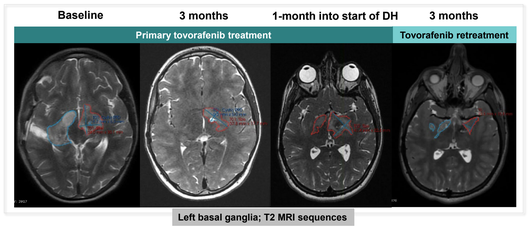
Conclusions

- While the FIREFLY-1 arm 1 data in patients with r/r *BRAF*-altered pLGG are still maturing, tovorafenib provided encouraging durability of responses in patients off-treatment
  - 91% (30/33) remain on a DH and only 1 pt had signs of clinical progression
  - The safety profile in patients who were rechallenged with tovorafenib following a DH was consistent with known safety profile of tovorafenib

Figure 3. Tumor progression while on a DH followed by tovorafenib rechallenge

Patient 1: 10-year-old boy with a BRAF V600E posterior optic, brainstem, and thalamus tumor

- Initiated treatment with tovorafenib 600 mg QW for 23.7 months. BOR of SD (−55.3%) at 3 months on primary tovorafenib treatment
- All AEs were mild or moderate (none severe) and non-serious; TRAEs included G2 anemia, rash, growth failure, generalized skin lesions, increased CPK, and paronychia, and G1 fatigue, hair color change, aphthous ulcers, AV block, photosensitivity reaction, increased LFTs, hypophosphatemia, and hypocalcemia
- While on a DH, progressed within 1 month (INV RANO-HGG; ≥25% in tumor size); clinical status was deteriorating
- Rechallenged with tovorafenib 600 mg QW. At first assessment, SPPD decrease of 49%*; subsequent clinical status improved
  - Retreatment ongoing for 5+ months at time of data cutoff
- All AEs during retreatment with tovorafenib were mild or moderate (none severe) and non-serious; clinically relevant TRAEs included G1 rash, alopecia, increased CPK, and increased LDH



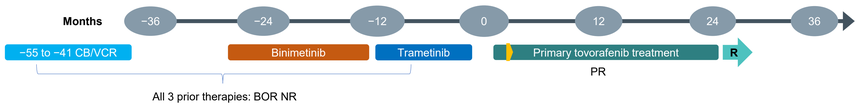
*Relative to the retreatment baseline.
AE, adverse events; AV, atrioventricular; BOR, best overall response; CB, carboplatin; CPK, creatine phosphokinase; G, grade; LDH, lactate dehydrogenase; LFT, liver function test; MRI, magnetic resonance imaging; R, retreatment; SD, stable disease; SPPD, Sum of Perpendicular Diameters; TRAEs, treatment-related adverse events; VCR, vincristine.

Patient 2: 15-year-old boy with BRAF V600E mutated mid-brain, dorsal pons tumor

- Initiated treatment with tovorafenib 600 mg QW for 24.6 months. BOR of PR (−67.1%) on primary tovorafenib treatment; TTR 2.73 months
- Clinically relevant TRAEs included G2 keratosis pilaris, hypophosphatemia, and hypokalemia, and G1 increased CPK, hair color change, rash, anemia, and hypocalcemia
- While on a DH, radiographic progression (INV RANO-HGG; ≥25% in tumor size) with no symptoms after 3 months
- Rechallenged with tovorafenib 600 mg QW. Subsequent clinical status was stable
  - Retreatment ongoing for 1+ month at time of data cutoff; will be evaluated for response at 3 months
- No TRAEs during retreatment with tovorafenib

BVZ, bevacizumab; IRI, Irinotecan.

Patient 3: 6-year-old boy with a *BRAF* fusion OPG



- Initiated treatment with tovorafenib 400 mg QW for 23.7 months. BOR of PR (−55.0%) on primary tovorafenib treatment; TTR 2.76 months
- Clinically relevant TRAEs included G2 rash, increased CPK, and decreased growth velocity, and G1 hair color change, dermatitis, facial and limb edema, hypocalcemia, hypophosphatemia, increased LFTs, alopecia, anemia, paronychia, and cheilitis
- While on a DH, progressed after 8.5 months (tumor size increase of 28%; considered slow progression and family elected to restart treatment). Rechallenged with tovorafenib 500 mg QW. At first assessment, tumor size decrease of 1.1%; no signs of clinical progression
  - Retreatment ongoing for 3+ months at time of data cutoff, will be evaluated for response at 6 months
- No reported AEs since retreatment with tovorafenib commenced

NR, not reported; OPG, optic pathway glioma.

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The phase 3 LOGGIC/FIREFLY-2 (NCT05566795) comparing tovorafenib with SOC chemotherapy in front-line *BRAF*-altered pLGG is enrolling globally.

More information on the FIREFLY-1 clinical trial (NCT04775485) can be found at www.clinicaltrials.gov
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