Clinical activity of pan-RAF inhibitor tovorafenib in the registrational pediatric low-grade glioma arm of the phase 2 FIREFLY-1 (PNOC026) study

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Pediatric low-grade glioma (pLGG)

- **pLGG is the most common brain tumor in children**
  - Accounts for ~30% of all CNS tumors
  - Is associated with significant disease- and treatment-associated morbidity
- **~70% of pLGGs are driven primarily by BRAF alterations**
  - KIAA1549-BRAF fusions are the most common genomic alterations in pLGG and occur in ~80% of pilocytic astrocytomas
  - BRAF alterations enable constitutive activation of the protein as a monomer (V600 mutations) or dimer (fusions), independent of extracellular stimuli or RAS activation
- **Tovorafenib is an investigational, oral, selective, CNS-penetrant, type II RAF inhibitor**
  - Activity against monomeric (class I alterations) and dimeric (class II alterations, including fusions) forms of RAF signaling
  - Does not cause paradoxical activation of the MAPK pathway observed with type I BRAF inhibitors
  - Available as tablets and a pediatric-friendly oral suspension
  - Once-weekly dosing
**FIREFLY-1: phase 2 study of tovorafenib monotherapy in LGG**

- Patients aged 6 months–25 years, with a RAF-altered tumor, and ≥1 prior line of systemic therapy with radiographic progression
- Prior use of MAPK pathway targeted therapy was permitted

### Arm 1 (LGG: registrational, n=77)
Children and young adults with recurrent or progressive LGG harboring a known activating BRAF alteration, including BRAF fusions and BRAF V600 mutations

### Arm 2 (LGG extension, n=59)
Children and young adults with recurrent or progressive LGG harboring a known activating RAF alteration, including BRAF or CRAF/RAF1 fusions or BRAF V600 mutations

### Arm 3 (advanced solid tumors)
Children and young adults with a locally advanced or metastatic solid tumor harboring a known activating RAF fusion that has relapsed or progressed or was nonresponsive to available therapies

### Endpoints

**Primary**
- ORR (RANO-HGG)\(^1\) per IRC

**Secondary include**
- Safety
- ORR (RAPNO-LGG)\(^2\) per IRC
- DOR
- PFS
- TTR
- CBR

**Exploratory include**
- ORR and CBR (RANO-LGG)\(^3\) per IRC

- Tovorafenib, 420 mg/m\(^2\) (not to exceed 600 mg), QW in 28-day cycles
- Patients treated for a planned period of 26 cycles (~24 months), after which, they may continue tovorafenib or opt to enter a drug holiday discontinuation period

- Arms 1 and 2 have fully accrued and are closed to further screening and enrollment
  - Arm 1 represents the efficacy dataset
  - Arms 1 and 2 are included for the safety analysis
- Arm 3 is actively recruiting patients

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CBR, clinical benefit rate; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; QW, once weekly; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; TTR, time to response.
### FIREFLY-1 registrational arm: baseline characteristics

**Dec 22, 2022 data cutoff.**

*Includes tumors that were extending into multiple regions of the brain, leptomeningeal disease, and/or spinal disease. 

*Includes 6 patients with BRAF duplication and 2 with BRAF rearrangement per FISH (fluorescence in situ hybridization) or ISH (in situ hybridization).

**MAPK, mitogen-activated protein kinase.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm 1 (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>8 (2–21)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>37 (48)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (6)</td>
</tr>
<tr>
<td>White</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Multiple</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Not reported</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Number of lines of prior lines of systemic therapy</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (1–9)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>38 (49)</td>
</tr>
<tr>
<td>Prior MAPK pathway targeted therapy, n (%)</td>
<td>46 (60)</td>
</tr>
</tbody>
</table>

**Location (n=77)**

- Optic pathway: 51%
- Deep midline structures: 12%
- Cerebellum: 6%
- Cerebral hemisphere: 8%
- Brain stem: 8%
- Other: 16%

**BRAF alteration (n=77)**

- BRAF V600E: 17%
- BRAF fusion*: 83%

*Includes 6 patients with BRAF duplication and 2 with BRAF rearrangement per FISH (fluorescence in situ hybridization) or ISH (in situ hybridization).
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.
Two of 69 patients are not shown in the waterfall plot; one patient passed away due to progressive disease (not related to tovorafenib) before the first imaging assessment and one did not receive T1 Gd+ follow-up imaging. *P < 0.001 from two-sided exact binomial test to test null hypothesis of ORR=21% based on Bouffet et al. 2

-100
-80
-60
-40
-20
0
20
40
60
80
100

Best tumor response (%)

MAPKi-naive
Prior MAPKi therapy
BRAF mutation

Response (IRC) RANO-HGG\(^1\) n=69

<table>
<thead>
<tr>
<th>Response (IRC)</th>
<th>RANO-HGG(^1) n=69</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (cCR + cPR/uPR), n (%)</td>
<td>46 (67%)*</td>
</tr>
<tr>
<td>Clinical benefit rate, n (%)</td>
<td></td>
</tr>
<tr>
<td>cCR, cPR/uPR, or SD</td>
<td>64 (93%)</td>
</tr>
<tr>
<td>cCR, cPR/uPR or patients with SD for 12 months or more</td>
<td>47 (68%)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>PR (includes 3 uPR, of which all remain on treatment)</td>
<td>42 (61%)</td>
</tr>
<tr>
<td>SD</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

CBR, clinical benefit rate; cCR, confirmed complete response; cPR, confirmed partial response; CR, complete response; HGG, high-grade glioma; IRC, independent radiology review committee; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; uPR, unconfirmed partial response.
As of data cutoff:

- The median duration of tovorafenib treatment was 10.8 months, with 74% (n=57) of all 77 patients enrolled still on treatment at data cutoff.
- Median IRC-assessed DOR* in months based on RANO-HGG criteria was not yet reached (95% CI: 9.0, not estimable)

* Analysis includes only confirmed responses. CI, confidence interval; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; RANO, Response Assessment in Neuro-Oncology.
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.

Two of 76 patients are not shown in the waterfall plot; one patient passed away due to progressive disease (not related to tovorafenib) before the first imaging assessment, and one patient with missing T1 Gd+ imaging at BL was deemed NE at all timepoints but had a best SPPD decrease of 65% on T2 imaging.

**FIREFLY-1 registrational arm: antitumor activity (RANO-LGG, n=76)**

<table>
<thead>
<tr>
<th>Response (IRC)</th>
<th>RANO-LGG(^1) n=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (cCR + cPR/uPR + cMR/uMR), n (%)</td>
<td>37 (49%)</td>
</tr>
<tr>
<td>Clinical benefit rate, n (%)</td>
<td></td>
</tr>
<tr>
<td>cCR, cPR/uPR, cMR/uMR, or SD</td>
<td>63 (83%)</td>
</tr>
<tr>
<td>cCR, cPR/uPR, cMR/uMR, or with SD for 12 months or more</td>
<td>36 (47%)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PR (includes 8 uPR, of which all remain on treatment)</td>
<td>20 (26%)</td>
</tr>
<tr>
<td>MR (includes 2 uMR, of which all remain on treatment)</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>SD</td>
<td>26 (34%)</td>
</tr>
<tr>
<td>PD</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Not evaluable§</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

**MAPKi-naive**
**Prior MAPKi therapy**
**BRAF mutation**

**Response (IRC)**
- PD
- SD
- MR
- PR
- CR


1. MAPKi-naive: Prior MAPKi therapy
2. Prior MAPKi therapy: BRAF mutation

BL, baseline; CBR, clinical benefit rate; cCR, confirmed complete response; cMR, confirmed minor response; cPR, confirmed partial response; CR, complete response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; SPPD, sum of the products of perpendicular diameters; uMR, unconfirmed minor response; uPR, unconfirmed partial response.
FIREFLY-1 registrational arm: duration of therapy (RANO-LGG, n=76)

Best overall response is shown: circles indicate start of response; PD for RANO-LGG was not used to determine treatment discontinuation; patients could continue treatment if there was no PD by RANO-HGG.

* Analysis includes only confirmed responses.

CI, confidence interval; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; PD, progressive disease; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; TTR, time to response; SD, stable disease.

As of data cutoff
- Median IRC-assessed DOR* in months based on RANO-LGG criteria was 14.4 months (95% CI: 8.4, not estimable)

Best overall response is shown: circles indicate start of response; PD for RANO-LGG was not used to determine treatment discontinuation; patients could continue treatment if there was no PD by RANO-HGG.

* Analysis includes only confirmed responses.
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding. Two of 69 patients not shown in waterfall plot; one patient passed away due to progressive disease (not related to tovorafenib) before the first imaging assessment and one patient had visual progressive disease but no evaluable T2 measurements at the time of progression.

*Pending adjudication. #PD for RAPNO-LGG was not used to determine treatment discontinuation; patients could continue treatment if there was no PD based on RANO-HGG per investigator’s assessment.


CBR, clinical benefit rate; cCR, confirmed complete response; cMR, confirmed minor response; cPR, confirmed partial response; CR, complete response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease; uMR, unconfirmed minor response; uPR, unconfirmed partial response.
FIREFLY-1: Safety, n=136 (treatment-emergent AEs ≥25% any grade)

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Treatment-emergent AEs</th>
<th>Treatment-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any AE</td>
<td>136 (100)</td>
<td>68 (50)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>96 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68 (50)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (43)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>56 (41)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (39)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>43 (32)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>40 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>39 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>37 (27)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>36 (26)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35 (26)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>34 (25)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Most commonly reported lab abnormalities were CPK elevation, anemia, hypophosphatemia, and AST elevation
  - Nearly all had no clinical manifestations and did not require clinical intervention or change in study treatment
- 5 patients (4%)* discontinued treatment due to an AE; 4 (3%) were treatment-related
  - Reasons for discontinuation included autoimmune hemolytic anemia (not treatment-related), hemolysis, ventricular extrasystoles, growth retardation, shunt malfunction* (not treatment-related) and tumor hemorrhage*
- 39 patients (29%) required dose reductions/interruptions due to treatment-related AEs

Dec 22, 2022 data cutoff.
Rash erythematous treatment-emergent: any grade, 14 (10%); grade ≥3 1 (1%); treatment-related: any grade, 14 (10%), grade ≥3 1 (1%).
*One patient had 2 events (shunt malfunction [not related to tovorafenib] and tumor hemorrhage [related to tovorafenib]).
AEs, adverse events; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
Case study: activity of tovorafenib in *KIAA1549-BRAF* fusion optic pathway glioma

8-year-old boy with relapsed pilomyxoid astrocytoma of the optic pathway, with visual loss in right eye, visual field loss in left eye, fatigue, intermittent nausea/vomiting, intermittent headaches, anorexia, and temperature regulation disorder

- Initiated treatment with tovorafenib 400 mg/QW following 3 prior therapies, including binimetinib and trametinib, which were discontinued due to PD
- At cycle 3, PR (~88%) per RANO-HGG, and MR (~32% and ~40%) per RAPNO-LGG and RANO-LGG, respectively
  - Sustained improvements in visual acuity reported; logMAR change 0.2 → 0
  - PD criteria met (~94% to ~91%) with RANO-HGG at cycle 15; continued treatment as investigator deemed no radiographic progression with subsequent reduction in target lesion (~97%)
- AEs were G2 (drug eruption, CPK elevation) and G1 (hair color change, paronychia, growth retardation)
Conclusions: FIREFLY-1 registrational arm

- Clinically meaningful and rapid tumor responses to monotherapy tovorafenib seen on both T1-Gd+ and T2/FLAIR sequences in this heavily pretreated population
  - RANO-HGG: 67% ORR and 26% of patients with SD
  - RANO-LGG: 49% ORR and 34% of patients with SD
  - RAPNO-LGG: 51% ORR, and 36% of patients with SD
- The median duration of tovorafenib treatment was 10.8 months, with 74% (57/77) still on treatment at data cut off
- Median IRC-assessed Time to Response was 2.8 months with RANO-HGG, 4.2 months with RANO-LGG, and 5.5 months with RAPNO-LGG*
- Tumor response independent of histologic subtype, BRAF alteration type (fusion vs mutation), number of prior lines of therapy, or prior MAPKi use
- Encouraging safety and tolerability profile with only 4% discontinuations; most treatment-related AEs were grade 1 or 2
  - 29% (39/136) of patients required dose reduction or interruption due to treatment-related AEs
- Phase 3 LOGGIC/FIREFLY-2 in front-line pLGG is enrolling; first patient dosed in March 2023

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Mon. 6/5, 1:15-4:15 pm CDT; “Pediatric Oncology” Poster Session
Poster Board #372b; TPS10067. 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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Hopp Children’s Cancer Center Heidelberg [KiTZ], Heidelberg University Hospital and German Cancer Research Center [DKFZ], and National Center for Tumor Diseases [NCT]), Heidelberg, Germany
Acknowledgments

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

FIREFLY-1 is funded by Day One Biopharmaceuticals.