# Clinical activity and safety of tovorafenib in patients with optic pathway gliomas in FIREFLY-1

Sarah E. S. Leary,[1] E. de Vos-Kerkhof,[2] Sébastien Perreault,[3] Olaf Witt,[4-8] David S. Ziegler,[9-11] Pablo Hernáiz Driever,[12] Andrea T. Franson,[13] Patricia A. Baxter,[14] Nicholas S. Whipple,[15] Cassie Kline,[16] Devorah Segal,[17] Nada Jabado,[18] Simon Bailey,[19] Geoffrey McCowage,[20] Jordan R. Hansford,[21,22] Dong-Anh Khuong-Quang,[23] Nicholas G. Gottardo,[24] Timothy Hassall,[25] Jung Woo Han,[26] Michal Yalon Oren,[27] Susan N. Chi,[28] Lisa McLeod,[29] Jiaheng Qiu,[29] Chris McKenna,[29] Daniel Da Costa,[29] Sandya Govinda Raju,[29] Darren Hargrave,[30] Lindsay B. Kilburn,[31] Daniel B. Landi,[32] Karsten Nysom[33]

[1]Cancer and Blood Disorders Center, Seattle Children's, Seattle, WA, USA; [2]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; [3]CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada; [4]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany; [5]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [6]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany; [7]German Cancer Consortium (DKTK), Heidelberg, Germany; [8]National Center for Tumor Diseases (NCT), Heidelberg, Germany; [9]Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia; [10]Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW, Australia; [11]School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia; [12]Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität Berlin, German HIT-LOGGIC-Registry for LGG in children and adolescents, Berlin, Germany; [13]CS Mott Children's Hospital, University of Michigan Medical School, Ann Arbor, Michigan, USA; [14]Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [15]Primary Children's Hospital and University of Utah, Salt Lake City, UT, USA; [16]Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA; [17]NYU Langone Health, New York, NY, USA; [18]McGill University Health Centre (MUHC) - The Montreal Children's Hospital (MCH), Montréal, QC, Canada; [19]Great North Children's Hospital and Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK; [20]Sydney Children's Hospitals Network, Westmead, NSW, Australia; [21]Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital, Adelaide, SA, Australia; [22]South Australia Health and Medical Research Institute, Adelaide, Australia and South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia; [23]Children's Cancer Centre, The Royal Children's Hospital Melbourne, Melbourne, Victoria, Australia; [24]Department of Pediatric and Adolescent Oncology and Hematology, Perth Children's Hospital, Perth, Australia and Brain Tumor Research Program, Telethon Kids Cancer Centre, Telethon Kids Institute, University of Western Australia, Perth, WA, Australia; [25]Children's Health Queensland Hospital and Health Service, South Brisbane, Australia; [26]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [27]Pediatric Hemato-Oncology Department, Sheba Medical Center, Ramat Gan, Israel; [28]Pediatric Neuro-Oncology, Department of Pediatrics, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [29]Day One Biopharmaceuticals, Brisbane, CA, USA; [30]UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; [31]Children's National Hospital, Washington, DC, USA; [32]Duke University, Durham, NC, USA; [33]Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark

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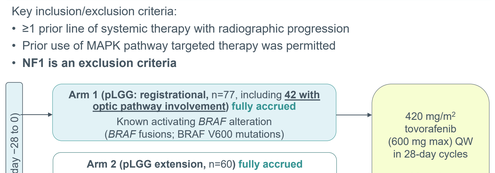
**Presenting author: Sarah E. S. Leary, MD, MS sarah.leary@seattlechildrens.org**

## Background

- ~30% of brain tumors in children are pediatric low-grade gliomas (pLGGs); a third of pLGGs are optic pathway gliomas (OPGs), most of which are pilocytic astrocytomas (PAs)[1,2]
- OPGs can be sporadic and present throughout childhood, or occur in association with neurofibromatosis type 1 (NF1), typically appearing ~3–6 years of age:[3]
  - Sporadic OPGs are more likely to cause clinical symptoms/ visual impairment and progress, with >90% requiring treatment[2]
    - *KIAA1549*::*BRAF* fusions are the most common genomic alterations in pLGG and occur in ~80% of PAs[4–7]
    - *BRAF* alterations result in constitutive activation of the protein as a monomer (V600 mutations) or dimer (fusions), independent of extracellular stimuli or RAS activation[8,9]
- Tovorafenib is an investigational, 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:[10]
  - Does not cause paradoxical mitogen-activated protein kinase (MAPK) pathway activation observed with type I BRAF inhibitors (BRAFis)
  - Once-weekly (QW) dosing (tablets or a pediatric-friendly oral suspension)
- FIREFLY-1 (NCT04775485) is an ongoing global, phase 2, multi-center, open-label, single intervention study of tovorafenib in patients 6 months–25 years of age with *RAF*-altered relapsed/refractory pLGG (arms 1 and 2) and advanced solid tumors (arm 3); **efficacy (arm 1, n=77)** and **safety (arms 1 and 2, n=137)** results (June 5, 2023 data cutoff) have been reported[11,12]
- This analysis evaluated the efficacy and safety of tovorafenib in patients in arm 1 with OPGs (June 5, 2023 data cutoff)[13]

## Study design

Key inclusion/exclusion criteria:
- ≥1 prior line of systemic therapy with radiographic progression
- Prior use of MAPK pathway targeted therapy was permitted
- **NF1 is an exclusion criteria**




**Endpoints (arm 1)**

| Primary | Secondary | Exploratory |
|---|---|---|
| ORR per RANO-HGG†,[14] | Safety, ORR per RAPNO-LGG (RAPNO)†,[15] , CBR, TTR, DOR, PFS | ORR and CBR per RANO-LGG†,[16,17] |

*That relapsed, progressed, or was nonresponsive to available therapies. †IRC-assessed.
CBR, clinical benefit rate; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; ORR, overall response rate; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; TTR, time to response.

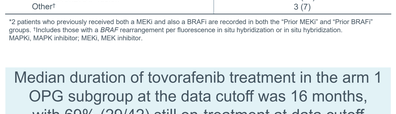
## Baseline characteristics and radiographic response results

### Table 1. Baseline characteristics

| Characteristic | Arm 1 OPG subgroup (n=42) |
|---|---|
| **Median age, years (range)** | 8 (2–16) |
| **Sex, n (%)** | |
| Male | 24 (57) |
| Female | 18 (43) |
| **Race, n (%)** | |
| Black or African American | 1 (2) |
| Asian | 2 (5) |
| White | 24 (57) |
| Multiple | 2 (5) |
| Other | 3 (7) |
| Not reported | 10 (24) |
| **Ethnicity, n (%)** | |
| Hispanic or Latino | 2 (5) |
| Not Hispanic or Latino | 29 (69) |
| Not stated | 10 (24) |
| Unknown | 1 (2) |
| **Number of prior lines of systemic therapy** | |
| **Median (range)** | **3 (1–9)** |
| 1, n (%) | 5 (12) |
| 2, n (%) | 11 (26) |
| ≥3, n (%) | 26 (62) |
| **Prior MAPK pathway targeted therapy, n (%)** | |
| Prior MEKi | 28 (67) |
| Prior BRAFi | 3 (7) |
| Prior BRAFi and MEKi* | 2 (5) |
| Any MAPKi | 29 (69) |
| ***BRAF* alteration status, n (%)** | |
| *BRAF* V600E mutation | 5 (12) |
| *KIAA1549*::*BRAF* fusion | 34 (81) |
| Other† | 3 (7) |

*2 patients who previously received both a MEKi and also a BRAFi are recorded in both the "Prior MEKi" and "Prior BRAFi" groups. †Includes those with a *BRAF* rearrangement per fluorescence in situ hybridization or in situ hybridization.
MAPKi, MAPK inhibitor; MEKi, MEK inhibitor.

Median duration of tovorafenib treatment in the arm 1 OPG subgroup at the data cutoff was 16 months, with 69% (29/42) still on-treatment at data cutoff



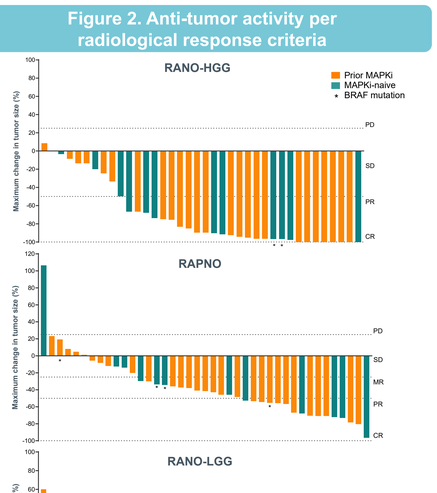

‡Six patients are not included in the analysis; 4 had no visual acuity (VA) assessments performed due to bilateral blindness, 1 had no baseline (BL) VA assessment, and 1 discontinued treatment and had no follow-up assessment after BL. logMAR, logarithm of the minimum angle of resolution.

### Table 2. Response by radiological criteria

| Response (IRC) | RANO-HGG[14] | | RAPNO[15] | | RANO-LGG[16,17] | |
|---|---|---|---|---|---|---|
| | n | | n | | n | |
| **ORR, n (%)*** | **39** | **25 (64)** | **42** | **21 (50)** | **42** | **23 (55)** |
| 95% CI | | 47–79 | | 34–66 | | 39–70 |
| **CBR, n (%)*** | | | | | | |
| **SD of any length of time** | | **37 (95)** | | **37 (88)** | | **38 (90)** |
| **SD ≥12 months** | | **31 (79)** | | **25 (60)** | | **28 (67)** |
| **BOR, n (%)*** | | | | | | |
| CR | | 7 (18) | | 0 | | 0 |
| PR | | 18 (46) | | 12 (29) | | 8 (19) |
| MR | | N/A | | 9 (21) | | 15 (36) |
| SD | | 12 (31) | | 16 (38) | | 15 (36) |
| SD <12 months | | 6 (15) | | 12 (29) | | 10 (24) |
| SD ≥12 months | | 6 (15) | | 4 (10) | | 5 (12) |
| PD† | | 2 (5) | | 5 (12) | | 3 (7) |
| Not evaluable | | 0 | | 0 | | 1 (2) |
| **Median DOR, months (95% CI)‡** | **25** | **16.8 (9.0–NR)** | **21** | **13.8 (11.3–NR)** | **23** | **14.4 (5.8–NR)** |
| **Median TTR, months (range)** | **25** | **5.5 (2.6–16.6)** | **21** | **5.5 (2.6–11.2)** | **23** | **5.5 (2.6–11.1)** |

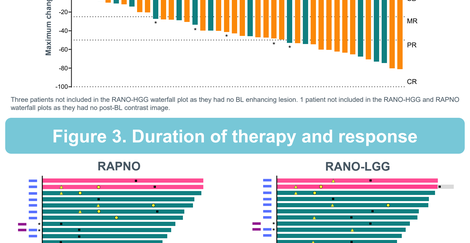
Percentages may not add to 100% due to rounding. *ORR, CBR, and BOR for RAPNO and RANO-LGG included MRs (ie, ORR=CR+PR+MR; CBR=CR+PR+MR+SD [calculated based on SD of any length and SD ≥12 months]). †PD per RAPNO and RANO-LGG were not used to determine treatment discontinuation; patients could continue treatment if there was no PD based on RANO-HGG per investigator's assessment. ‡Kaplan Meier estimate with the corresponding log-log transformed 95% CI.
BOR, best overall response; CI, confidence interval; CR, complete response; MR, minor response; N/A, not applicable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

### Figure 2. Anti-tumor activity per radiological response criteria




Three patients not included in the RANO-HGG waterfall plot as they had no BL enhancing lesion. 1 patient not included in the RANO-HGG and RAPNO waterfall plots as they had no post-BL contrast image.

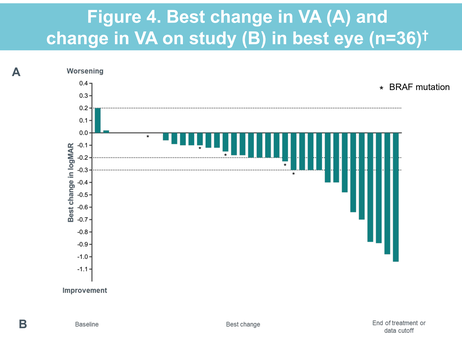
### Figure 3. Duration of therapy and response




In patients with confirmed response, symbols indicate the start of response (MR or PR). If initial responses improved with continued treatment (from MR to confirmed PR), both the timepoint of the initial response and the timepoint that the response initially improved are marked accordingly.

## Visual acuity response results

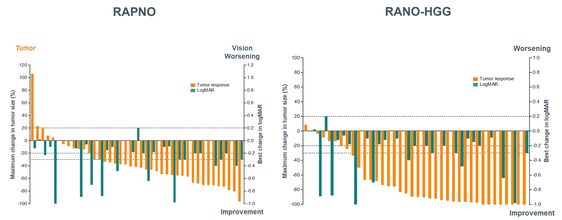
### Figure 4. Best change in VA (A) and change in VA on study (B) in best eye (n=36)†




Percentages may not add up to 100% due to rounding. †Six patients are not included in the analysis; 4 had no VA assessments performed due to bilateral blindness, 1 had no BL VA assessment, and 1 discontinued treatment and had no follow-up assessment after BL.

**Vision remained stable** (n=24, 67%) **or improved** (n=8, 22%) in **89%** (n=32) **of evaluable patients** (n=36) per VA assessment (best eye)

### Figure 5. Radiological response correlation with VA response




**Stable or improved VA was observed even with small decreases in tumor size across radiographic assessment criteria**

## Safety results

### Table 3. TEAEs in ≥25% any grade in arms 1 + 2 (n=137)

| | TEAEs | | TRAEs | |
|---|---|---|---|---|
| **Preferred term, (%)** | **Any grade** | **Grade ≥3** | **Any grade** | **Grade ≥3** |
| Any AE | 137 (100) | 86 (63) | 134 (98) | 58 (42) |
| Hair color change | 104 (76) | 0 | 104 (76) | 0 |
| Anemia | 81 (59) | 15 (11) | 67 (49) | 14 (10) |
| Elevated CPK | 80 (58) | 16 (12) | 77 (56) | 16 (12) |
| Fatigue | 76 (55) | 6 (4) | 60 (44) | 6 (4) |
| Vomiting | 68 (50) | 6 (4) | 28 (20) | 3 (2) |
| Hypophosphatemia | 64 (47) | 0 | 48 (35) | 0 |
| Headache | 61 (45) | 2 (1) | 29 (21) | 0 |
| Maculopapular rash | 60 (44) | 11 (8) | 56 (41) | 11 (8) |
| Pyrexia | 53 (39) | 5 (4) | 17 (12) | 1 (1) |
| Dry skin | 49 (36) | 0 | 45 (33) | 0 |
| Elevated LDH | 48 (35) | 0 | 42 (31) | 0 |
| Increased AST | 47 (34) | 4 (3) | 41 (30) | 4 (3) |
| Constipation | 45 (33) | 0 | 31 (23) | 0 |
| Nausea | 45 (33) | 0 | 25 (18) | 0 |
| Upper RTI | 43 (31) | 2 (1) | 2 (1) | 0 |
| Dermatitis acneiform | 42 (31) | 1 (1) | 41 (30) | 1 (1) |
| Epistaxis | 42 (31) | 1 (1) | 27 (20) | 0 |
| Decreased appetite | 39 (28) | 5 (4) | 28 (20) | 4 (3) |
| Paronychia | 36 (26) | 2 (1) | 32 (23) | 2 (1) |
| Pruritus | 35 (26) | 1 (1) | 32 (23) | 1 (1) |
| COVID-19 | 34 (25) | 0 | 0 | 0 |

ALT, alanine transaminase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; RTI, respiratory tract infection; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

- 9 patients (7%) had TRAEs leading to discontinuation
  - The most common were intratumoral hemorrhage (n=3) and decrease in growth velocity (n=2)
- 33 patients (24%) had TRAEs leading to dose reduction; the median dose reduction was 1 level; 50 patients (37%) had TRAEs leading to dose interruption; the median dose interruption was 7 days (1 week)

## Conclusions

- Clinically meaningful and rapid tumor responses seen on T2/FLAIR sequences in *BRAF*-altered/non-NF1 relapsed/refractory OPGs:
  - Similar to the full cohort,[12] responses were demonstrated across all 3 response criteria, *BRAF*-alteration type (mutation vs fusion) and prior MAPKi use (prior MAPKi/no prior MAPKi)
- Vision was stable or improved in 89% of evaluable patients (VA, best eye):
  - Preservation of vision through stabilizing or reducing the size of the tumor that may impact optic nerve function is an important treatment outcome
- Encouraging safety and tolerability profile with only 7% having TRAEs leading to discontinuation; most TRAEs were grade 1/2
- Phase 3 LOGGIC/FIREFLY-2 (NCT05566795) study in front-line pLGG is enrolling globally;[20,21] the first patient was dosed in March 2023[22]

## References

1. Ostrom QT, et al. *Neuro Oncol.* 2015;16(10):x1–x36.
2. Samples DC, et al. *Front Surg.* 2022;9:864250.
3. Packer RJ, et al. *Neuro Oncol.* 2020;22(6):773–784.
4. Johnson A, et al. *Oncologist.* 2017; 22(12):1478–1490.
5. Ryall S, et al. *Cancer Cell.* 2020;37(4):569–583 e565.
6. Acharya S, et al. *J Neurooncol.* 2019;144(3):603–610.
7. Li X, et al. *Neuro Oncol.* 2023; 25(4):750–760.
8. Davies H, et al. *Nature.* 2002;417(6892):949–954.
9. Yaeger R and Corcoran RB. *Cancer Discov.* 2019;9(3):329–341.
10. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774–785.
11. ClinicalTrials.gov website. https://classic.clinicaltrials.gov/ct2/show/NCT04775485. Accessed March 13, 2024.
12. Kilburn LB, et al. *Lancet Med.* 2024;30(1):207–217.
13. Nysom K, et al. *Neuro Oncol.* 2023;25(suppl 5):v79.
14. Wen PY, et al. *J Clin Oncol.* 2010;28(11):1963–1972.
15. Fangusaro J, et al. *Lancet Oncol.* 2020;21(6):e305–316.
16. van den Bent MJ, et al. *Lancet Oncol.* 2011;12(6):583–593.
17. Wen PY, et al. *J Clin Oncol.* 2017;35(21):2439–2449.
18. Schultz-Bonel K, et al. *Invest Ophthalmol Vis Sci.* 2006;47(3):1236–1240.
19. Grekow AK, et al. *Glioma Klin Padiatr.* 2019;231(3):107–135.
20. van Tilburg CM, et al. *BMC Cancer.* 2024;24(1):147.
21. ClinicalTrials.gov website. https://clinicaltrials.gov/study/NCT05566795. Accessed March 15, 2024.
22. Day One website. March 6, 2023 news release: https://ir.dayonebio.com/news-releases/news-release-details/day-one-reports-fourth-quarter-and-full-year-2022-financial. Accessed March 26, 2024.