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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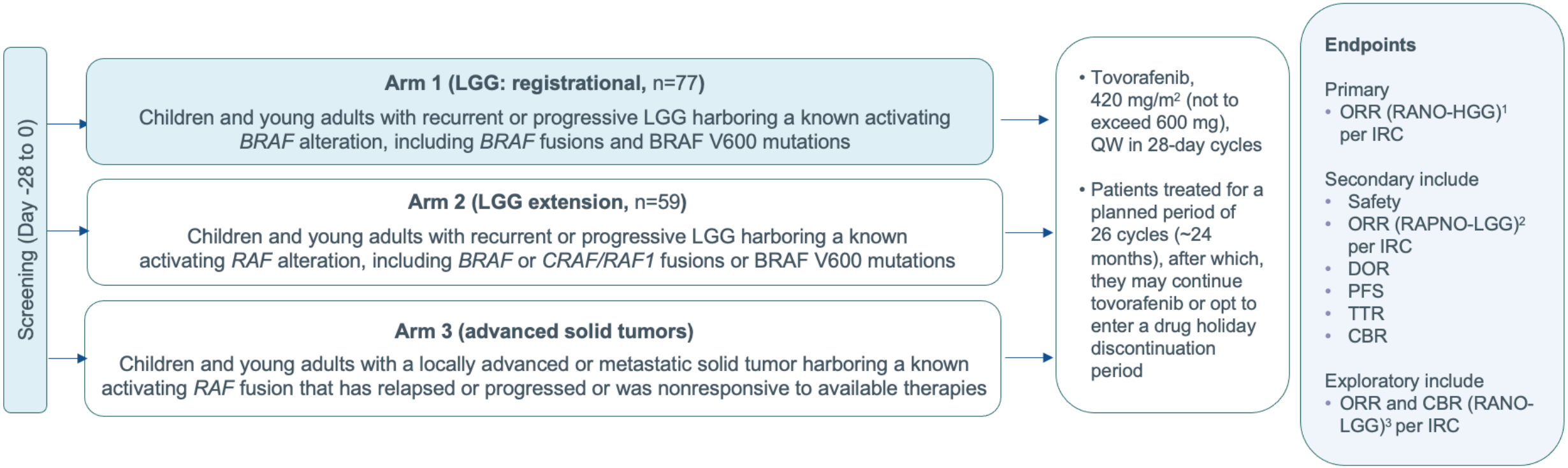
Pediatric low-grade glioma (pLGG)

- **pLGG is the most common brain tumor in children[1]**
  - 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[2,3]**
  - *KIAA1549-BRAF* fusions are the most common genomic alterations in pLGG and occur in ~80% of pilocytic astrocytomas[4,5]
  - *BRAF* alterations enable constitutive activation of the protein as a monomer (V600 mutations) or dimer (fusions), independent of extracellular stimuli or RAS activation[6,7]
- **Tovorafenib is an investigational, oral, selective, CNS-penetrant, type II RAF inhibitor[8]**
  - Activity against monomeric (class I alterations) and dimeric (class II alterations, including fusions) forms of RAF signaling[8]
  - Does not cause paradoxical activation of the MAPK pathway observed with type I BRAF inhibitors[8]
  - Available as tablets and a pediatric-friendly oral suspension
  - Once-weekly dosing

1. Ostrom QT, et al. *Neuro Oncol*. 2015;16(Suppl 10):x1–x36. 2. Chen Y-H, Gutmann DH. *Oncogene*. 2014;33(16):2019-2026. 3. Packer RJ et al. *Neuro Oncol.* 2017;19(6)750-761. 4. Ryall S, et al. *Cancer Cell*. 2020;37(4):569-583. 5. Ryall S, Tabori U, Hawkins C *Acta Neuropathol Commun*. 2020;8(1):30. 6. Davies H. et al, *Nature*. 2002;417(6892):949-954. 7. Yaegar R; Cochran RB. *Cancer Discov*. 2019;9(3):329-341. 8. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774-785.
CNS, central nervous system; MAPK, mitogen-activated protein kinases; RAF, rapidly accelerated fibrosarcoma.

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



- 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

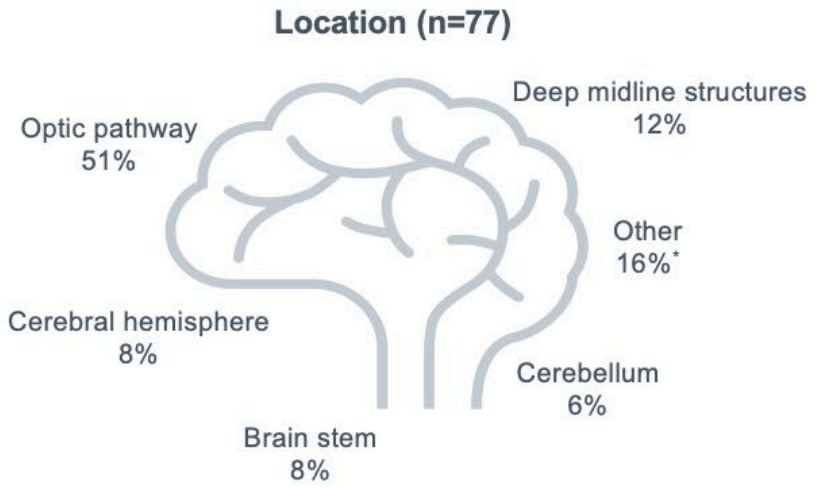
Dec 22, 2022 data cutoff.

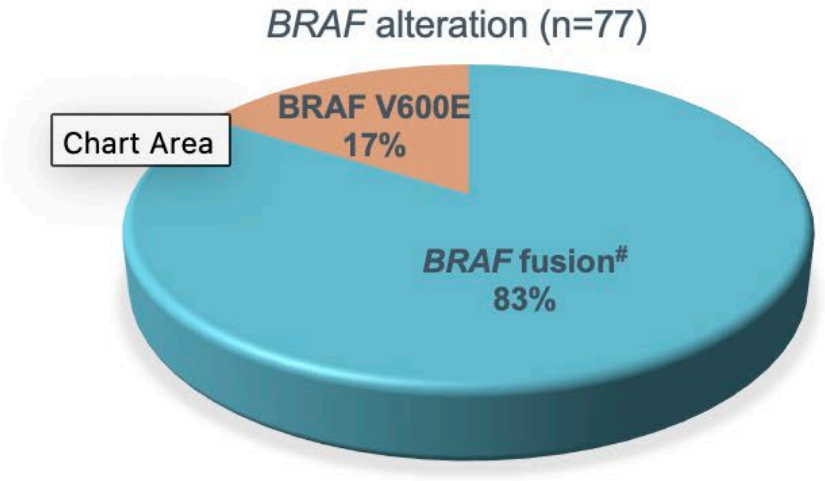
1. Wen PY, et al. *J Clin Oncol.* 2010;28(11):1963-1972. 2. Fangusaro J, et al. *Lancet Oncol.* 2020;21(6):e305–316. 3. van den Bent MJ, et al. *Lancet Oncol.* 2011;12(6):583-593.

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

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

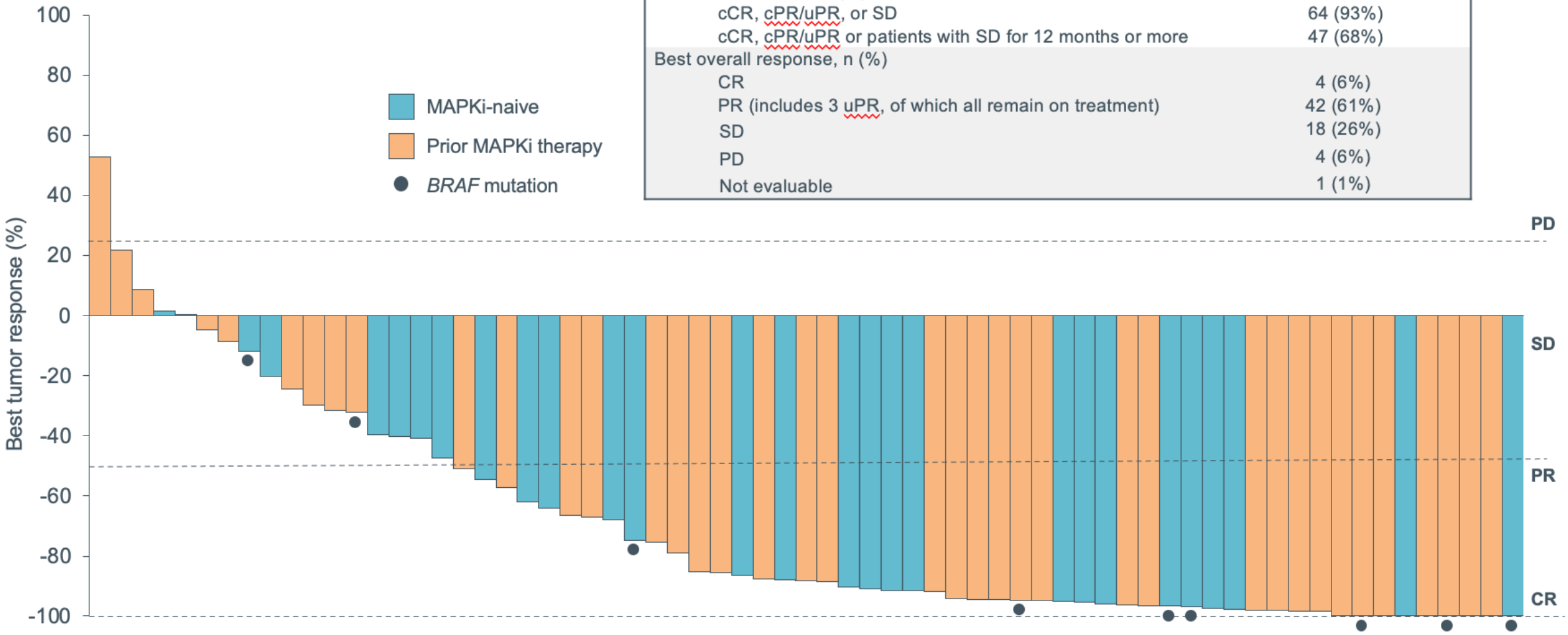




Dec 22, 2022 data cutoff.
*Includes tumors that were extending into multiple regions of the brain, leptomeningeal disease, and/or spinal disease. #Includes 6 patients with *BRAF* duplication and 2 with *BRAF* rearrangement per FISH (fluorescence in situ hybridization) or ISH (in situ hybridization).
MAPK, mitogen-activated protein kinase.

FIREFLY-1 registrational arm: antitumor activity (RANO-HGG, n=69)

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

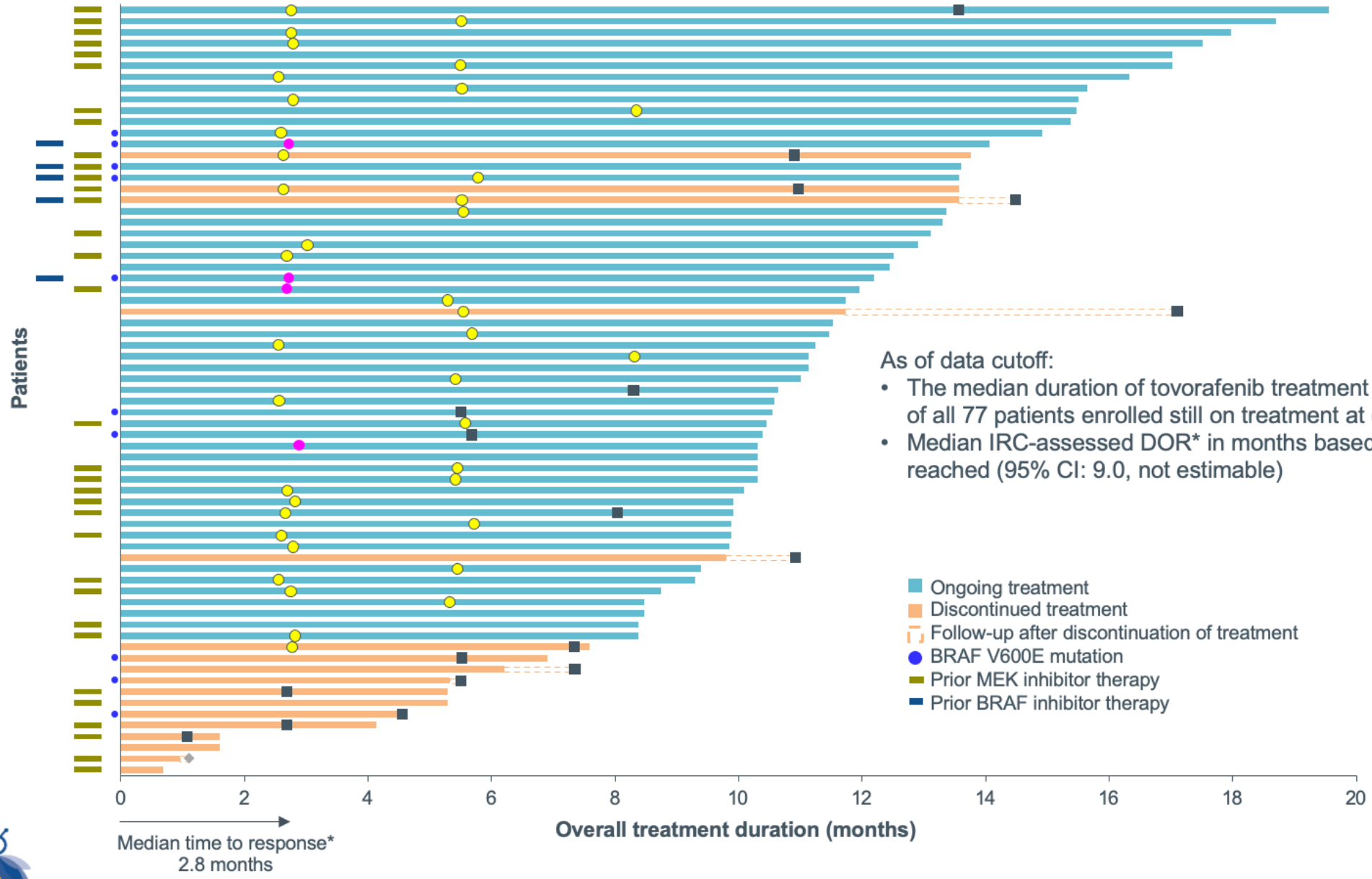


Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.
Two of 69 patients are not shown in the waterfall plot; one patient passed away due to progressive disease (not related to tovorafenib) before the first imaging assessment and one did not receive T1 Gd+ follow-up imaging. *P<0.001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

1. Wen PY, et al. *J Clin Oncol.* 2010;28(11):1963-1972. 2. Bouffet E, et al. *J Clin Oncol.* 2012;30(12):1358-1363.

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.

FIREFLY-1 registrational arm: duration of therapy (RANO-HGG, n=69)



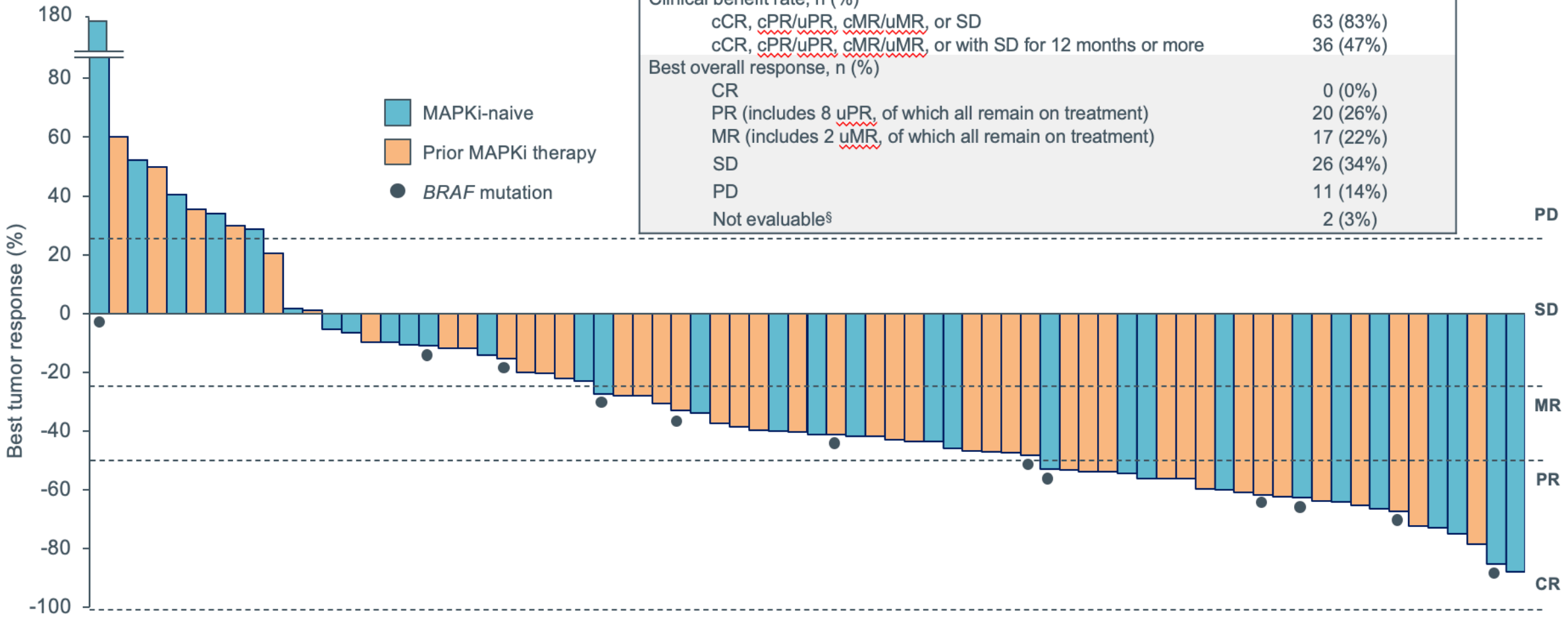
As of data cutoff:

- 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.

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

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



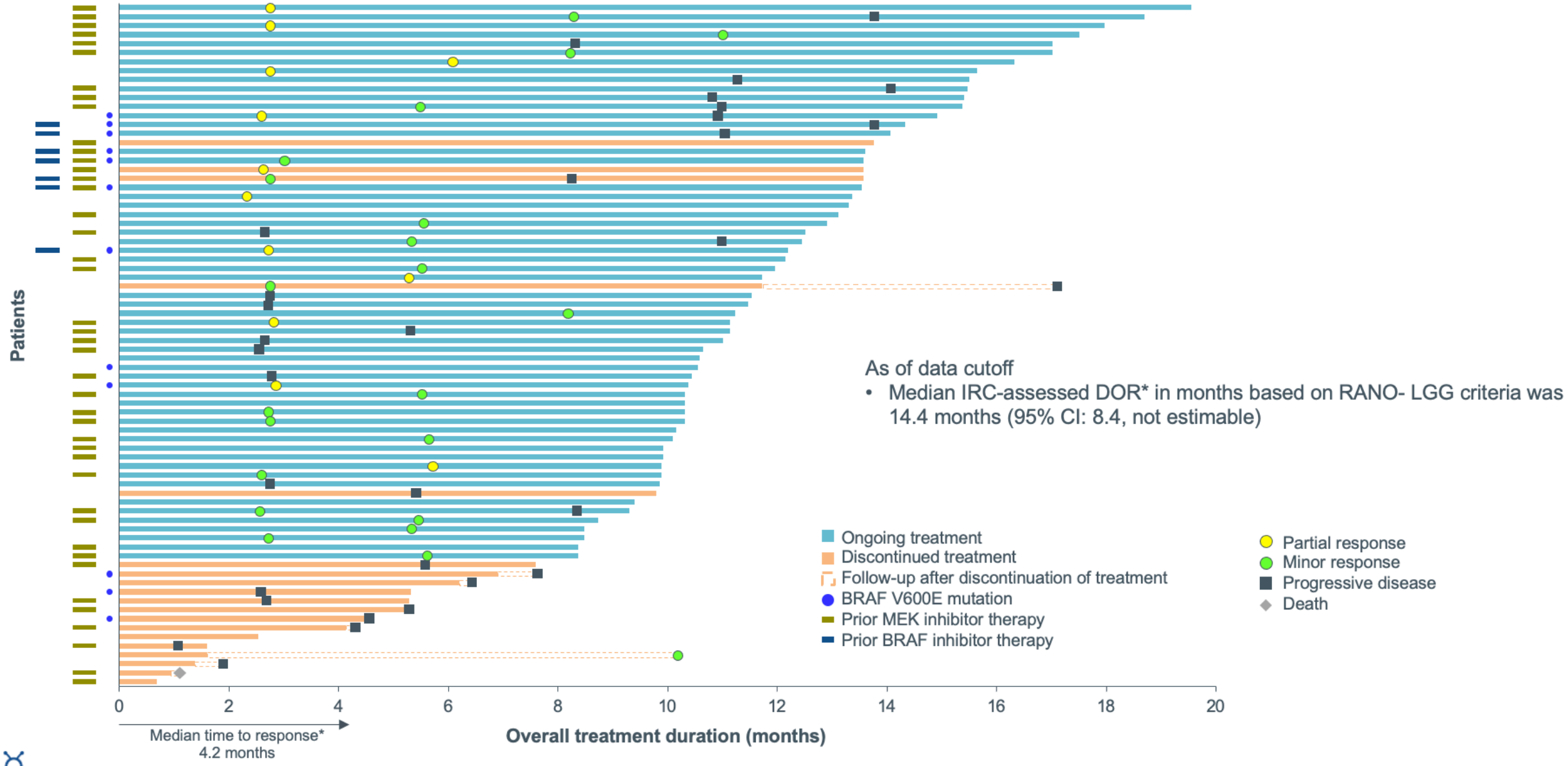
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.

§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

1. van den Bent MJ, et al. *Lancet Oncol.* 2011;12(6):583-593.

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.

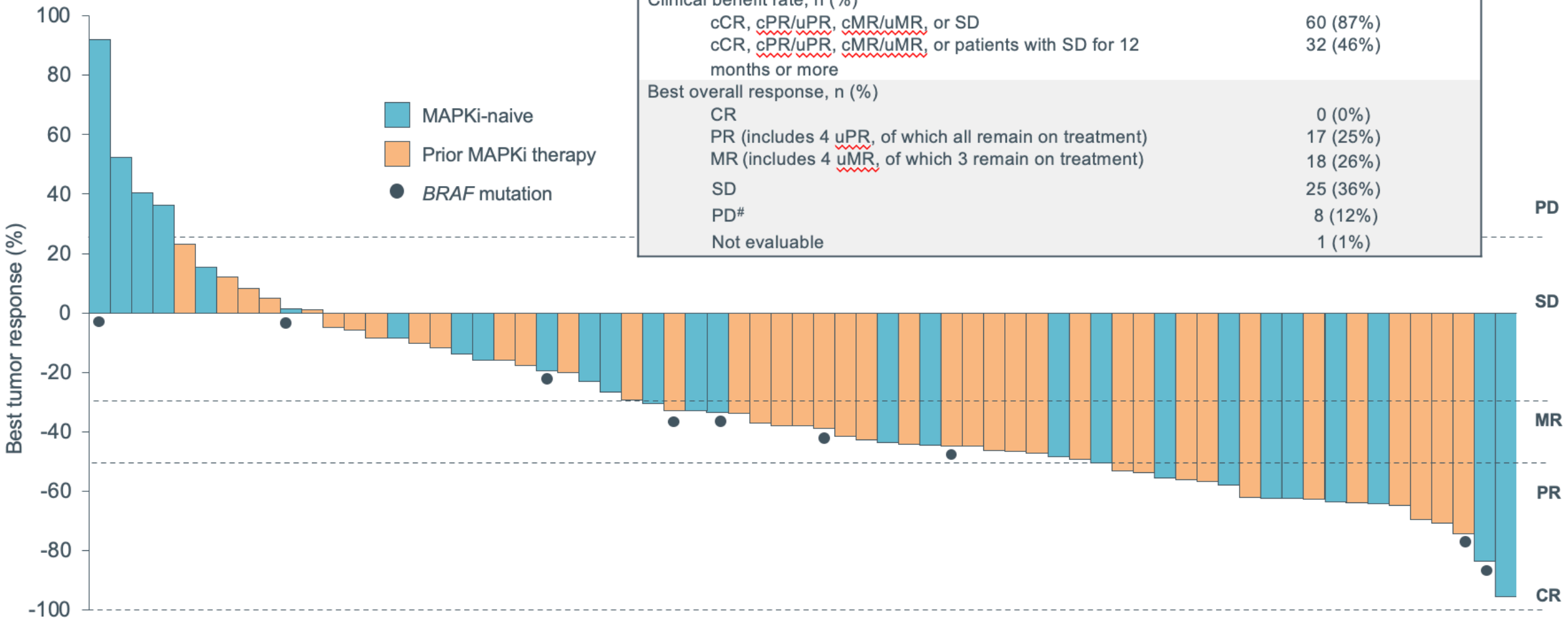
FIREFLY-1 registrational arm: duration of therapy (RANO-LGG, n=76)



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.

FIREFLY-1 registrational arm: antitumor activity (RAPNO-LGG, n=69*)

Response (IRC)	RAPNO-LGG[1] n=69
ORR (cCR + cPR/uPR + cMR/uMR), n (%)	35 (51%)
Clinical benefit rate, n (%)	
cCR, cPR/uPR, cMR/uMR, or SD	60 (87%)
cCR, cPR/uPR, cMR/uMR, or patients with SD for 12 months or more	32 (46%)
Best overall response, n (%)	
CR	0 (0%)
PR (includes 4 uPR, of which all remain on treatment)	17 (25%)
MR (includes 4 uMR, of which 3 remain on treatment)	18 (26%)
SD	25 (36%)
PD[#]	8 (12%)
Not evaluable	1 (1%)



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.

1. Fangusaro J, et al. *Lancet Oncol.* 2020;21(6):e305–316.

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)

	Treatment-emergent AEs		Treatment-related AEs	
Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	136 (100)	68 (50)	133 (98)	47 (35)
Hair color changes	96 (71)	0	96 (71)	0
Fatigue	68 (50)	4 (3)	54 (40)	4 (3)
Vomiting	59 (43)	3 (2)	24 (18)	3 (2)
Rash maculo-papular	56 (41)	10 (7)	51 (38)	10 (7)
Headache	53 (39)	1 (1)	27 (20)	0
Pyrexia	43 (32)	2 (1)	15 (11)	1 (1)
Nausea	40 (29)	0	21 (15)	0
Dry skin	39 (29)	0	34 (25)	0
Dermatitis acneiform	37 (27)	1 (1)	36 (26)	1 (1)
Constipation	36 (26)	0	28 (21)	0
Decreased appetite	35 (26)	4 (3)	25 (18)	3 (2)
Epistaxis	34 (25)	0	22 (16)	0

- **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**

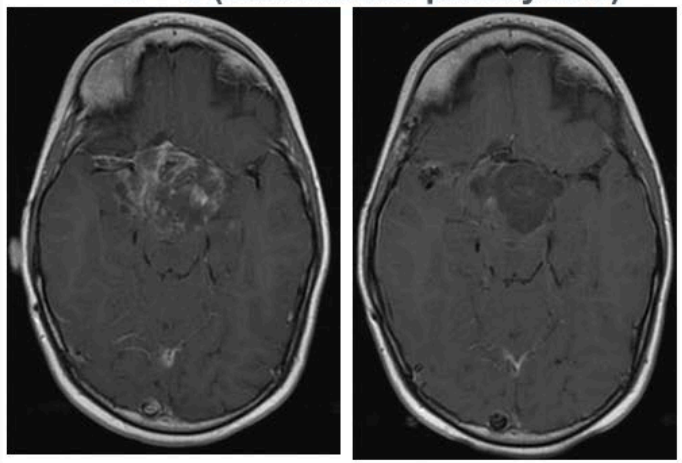
Dec 22, 2022 data cutoff.
Rash erythematous treatment-emergent: any grade, 14 (10%); grade ≥3 1 (1%); treatment-related: any grade, 14 (10%), grade ≥3 1 (1%).
*One patient had 2 events (shunt malfunction [not related to tovorafenib] and tumor hemorrhage [related to tovorafenib]).
AEs, adverse events;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

Case study: activity of tovorafenib in *KIAA1549-BRAF* fusion optic pathway glioma

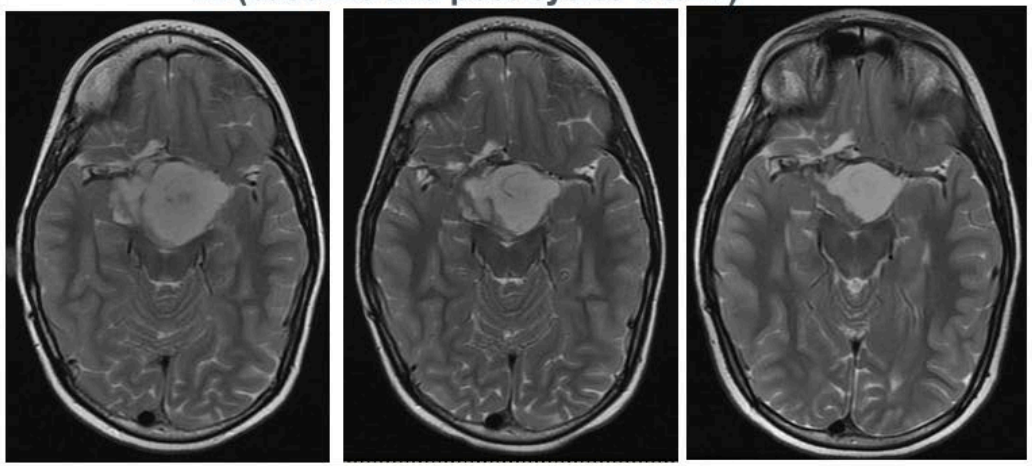
8-year-old boy with relapsed pilomyxoid astrocytoma of the optic pathway, with visual loss in right eye, visual field loss in left eye, fatigue, intermittent nausea/vomiting, intermittent headaches, anorexia, and temperature regulation disorder

- 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)

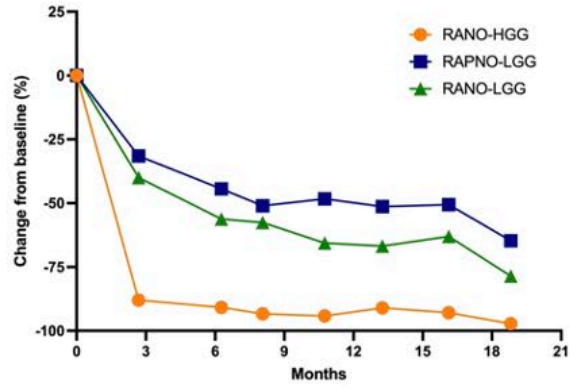
T1 + C (baseline and post-cycle 3)



T2 (baseline and post-cycles 3 & 12)



Tumor kinetics



Dec 22, 2022, data cutoff.

AEs, adverse events; C, contrast; CPK, creatine phosphokinase; G, grade; HGG, high-grade glioma; LGG, low-grade glioma; logMAR, Logarithm of the Minimum Angle of Resolution; MR, minor response; PD, progressive disease; PR, partial response; QW, once weekly; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; VC, vincristine-carboplatin.

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**

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

Dec 22, 2022 data cutoff.
*Analysis includes confirmed responses only.

Acknowledgments

Thank you to all patients, families, caregivers, and clinical investigators for their participation in this study

We are deeply grateful for the site coordinators and study staff who are instrumental in making this work possible

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

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