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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Disclosures

- Consulting Fee (eg, Advisory Board): Blueprint Medicine (DSMB Chair) 11/2021 – 2/2023
- Contracted Research:
  - Novartis
  - Regeneron Pharmaceuticals
  - Day One Biopharmaceuticals
  - Spring Works Therapeutics
  - Bristol Myers Squibb
  - SonALAsense
- Stock Shareholder: Onconova Therapeutics

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

Screening (Day -28 to 0)

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

- 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

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

- 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

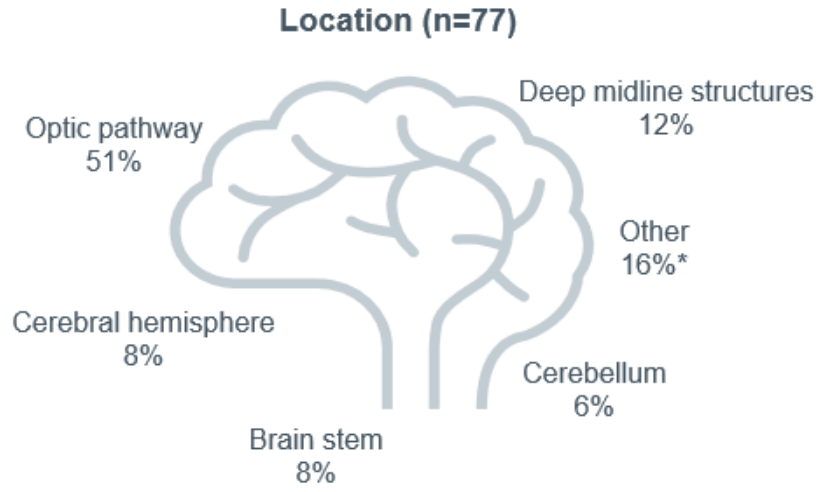
Dec 22, 2022 data cutoff.

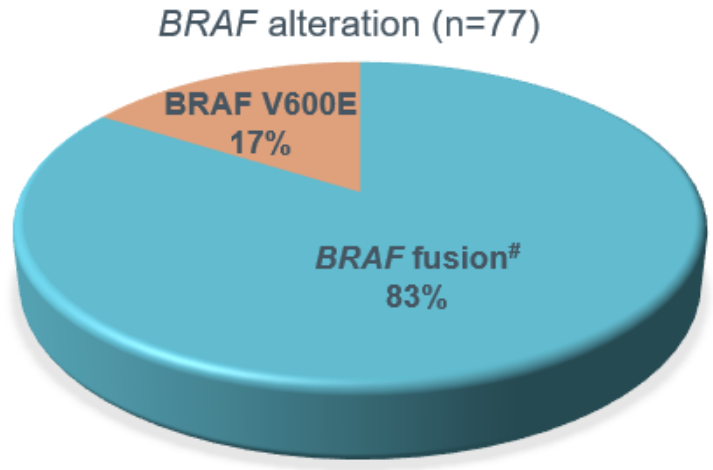
1. Wen PY, et al. *J Clin Oncol.* 2010;28(11):1963-1972. 2. Fangusaro J, et al. *Lancet Oncol.* 2020;21(6):e305–316. 3. van den Bent MJ, et al. *Lancet Oncol.* 2011;12(6):583-593.

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)
Prior MEK inhibitor	43 (56)
Prior BRAF inhibitor	8 (10)

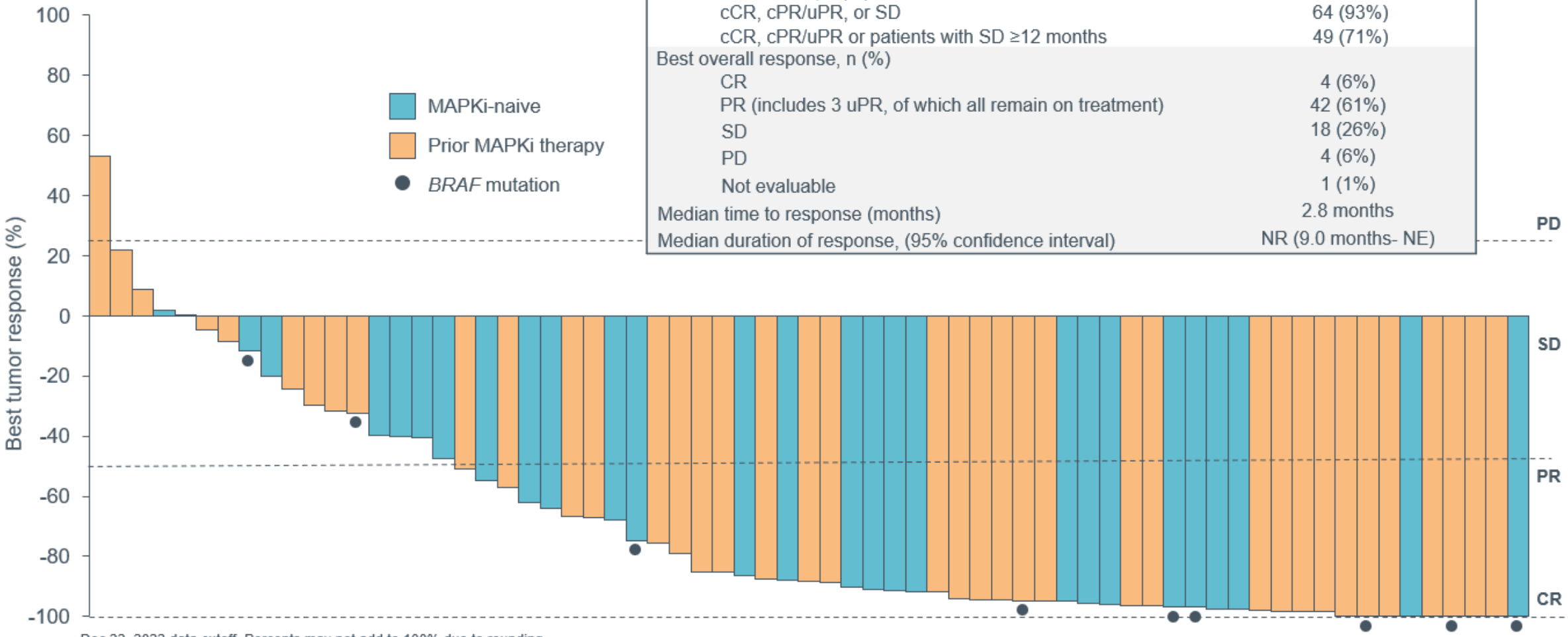




Dec 22, 2022 data cutoff.
*Includes tumors that were extending into multiple regions of the brain, leptomeningeal disease, and/or spinal disease. #Includes 6 patients with *BRAF* duplication and 2 with *BRAF* rearrangement per FISH (fluorescence in situ hybridization) or ISH (in situ hybridization).
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 ≥12 months	49 (71%)
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%)
Median time to response (months)	2.8 months
Median duration of response, (95% confidence interval)	NR (9.0 months- NE)

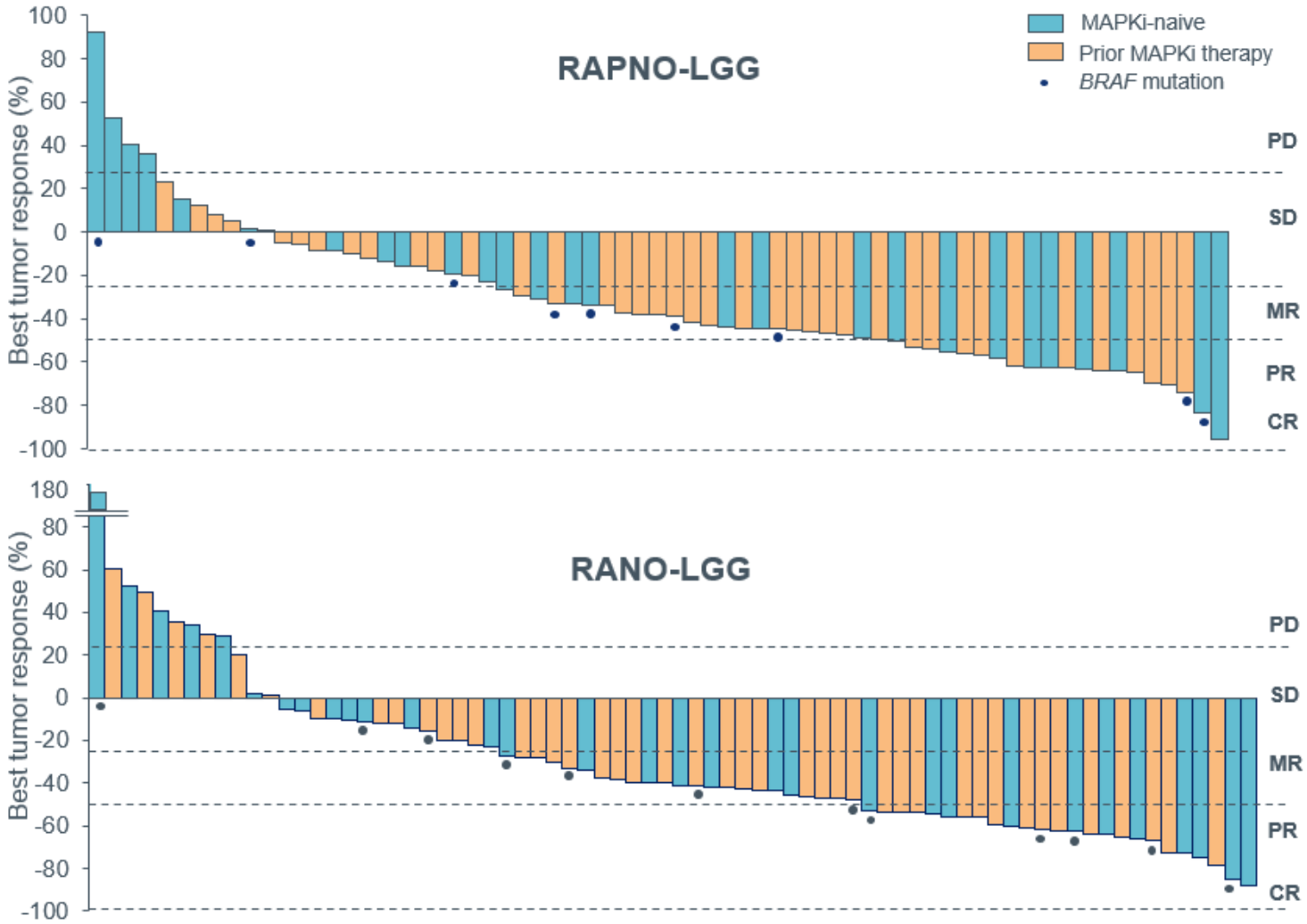


Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.
Two of 69 patients are not shown in the waterfall plot; one patient passed away due to progressive disease (not related to tovorafenib) before the first imaging assessment and one did not receive T1 Gd+ follow-up imaging. *P<0.001 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; NE, not estimable; NR, not reached; 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: antitumor activity



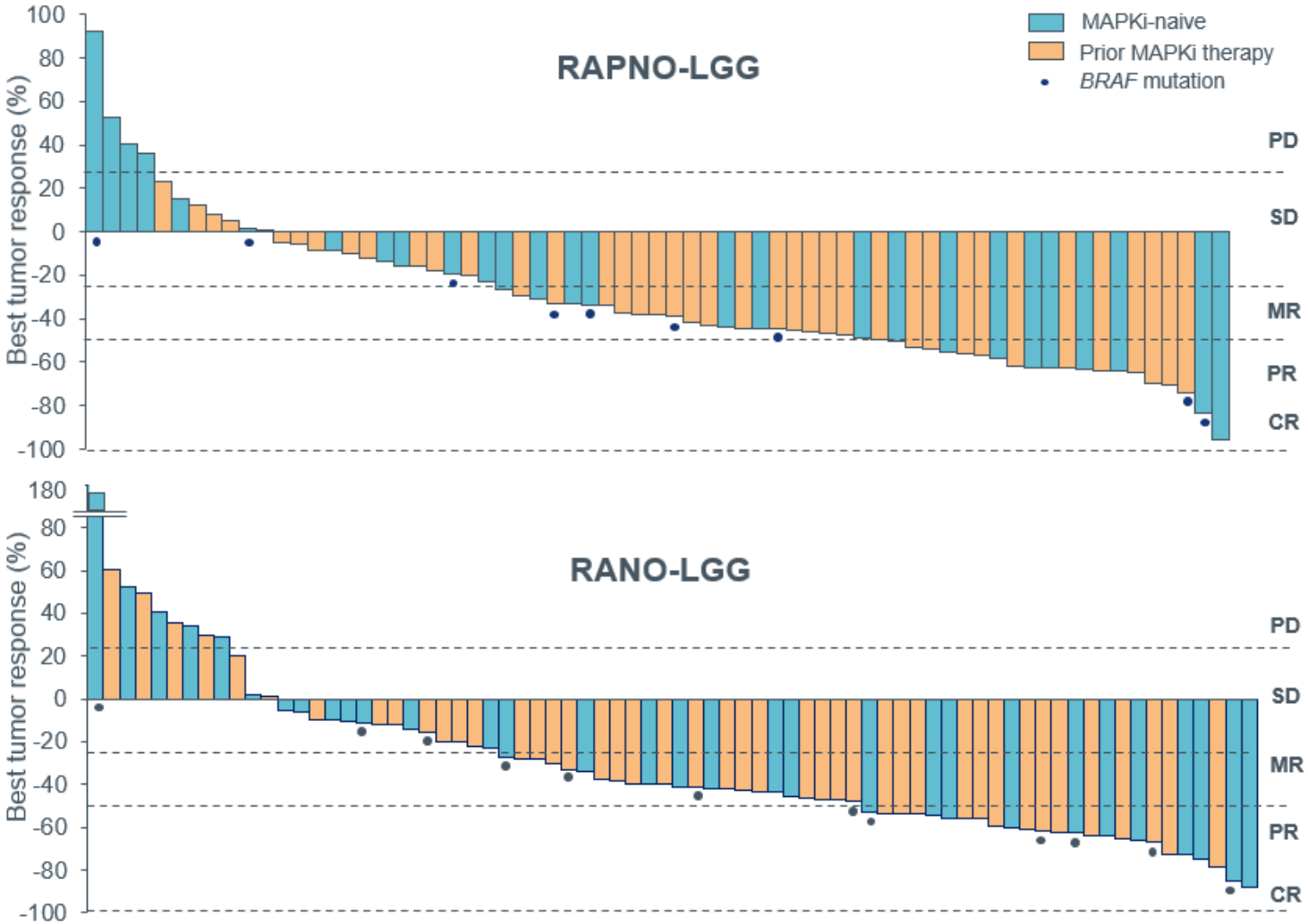
Response (IRC)	RAPNO-LGG[1,*] n=69	RANO-LGG[2] n=76
ORR (cCR + cPR/uPR + cMR/uMR), n (%)	35 (51%)	37 (49%)
Clinical benefit rate, n (%)		
cCR, cPR/uPR, cMR/uMR or SD	60 (87%)	63 (83%)
cCR, cPR/uPR, cMR/uMR or SD ≥12 months	36 (52%)	39 (51%)
Best overall response, n (%)		
CR	0 (0%)	0 (0%)
PR	17 (25%)	20 (26%)
MR	18 (26%)	17 (22%)
SD	25 (36%)	26 (34%)
PD[§]	8 (12%)	11 (14%)
Not evaluable	1 (1%)	2 (3%)

Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding. Two patients are not shown in the waterfall plots; One patient passed away due to PD (not tovorafenib-related) before first assessment and one patient with missing T1 Gd+ imaging at BL was deemed NE. [§]PD for RAPNO-LGG and RANO-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. 2. 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; 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 registrational arm: antitumor activity



Response (IRC)	RAPNO-LGG[1,*] n=69	RANO-LGG[2] n=76
ORR (cCR + cPR/uPR + cMR/uMR), n (%)	35 (51%)	37 (49%)
Clinical benefit rate, n (%)		
cCR, cPR/uPR, cMR/uMR or SD	60 (87%)	63 (83%)
cCR, cPR/uPR, cMR/uMR or SD ≥12 months	36 (52%)	39 (51%)
Best overall response, n (%)		
CR	0 (0%)	0 (0%)
PR	17 (25%)	20 (26%)
uPR[#]	4 (6%)	8 (11%)
MR	18 (26%)	17 (22%)
uMR[#]	4 (6%)	2 (3%)
SD	25 (36%)	26 (34%)
PD[§]	8 (12%)	11 (14%)
Not evaluable	1 (1%)	2 (3%)

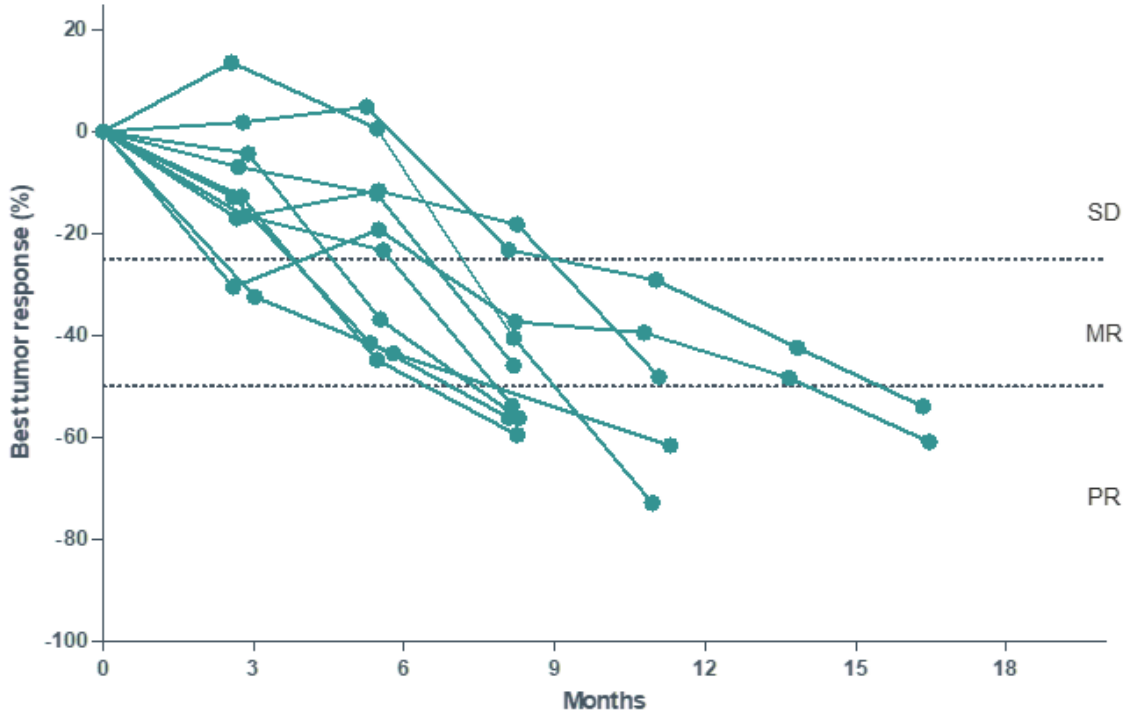
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding. Two patients are not shown in the waterfall plots; One patient passed away due to PD (not tovorafenib-related) before first assessment and one patient with missing T1 Gd+ imaging at BL was deemed NE. [#]4/4 uPR and 3/4 uMR per RAPNO-LGG and all unconfirmed responses per RANO-LGG remain on treatment. [§]PD for RAPNO-LGG and RANO-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. 2. van den Bent MJ, et al. *Lancet Oncol.* 2011;12(6):583-593.

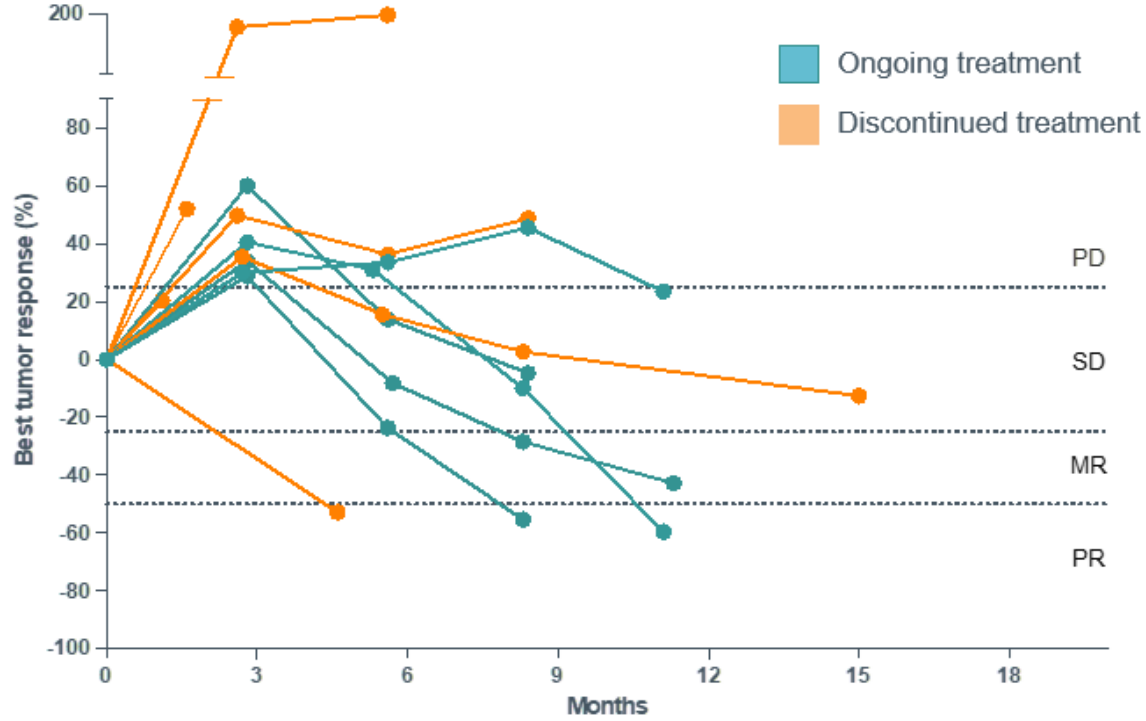
BL, baseline; CBR, clinical benefit rate; cCR, confirmed completed response; cMR, confirmed minor response; cPR, confirmed partial response; CR, complete response; IRC, independent radiology review committee; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; 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.

Tumor kinetics in patients uMR, uPR or PD (RANO-LGG)

Patients with uMR or uPR (n=10)*

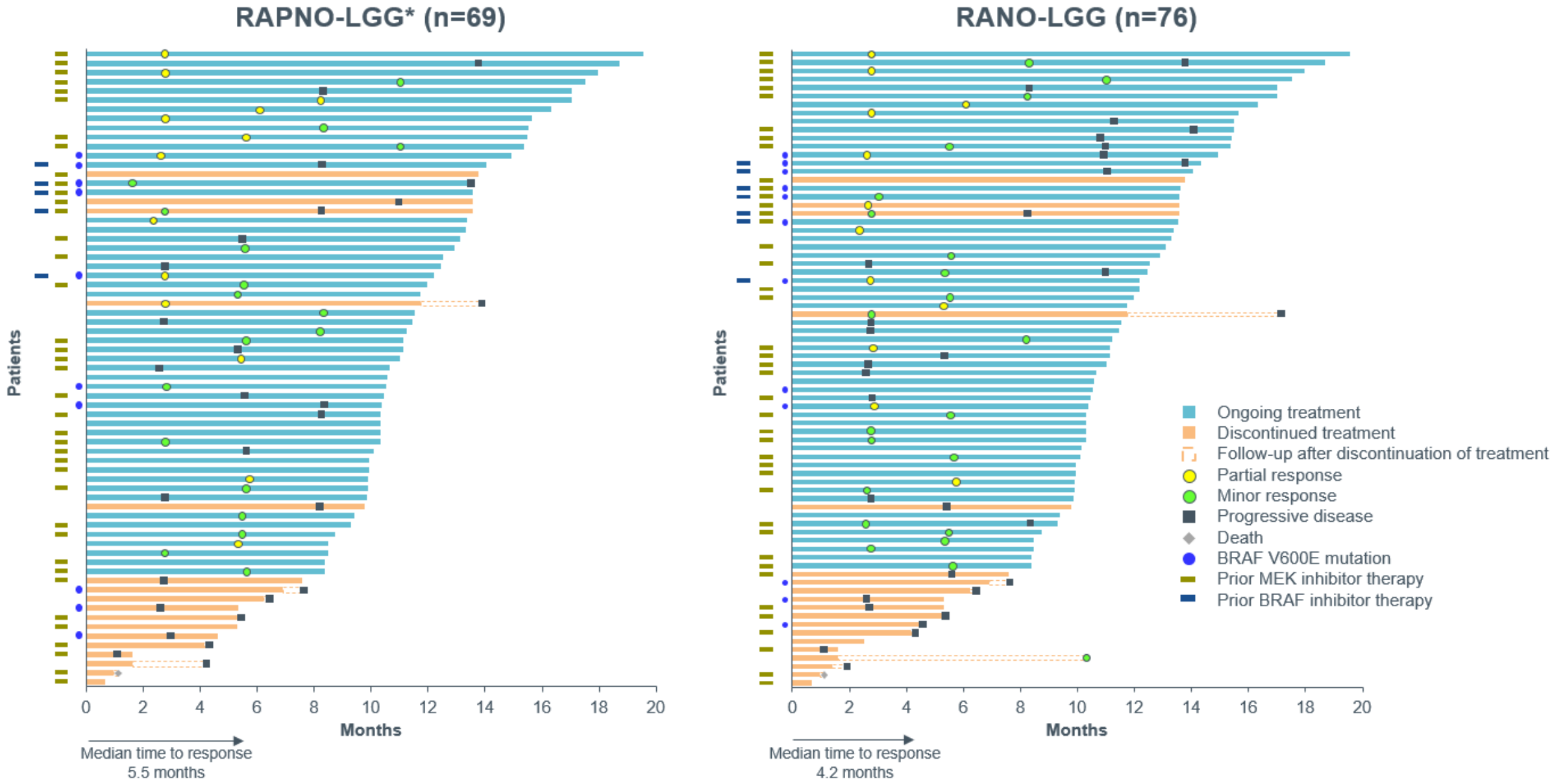


Patients with best response of PD (n=11)



Dec 22, 2022 data cutoff
*All unconfirmed responses remain on treatment as of May 2023.
LGG, low-grade glioma; PD, progressive disease; RANO, Response Assessment in Neuro-Oncology; uMR, unconfirmed minor response; uPR, unconfirmed partial response.

FIREFLY-1 registrational arm: duration of therapy



BOR is shown; circles indicate start of response. PD for the purpose of treatment was based on RANO-HGG, not RAPNO-LGG or RANO-LGG. *Pending adjudication.
BOR, best overall response; LGG, low-grade glioma; PD, progressive disease; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

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**

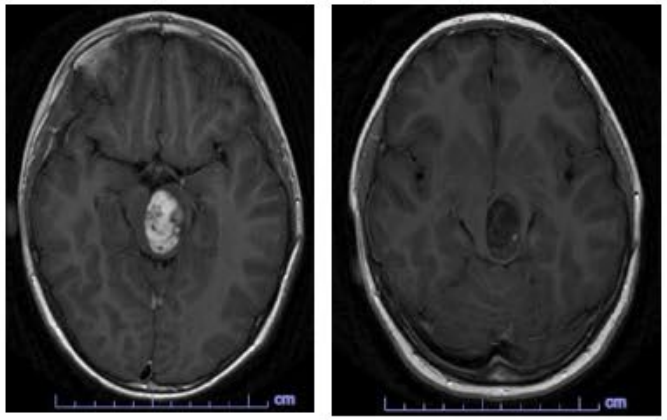
Dec 22, 2022 data cutoff.
Rash erythematous treatment-emergent: any grade, 14 (10%); grade ≥3 1 (1%); treatment-related: any grade, 14 (10%), grade ≥3 1 (1%).
*One patient had 2 events (shunt malfunction [not related to tovorafenib] and tumor hemorrhage [related to tovorafenib]).
AEs, adverse events;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

Case study: activity of tovorafenib in *KIAA1549-BRAF* fusion pilocytic astrocytoma

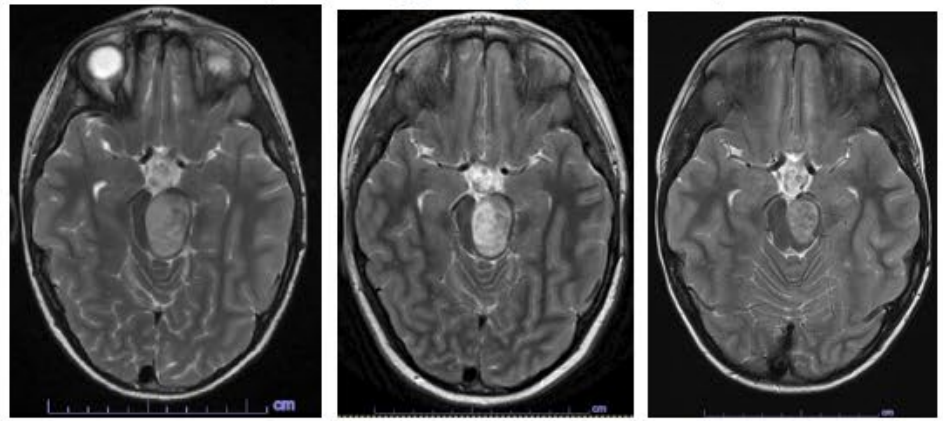
9-year-old boy with progressive pilocytic astrocytoma in the brain stem, with right hemiparesis, right facial nerve palsy, gait disturbance, intermittent headaches, word-finding difficulty, mirror/reverse writing, increased impulsivity, bilateral esophoria, mild right esotropia, ptosis of left eye, double/blurry vision, and hypocalcemia

- Initiated treatment with tovorafenib 500 mg/QW following 3 prior therapies, including 2 courses of trametinib/bevacizumab, which were discontinued due to PD
- **PR** (−97%) at cycle 3 per RANO-HGG, **MR** (−45%) and **uPR** (−57% and −60%) per RAPNO-LGG and RANO-LGG at cycles 6 and 9, respectively
  - **Improvements in hemiparesis, regained ability to walk/run at near-normal function and functional improvements in right hand enabling him to write**
- AEs were G3 hypocalcemia, CPK elevation and fatigue, and G1 acneiform rash, hair color change

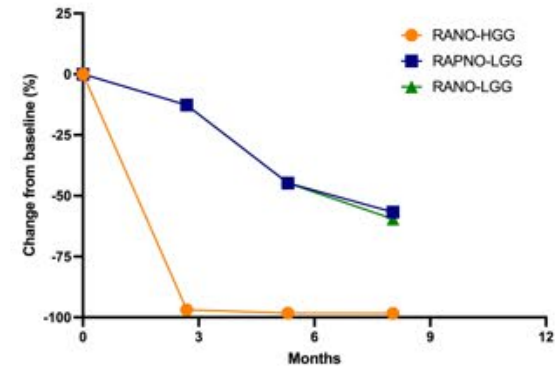
T1 (baseline and post-cycle 3)



T2 (baseline, post-cycles 3 and 6)



Tumor kinetics



Dec 22, 2022 data cutoff.

AEs, adverse events; CPK, creatine phosphokinase; G, grade; HGG, high-grade glioma; LGG, low-grade glioma; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; QW, once weekly; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; uPR, unconfirmed partial response; VC, vincristine-carboplatin.

Conclusions: FIREFLY-1 registrational arm

- Clinically meaningful and rapid tumor responses seen on both T1-Gd+ and T2/FLAIR sequences in this heavily pretreated population
  - RANO-HGG: 67% ORR (includes 3 uPR) and 26% of patients with SD
  - RAPNO-LGG: 51% ORR (includes 4 uPR and 4 uMR) and 36% of patients with SD
  - RANO-LGG: 49% ORR (includes 8 uPR and 2 uMR) and 34% 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 TTR was 2.8 months with RANO-HGG, 5.5 months with RAPNO-LGG*, and 4.2 months with RANO-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
- Ph 3 LOGGIC/FIREFLY-2 (NCT05566795) in front-line pLGG is enrolling; first patient dosed in March 2023

Dec 22, 2022 data cutoff.
*Pending adjudication.

Acknowledgments

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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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