

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

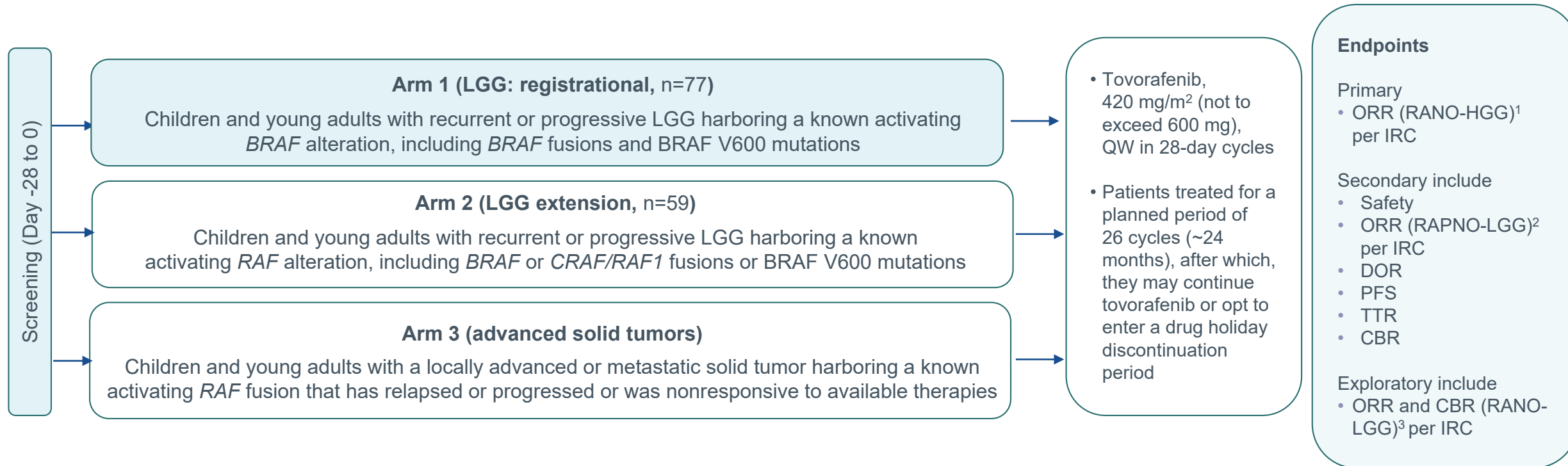
Pediatric low-grade glioma (pLGG)

- **pLGG is the most common brain tumor in children¹**
 - 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 inhibitor⁸**
 - Activity against monomeric (class I alterations) and dimeric (class II alterations, including fusions) forms of RAF signaling⁸
 - Does not cause paradoxical activation of the MAPK pathway observed with type I BRAF inhibitors⁸
 - 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



- 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

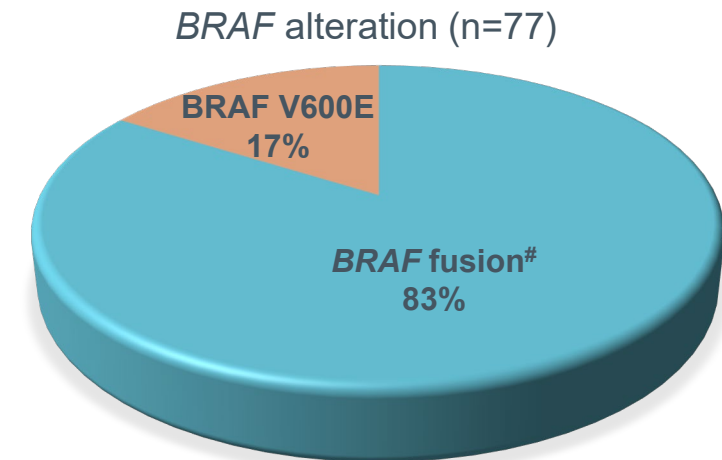
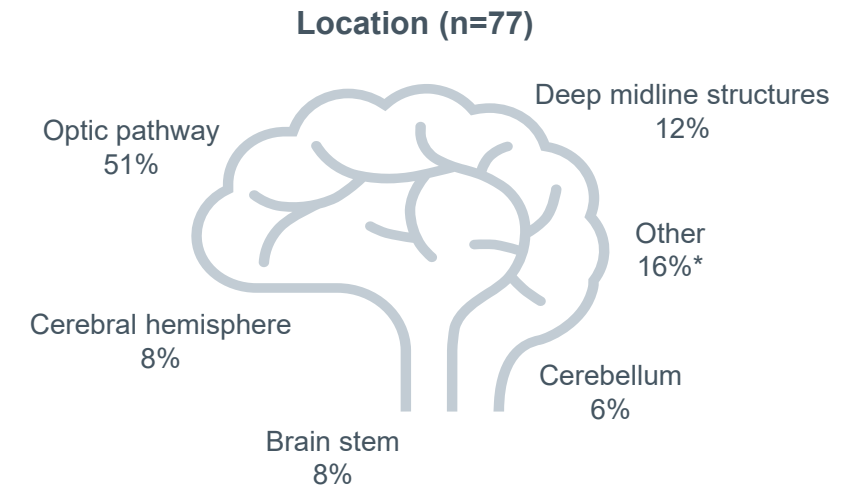
Dec 22, 2022 data cutoff.

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)

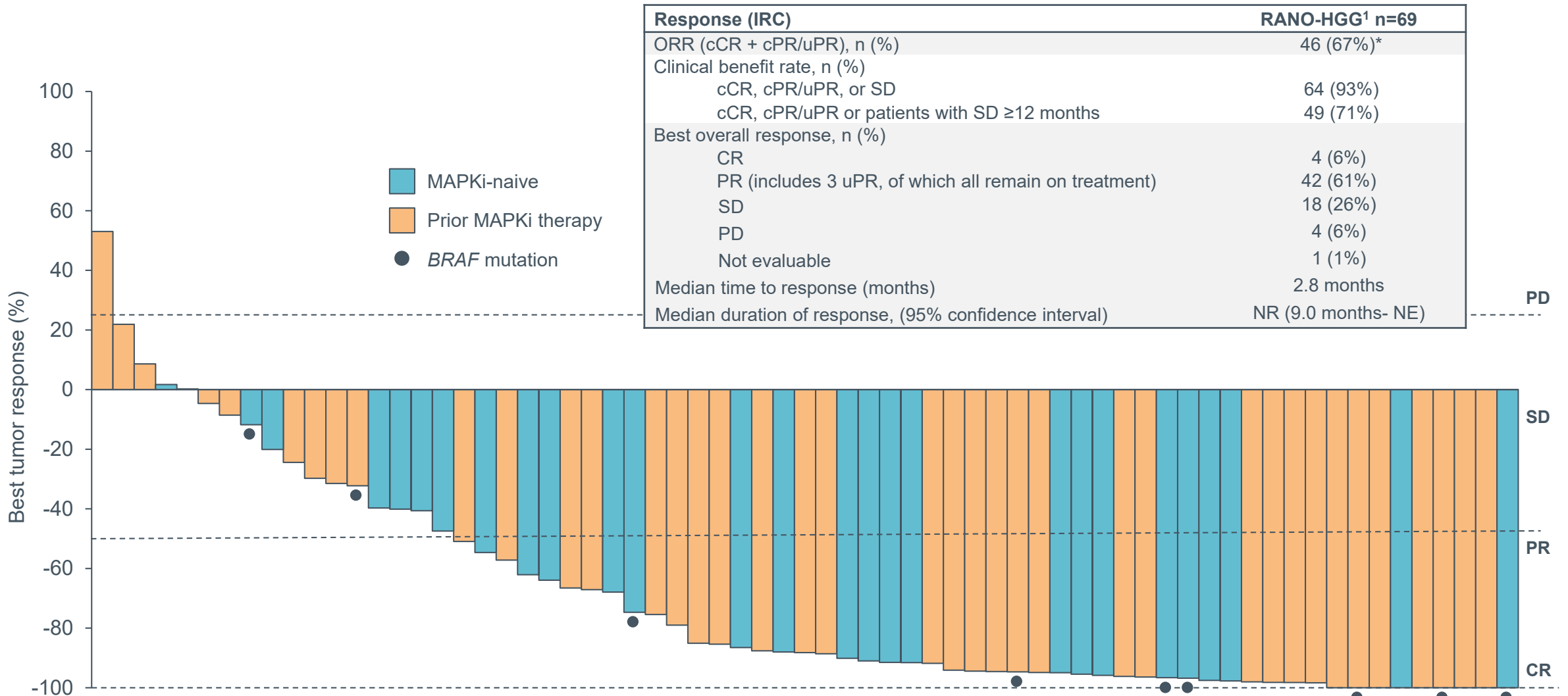


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*Includes tumors that were extending into multiple regions of the brain, leptomeningeal disease, and/or spinal disease. #Includes 6 patients with *BRAF* duplication and 2 with *BRAF* rearrangement per FISH (fluorescence in situ hybridization) or ISH (in situ hybridization).

MAPK, mitogen-activated protein kinase.

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



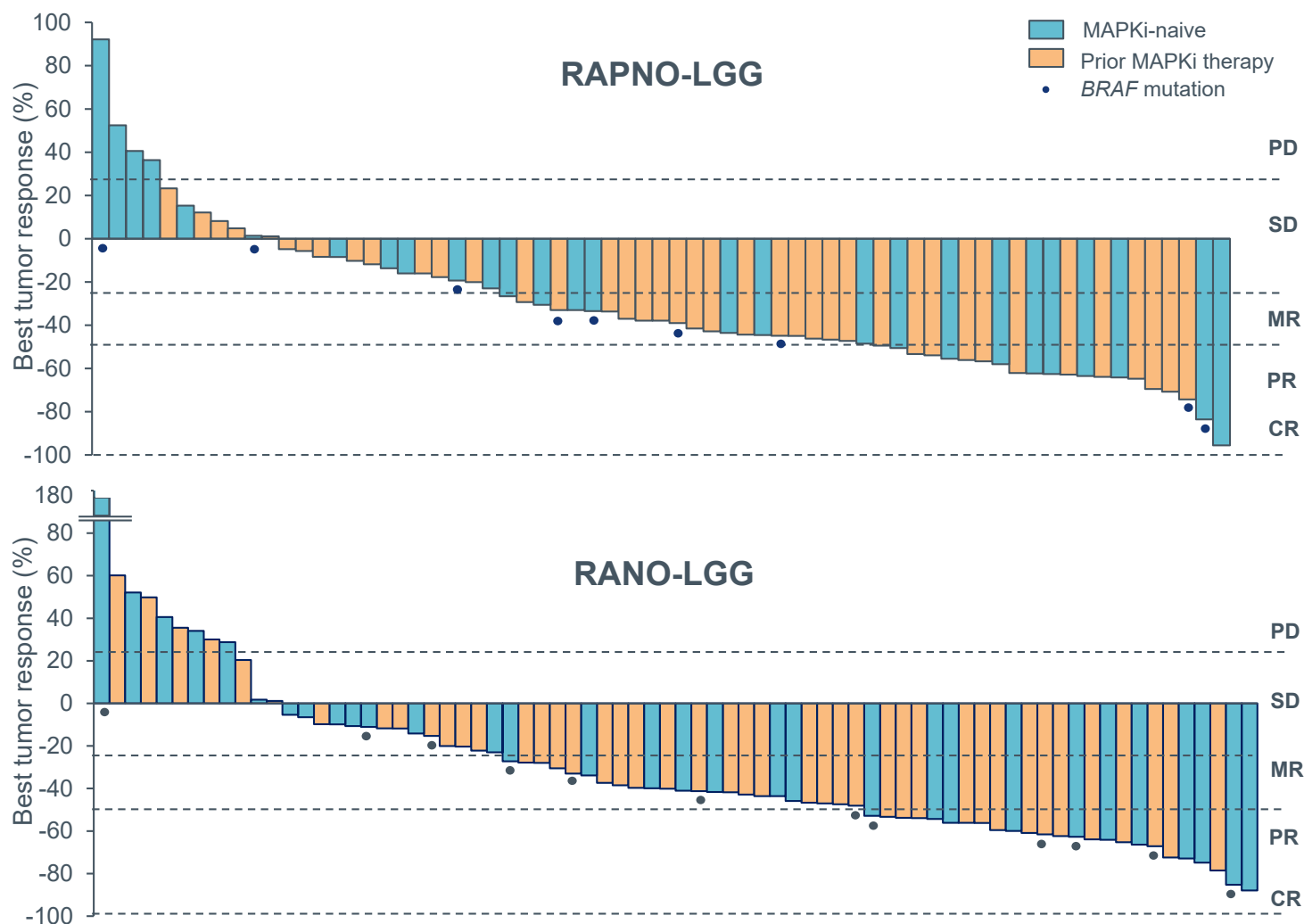
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding.

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



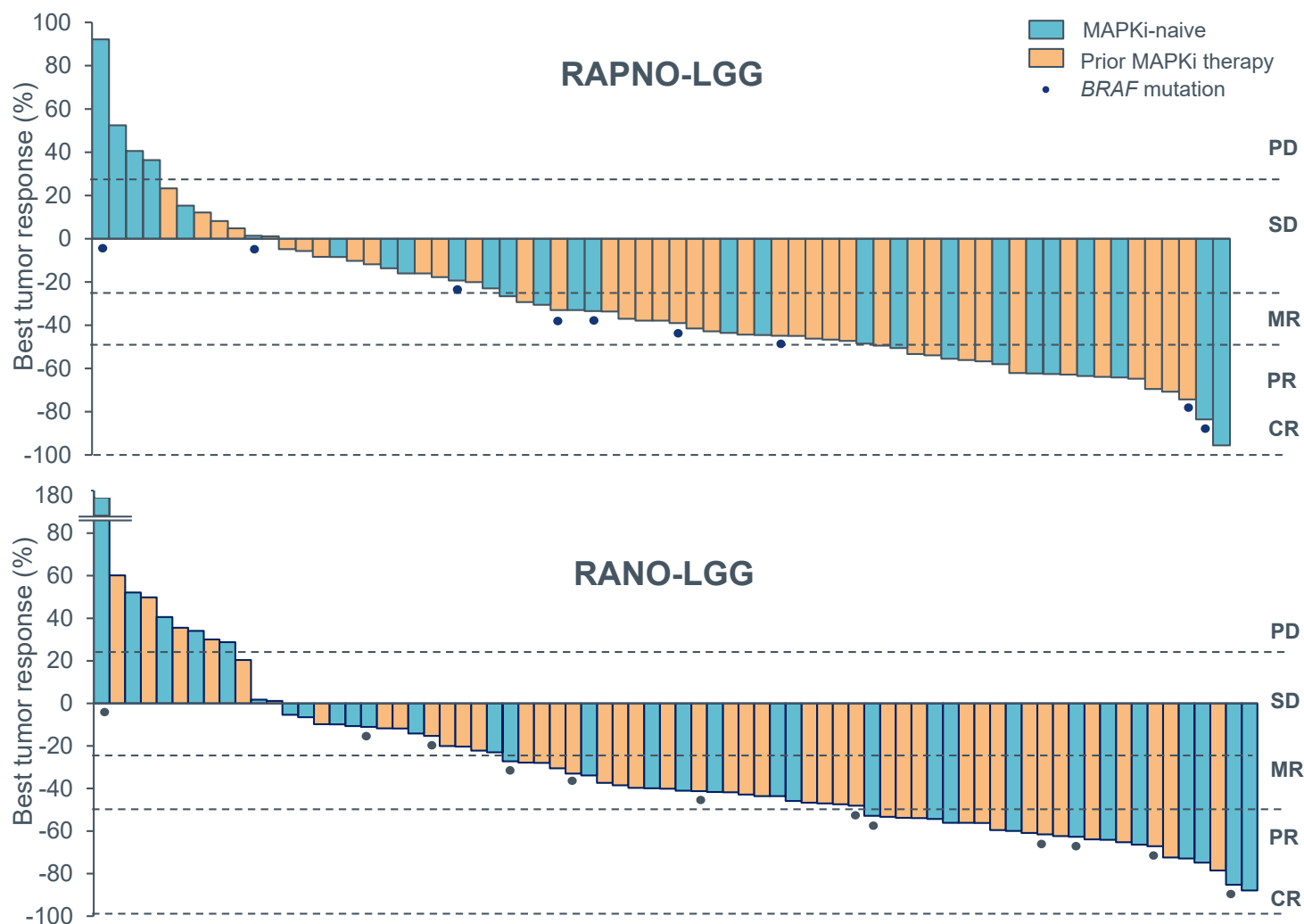
Response (IRC)	RAPNO-LGG ^{1,*} n=69	RANO-LGG ² n=76
ORR (cCR + cPR/uPR + cMR/uMR), n (%)	35 (51%)	37 (49%)
Clinical benefit rate, n (%)		
cCR, cPR/uPR, cMR/uMR or SD	60 (87%)	63 (83%)
cCR, cPR/uPR, cMR/uMR or SD ≥12 months	36 (52%)	39 (51%)
Best overall response, n (%)		
CR	0 (0%)	0 (0%)
PR	17 (25%)	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



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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%)

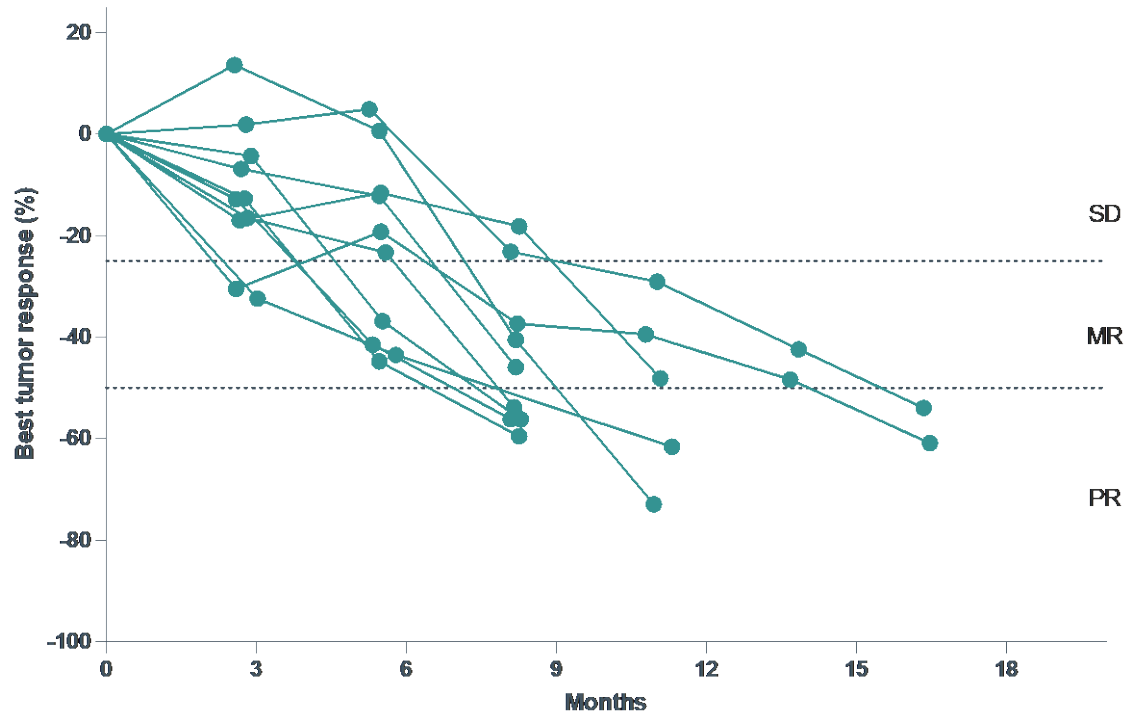
Dec 22, 2022 data cutoff. Percents may not add to 100% due to rounding. Two patients are not shown in the waterfall plots; One patient passed away due to PD (not tovorafenib-related) before first assessment and one patient with missing T1 Gd+ imaging at BL was deemed NE. [#]4/4 uPR and 3/4 uMR per RAPNO-LGG 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.

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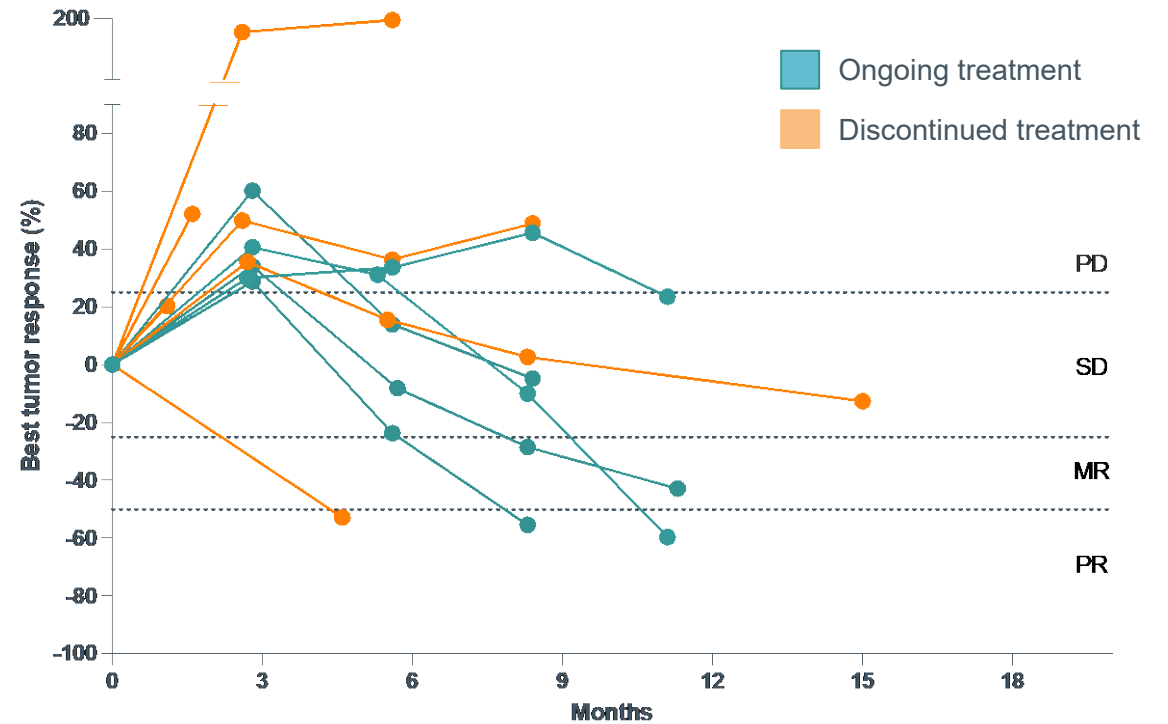
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Tumor kinetics in patients uMR, uPR or PD (RANO-LGG)

Patients with uMR or uPR (n=10)*



Patients with best response of PD (n=11)

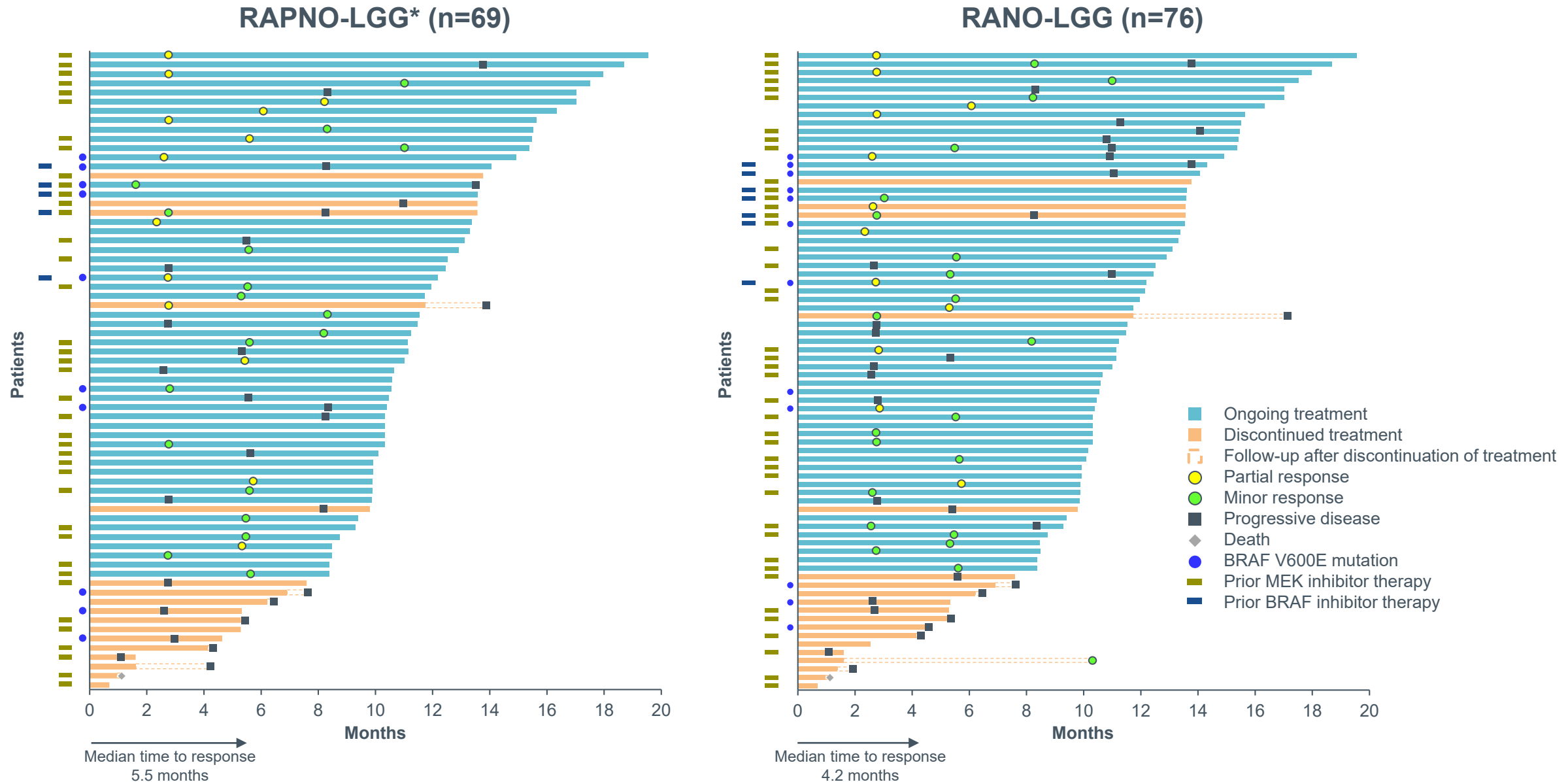


Dec 22, 2022 data cutoff

*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)

Preferred term, n (%)	Treatment-emergent AEs		Treatment-related AEs	
	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.

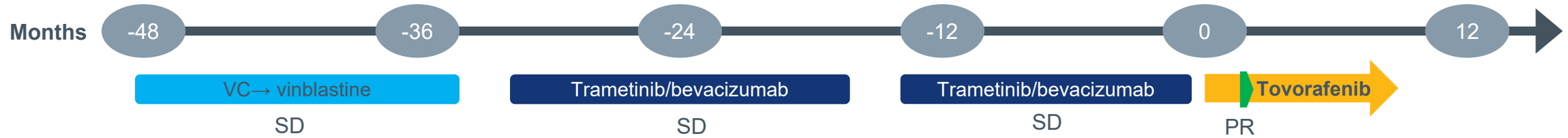
Rash erythematous treatment-emergent: any grade, 14 (10%); grade ≥3 1 (1%); treatment-related: any grade, 14 (10%), grade ≥3 1 (1%).

*One patient had 2 events (shunt malfunction [not related to tovorafenib] and tumor hemorrhage [related to tovorafenib]).

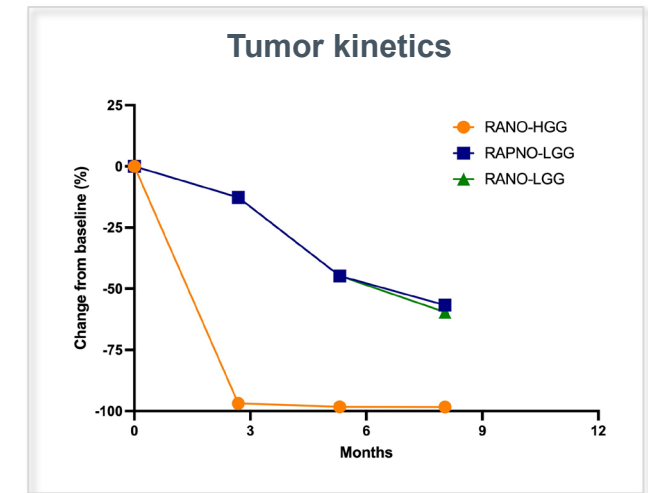
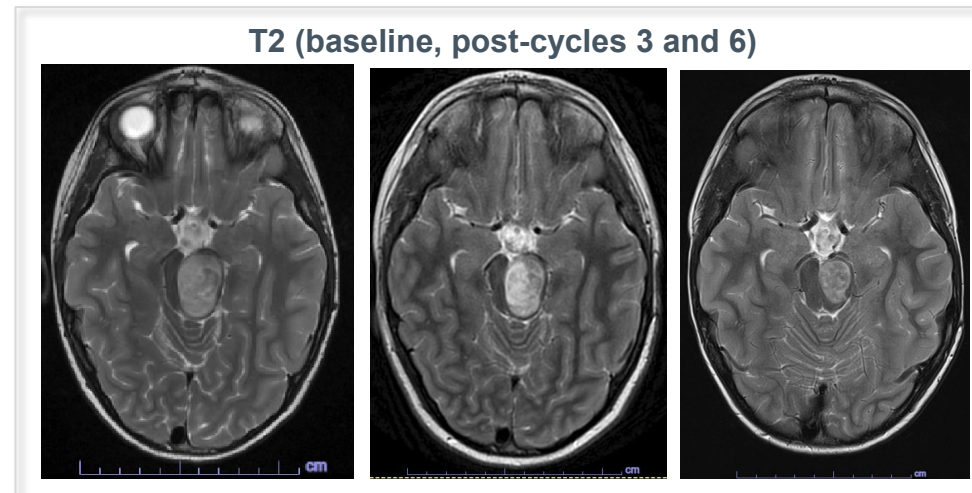
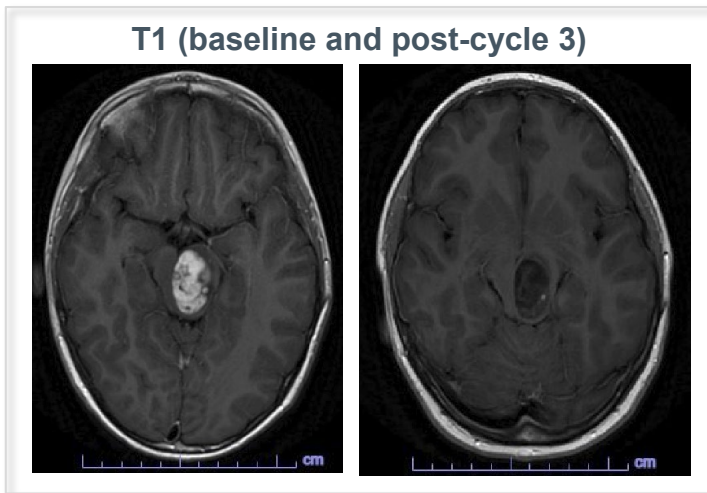
AEs, adverse events; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

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



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

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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