Clinical activity and safety of the RAF inhibitor tovorafenib in patients with optic pathway gliomas in the registrational pediatric low-grade glioma arm of the phase 2 FIREFLY-1 (PNOC026) study

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Pediatric low-grade gliomas in the optic-pathway/hypothalamic region can irreversibly affect and threaten visual and/or endocrine functions

- **~30% of brain tumors are pLGGs; a third of pLGGs are OPGs, most of which are pilocytic astrocytomas[1,2]**

- **OPGs can be sporadic and present throughout childhood, or occur in association with 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 pilocytic astrocytomas[4-7]
    - *BRAF* alterations enable 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 activation of the MAPK pathway observed with type I BRAF inhibitors[10]
  - Available as tablets and a pediatric-friendly oral suspension
  - Once-weekly dosing

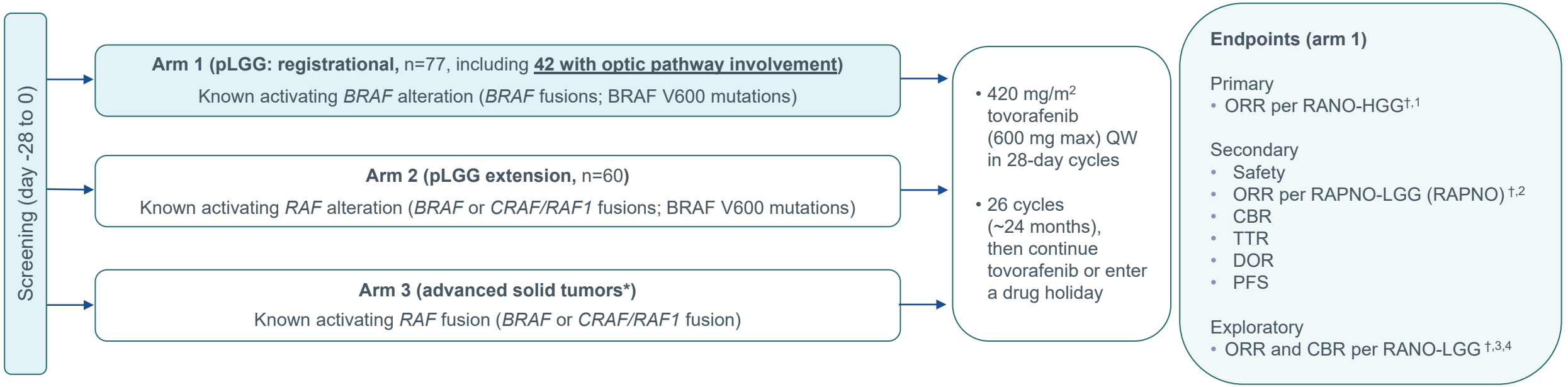
MAPK, mitogen-activated protein kinases; NF1, Neurofibromatosis 1; OPG, optic pathway glioma; pLGG, pediatric low-grade glioma.

1. Ostrom QT, et al. *Neuro Oncol*. 2015;16(Suppl 10):x1–x36. 2. Samples DC, et al. *Front Surg.* 2022;9:884250. 3. Packer RJ, et al. *Neuro Oncol*. 2020; 22(6):773–784. 4. Chen Y-H, Gutmann DH. *Oncogene*. 2014;33(16):2019-2026. 5. Packer RJ et al. *Neuro Oncol.* 2017;19(6)750-761. 6. Ryall S, et al. *Cancer Cell*. 2020;37(4):569-583. 7. Ryall S, Tabori U, Hawkins C *Acta Neuropathol Commun.* 2020;8(1):30. 8. Davies H. et al*, Nature*. 2002;417(6892):949-954. 9. Yaegar R and Cochran RB. *Cancer Discov*. 2019;9(3):329-341. 10. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774-785.

CNS, central nervous system; MAPK, mitogen-activated protein kinase; NF1, neurofibromatosis type 1; OPG, optic pathway glioma; pLGG, pediatric low-grade glioma.

FIREFLY-1: phase 2 study of tovorafenib monotherapy in relapsed/refractory pLGG

- 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
- **Neurofibromatosis type 1 (NF1) is an exclusion criteria**



- Arms 1 and 2: **fully accrued**
  - Arm 1: **efficacy analysis**
  - Arms 1 and 2: **safety analysis**
- Arm 3: actively recruiting patients

June 5, 2023 data cutoff. *That has relapsed or progressed or was nonresponsive to available therapies †IRC-assessed.

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. 4. Wen PY, et al. J. *Clin Oncol*. 2017;35(21),2439-2449.

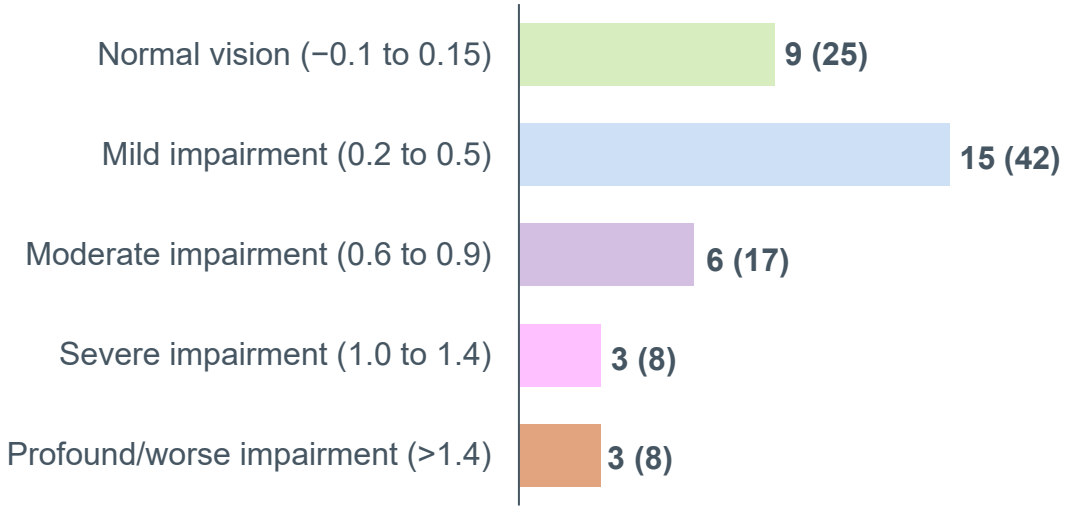
CBR, clinical benefit rate; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; MAPK, mitogen-activated protein kinase; ORR, overall response rate; PFS, progression-free survival; pLGG, pediatric low-grade glioma; QW, once weekly; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; TTR, time to response.

Baseline characteristics: pLGG with optic pathway involvement

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 MEK inhibitor	28 (67)
Prior BRAF inhibitor	3 (7)
Prior BRAF and MEK inhibitors*	2 (5)
Any MAPK inhibitor	29 (69)

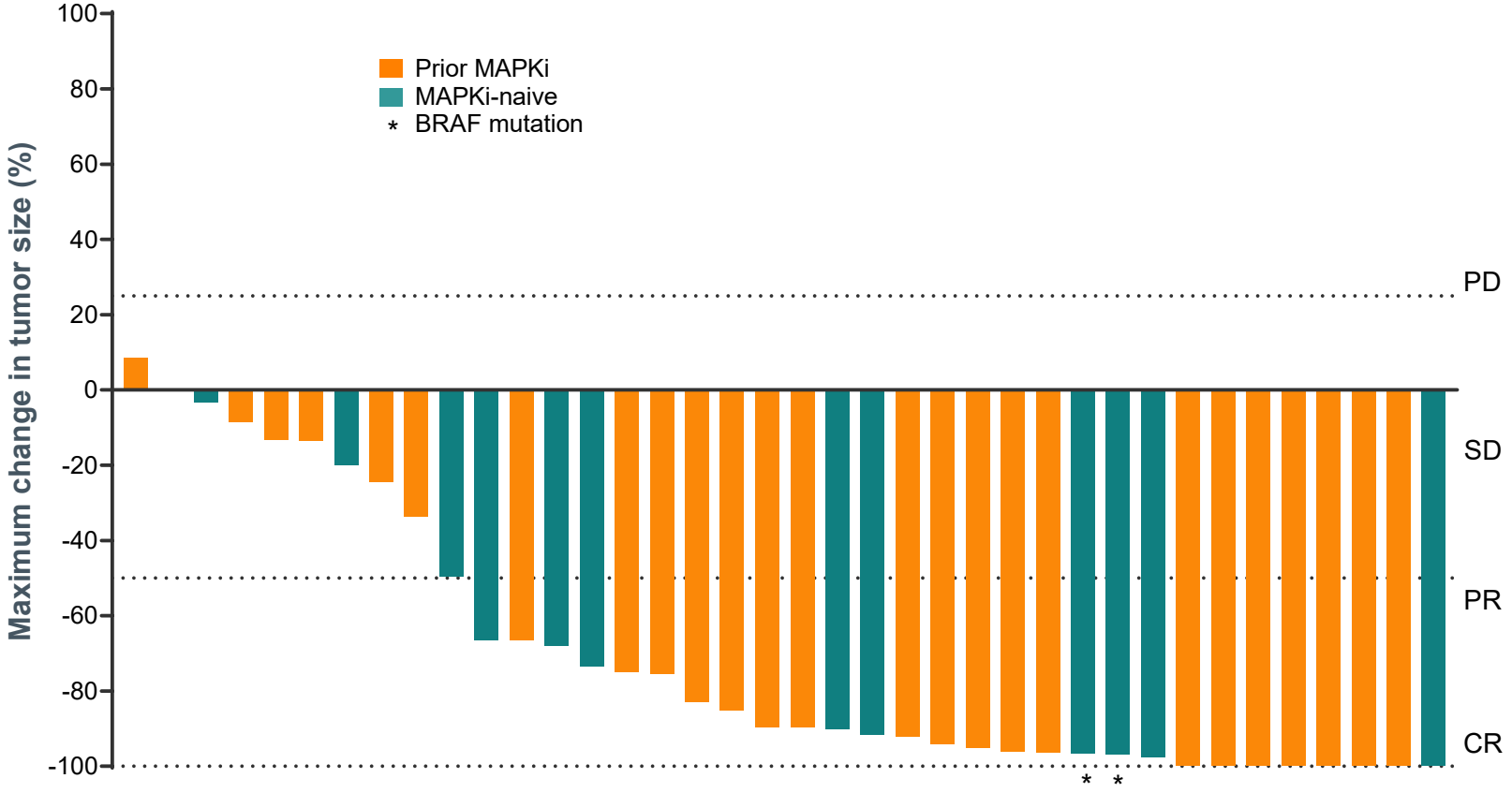
Characteristic (cont.)	Arm 1 OPG subgroup (n=42)
BRAF alteration status, n (%)	
BRAF V600E mutation	5 (12)
KIAA1549::*BRAF* fusion	34 (81)
Other†	3 (7)

Baseline vision, best eye (logMAR range) (n=36)‡, n (%)



June 5, 2023 data cutoff. LogMAR ranges adapted from Schultz-Bonsel K, et al. *Invest Ophthalmol Vis Sci*. 2006;47(3):1236-1240 and Gnekow AK, et al. *Glioma Klin Padiatr*. 2019;231(3):107-135.
*The 2 patients that had previously received both a MEK inhibitor and also a BRAF inhibitor are recorded in both the "Prior MEK inhibitor" and "Prior BRAF inhibitor" groups. †Includes those with a *BRAF* rearrangement per fluorescence in situ hybridization or in situ hybridization. ‡Six patients are not included in the analysis; 4 had no visual acuity assessments done, 1 had no baseline assessment and 1 had no follow-up assessment after baseline
logMAR, logarithm of the minimum angle of resolution; MAPK, mitogen-activated protein kinase: OPG, optic pathway glioma.

Antitumor activity per RANO-HGG: OPG subgroup analysis



Response (IRC)	RANO-HGG[1]	
	N	
ORR, n (%)	**39**	**25 (64)**
95% CI		47–79
CBR, n (%)		
SD of any length of time		**37 (95)**
SD ≥12 months		**31 (79)**
BOR, n (%)		
CR		7 (18)
PR		18 (46)
SD		12 (31)
SD <12 months		6 (15)
SD ≥12 months		6 (15)
PD		2 (5)
Median DOR, months (95% CI)*	**25**	**16.8 (9.0–NR)**
Median TTR, months (range)	**25**	**5.5 (2.6–16.6)**

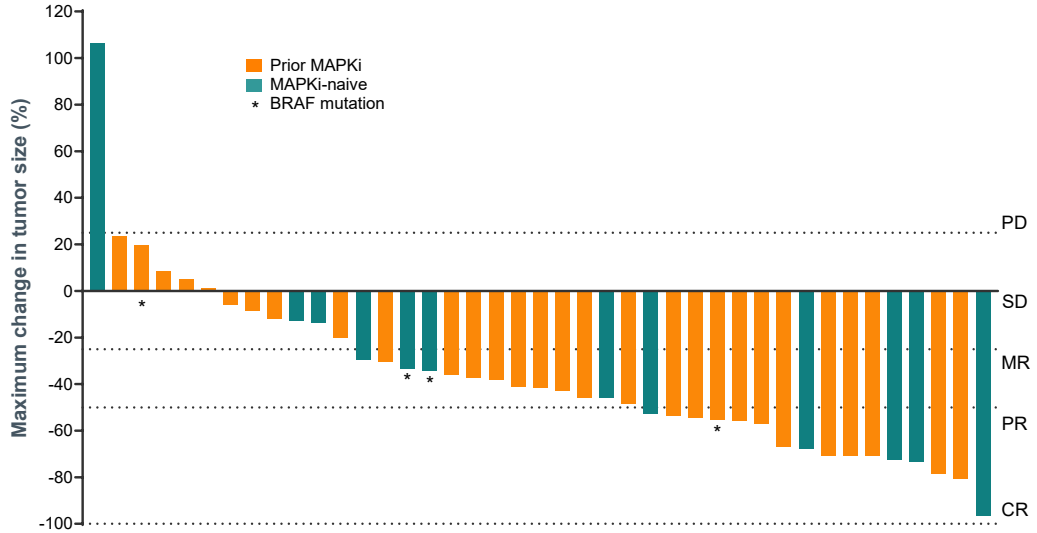
June 5, 2023 data cutoff. There were no patients deemed NE. *Kaplan Meier estimate with the corresponding log-log transformed 95% CI.

1. Wen PY, et al. *J Clin Oncol.* 2010;28(11):1963-1972.

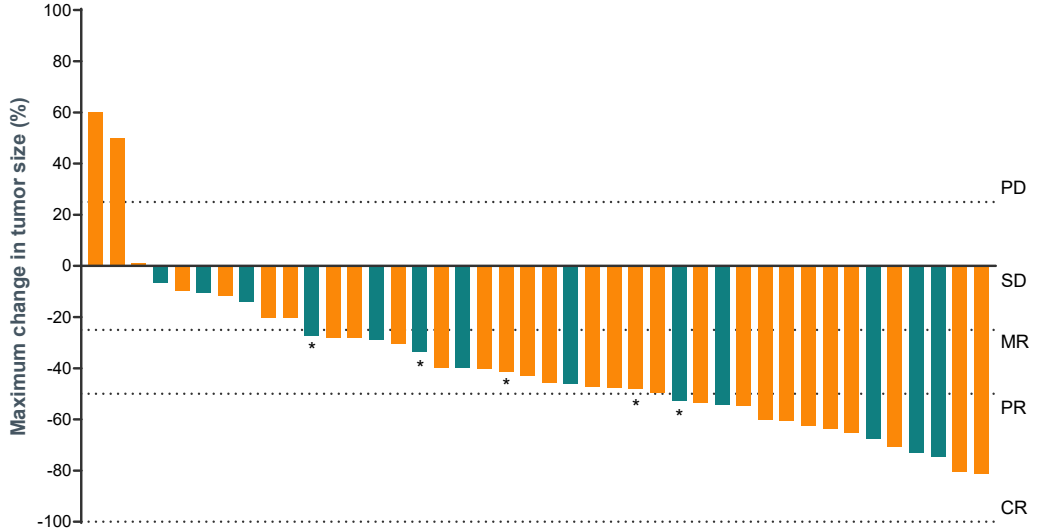
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; NE, not evaluable; NR, not reached; OPG, optic pathway glioma; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; TTR, time to response.

Antitumor activity per RAPNO and RANO-LGG: OPG subgroup analysis

RAPNO



RANO-LGG



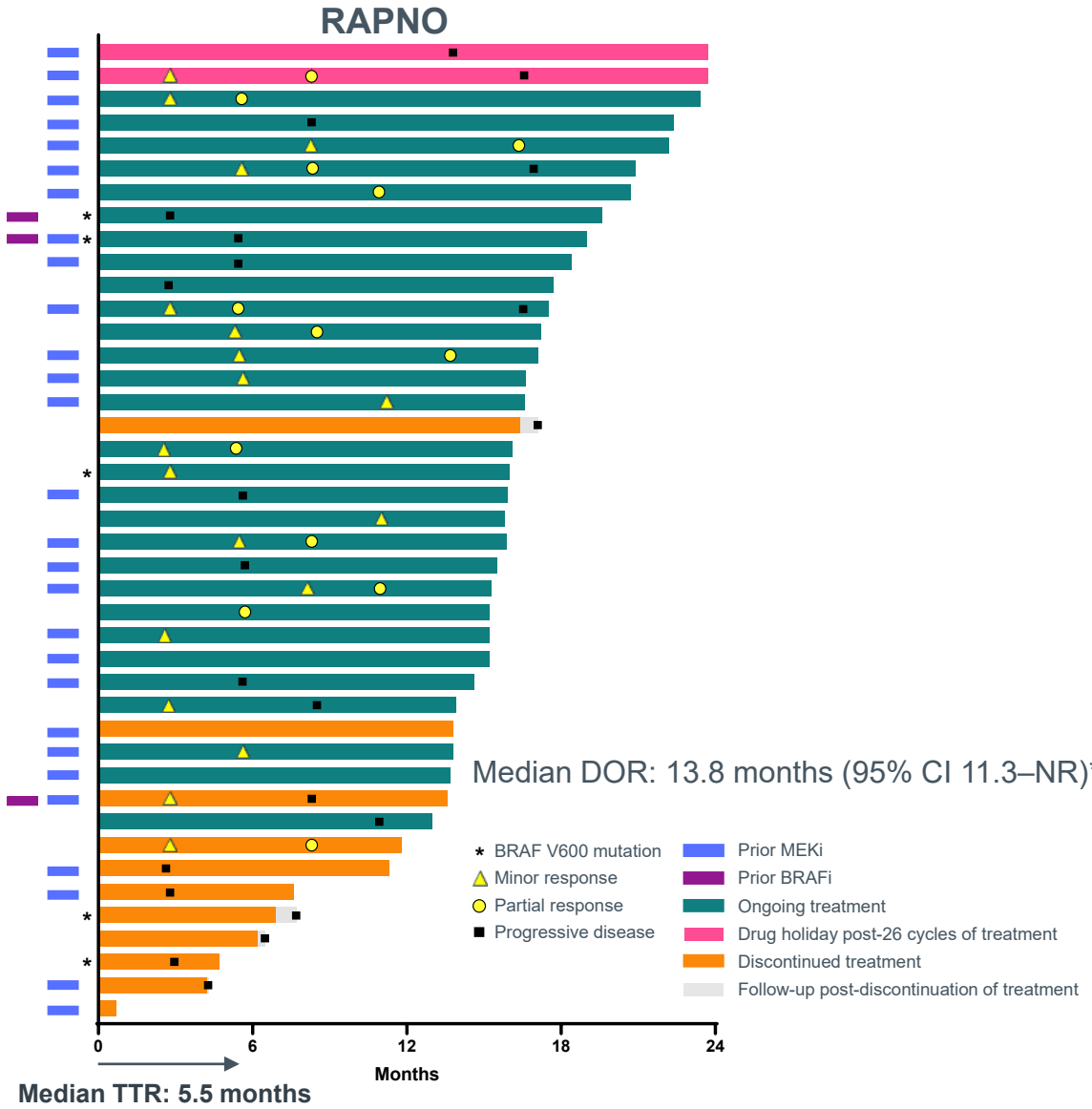
Response (IRC)	RAPNO[1]		RANO-LGG[2,3]	
	N		N	
ORR,* n (%)	**42**	**21 (50)**	**42**	**23 (55)**
95% CI		34–66		39–70
CBR,* n (%)				
SD of any length of time		**37 (88)**		**38 (90)**
SD ≥12 months		**25 (60)**		**28 (67)**
BOR,* n (%)				
CR		0		0
PR		12 (29)		8 (19)
MR		9 (21)		15 (36)
SD		16 (38)		15 (36)
SD <12 months		12 (29)		10 (24)
SD ≥12 months		4 (10)		5 (12)
PD†		5 (12)		3 (7)
Not evaluable		0		1 (2)

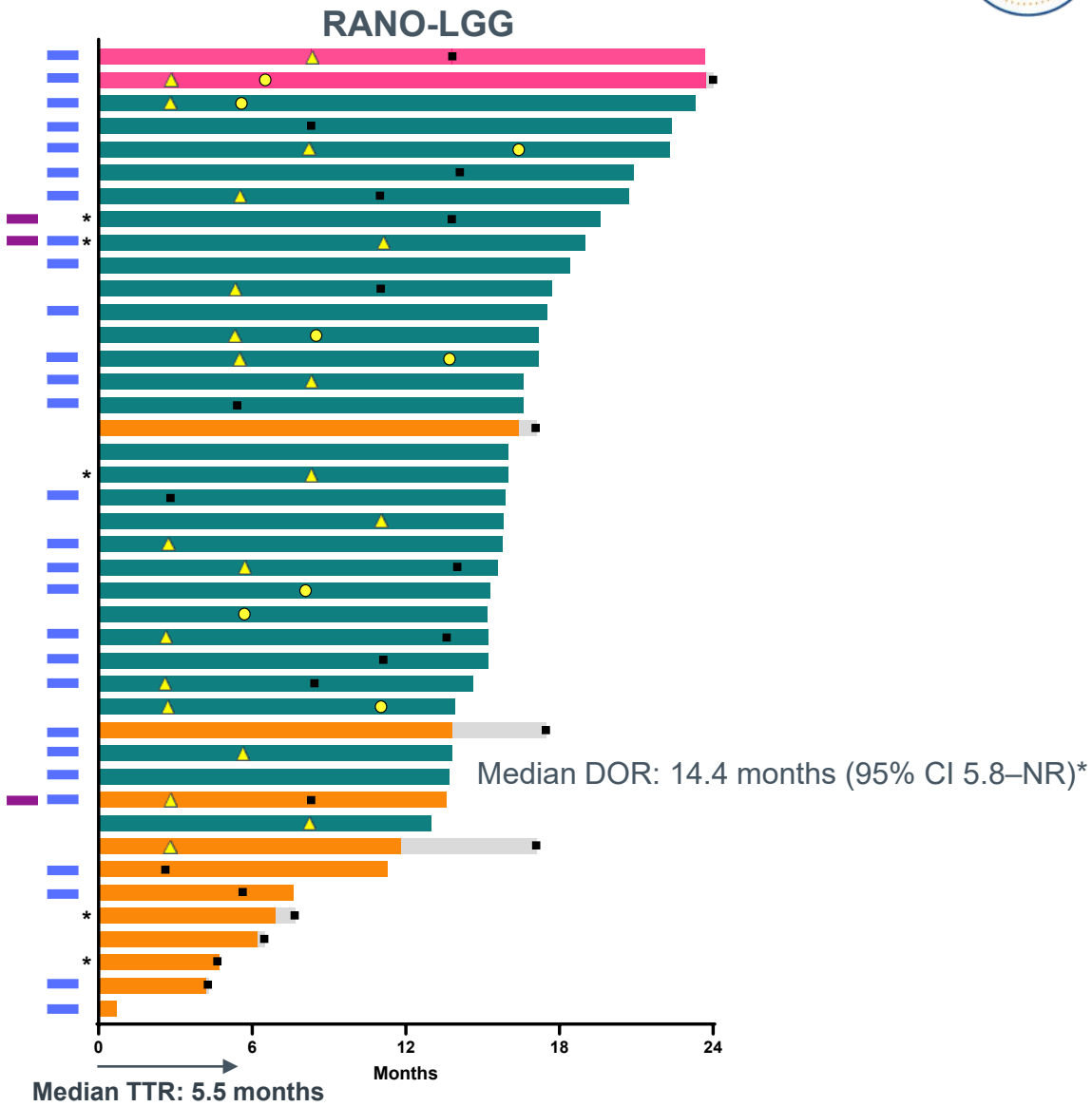
June 5, 2023 data cutoff. Percentages may not add to 100% due to rounding. *ORR, CBR, and BOR for RAPNO and RANO-LGG included MRs (ie, ORR=CR+PR+MR; CBR=CR+PR+MR+SD [calculated based on SD of any length and SD ≥12 months]). †PD per RAPNO and RANO-LGG were not used to determine treatment discontinuation; patients could continue treatment if there was no PD based on RANO-HGG per investigator's assessment.

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. 3. Wen PY, et al. *J. Clin Oncol.* 2017;35(21),2439-2449.

BOR, best overall response; CBR, clinical benefit rate; 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; OPG, optic pathway glioma; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology Response Assessment in Pediatric Neuro-Oncology; SD, stable disease.

Duration of therapy and response per RAPNO and RANO-LGG: OPG subgroup

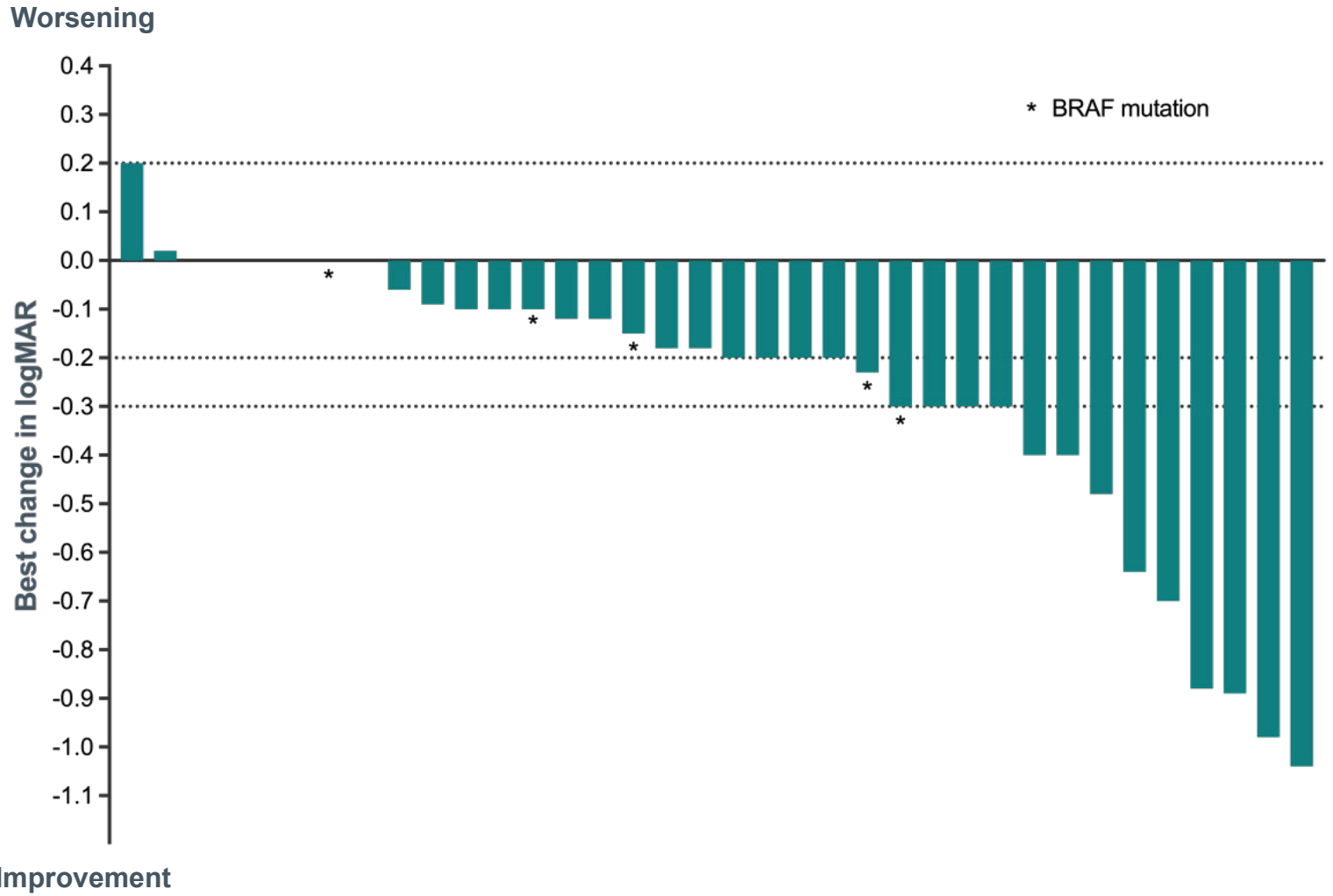




In patients with confirmed response, symbols indicate the start of response (MR or PR). If initial responses improved with continued treatment (from MR to confirmed PR), both the timepoint of the initial response and the timepoint that the response initially improved are marked accordingly. *Kaplan Meier estimate with the corresponding log-log transformed 95% CIs.

BRAFi, BRAF inhibitor; CI, confidence interval; DOR, duration of response; LGG, low-grade glioma; MEKi, MEK inhibitor; MR, minor response; NR, not reached; PR, partial response; OPG, optic pathway glioma; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; TTR, time to response.

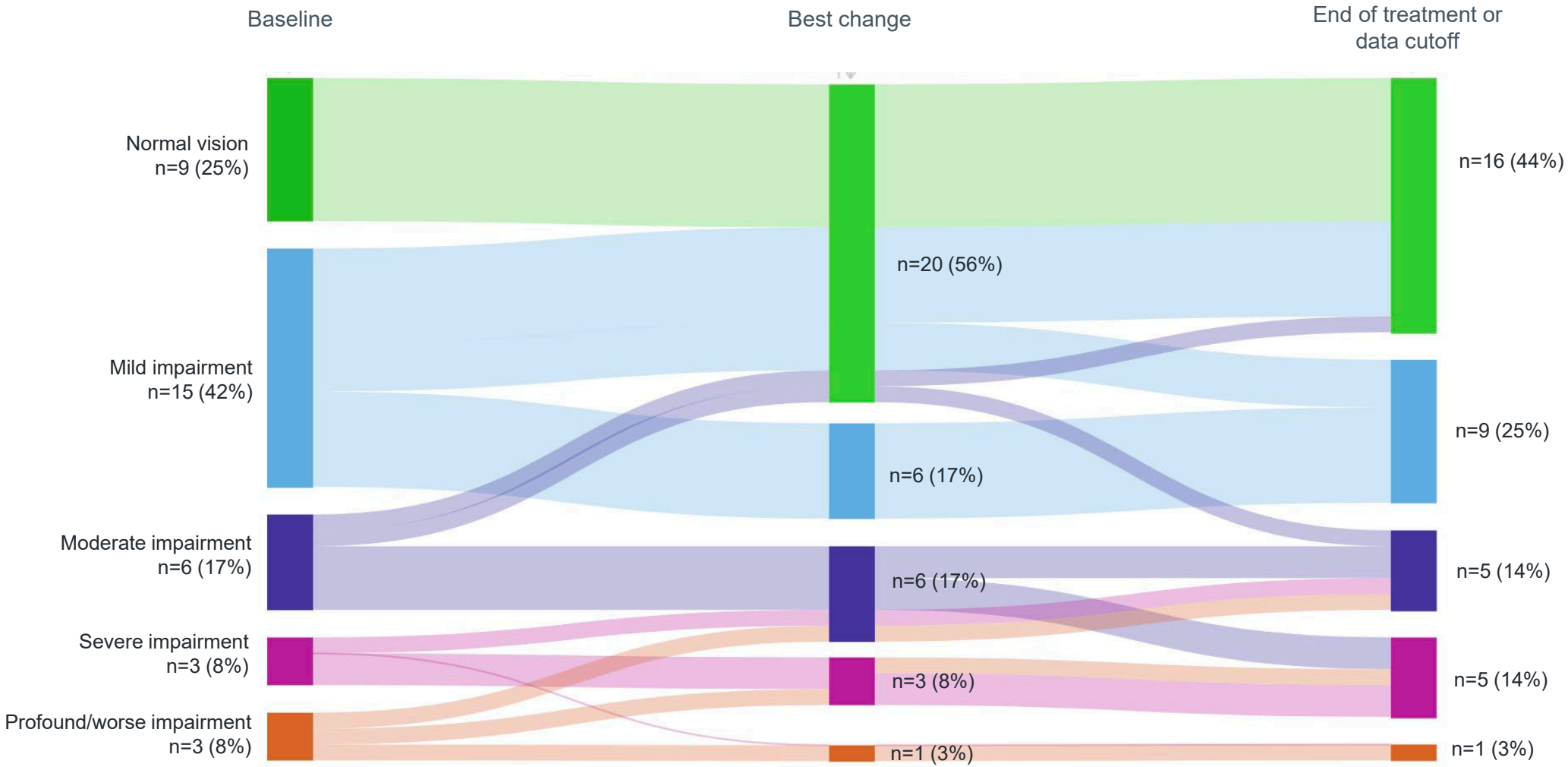
Best change in visual acuity in best eye: OPG subgroup analysis (n=36*)



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

Percents may not add up to 100 due to rounding.
*Six patients are not included in the analysis; 4 had no visual acuity assessments done due to bilateral blindness, 1 had no baseline assessment, and 1 discontinued treatment and had no follow-up assessment after baseline.
logMAR, logarithm of the minimum angle of resolution; OPG, optic pathway glioma.

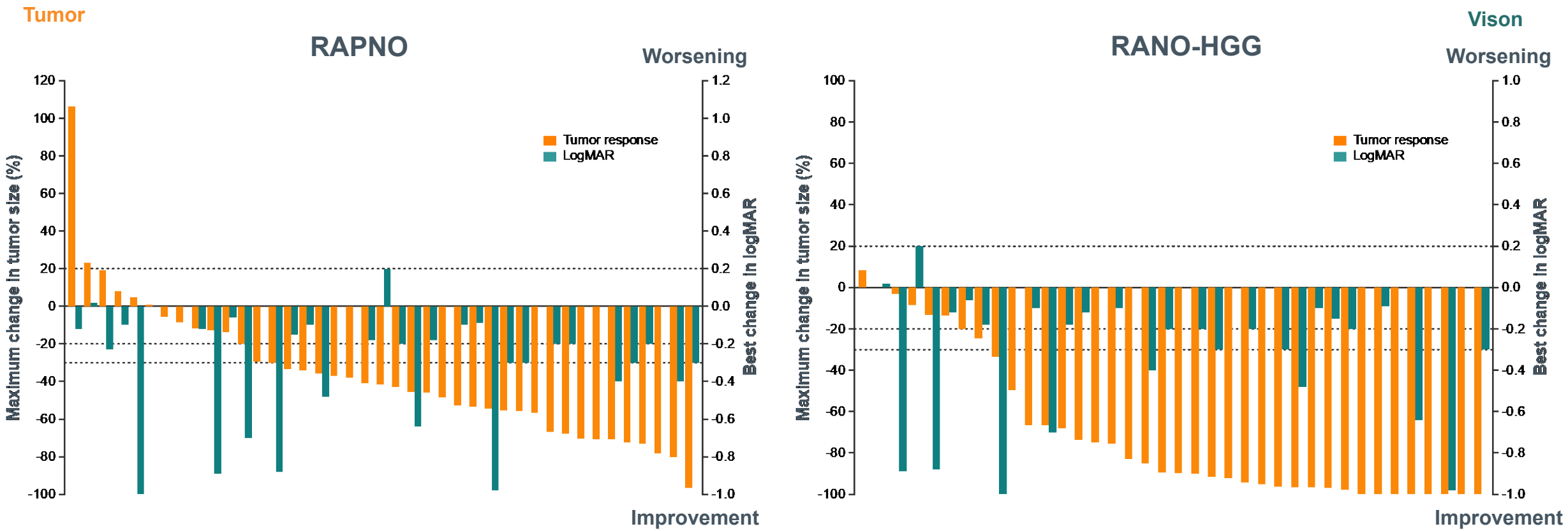
Change in visual acuity on study in best eye: OPG subgroup analysis (n=36*)



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

Percents may not add up to 100 due to rounding.
*Six patients are not included in the analysis; 4 had no visual acuity assessments done due to bilateral blindness, 1 had no baseline assessment, and 1 discontinued treatment and had no follow-up assessment after baseline.
OPG, optic pathway glioma.

Neuro-radiological correlation with visual acuity: OPG subgroup analysis



- Stable or improved visual acuity observed even with small decreases in tumor size regardless of imaging modality

HGG, high-grade glioma; LGG, low-grade glioma; logMAR, logarithm of the minimum angle of resolution; OPG, optic pathway glioma; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology-low-grade glioma.

Safety (treatment-emergent AEs ≥25% any grade in arms 1 & 2 [n=137])

	TEAEs		TRAEs	
Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	137 (100)	86 (63)	134 (98)	58 (42)
Hair color changes	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

- **9 patients (7%) had TRAEs leading to discontinuation**
  - The most common were tumor hemorrhage (3 patients) and decrease in growth velocity (2 patients)
- **33 patients (24%) had TRAEs leading to dose reduction; 50 patients (37%) had TRAEs leading to dose interruption**

June 5, 2023 data cutoff.

AE, adverse event; 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.

Summary and Conclusions: OPG subgroup analysis

- Clinically meaningful and rapid tumor responses seen on T2/FLAIR sequences in this important subgroup
- The median duration of tovorafenib treatment in the OPG subgroup analysis was 16 months, with 69% (29/42) still on treatment at data cut off
- Vision remained stable or improved in 89% of evaluable patients per visual acuity of 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 or 2

Response (IRC)	RANO-HGG	RAPNO	RANO-LGG
OPG subgroup analysis			
ORR	64%	50%	55%
Patients with SD at any length of time	31%	38%	36%
CBR (SD of any length of time)	95%	88%	90%
Median DOR	16.8 mo	13.8 mo	14.4 mo
Median TTR	5.5 mo	5.5 mo	5.5 mo

Phase 3 LOGGIC/FIREFLY-2 in front-line pLGG is enrolling globally; first patient dosed in March 2023

June 5, 2023 data cutoff.
CBR, clinical benefit rate; DOR, duration of response; FLAIR, fluid-attenuated inversion recovery; IRC, independent radiology review committee; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; mo, months; NR, not reached; ORR, overall response rate; pLGG, pediatric low-grade glioma; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology, SD, stable disease; TRAEs, treatment-related adverse events; TTR, time to response.

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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