Clinical activity of RAF inhibitor tovorafenib according to prior MAPK inhibitor treatment in the registrational low-grade glioma arm of the phase 2 FIREFLY-1 (PNOC026) study

Dong-Anh Khuong-Quang,[1] Karsten Nysom,[2] Daniel B. Landi,[3] David S. Ziegler,[4-6] Pablo Hernáiz Driever,[7] Sarah E. S. Leary,[8] Simon Bailey,[9] Jasper van der Lugt,[10] Sébastien Perreault,[11] Angela J. Waanders,[12] Patricia A. Baxter,[13] Olaf Witt,[14-18] Darren Hargrave,[19] Geoffrey McCowage,[20] Jordan R. Hansford,[21,22] Helen Toledano,[23] Liat Oren,[24] Enrica E. K. Tan,[25] Nicolas U. Gerber,[26] Hyoung Jin Kang,[27] Valérie Larouche,[28] Mohamed S. Abdelbaki,[29] Izzy Cornelio,[30] Yeonhee Kim,[30] Ashley Walter,[30] Peter Manley,[30] Lindsay B. Kilburn[31]

[1]Children's Cancer Centre, The Royal Children's Hospital Melbourne, Melbourne, Victoria, Australia; [2]Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [3]Duke University, Durham, NC, USA; [4]Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia; [5]Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, NSW, Australia; [6]School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia; [7]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; [8]Cancer and Blood Disorders Center, Seattle Children's, Seattle, WA, USA; [9]Great North Children's Hospital and Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK; [10]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; [11]CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada; [12]Ann & Robert H Lurie Children's Hospital, Chicago, IL, USA; [13]Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [14]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany; [15]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [16]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany; [17]German Cancer Consortium (DKTK), Heidelberg, Germany; [18]National Center for Tumor Diseases (NCT), Heidelberg, Germany; [19]UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, 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; South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia; [23]Department of Pediatric Oncology, Schneider Children's Medical Center, Petach Tikva, and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [24]Department of Hematology & Oncology, Rambam Healthcare Campus, Haifa, Israel; [25]Haematology/Oncology Service, KK Women's and Children's Hospital, Singapore; [26]Department of Oncology, University Children's Hospital, Zurich, Switzerland; [27]Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Cancer Research Institute, Seoul National University Children's Hospital, Seoul, Republic of Korea; [28]Department of Pediatrics, Centre Mère-Enfant Soleil du CHU de Québec-Université Laval, Quebec City, Quebec, Canada; [29]Division of Hematology and Oncology, Department of Pediatrics, School of Medicine, Washington University, St. Louis, MO, USA; [30]Day One Biopharmaceuticals, Brisbane, CA, USA; [31]Children's National Hospital, Washington, DC, USA

28th Annual Meeting and Education Day of the Society for Neuro-Oncology, November 16–19, 2023, Vancouver, Canada

Disclosures

- Contracted research
  - Day One Biopharmaceuticals

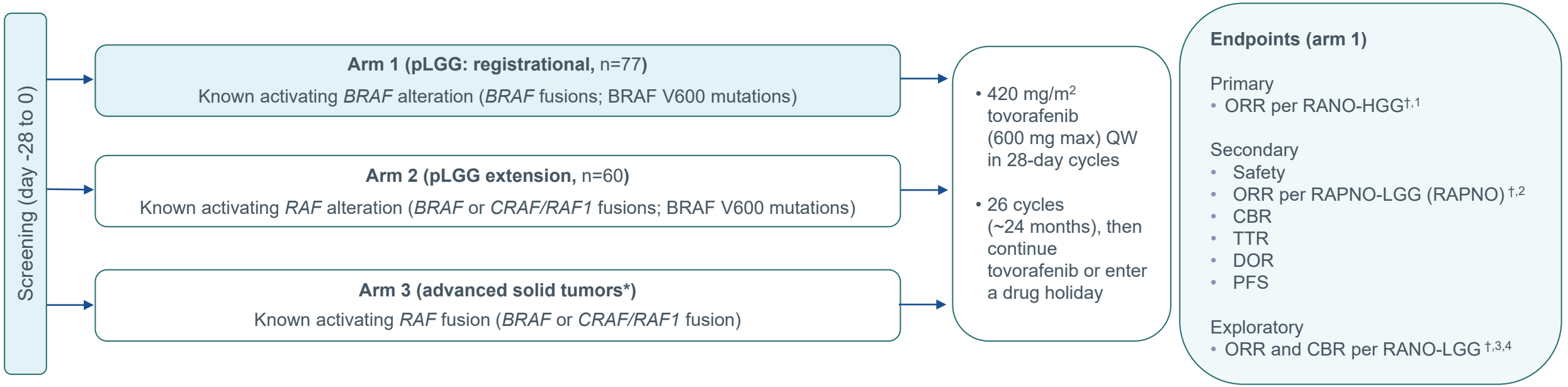
Patients with pediatric low-grade glioma often require multiple lines of therapy

- **At ~30%, pLGGs are the most common pediatric brain tumor[1]**
- **70% of pLGGs are driven primarily by *BRAF* alterations**
  - *KIAA1549*::*BRAF* fusions are the most common genomic alterations in pLGG and occur in ~80% of pilocytic astrocytomas[2-5]
  - *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]
- **~60% of patients with pLGG are not cured by resection and have chronic, progressive disease often requiring multiple and multimodal treatment regimens[8,9]**
  - Each adjuvant therapy increases risk of long-term sequelae such as cognitive deficits, blindness, hearing loss, hormonal disturbance, obesity, etc[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

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 and Cochran RB. *Cancer Discov.* 2019;9(3):329-341. 8. Lim YJ. *Brain Tumor Res Treat.* 2022;10(4):221-225.
9. Goebel A-M, et al. *J Cance*r. 2019;10(25):6314–6326. 10. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774-785.
CNS, central nervous system; MAPK, mitogen-activated protein kinase; pLGG, pediatric low-grade glioma.

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

- Patients 6 months–25 years of age, 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: **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.

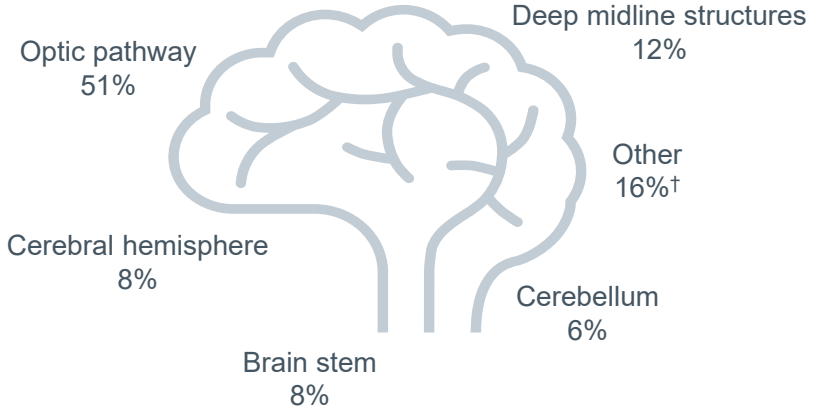
1. Wen PY, et al. *J Clin Oncol*. 2010;28(11):1963-1972. 2. Fangusaro J, et al. *Lancet Oncol*. 2020;21(6):e305–316. 3. van den Bent MJ, et al. *Lancet Oncol*. 2011;12(6):583-593. 4. Wen PY, et al. J. *Clin Oncol*. 2017;35(21),2439-2449.

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.

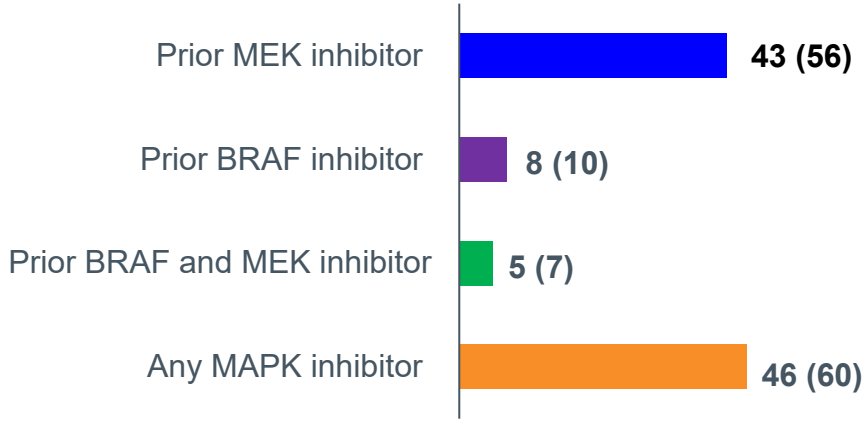
Patient and baseline characteristics

Characteristic	Arm 1 (n=77)
Median age, years (range)	8 (2–21)
Gender, n (%)	
Male	40 (52)
Female	37 (48)
Race, n (%)	
White	41 (53)
Asian	5 (6)
Black	2 (3)
Multiple	3 (4)
Other	6 (8)
Not specified	20 (26)
Ethnicity, n (%)	
Hispanic or Latino	3 (4)
Not Hispanic or Latino	51 (66)
Not stated	21 (27)
Missing	2 (3)
Number of prior lines of systemic therapy	
Median (range)	3 (1–9)
1, n (%)	17 (22)
2, n (%)	21 (27)
≥3, n (%)	39 (51)
BRAF alteration status, n (%)	
BRAF fusion	64 (83)
KIAA1549::BRAF fusion	56 (73)
Other	8* (10)
BRAF V600E mutation	13 (17)

Location (n=77)

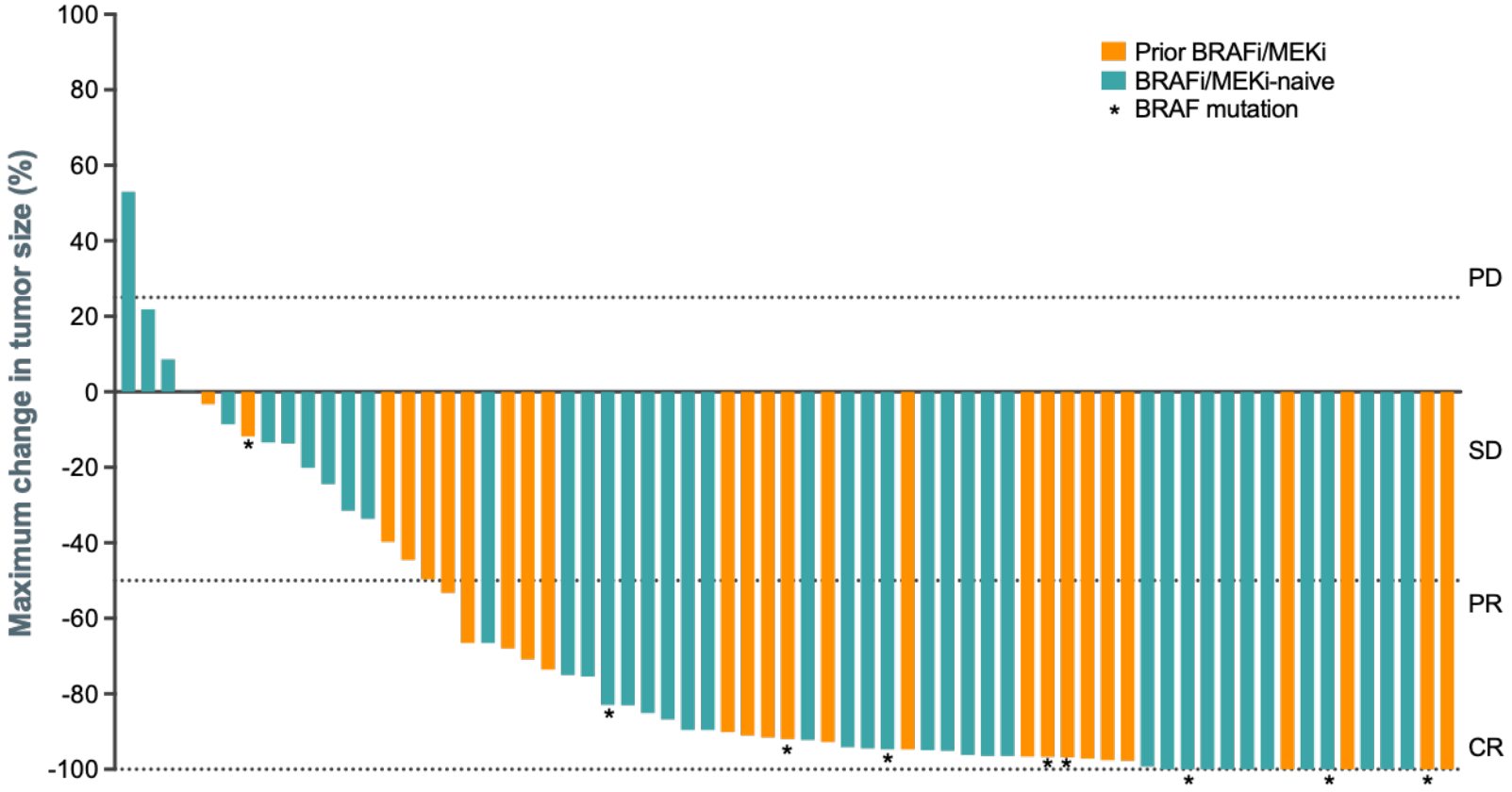


Prior MAPK pathway targeted therapy, n (%)‡



June 5, 2023 data cutoff.
*Includes 6 patients with *BRAF* duplication and 2 with *BRAF* rearrangement per fluorescence in situ hybridization or in situ hybridization. †Includes tumors that were extending into multiple regions of the brain, leptomeningeal disease, and/or spinal disease.
‡The 5 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.
MAPK, mitogen-activated protein kinase.

Antitumor activity per RANO-HGG



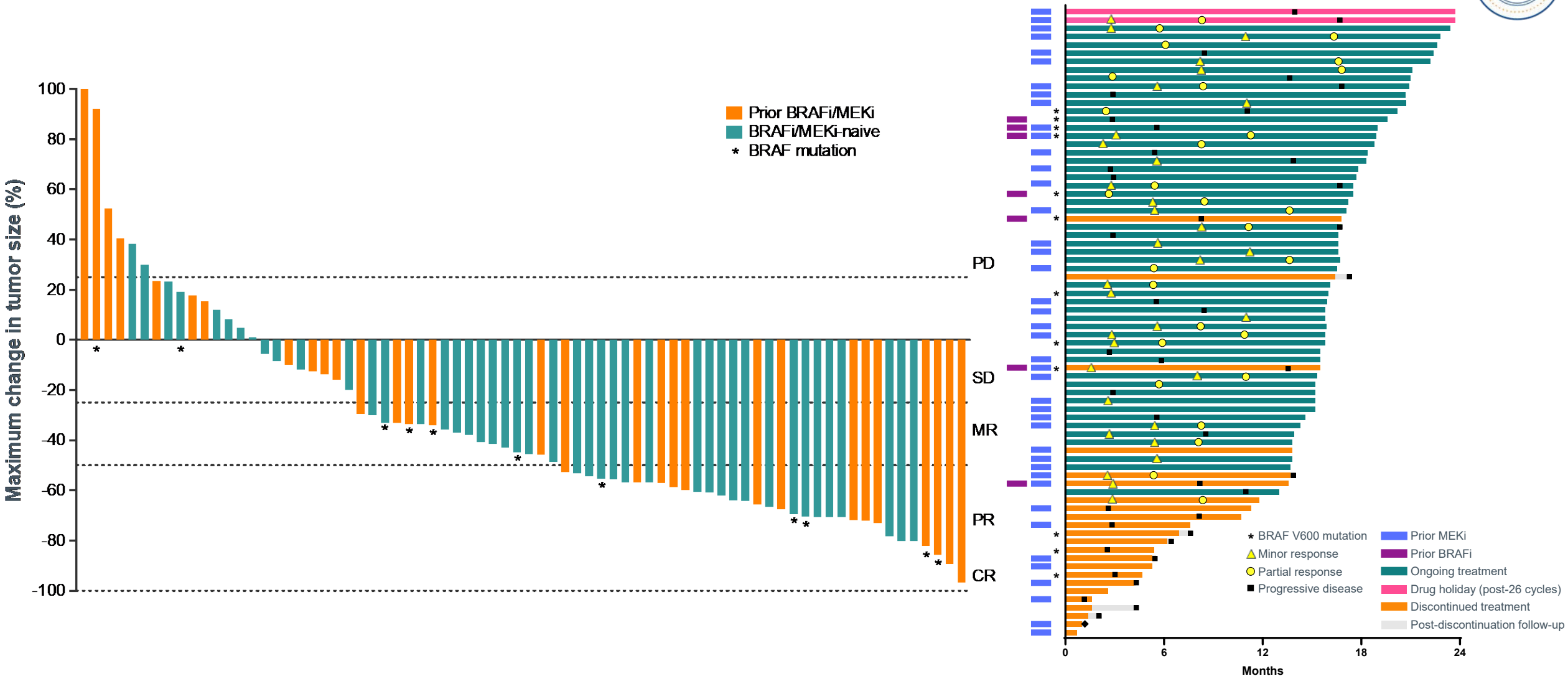
Response (IRC)	RANO-HGG[1]	
	n	
ORR, (primary endpoint), n (%)	**69**	**46 (67)***
Prior MAPKi	41	29 (71)
MAPKi-naïve	28	17 (61)
CBR, n (%) (SD of any length of time)	**69**	**64 (93)**
Prior MAPKi	41	37 (90)
MAPKi-naïve	28	27 (96)
CBR, n (%) (SD ≥12 months)	**69**	**54 (78)**
Prior MAPKi	41	33 (80)
MAPKi-naïve	28	21 (75)
BOR, n (%)	**69**	
CR		12 (17)
PR		34 (49)
SD		18 (26)
SD <12 months		10 (14)
SD ≥12 months		8 (12)
PD		4 (6)
Not evaluable		1 (1)
Median DOR, months (95% CI)†	**46**	**16.6 (11.6–NR)**
Prior MAPKi	29	15.1 (9.0–16.8)
MAPKi-naive	17	NR (11,6–NR)
Median TTR, months (range)	**46**	**3.0 (2.6–16.6)**
Prior MAPKi	29	2.8 (2.6–16.6)
MAPKi-naive	17	5.3 (2.6–11.1)

June 5, 2023 data cutoff. Percentages 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. Fangusaro J, et al. *Lancet Oncol.* 2020;21(6):e305–316. 2. Bouffet E, et al. *J Clin Oncol.* 2012;30(12):1358-1363.

BOR, best overall response; CBR, clinical benefit rate, CI, confidence interval; CR, complete response; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; MAPKi, mitogen-activated protein kinase inhibitor; NR, not reached; 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 and duration of therapy per RAPNO



June 5, 2023 data cutoff. Percentages 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 imaging at post-BL was deemed NE.

MAPKi, mitogen-activated protein kinase inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

Antitumor activity per RAPNO and RANO-LGG

Response (IRC)	RAPNO[1]		RANO-LGG[2,3]	
	n		n	
ORR,* n (%)	**76**	**39 (51)**	**76**	**40 (53)**
Prior MAPKi	45	22 (49)	45	23 (51)
MAPKi-naïve	31	17 (55)	31	17 (55)
CBR,* n (%) (SD of any length of time)	**76**	**62 (82)**	**76**	**63 (83)**
Prior MAPKi	45	38 (84)	45	38 (84)
MAPKi-naive	31	24 (77)	31	25 (81)
CBR,* n (%) (SD ≥12 months)	**76**	**43 (57)**	**76**	**46 (61)**
Prior MAPKi	45	25 (56)	45	26 (58)
MAPKi-naive	31	18 (58)	31	20 (65)
BOR,* n (%)	**76**		**76**	
CR		0		0
PR		28 (37)		20 (26)
MR		11 (14)		20 (26)
SD		23 (30)		23 (30)
SD <12 months		19 (25)		17 (22)
SD ≥12 months		4 (5)		6 (8)
PD†		13 (17)		11 (14)
Not evaluable		1 (1)		2 (3)
Median DOR, months (95% CI)‡	**39**	**13.8 (11.3–NR)**	**40**	**14.4 (11.0–NR)**
Prior MAPKi	22	13.8 (11.3–NR)	23	12.0 (8.5–NR)
MAPKi-naïve	17	NR (8.4–NR)	17	16.3 (8.4–NR)
Median TTR, months (range)	**39**	**5.3 (1.6–11.2)**	40	**5.5 (1.6–11.3)**
Prior MAPKi	22	5.4 (1.6–11.2)	23	5.5 (1.6–11.3)
MAPKi-naïve	17	5.3 (2.3–11.0)	17	5.3 (2.3–11.0)

June 5, 2023 data cutoff. *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. ‡The exact 95% CIs were calculated using Clopper-Pearson method.

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, CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent radiology review committee; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; MR, minor response; NE, not evaluable; NR, not reached; 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; TTR, time to response.

Response to tovorafenib in patients who progressed on a MAPKi*

Assessment criteria, Evaluable patients	Radiographic progression while on a prior MAPKi		ORR in patients previously-treated with a MAPKi	
	Any line of therapy n (%)	Most recent treatment n (%)	Any line of therapy n (%)	Most recent treatment n (%)
RANO-HGG n=69	25 (36)	19 (28)	17 (68)	14 (74)
RAPNO* n=76	28 (37)	22 (29)	16 (57)	13 (59)
RANO-LGG* n=76	28 (37)	22 (29)	14 (50)	11 (50)

*RAPNO-LGG and RANO-LGG response assessments include MR.
HGG, high-grade glioma; LGG, low-grade glioma; MAPKi, mitogen-activated protein kinase inhibitor; ORR, overall response rate; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology.

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

- Clinically meaningful and rapid tumor responses seen on both T1-Gd+ and T2/FLAIR sequences
- Median duration of tovorafenib treatment in arm 1 was 15.8 months, with 66% (51/77) still on treatment at data cutoff
- 1 in 3 patients progressed while on treatment with a MAPKi; more than half responded to tovorafenib
- Encouraging safety and tolerability profile with only 7% (n=9) of patients having TRAEs leading to tovorafenib discontinuation; most TRAEs were grade 1 or 2

Response (IRC)	RAPNO	RANO-LGG
Arm 1 overall		
ORR	51%	53%
Patients with SD of any length of time	30%	30%
CBR (SD of any length of time)	82%	83%
Median DOR	13.8 mo	14.4 mo
Median TTR	5.3 mo	5.5 mo
Prior MAPKi		
ORR	49%	51%
Patients with SD at any length of time	36%	33%
CBR (SD of any length of time)	84%	84%
Median DOR	13.8 mo	12.0 mo
Median TTR	5.4 mo	5.5 mo
MAPKi-naive		
ORR	55%	55%
Patients with SD with SD at any length	23%	26%
CBR (SD of any length of time)	77%	81%
Median DOR	NR	16.3 mo
Median TTR	5.3 mo	5.3 mo

Published online this morning in *Nature Medicine*
https://doi.org/10.1038/s41591-023-02668-y

Kilburn LB, et al. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial

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

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

FIREFLY-1 is funded by Day One Biopharmaceuticals