Type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma (pLGG): Reversible decreases in growth velocity in the phase 2 FIREFLY-1 trial

Cassie Kline,[1] Angela J. Waanders,[2] David S. Ziegler,[3-5] Lindsay B. Kilburn,[6] Karsten Nysom,[7] Jasper van der Lugt,[8] Timothy E. Hassall,[9] Nicolas U. Gerber,[10] Devorah Segal,[11] Valérie Larouche,[12] Dong-Anh Khuong-Quang,[13] Jordan R. Hansford,[14,15] Sarah E. S. Leary,[16] Pablo Hernáiz Driever,[17] Simon Bailey,[18] Sébastien Perreault,[19] Geoffrey McCowage,[20] Olaf Witt,[21-25] Patricia A. Baxter,[26] Hyoung Jin Kang,[27] Jung Woo Han,[28] Darren Hargrave,[29] Andrea T. Franson,[30] Michal Yalon Oren,[31] Helen Toledano,[32] Mohamed S. Abdelbaki,[33] Nada Jabado,[34] Nicholas G. Gottardo,[35] Nicholas S. Whipple,[36] Susan N. Chi,[37] Liat Oren,[38] Enrica E. K. Tan,[39] Sabine Mueller,[40] Karen D. Wright,[37] Samuel C. Blackman,[41] Jiaheng Qiu,[41] Dolores Podesta,[41] Ashley Walter,[41] Daniel Da Costa,[41] Peter Manley,[41] Lisa McLeod,[41] Daniel B. Landi,[42]

[1]Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [2]Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA; [3]Kids Cancer Centre, Sydney Children's Hospital, Randwick, New South Wales, Australia; [4]Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, New South Wales, Australia; [5]School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia; [6]Children's National Hospital, Washington, DC, USA; [7]Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [8]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; [9]Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, Australia; [10]Department of Oncology, University Children's Hospital, Zurich, Switzerland; [11]NYU Langone Health, New York, NY, USA; [12]Department of Pediatrics, Centre Mère-Enfant Soleil du CHU de Québec-Université Laval, Quebec City, Quebec, Canada; [13]Children's Cancer Centre, Royal Children's Hospital Melbourne, Melbourne, Victoria, Australia; [14]Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital, Adelaide, South Australia, Australia; [15]South Australia Health and Medical Research Institute, Adelaide, Australia; South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, South Australia, Australia; [16]Cancer and Blood Disorders Center, Seattle Children's, Seattle, WA, USA; [17]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; [18]Great North Children's Hospital and Newcastle University Centre for Cancer, Newcastle-upon-Tyne, UK; [19]Department of Neurosciences, Division of Child Neurology, CHU Sainte-Justine, Université de Montréal, Montréal, Quebec, Canada; [20]Sydney Children's Hospitals Network, Westmead, New South Wales, Australia; [21]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany; [22]Clinical Cooperation Unit, Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [23]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany; [24]German Cancer Consortium (DKTK), Heidelberg, Germany; [25]National Center for Tumor Diseases (NCT), Heidelberg, Germany; [26]Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; [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]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [29]UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; 30C.S. Mott Children's Hospital, University of Michigan Medical School, Ann Arbor, MI, USA; [31]Pediatric Hemato-Oncology, Sheba Medical Center, Ramat Gan, Israel; [32]Department of Pediatric Oncology, Schneider Children's Medical Center, Petach Tikva, and Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [33]The Division of Hematology and Oncology, St. Louis Children's Hospital, Washington University, School of Medicine in St. Louis, Washington University, St. Louis, MO, USA; [34]McGill University Health Centre (MUHC), Montreal Children's Hospital (MCH), Montreal, Quebec, Canada; [35]Department of Pediatric and Adolescent Oncology and Hematology, Perth Children's Hospital, Perth, Australia, and Brain Tumor Research Program, Telethon Kids Cancer Centre, Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia; [36]Primary Children's Hospital and University of Utah, Salt Lake City, UT, USA; [37]Pediatric Neuro-Oncology, Department of Pediatrics, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [38]Department of Hematology & Oncology, Rambam Healthcare Campus, Haifa, Israel; [39]Paediatric Haematology/Oncology Service, KK Women's and Children's Hospital, Singapore, Singapore; [40]Department of Neurology, Neurosurgery and Pediatrics, University of California, San Francisco, San Francisco, CA, USA; [41]Day One Biopharmaceuticals, Brisbane, CA, USA; [42]Duke University, Durham, NC, USA

21st International Symposium on Pediatric Neuro-Oncology (ISPNO 2024), June 28–July 2, 2024, Philadelphia, PA. LGG-40

Disclosures

- Contract for clinical trial/grant support: Chimerix Inc., Curis, Inc., Day One Biopharmaceuticals, Inc., Ipsen, Kazia Therapeutics Limited, Midatech Pharma PLC (completed), Regeneron Pharmaceuticals, Inc.
- Contract for clinical trial/grant support: Bristol Myers Squibb

- FIREFLY-1 is funded by Day One Biopharmaceuticals

Background

- The ongoing, open label, three-arm, phase 2 FIREFLY-1 (PNOC026; NCT04775485) trial is investigating the efficacy (arm 1, n=77), and safety and tolerability (arms 1/2) of tovorafenib (420 mg/m^2 QW; 600 mg maximum) in children, adolescents, and young adults with *BRAF*-altered relapsed/refractory pLGG who have received at least one prior systemic therapy[1]
  - Clinically meaningful tumor responses and a manageable safety profile have been demonstrated[2]
    - Recently granted accelerated approval by the US FDA in patients ≥6 months of age with r/r pLGG with a *BRAF* alteration[3]
  - Reversible decreases in GV have been reported[2]

- Children with CNS tumors are likely to have growth-related conditions at baseline[4-7]
- **Decreased linear growth or other effects on bone health are sometimes observed with pediatric oncology treatments:**

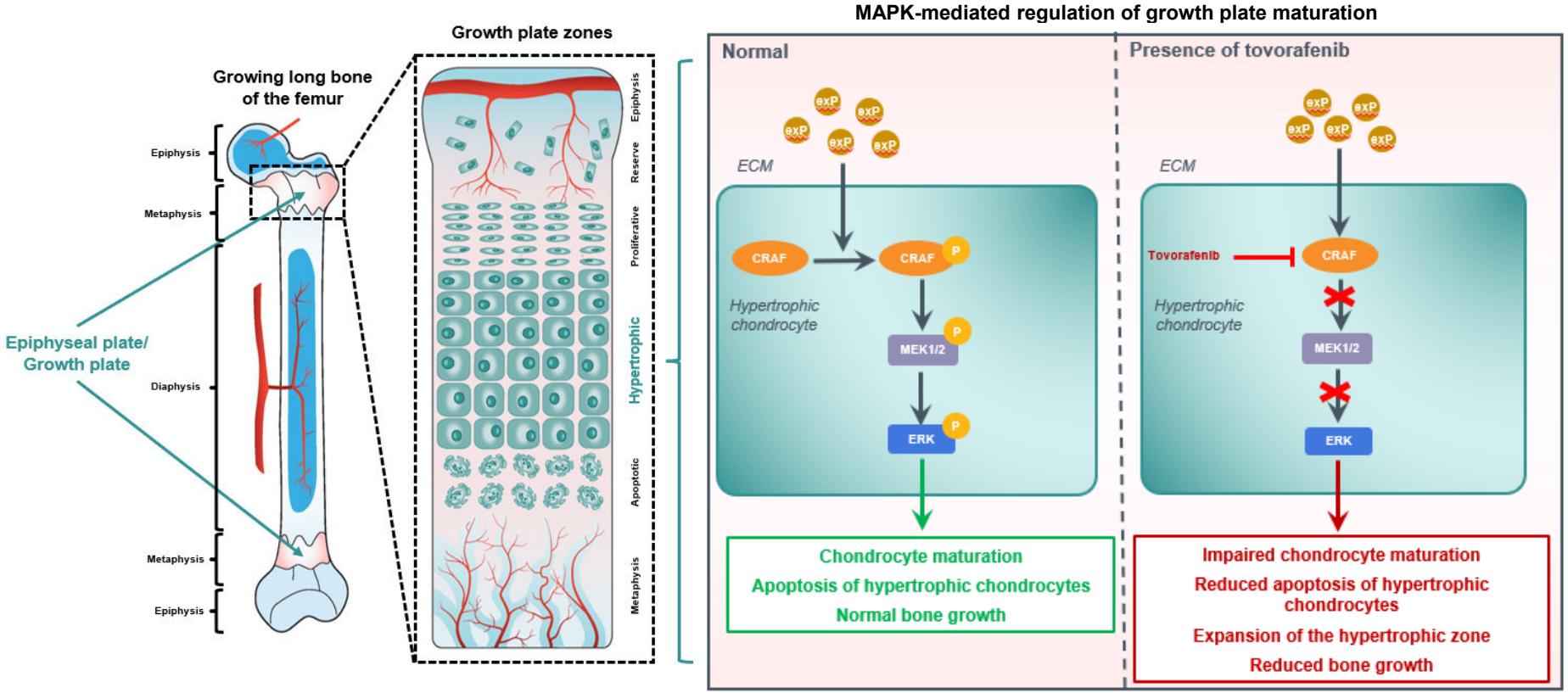
Treatment class	Reported impact on growth
Cranial radiotherapy[8]	GH deficiency, hypothyroidism
Spinal radiotherapy[8]	Vertebral growth plate toxicity
Prolonged steroids[8]	Growth plate damage, decreased endogenous GH release, decreased proliferation of chondrocytes
Retinoids and hedgehog inhibitors[8,9]	Premature fusion of growth plates
TKIs[8] • TRK inhibitors (eg, entrectinib,[10] larotrectinib[11]) • VEGF/VEGFR inhibitors (eg, sunitinib, pazopanib[12]) • MAPK inhibitors (eg, dabrafenib/trametinib[13])	Growing evidence suggests an impact on bone health, mostly while on treatment • Increased risk of fractures • Altered growth velocity

GH, growth hormone; GV, growth velocity; MAPK, mitogen-activated protein kinase; TKIs, tyrosine kinase inhibitors; QW, once weekly.

1. ClinicalTrials.gov website. https://classic.clinicaltrials.gov/ct2/show/NCT04775485. Accessed May 6, 2024. 2. Kilburn LB, et al. *Nat. Med*. 2024;30(1):207–217. 3. US FDA website. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tovorafenib-patients-relapsed-or-refractory-braf-altered-pediatric. Accessed May 14, 2024. 4. Chemaitilly W, et al. *Clin Endocrinol (Oxf)*. 2016;84(3):361–371. 5. Meacham LR, et al. *J Pediatr Endocrinol Metab*. 2004;17(5):711–717. 6. Mostoufi-Moab S, et al. *Pediatr Endocrinol Rev*. 2010;8(1):6. 7. Müller HL, et al. *Pediatr Blood Cancer*. 2019;66(2):e27487. 8. Mostoufi-Moab G. Endocrine Late Effects in Survivors of Childhood Cancer. Oral presentation at: 2024 ASPHO (American Society of Pediatric Hematology/Oncology); April 5, 2024; Seattle, WA. 9. Robinson GW, et al. *Oncotarget*. 2017;8(41):69295–69302. 10. Desai AV, et al. *J Clin Oncol*. 2024:42(16_suppl):10000 & associated presentation. 11. Laetsch TW, et al. *Ann Oncol*. 2021;32(suppl_5):S583-S620. 12. Voss SD, et al. *Pediatr Blood Cancer*. 2015; 62(1):45–51. 13. Caspi S, et al. *Authorea*. October 9, 2020. DOI: 10.22541/au.160225762.21068105/v1 (preprint).

Pharmacologic inhibition of CRAF is hypothesized to cause a reversible decrease in GV[1]

- CRAF is the predominant RAF isoform expressed in hypertrophic chondrocytes[2]
- In GEMMs, chondrocyte-specific CRAF ablation reduced the rate of apoptosis in the hypertrophic chondrocyte layer, and in turn, reduced the rate of new bone formation, indicating that CRAF plays an important role in growth plate maturation[2-4]
- Tovorafenib is a type II RAF inhibitor with potent (IC_{50}=0.7 nM) activity against CRAF, in addition to activity against BRAF[4-7]



ECM, extracellular matrix; exP, extracellular phosphate; GEMM, genetically engineered mouse model. Adapted from Hallett SA, et al. *Int. J. Mol. Sci.* 2019;20(23):6009, Binder G. *Horm Res.* 2009;71(suppl 2):64–70, and Allen DB, et al. *Horm Res Paediatr.* 2021;94:319–332.

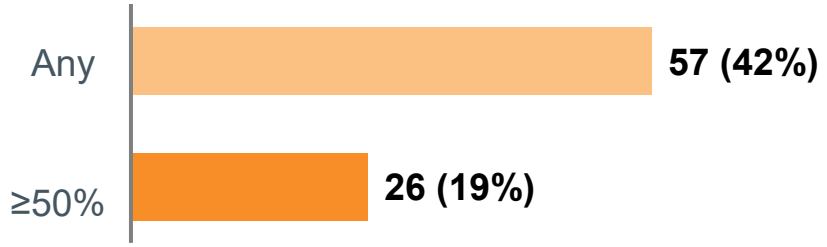
1. Kilburn LB, et al. *Nat. Med.* 2024;30(1):207–217. 2. Liu ES, et al. *Development.* 2016;143(2):348-355. 3. Provot S, et al. *Mol Cell Biol.* 2008;28(1):344–357. 4. Papaioannou G, et al. *J Biol Chem.* 2017;292(8):3164-3171. 5. Sun Y, et al. *Neuro Oncol.* 2017;19(6):774–785. 6. Tkacik E, et al. *J. Biol. Chem.* 2023;299(5):104634. 7. Rasco DW, et al. *Cancer Chemother Pharmacol.* 2023;92(1):15-28.

Patient characteristics and frequency of reported events of decreased GV

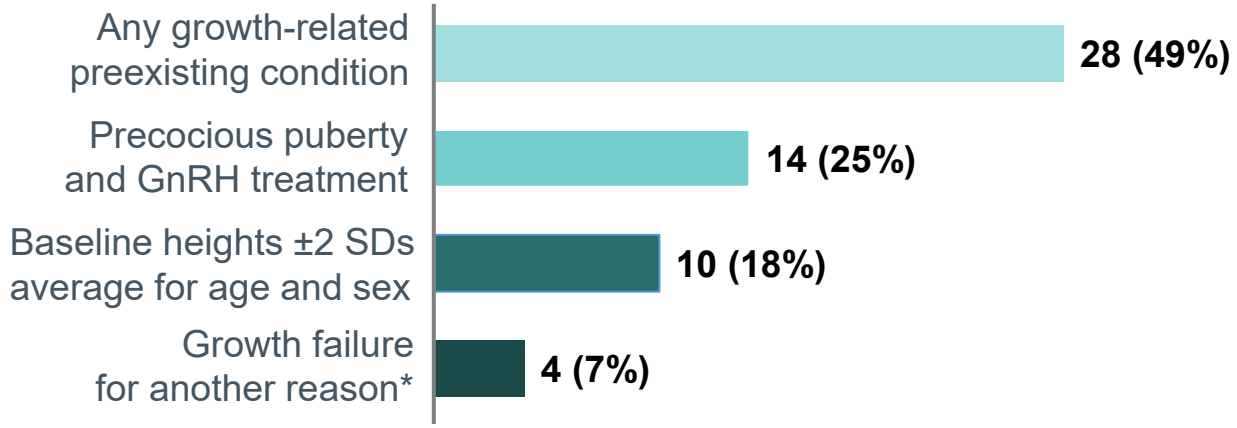
Objective: assess if decreases in GV are transient and reversible based on available patient data on and off tovorafenib

- There have been 69 positively adjudicated cases of decreased GV reported to the tovorafenib GSDB:
  - 57 from FIREFLY-1, 7 from the EAP/CUP, and 5 from 2 IISs

Reported events of decreases in GV from baseline in FIREFLY-1 arms 1 & 2 (n=137)



Growth-related conditions at baseline in patients with reported events of decreased GV (n=57)

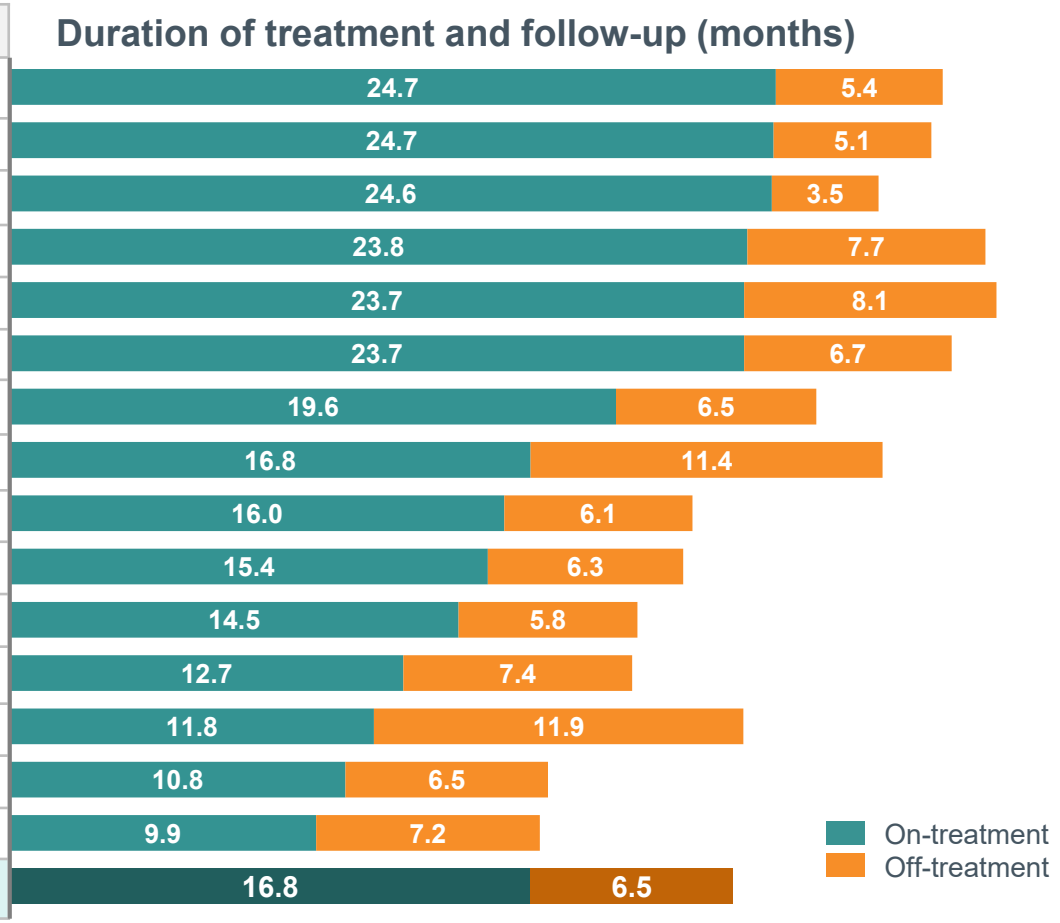


April 19, 2024 data cutoff. *GH deficiency (1 patient). growth failure (2 patients), and growth delay (1 patient). CUP, compassionate use program; EAP, expanded access program; GnRH, Gonadotropin hormone-releasing hormone; GSDB, global safety database; GV, growth velocity, IIS, investigator-initiated studies; SD, standard deviation.

Duration of treatment and follow-up in patients with decreased GV

Among the 57 patients with reported decreased GV, **15 had interrupted or discontinued treatment for ≥3 months and had post-treatment heights provided**, including 2 permanent discontinuations and 3 interruptions due to decreased GV

Age (years)*	Sex	Tumor location	Baseline condition	AGV on-treatment (cm/year)	AGV off-treatment (cm/year)
4	Male	Deep midline	GH deficiency/GF; adv bone age	2.73	8.52
8	Male	Optic pathway		1.25	10.91
4	Male	Cerebral hemisphere		2.51	10.18
3	Male	Deep midline		1.00	10.97
6	Male	Optic pathway		1.99	11.83
8	Female	Posterior fossa		1.54	9.54
12	Female	4th ventricle		0.50	2.05
9	Female	Deep midline	PP	0.82	8.05
12	Male	Optic pathway		0.91	13.50
5	Male	Optic pathway		0.77	6.88
12	Male	Cerebral hemisphere	Height >2 SD	0.00	11.69
10	Female	Optic pathway	Tanner stage 4 at study entry	1.03	4.40
9	Female	Optic pathway	PP, adv bone age	2.02	4.84
7	Male	Deep midline		0.22	7.38
3	Female	Deep midline		1.43	8.51
Median				**1.03**	**8.52**

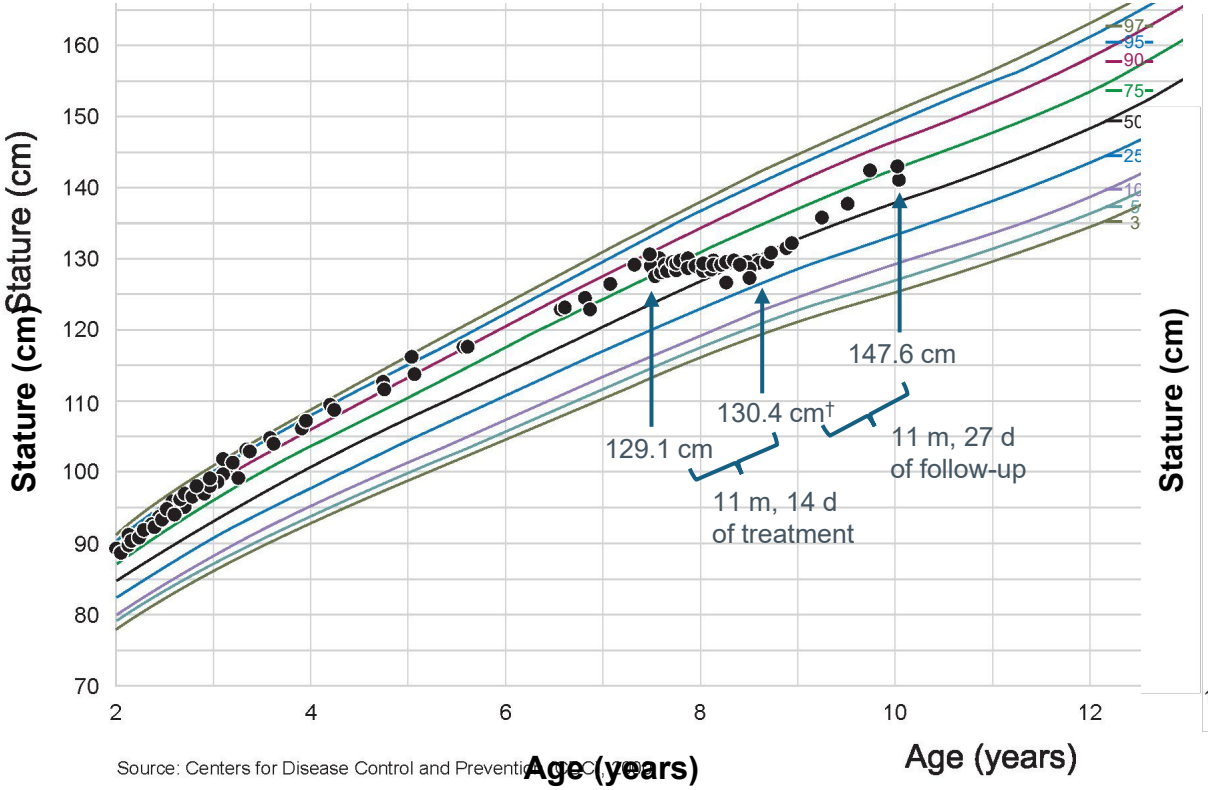


- **All 15 patients with post-treatment heights showed recovery of AGV**; **13/15 (87%) showed evidence of catch-up growth**
- 12/15 (80%) patients had bone age or endocrine evaluation at follow-up
  - **All had normal on-treatment bone age and endocrine evaluations showed no deficiencies (2 were low/borderline)**

April 19, 2024 data cutoff. *Age at C1D1 (cycle 1 day 1). One additional 4-year-old boy with on-treatment AGV of 1.2 cm/y had an off-treatment AGV of 12.3 cm/y after 2 months of off-treatment follow-up. This patient withdrew consent so no additional follow-up will be obtained. AGV, annualized growth velocity; cm, centimeters; GF, growth failure; GH, growth hormone, PP, precocious puberty; SD, standard deviation.

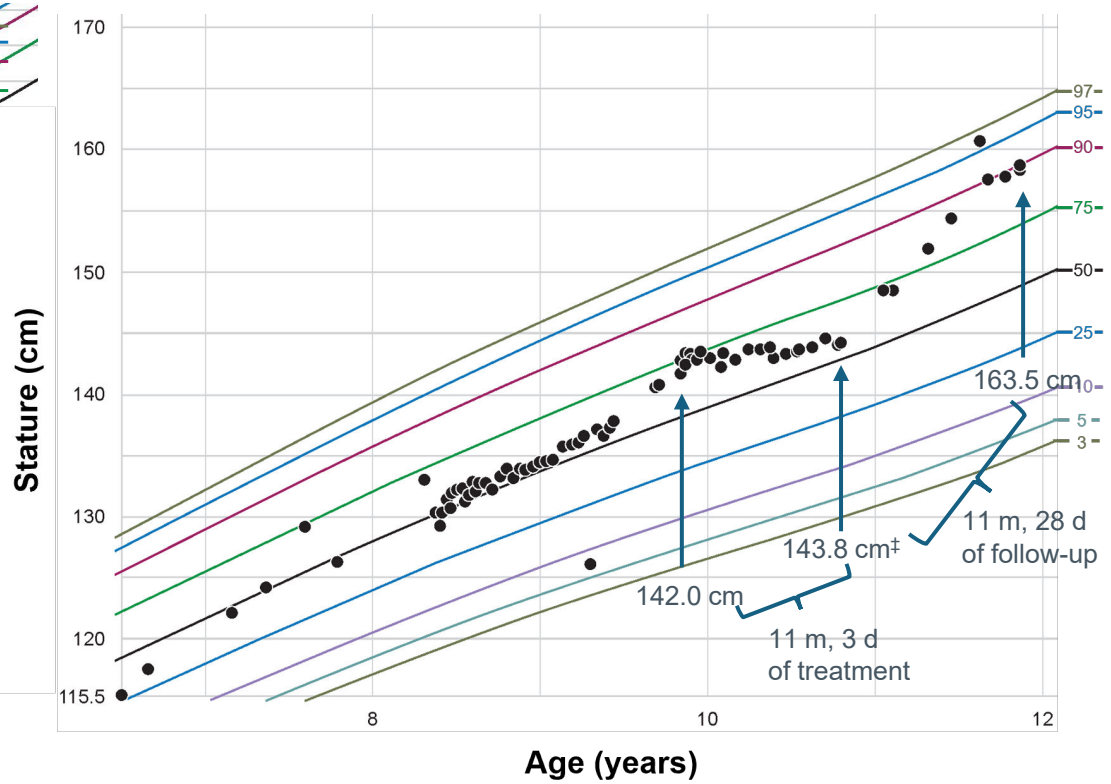
Representative Growth Charts

- 7-year-old* boy with a *BRAF* fusion suprasellar PA who had received 1 prior line of systemic therapy (chemotherapy [CP/VCR])
- BSA <1.5 mg/m^2; dose level 530 mg/m^2 (480 mg dose)
- Pre-existing G1 hypophosphatemia
- Normal bone age on study and no GH deficiencies
- 10 years of age at follow-up



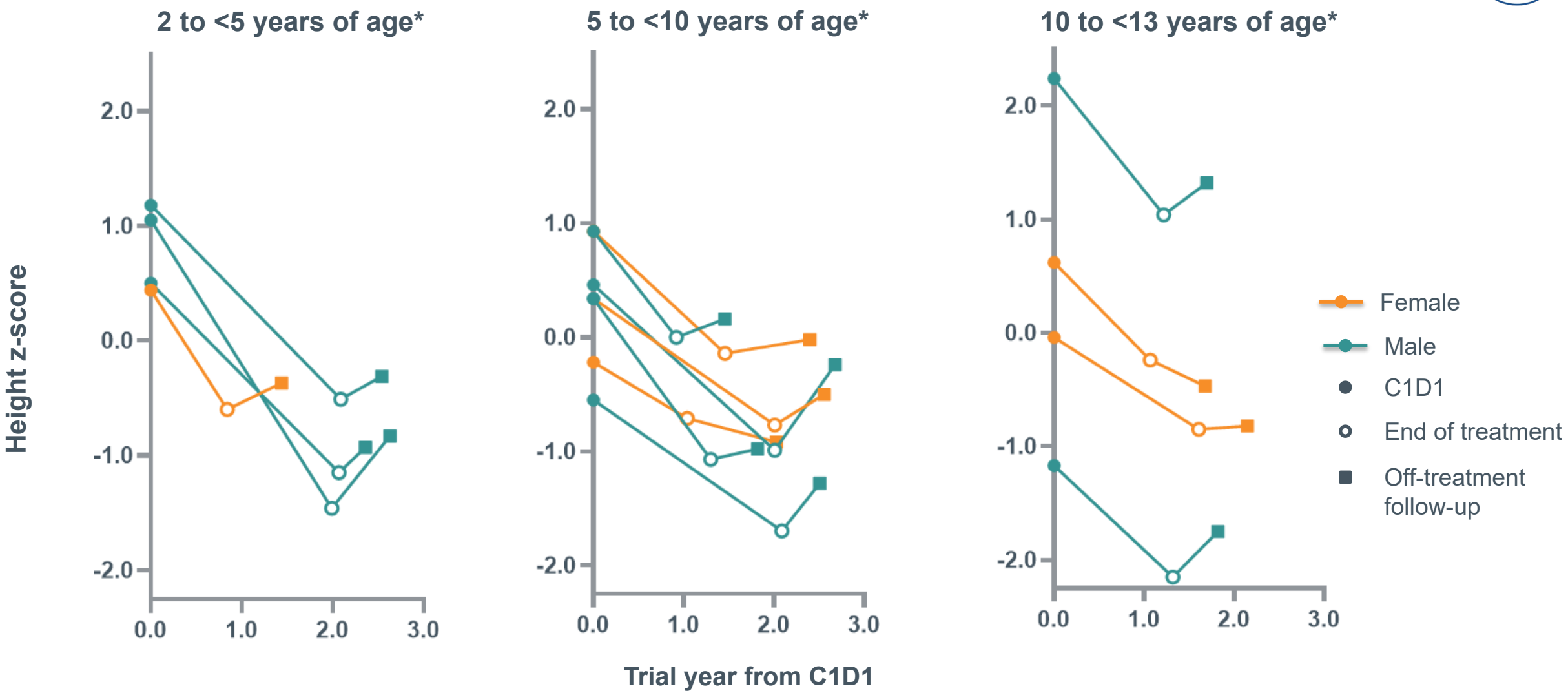
Source: Centers for Disease Control and Prevention CDC.gov

- 9-year-old* boy with a *BRAF* fusion chiasmatic hypothalamic glioma (PA) who had received 2 prior lines of systemic therapy (chemotherapy: CP/VCR, then VBL/BVZ)
- BSA <1.5 mg/m^2; dose level 530 mg/m^2 (640 mg dose)
- No pre-existing growth failure or growth hormone deficiency
- Normal bone age on study and no GH deficiencies
- 11 years of age at follow-up



2 male patients from an IIS. *Age at study entry. †Patient discontinued in November 2021; last follow-up bone age assessment on August 29, 2023. ‡Patient discontinued March 28, 2022.
BL, baseline; BSA, body surface area; BVZ, bevacizumab; CP, carboplatin; G, grade; GH, growth hormone; PA, pilocytic astrocytoma; VBL, vinblastine; VCR, vincristine.

Per patient height z-scores: baseline, end of treatment, and off-treatment follow-up



13 of 15 patients showed increases in height z-score indicative of catch-up growth

April 19, 2024 data cutoff. *Age at C1D1.

GSDB reports of decreased GV: Patients treated outside of FIREFLY-1

Program/study	Reports of decreased GV to the tovorafenib GSDB	Follow-up status
EAP/CUP	7 patients • 6 males between 5–9 years of age • 13-year-old female with advanced bone age at the start of treatment	• All 7 (100%) continue on treatment; follow-up pending

2 IISs	5 (10.2%)† of 49 patients
	• 4 retrospective reports after completing the study
	  • 3 males between 10–14 years of age
	  • 7-year-old female 97th percentile >2 SD above average for height at start of treatment
	• 1 discontinuation (14-year-old male) due to decreased GV after nearly 2 years of treatment
		• 4 (80%), including the patient who discontinued, had ≥3 months of off-treatment follow-up reported
		  • All 4 (100%) showed evidence of recovery of GV, some as early as 3 months (7-year-old female) and 2 had full catch-up (10- and 12-year-old males)
		• The 5th patient (14-year-old male) passed away due to PD shortly after coming off study

*EAP/CUP: April 19, 2024 data cufoff; Ph 1 IISs: August 8, 2023 data cutoff (90DSU).
†Received 530 mg/m^2 tovorafenib.
90DSU, 90 Day Safety Update; CUP, compassionate use program; EAP, expanded access program; GSDB, global safety database; GV, growth velocity; IIS, investigator-initiated study; PD, progressive disease.

Conclusions

- In FF-1, reversible decreases in GV were reported in <50% of patients, causing only 1.5% (2/137) to discontinue
- GV decrease is confounded by growth-related conditions at baseline and comparison to GV data for healthy children; of the 42% (n=57) with GV changes, 49% (n=28) had pre-existing growth-related conditions
- Based on previously published GEMM studies, it is hypothesized that reversible GV decrease with tovorafenib is due to inhibition of CRAF signaling which slows maturation of chondrocytes in long bone growth plates
- Data to date from the tovorafenib GSDB* shows off-treatment growth measurements indicate GV recovery and catch-up growth in the majority of patients
  - No deficiencies in bone integrity were observed
  - Ongoing analysis and assessments continue, including in those with early puberty onset
- Long-term monitoring of growth and development and routine bone age monitoring on- and off-treatment is included in the ph 3 LOGGIC/FIREFLY-2 trial (NCT05566795) in front-line pLGG which is currently enrolling

*FF-1 & EAP/CUP: April 19, 2024 data cufoff; 2 IISs: August 8, 2023 data cutoff (90DSU).
90DSU, 90-day safety update; CUP, compassionate use program; EAP, expanded access program; FF-1, FIREFLY-1; GEMM, genetically engineered mouse model; GH, growth hormone; GSDB, global safety database; GV, growth velocity.

Acknowledgments

- Day One Bio Clinical Pharmacology (Loan Tran, PharmD; Yang Zhang, PhD, RPh; Jing Wang, PhD)
- Certara Quantitive Science (Yin Edwards, PharmD, PhD; YuWei Lin, PhD; S. Y. Amy Cheung, PhD)
- Pediatric Neuro-Oncology Consortium (PNOC) and the PNOC014 investigators and trial team

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

We are deeply grateful for the site coordinators and trial 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