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

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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 once weekly (QW); 600 mg maximum) in children, adolescents, and young adults with *BRAF*-altered relapsed/refractory pLGG who received at least one prior systemic therapy[1]
  - Clinically meaningful tumor responses and a manageable safety profile have been demonstrated[2]
    - US FDA recently granted accelerated approval in patients ≥6 months of age with r/r pLGG with a *BRAF* alteration[3]
  - Reversible decreases in growth velocity (GV) have been reported[2]

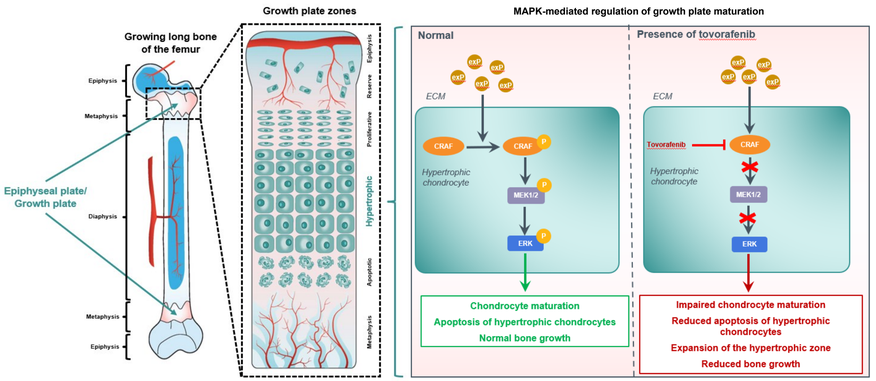
- Children with CNS tumors are likely to have growth-related conditions at baseline[4-7]
- Decreased linear growth is sometimes observed with pediatric oncology treatments:

Treatment Class	Reported Impact on Growth
Cranial radiotherapy[8]	• Growth hormone (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[8,10,11]	• Growing evidence suggests association with altered GV
	  • A review of targeted radiographic studies of 53 patients* from 6 COG ph 1 & pilot consortium clinical trials of new anti-angiogenic agents for refractory cancer found reversible growth plate abnormalities in 5 children (9.4%) on VEGF/VEGFR inhibitors[10]
	  • Growth plate monitoring in children with open growth plates receiving anti-angiogenic therapy was recommended
	  • In a single center report, 6 of 18 (33.3%) pediatric patients with MAPK-pathway driven tumors had growth impairment during dabrafenib/trametinib treatment; 2 (11.1%) had significant decreased GV on prolonged dabrafenib treatment (31 & 36 months)[11]

- **Objective:** assess if decreased GV is transient and reversible based on available patient data on and off tovorafenib

Figure 1. Hypothesized mechanism for tovorafenib-associated reversible decreases in GV



ECM, extracellular matrix; exP, extracellular phosphate.

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.

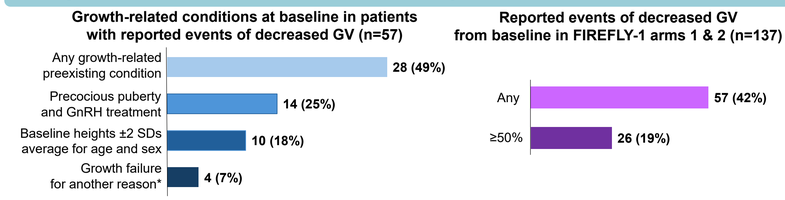
- CRAF is the predominant RAF isoform expressed in hypertrophic chondrocytes[12]
- Chondrocyte-specific CRAF ablation in genetically engineered mouse models (GEMMs) reduced the rate of apoptosis in the hypertrophic chondrocyte layer, thereby reducing the rate of new bone formation and indicated that CRAF plays an important role in growth plate maturation[12-14]
- Tovorafenib is a type II RAF inhibitor with potent (IC_{50}=0.7 nM) activity against CRAF, in addition to activity against BRAF[14-17]
- Pharmacologic inhibition of CRAF is hypothesized to cause a reversible decrease in GV, potentially validating the GEMM studies[2]

Methods

- There have been 69 positively adjudicated cases of decreased GV reported to the tovorafenib global safety database (GSDB): 57 from FIREFLY-1 **(Figure 2)**, 7 from the Expanded Access Program (EAP)/Compassionate Use Program (CUP), and 5 from 2 Investigator-Initiated Studies (IISs) **(Table 1)**
  - Follow-up on decreased GV reported to the GSDB is provided

Results

Figure 2. Patient characteristics and frequency of reported events of decreased GV

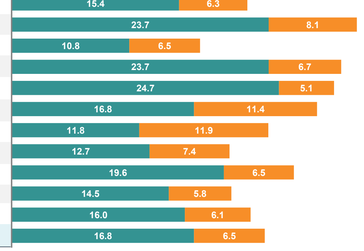


April 19, 2024 data cutoff. *GH deficiency (1 patient). growth failure (2 patients) and growth delay (1 patient). GnRH, gonadotropin-releasing hormone; SD, standard deviation.

Figure 3. 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)
3	Female	Deep midline		1.43	8.51
3	Male	Deep midline		1.00	10.97
4	Male	Cerebral hemisphere		2.51	10.18
4	Male	Deep midline	GH deficiency/GF; adv bone age	2.73	8.52
5	Male	Optic pathway		0.77	6.88
6	Male	Optic pathway		1.99	11.83
7	Male	Deep midline		0.22	7.38
8	Female	Posterior fossa		1.54	9.54
8	Male	Optic pathway		1.25	10.91
9	Female	Deep midline	PP	0.82	8.05
9	Female	Optic pathway	PP; adv bone age	2.02	4.84
10	Female	Optic pathway	Tanner stage 4 at study entry	1.03	4.40
12	Female	4th ventricle		0.50	2.05
12	Male	Cerebral hemisphere	height >2 SD	0.00	11.69
12	Male	Optic pathway		0.91	13.50
Median				**1.03**	**8.52**

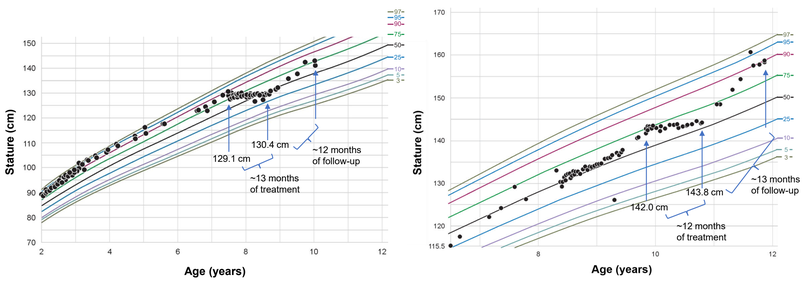


- All 15 patients with post-treatment heights showed recovery of AGV; 13/15 (87%) showed evidence of catch-up growth (**Figure 5**)
- 12/15 (80%) patients had bone age or endocrine evaluation at follow-up
  - All had normal on-treatment bone age and endocrine evaluations showed no deficiencies (2 were low/borderline)

- 38 (67%) patients with decreased GV had GH assessments on treatment; 3 had low/borderline results
  - 1 had a baseline GH deficiency
  - 2 had a tumor-associated GH deficiency first identified during treatment (both had OPG and pre-existing hypothyroidism)
- 32 (56%) patients with decreased GV had on-treatment bone age assessments
  - None showed advancement of bone age (relative to chronological age) from baseline or premature closure of growth plates
  - No osteopenia or abnormal fractures were reported

April 19, 2024 data cutoff. *Age at C1D1 (cycle 1 day one). 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; PP, precocious puberty.

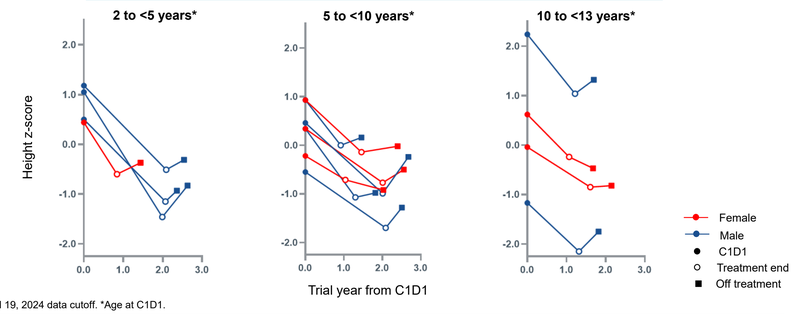
Figure 4. Representative Growth Charts



2 male patients from an IIS.

Figure 5. Per patient height z-scores: Baseline, end of treatment, and off treatment

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



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

Table 1. 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 Ph 1 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 >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 cutoff; Ph 1 ISSs: August 8, 2023 data cutoff (90DSU).
*Received 530 mg/m^2 tovorafenib.
Ph, phase; PD, progressive disease.

Conclusions

- Reversible GV changes reported in <50% of patients in FF-1, causing only 2 of 137 patients (1.5%) to discontinue
- GV change is confounded by growth-related conditions at baseline and comparison to GV data for healthy children; of the 42% (n=57) of with GV changes, 49% (n=28) had pre-existing growth-related conditions
- Based on previously published GEMM studies, it is hypothesized that GV change with tovorafenib is due to inhibition of CRAF signaling, slowing maturation of chondrocytes in long bone growth plates[2,12-17]
- 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 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 long-term extension of FIREFLY-1 and the ph 3 LOGGIC/FIREFLY-2 trial (NCT05566795) in front-line pLGG which is currently enrolling
  - Comparison between model predictions and observed GV recovery data following treatment discontinuation is underway for patients enrolled on FIREFLY-1

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More information on the FIREFLY-1 clinical trial (NCT04775485) can be found at www.clinicaltrials.gov
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