Growth recovery in patients with *BRAF*-altered pediatric low-grade gliomas (pLGGs) after discontinuation of tovorafenib

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Background

- Tovorafenib is a type II RAF inhibitor with potent (IC_{50}=0.7 nM) activity against CRAF, in addition to BRAF[1–3]
- Based on preclinical data, CRAF plays an essential role in chondrocyte maturation, a required step in linear bone growth
  - CRAF is the predominant RAF isoform expressed in hypertrophic chondrocytes[4]
  - Chondrocyte-specific CRAF ablation in genetically engineered mouse models reduced the rate of apoptosis in the hypertrophic chondrocyte layer, thereby reducing the rate of new bone formation; indicating an important role of CRAF in growth plate maturation[4–6]
- Children treated with tovorafenib in the investigator-initiated phase 1 PNOC014 (NCT03429803) and pivotal phase 2 FIREFLY-1 (NCT04775485) trials demonstrate a reversible decrease in growth velocity consistent with CRAF inhibition, with no signs of premature closure of growth plates or adverse effects on bone such as fractures or treatment-emergent osteopenia[7,8]
- Here, we report a combined analysis of off treatment growth recovery in patients treated with tovorafenib in 3 clinical trials[7–9]

Methods

- Patients <18 years (yrs) of age with *BRAF*-altered relapsed/refractory pLGG treated with tovorafenib in the investigator-initiated phase 1 PNOC014 trial,[7] phase 2 FIREFLY-1 trial,[8] or Expanded Access Program for tovorafenib (NCT05760586)[9] were included
- Eligible patients had a minimum of 5 cycles of treatment (140 days), with height measurements at baseline (BL) and at least 1 ≥90 days after the last dose of tovorafenib as of November 15, 2024
- Heights and weights were measured every cycle on treatment to inform dosing; off treatment follow-up was variable
- **Z-scores** for height were calculated to quantify the number of standard deviations each measurement is from the median for age- and sex-specific reference populations based on Centers for Disease Control and Prevention (CDC) reference values[10]
- **Growth suppression on treatment** was defined as at least 0.1 decrease in height-for-age z-score/yr from BL in the piecewise linear mixed effect model (PLMM)
- **Growth recovery** was defined as an increase in post-treatment annualized growth velocity (AGV)[11,12] from on-treatment AGV (total AGV off treatment>total AGV on treatment) in patients with growth suppression on treatment
- **Catch-up growth** was defined as an increase in post-treatment height z-score and recovery towards BL z-score in patients with growth suppression on treatment and categorized as:
  - **Partial catch-up growth:** increase in height z-score, but not reaching BL z-score
  - **Complete catch-up growth**: height z-score increases to BL z-score
- The independent effects of key variables on on and off treatment growth velocity were assessed using a PLMM
  - Variables included in the final model were: on treatment time, off treatment time, BL z-score, BL age, and sex
  - A random effect was included to account for repeated measures in individual patients

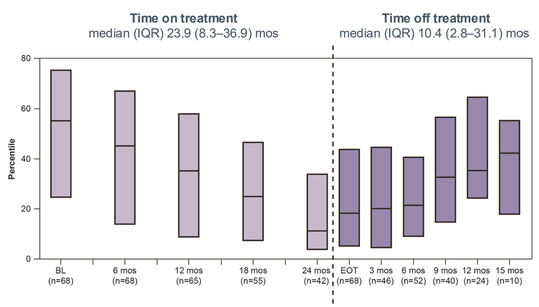
Results

Table 1. Patient BL characteristics

Trial	
FIREFLY-1	47 (69)
Expanded Access Program	4 (6)
PNOC014	17 (25)
Total	**68 (100)**
Sex	
Female	27 (40)
Male	41 (60)
BL age (yrs)	
2 to <6	12 (18)
6 to <12	33 (49)
12 to <16	22 (32)
16 to <18	1 (1)
End of treatment (EOT) age (yrs)	
2 to <6	2 (3)
6 to <12	37 (54)
12 to <16	19 (28)
16 to <25	10 (15)
Endocrinopathy[a]	
Any	29 (43)
Growth hormone (GH) deficiency	9 (13)
Hypothyroidism	13 (19)
Central precocious puberty (CPP)	7 (10)
Adrenal insufficiency	4 (6)
Panhypopituitarism	7 (10)
Diencephalic syndrome	3 (4)
Highest Tanner stage on trial	
Any	36 (53)
Stage 1	10 (15)
Stage 2	11 (16)
Stage 3	4 (6)
Stage 4	7 (10)
Stage 5	4 (6)
Not available	32 (47)
≥Grade 2 on treatment hypophosphatemia	31 (46)
On treatment gonadotropin-releasing hormone agonist (GnRHa) use	7 (10)
On treatment GH use	5 (7)[b]
BL z-score, median (interquartile range [IQR])	
Height	0.13 (−0.69–0.69)
Weight	0.74 (−0.47–1.84)
BL height	
<−2 standard deviations (SDs)	3 (4)
>+2 SDs	5 (7)
BL weight	
<−2 SDs	3 (4)
>+2 SDs	11 (16)

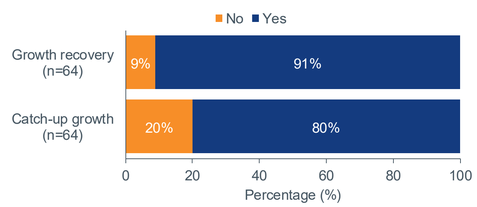
All values are n (%) unless specified otherwise.
[a]Based on medical history (at BL or reported at any time on treatment). A patient could have had more than 1 endocrinopathy.
[b]1 patient (1%) was started on GH treatment when treatment with tovorafenib was initiated.

Figure 1. Height-for-age percentiles on and off tovorafenib treatment



Median and IQR are shown for height percentile at 6-mo intervals during and 3-mo intervals after treatment with tovorafenib. Mos, months.

Figure 2. Growth recovery and catch-up growth post-treatment with tovorafenib



- 4 patients with no on treatment growth suppression were excluded from growth recovery and catch-up growth analyses (denoted with an 'X' in **Figure 3**)

Figure 3. Off treatment height z-score change from EOT

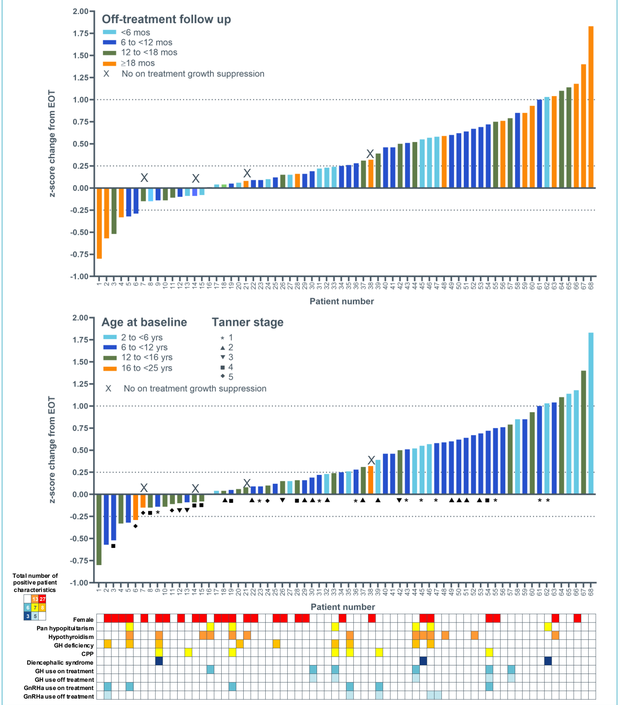
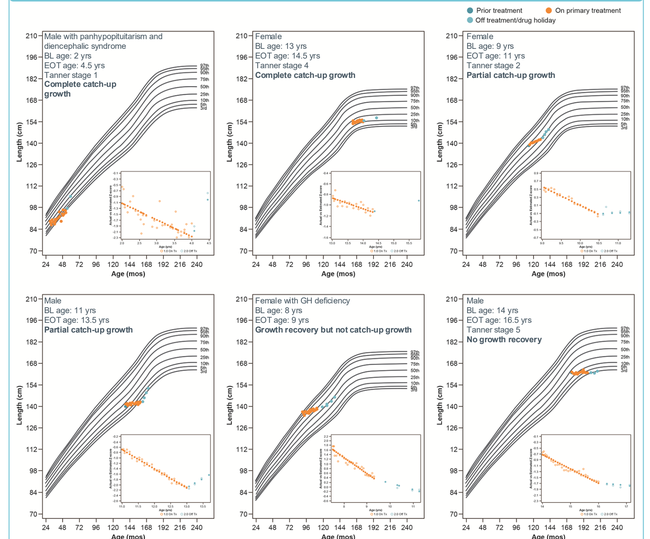


Figure 4. CDC-based growth chart examples



Inset shows fitted regression line from model predictions for z-score changes based on patient actual clinical data.

Table 2. Significant effects on annual height z-score changes from PLMM

		PLMM estimates				
			Annual on treatment change		Annual off treatment change	
	BL age (yrs)	n	AGV (cm)	z-score	AGV (cm)	z-score
Male (n=41)	2–<6	8	2.41	−0.88	11.63	1.12
	6–<12	21	1.63	−0.67	10.12	0.65
	12–<16	12	0.82	−0.45	4.96	0.43
	16–≤25	0	0.39	−0.13	3.63	0.40
Female (n=27)	2–<6	4	2.28	−0.74	8.11	0.72
	6–<12	12	1.50	−0.53	6.61	0.25
	12–<16	10	0.69	−0.31	1.44	0.03
	16–≤25	1	0.26	0.01	0.11	0.01

- Annual changes in on/off treatment z-score were significantly (P<0.05) associated with age and sex
- Duration of treatment was not associated with rate of off treatment z-score rebound
- Overall, post-treatment AGV exceeded on treatment AGV across age and sex groups
- Tanner stage, CPP/GnRHa, GH, and hypophosphatemia were not significantly associated with on/off height z-score changes (data not shown)

Conclusions

- Over a median off treatment follow up of 10 mos, a majority of patients across all age groups showed **growth recovery** (91%) and **catch-up growth** (80%) after stopping tovorafenib
  - According to PLMM estimates, growth recovery after treatment cessation was observed for both males and females
  - Males had more robust rebound growth compared with age-matched females, despite experiencing a faster z-score decrease
  - Slower post-treatment growth was observed in older patients, which may reflect the natural growth rate decrease with age; assessment of bone age and Tanner stage may better inform longer-term growth potential
  - The degree to which tumor-associated endocrinopathies/treatments and later Tanner stage impacted growth rates is unclear, and early consultation with endocrinologists may identify other potential impacts on growth potential
- Growth effects of tovorafenib appear to be reversible in most patients and catch-up growth is observed early in the post-treatment period. Monitoring of patients through completion of growth is ongoing and will further characterize off treatment growth and catch-up patterns

References

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