Analysis of reversible decreases in growth rate* in pediatric patients with relapsed/recurrent low-grade glioma who received tovorafenib

This summary is based on presentations at 2 medical meetings–the 2024 ASCO (American Society of Clinical Oncology) Annual Meeting and ISPNO 2024 (the 21st International Symposium on Pediatric Neuro-Oncology), which were entitled:

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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

Study start date: April 22, 2021
Study end date: (estimated) June 10, 2024
Study number: NCT04775485
Other study names: DAY101-001; PNOC026

More information on the FIREFLY-1 study can be found at: https://clinicaltrials.gov/ct2/show/NCT04775485

Background

What is pediatric low-grade glioma (pLGG)?

- pLGGs are a group of slow growing tumors in the brain and/or spinal cord and are the most common type of cancer in these areas in children and adolescents and young adults (AYAs)
- **~70%** of pLGGs have changes in the *BRAF* gene and therefore, the BRAF protein, which causes tumors to grow
- Depending on where the tumor is in the brain, pLGGs may cause people to feel tired, have headaches, have difficulties with concentration, thinking, walking or balance, and sometimes, with vision
- "Relapsed" means that the tumor has returned after treatment (also known as "recurrent" or "progressive")

How is pLGG treated?

The ideal treatment, when possible, is **surgery** to completely remove the tumor

When surgery is not possible, anticancer treatments, known as **chemotherapy**, are often given to shrink the tumor

- Radiation is another type of treatment, but is used less often due to concerns about the impact on the brain in an age group that is still developing

"Targeted therapies" are a newer type of treatment that may be taken as a pill or a liquid. Many target a key cancer pathway, the mitogen-activated protein kinase (MAPK) pathway, and block proteins responsible for tumors, such as BRAF and MEK

Often multiple courses of therapies are needed over time to prevent the tumor from growing

*How fast a child grows taller.

What is tovorafenib?

- Is a targeted therapy taken as a pill or liquid once a week. It is designed to block the activity of BRAF, the protein made by the *BRAF* gene
- Is in a class of molecules known as "type II RAF inhibitors"
- Was granted accelerated approval by the US Food and Drug Administration (FDA) on April 23, 2024 for patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a *BRAF* fusion or rearrangement, or BRAF V600 mutation*
  - Was the first FDA approval of a systemic therapy for the treatment of patients with pLGG with either type of change in the *BRAF* gene

What is the FIREFLY-1 study?

FIREFLY-1 is an ongoing phase 2† study being conducted in 11 countries.‡ It is looking at tovorafenib in children and AYA participants with relapsed or recurrent pLGGs or other solid tumors that have spread beyond the initial site, with changes in the *BRAF* or another *RAF* gene. It is not being compared to other treatments; the study has 3 different groups (or "arms") and is investigating whether tovorafenib is safe and works to help keep tumors from growing. All participants in FIREFLY-1 have been previously treated with an anticancer treatment.

A PLS of the most recent results from FIREFLY-1 (study data cutoff June 5, 2023) that were published in November 2023 in *Nature Medicine* is available. It describes the efficacy, safety, and tolerability results to date, and notes that decreases in growth rate (how fast a child grows taller) were observed.

In this analysis, researchers wanted to look at a specific side effect, decreased growth rate, in all participants with relapsed or progressive pLGG who have received tovorafenib. This included participants in the ongoing FIREFLY-1 study, the Expanded Access Program (EAP), Compassionate Use Program (CUP), and investigator-initiated studies (IISs). Data used were from the Day One Global Safety Database (GSDB). Unless otherwise indicated, the data cutoff was April 19, 2024.

How do brain tumors and treatment of them impact growth?

- Children with brain tumors are likely to have growth-related conditions even before receiving treatment
- Decreased growth rate is sometimes observed with pediatric oncology treatments including:
  - Different types of radiation treatments
  - Using steroids for a long time
  - Small molecules designed to target different proteins involved in cancer like those that aim to reduce the growth of new blood vessels in tumors or those that target the MAPK pathway

*This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

†Phase 2 studies test whether a new treatment works for a specific type of cancer, in a dose and schedule determined in a phase 1 study. The tolerability and safety of the new treatment are also examined.

‡The 11 countries include: Australia, Canada, Denmark, Germany, Israel, Netherlands, Singapore, South Korea, Switzerland, United Kingdom, and United States.

Abbreviations: **AYAs**, adolescents and young adults; **CUP**, Compassionate Use Program; **EAP**, Expanded Access Program; **FDA**, Food and Drug Administration; **GSDB**, Global Safety Database; **IISs**, investigator-initiated studies; **MAPK**, mitogen-activated protein kinase; **pLGG**, pediatric low-grade glioma; **PLS**, plain language summary

Pronounciations: **BRAF**, be-raf; **Glioma**, glee-OH-ma; **Tovorafenib**, toe-voe-RAF-uh-nib

Why might tovorafenib cause decreases in growth rate?

- In children who are still growing, there is an important area of long bones, called the growth plate
  - The growth plate contains special cells that make RAF proteins, which when altered, can cause tumors to grow
    - There are 3 different kinds of RAF proteins, ARAF, BRAF, and CRAF, with CRAF the most common RAF protein found in these growth plate cells
  - Studies in mice whose genes had been altered have shown that when these special cells could not make the CRAF protein, the rate of new bone formation was slowed. This showed CRAF has an important role in maturing of the growth plate
  - Tovorafenib blocks CRAF most strongly, followed by BRAF and ARAF
    - Based on the studies in mice, it is likely that tovorafenib blockade of CRAF causes slowed growth

Analysis objective & results

Objective

Assess if decreases in growth rate are transient and reversible based on available participant data on and off **tovorafenib**

69 cases of decreases in growth rate have been reported to the tovorafenib Global Safety Database

Common terms used when discussing growth in children

Bone age: measure of a person's skeletal development, or biological maturity, as opposed to their chronological age. It is used by doctors to help diagnose conditions that cause short or tall stature (natural height).

Catch-up growth: growth rate above the normal limits for age for at least 1 year after a transient period of decreased growth rate; it can be complete or incomplete. It is not possible to know whether catch-up growth is complete for an individual child, but if the final height is within the target range, it is considered that catch-up growth is likely complete.

Endocrine evaluation: diagnostic tests used to check for hormonal-related issues.

Growth delay: temporary delay in a child's skeletal growth and height, with no physical abnormalities causing the delay.

Growth failure: occurs when a child's growth rate is slower than expected, and is defined as being below the third percentile for their age and gender, meaning that 97% of their peers are taller than them.

Growth hormone deficiency: occurs when the body doesn't produce enough growth hormone to allow for normal growth. Can be present at birth (congenital) or develop later in childhood (acquired).

Growth recovery: growth rate that increases after a period of decreased growth rate.

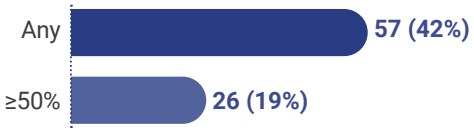
Standard deviation (SD): a number that tells how measurements for a group are spread out from the average (mean or expected value).

Tanner stage: a way to measure physical development as children transition into adolescence and adulthood; uses 5 different stages, with Tanner stage 1 being pre-puberty and Tanner stage 5 being adulthood.

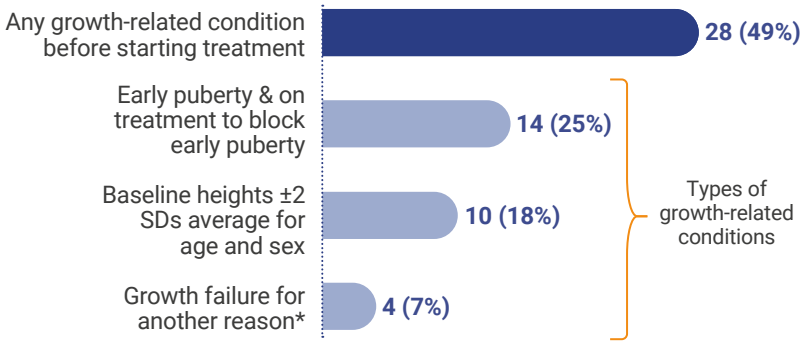
Abbreviations: CUP, Compassionate Use Program; **EAP**, Expanded Access Program; **IISs**, investigator-initiated studies; **SD**, standard deviation

Participant characteristics and frequency of reported events of decreased growth rate

Extent of decrease in growth rate in FIREFLY-1 arms 1 & 2 (n=137)



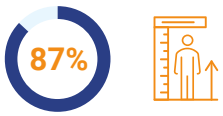
Growth-related conditions before starting treatment in participants with reported events of decreased growth rate (n=57 overall)



*Growth hormone deficiency (1 participant), growth failure (2 participants) and growth delay (1 participant).

Duration of treatment with tovorafenib and follow-up off treatment in participants with decreased growth rate

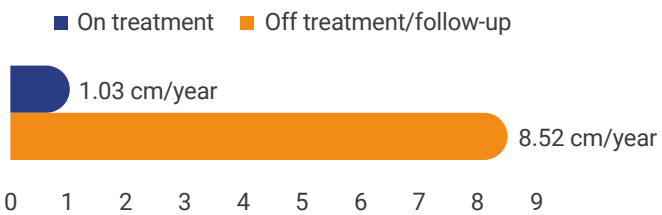
- In the 57 participants with reported decreased growth rate, 15 had interrupted or discontinued treatment with tovorafenib for ≥3 months and had post-treatment heights entered into the GSDB
  - Of those, 2 permanent discontinuations and 3 interruptions were due to decreased growth rate



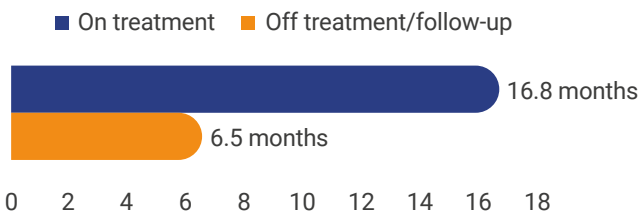
- All 15 participants with post-treatment heights showed recovery of annualized growth rate
  - **13/15 (87%)** showed evidence their growth had caught up

- **12/15 (80%)** participants had bone age or endocrine evaluation at follow-up
  - All had normal on-treatment bone age and endocrine (i.e., hormonal) evaluations showed no deficiencies (2 were low/borderline)

Median† annualized growth rate



Median† duration of treatment and follow-up

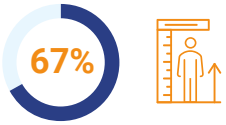


For these 15 patients:

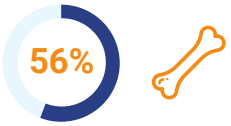
- The median† annualized growth rate was
  - 1.03 cm/year on treatment
  - 8.52 cm/year off treatment/follow-up
- The median† duration of:
  - Treatment: 16.8 months
  - Off treatment/follow-up: 6.5 months

†The median is the middle value of a set of numbers once all have been arranged in ascending order. It is usually a better measure of the true midpoint when there are extreme values or outliers because it is not affected by the precise numerical values of the outliers.

Abbreviations: **GSDB**, Global Safety Database; **SD**, standard deviation



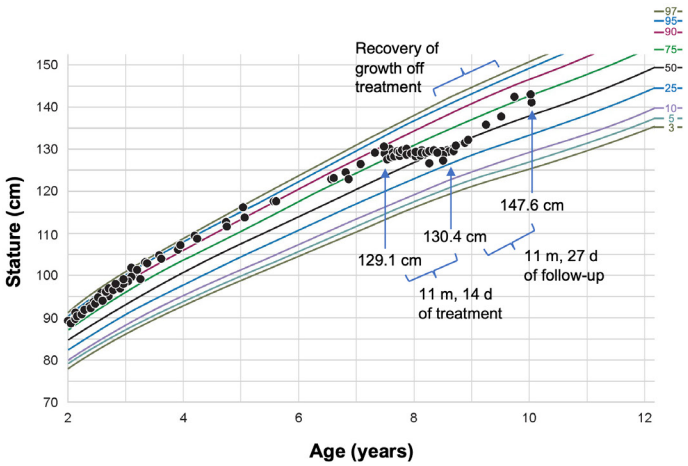
- **38 (67%)** participants with decreased growth rate had growth hormone assessments on treatment; 3 had low/borderline results
  - 1 had a baseline growth hormone deficiency
  - 2 had a tumor-associated growth hormone deficiency first identified during treatment (both had an optic pathway glioma and a hypoactive thyroid before starting treatment)



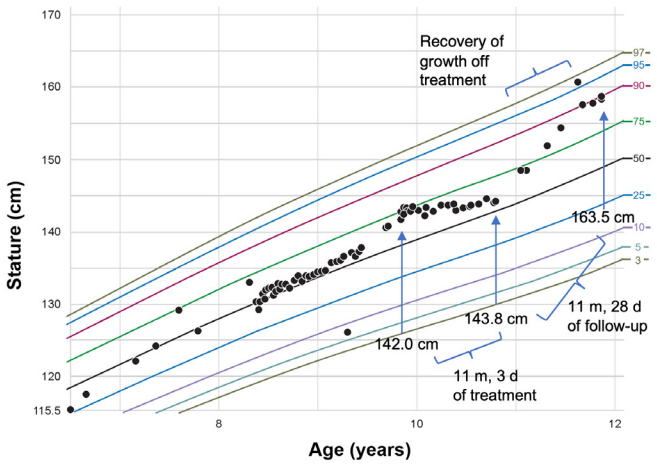
- **32 (56%)** participants with decreased growth rate had on-treatment bone age assessments
  - None showed advancement of bone age (relative to chronological age) from start of treatment or growth plates closing prematurely
  - No decreases in bone mineral density (i.e., amount of minerals in bone) or abnormal fractures were reported

Illustrative growth charts: 2 participants treated with tovorafenib in an IIS

- This participant was almost 8 years of age and at the 90th percentile for height at the start of the treatment, plateaued, and fell to the 50th percentile at the end of ~11 months of treatment. Around a year after stopping treatment, he is growing and currently at the 75th percentile



- This participant was almost 10 years of age and at the 75th percentile for height at the start of treatment and fell to 50th percentile after about a year of treatment. He has caught up on growth and has reached the 90th percentile ~12 months after stopping treatment



These are descriptions of outcome in two specific cases, which may not be applicable to other patients with similar tumors having these gene changes.

What is a growth chart?

- Allows the comparison of height, weight, and head circumference with others of the same assigned sex and age group. They are used to track a child's growth
- To use a growth chart to track height, find the measurement (cm) at the left side of the chart, follow until the lines intersect with the appropriate age, and then find the curve closest to the intersection. Each curve represents a different percentile, which is the number of 100 children who are that height. Follow the curve up to the right to find the matching percentile
  - The 50th percentile is exactly average in size
- It is important to remember it is not the best of 100 test score; each child lives somewhere on the growth curve. It is an individual record for a child and what matters more than a single point is how a child is tracking over time

Participants treated outside of FIREFLY-1 with decreased growth rate reported to the GSDB

Program/study	Reports of decreased growth rate to the tovorafenib GSDB	Follow-up status
EAP/CUP	7 participants • 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 participants • 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 growth rate after nearly 2 years of treatment	• 4 participants, including the participant who discontinued, had ≥3 months of off-treatment follow-up reported – All 4 showed evidence of recovery of growth rate, some as early as 3 months (7-year-old female) and 2 had fully caught up (10- and 12-year-old males) • The 5th participant (14-year-old male) passed away due to progressive disease shortly after coming off study

EAP/CUP: April 19, 2024 data cutoff; phase 1 IISs: August 8, 2023 data cutoff (90 day safety update for the FDA).
*Received 530 mg/m^2 tovorafenib (not to exceed 600 mg), once weekly

Abbreviations: **CUP**, Compassionate Use Program; **EAP**, Expanded Access Program; **FDA**, Food and Drug Administration; **GSDB**, Global Safety Database; **IISs**, investigator-initiated studies; **SD**, standard deviation

Overall summary

- Reversible decreases in growth rate were reported in <50% of participants in FIREFLY-1, and 2 of 137 participants (~2%) discontinued due to decreased growth rate
- Nearly half of the children with decreased growth rate in the trial had growth-related conditions before starting treatment and may not be comparable to children without pLGG. Therefore, it is hard to distinguish how much of the decreased growth is due to tovorafenib treatment and how much is due to pLGG
- It is likely that blocking of CRAF activity by tovorafenib is the cause of decreased growth rate in children with pLGG
- Growth measurements in children who have been off treatment indicate growth rate recovery, and that most participant's growth has caught up
  - No deficiencies in bone strength were observed
  - Ongoing analysis and assessments continue, including in those with puberty that has occurred at an earlier than expected age
- Long-term monitoring of growth and development and routine testing to monitor bone age on and off treatment is included in the related phase 3 LOGGIC/FIREFLY-2 trial (NCT05566795), which is in progress and is looking at how tovorafenib compares to a doctor's choice of chemotherapy in participants newly diagnosed with pLGG with a change in a *RAF* gene
  - A PLS of the study protocol that was published in January 2023 in *BMC Cancer* is available

Abbreviations: **pLGG**, pediatric low-grade glioma; **PLS**, plain language summary

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Day One, the study sponsor, is extremely grateful to all patients, families, caregivers, and clinical investigators for their participation in the FIREFLY-1 study.

Click here to view more information on the FIREFLY-1 study

Click here to view more information on clinical trials in general

Click here to view more information on clinical trials in childhood cancer

Writing support for this summary was provided by Molly Hoke, PhD, ISMPP CMPP™ of Day One Biopharmaceuticals, Inc.
MED-0110, June 2024