Study to evaluate the safety and efficacy of tovorafenib in pediatric patients with relapsed/recurrent low-grade glioma: updated results from the FIREFLY-1 study

This summary is based on the peer-reviewed manuscript published in ***Nature Medicine*** on November 17, 2023, which was entitled:

The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial

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

Click to view more information on the FIREFLY-1 study: 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 which 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

What is tovorafenib?

- Tovorafenib is an investigational 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
- It is in a class of molecules known as "type II RAF inhibitors"

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.

In this analysis, researchers wanted to look at the latest antitumor and safety results from participants with pLGG who received tovorafenib in the FIREFLY-1 study. These results from the Efficacy Group (Arm 1) and the Safety Group (Arm 1 and Arm 2) were used to support the US Food and Drug Administration (FDA) review and approval of this therapy. The study data cutoff was June 5, 2023.

*Phase 2 studies test if one type of specific cancer responds to a new treatment, 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; MAPK, mitogen-activated protein kinase; **pLGG**, pediatric low-grade glioma

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

Study design & results

Who took part in this analysis?

Arm 1 (*BRAF* gene changes)
77 participants with pLGG
= **Efficacy Group**

Select traits

8 years — **median‡ age** (range: 2–21 years)

52% Males | **48%** Females

53% White | **26%** Not specified | **8%** Other
- **6%** Asian
- **4%** Multiple
- **3%** Black

Type of *BRAF* gene change

83% *BRAF* fusion
17% BRAF V600E mutation

Prior anticancer treatments (chemotherapy or targeted therapy)

3 — **median‡ number** (range: 1–9)

- **60%** prior MAPK pathway targeted therapy¥
- **56%** prior MEK inhibitor
- **10%** prior BRAF inhibitor

Treatment:

- Tovorafenib, 420 mg/m^2 (600 mg max)
- Once weekly (pill or liquid form)
- 28-day cycles for ~2 years (26 cycles), or until the cancer starts growing or there are unacceptable side effects
- After the 2 years, can continue with tovorafenib or stop

Study inclusion requirements:

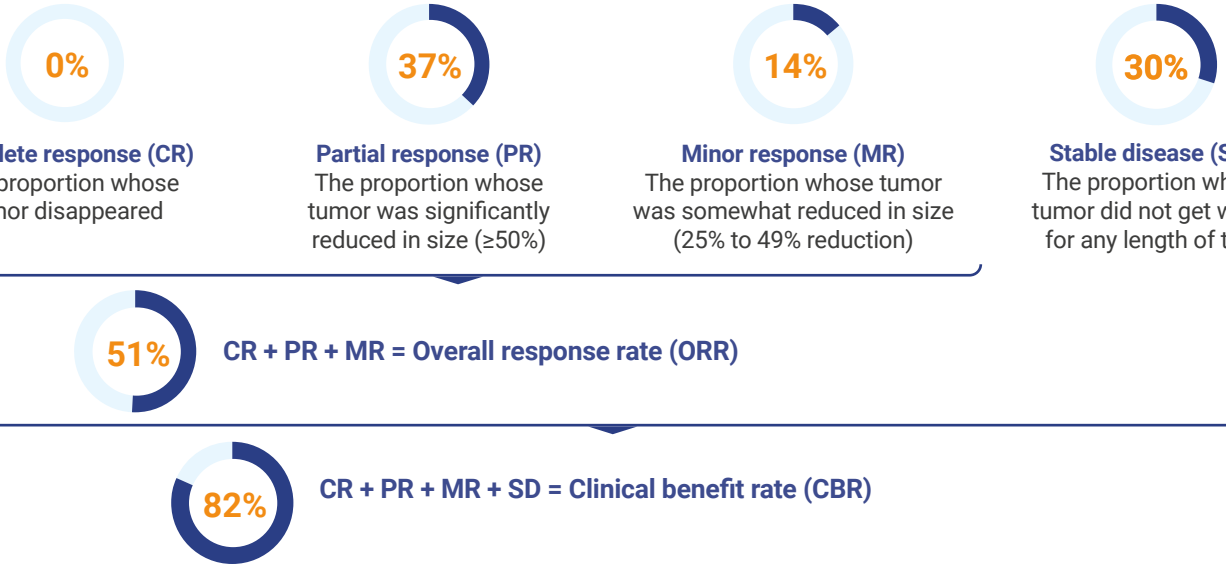
- 6 months to 25 years of age
- At least one prior anticancer treatment for pLGG
- pLGG that was growing, as seen by MRI

¥Five patients (7%) in arm 1 had previously received both a MEK inhibitor and also a BRAF inhibitor. These patients are recorded in both the 'prior MEK inhibitor' and 'prior BRAF inhibitor' groups

Abbreviations: **MRI**, magnetic resonance imaging; **pLGG**, pediatric low-grade glioma

How did tovorafenib impact tumors of Efficacy Group participants with pLGG?

Overall (76 patients met the evaluation criteria)*



Complete response (CR)
The proportion whose tumor disappeared

Partial response (PR)
The proportion whose tumor was significantly reduced in size (≥50%)

Minor response (MR)
The proportion whose tumor was somewhat reduced in size (25% to 49% reduction)

Stable disease (SD)†
The proportion whose tumor did not get worse for any length of time

CR + PR + MR = Overall response rate (ORR)

CR + PR + MR + SD = Clinical benefit rate (CBR)

Time to response (TTR), the median‡ time to when the tumor showed signs of shrinking or disappearing, following initiation of tovorafenib treatment: **5.3 months§**

Duration of response (DOR), the median‡ length of time while on tovorafenib during which the tumor did not grow: **13.8 months§**

Median‡ length of tovorafenib treatment: **15.8 months**

66% of participants were still receiving tovorafenib as of June 5, 2023 (study data cutoff)

Subgroups: Efficacy by type of *BRAF* gene change and prior/no prior MAPK targeted therapy

	BRAF fusion (64 participants)	BRAF mutation (12 participants)	Prior MAPK targeted therapy (45 participants)	No prior MAPK targeted therapy (31 participants)
ORR	52%	50%	49%	55%
CBR	83%	75%	84%	77%
Median‡ TTR§	5.5 months	2.8 months	5.4 months	5.3 months
Median‡ DOR§	13.8 months	NR	13.8 months	NR

NR, not reached; meaning the value could not be measured because fewer than 50% of the participants had tumors which had progressed at the study data cutoff.

An additional analysis showed that 1 in 3 participants had progressed while on treatment with a MAPK targeted therapy; >50% responded to tovorafenib

*These data are based on a type of MRI criteria called RAPNO-LGG. The FIREFLY-1 trial used two other types of MRI criteria, RANO-HGG and RANO-LGG, which are ways of scanning tumors in the brain that are different from each other and RAPNO-LGG. This trial was the first to use all 3 criteria and results across the 3 followed similar trends.

†"Stable disease" means that the tumor did not meet other criteria for response or progression and any growth from the start of the trial was below 25% (with a stable or reduced dose of corticosteroids).

‡The median is the middle value of a set of numbers once all have been arranged in ascending order or the midpoint time interval in a group of participants. 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.

§Only participants who responded were included.

Abbreviations: **CBR**, clinical benefit rate; **CR,** complete response; **DOR**, duration of response; **HGG,** high-grade glioma; **MAPK**, mitogen-activated protein kinase; **MR,** minor response; **MRI,** magnetic resonance imaging; **NR**, not reached; **ORR**, overall response rate; **pLGG**, pediatric low-grade glioma; **PR**, partial response; **RANO,** Response Assessment in Neuro-Oncology; **RAPNO;** Response Assessment in Pediatric Neuro-Oncology; **SD**, stable disease; **TTR**, time to response

What were the most common side effects of tovorafenib in the Safety Group?

Arm 1 (*BRAF* gene changes)
77 participants with pLGG

+

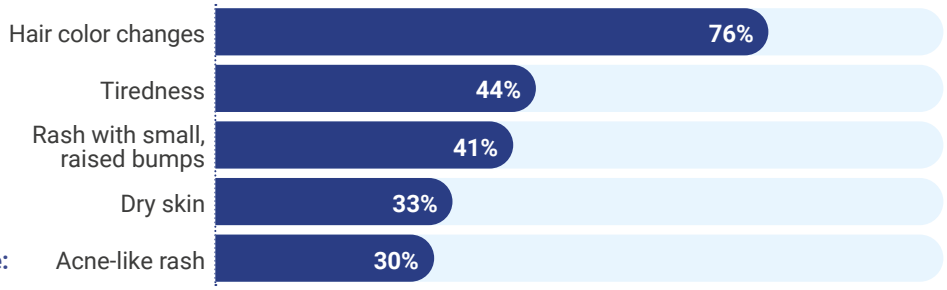
Arm 2 (*RAF* gene changes)
60 participants with pLGG

=

Safety Group (137 participants)

98%

experienced a side effect of any seriousness that was thought to be due to tovorafenib; the most common (25% or more) were:



- **42%** experienced a side effect that was thought to be due to tovorafenib that was considered serious:
  - The most frequently occurring were: **rash with small, raised bumps (8%) decreased growth rate* (5%), tiredness (4%), decreased appetite (3%),** and **tumor hemorrhage** and **vomiting (2% each)**

What other information about the Safety Group was discovered in participants who received tovorafenib?

Fever, diarrhea, and weight gain were reported less often as due to tovorafenib and did not significantly interfere with treatment

No signs of negative effects on the eyes or heart or abnormal weight gain were seen

Skin rashes were common; none were life-threatening

How many Safety Group participants had to stop or change tovorafenib treatment due to side effects thought to be due to tovorafenib?

Action taken with tovorafenib	Stopped	Dose lowered	Dose interrupted/ temporarily stopped
Participants (of 137) who had a side effect leading to action	9 (7%)	33 (24%)	50 (37%)
Most common side effects leading to action: participants who had it	• Tumor hemorrhage: 3 (2%) • Decreased growth rate:* 2 (1%)	• Rash with small, raised bumps: 6 (4%) • Decreased appetite: 4 (3%)	• Rash with small, raised bumps: 13 (9%) • Vomiting: 6 (4%) • Tiredness: 6 (4%)

- **14 days (2 doses):** median‡ duration of dose interruption due to any side effect

*How fast a child grows taller.
‡Midpoint time interval.

Abbreviations: pLGG, pediatric low-grade glioma

Overall summary

The FIREFLY-1 study is looking at whether a new investigational anticancer treatment called tovorafenib might be a safe and effective way to treat children and adolescents and young adults (AYAs) with a type of brain cancer called pediatric low-grade glioma (pLGG), which has begun to grow after previous treatment.

In this analysis of 77 participants in Arm 1 with pLGG with a change in the *BRAF* gene who met certain evaluation criteria, researchers found that following treatment with tovorafenib:

- Tumors decreased in size in 51% of participants overall, including in those with either type of *BRAF* gene change and whether or not MAPK targeted therapy had been received previously
- While almost all of the 137 participants treated with tovorafenib had side effects, most were mild to moderate in severity and did not impact most participants from continuing treatment; the most common determined to be related to tovorafenib were **hair color changes (76%), tiredness (44%),** and a **rash with small, raised bumps (41%)**
- These results provide additional support for the evaluation of tovorafenib as a potential treatment for patients with pLGG with a change in the *BRAF* gene whose cancer gets worse or comes back after previous treatment

A related phase 3 trial, LOGGIC/FIREFLY-2 (NCT05566795) 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.

Abbreviations: **AYAs**, adolescents and young adults; **MAPK**, mitogen-activated protein kinase; **pLGG**, pediatric low-grade glioma

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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

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