The LOGGIC/FIREFLY-2 study evaluating the efficacy and safety of tovorafenib vs SoC chemotherapy in pediatric patients with low-grade glioma requiring first-line systemic therapy

This summary is based on the **peer-reviewed manuscript** published in *BMC Cancer* in January 2024 and is entitled:

LOGGIC/FIREFLY-2: A phase 3, randomized trial of tovorafenib versus chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating *RAF* alteration

Click here to view this LOGGIC/Day One publication

Study start date: February 27, 2023

Study end date: (estimated) March 2030

Study number: NCT05566795

Other study names: DAY101-002

Click to view more information on the LOGGIC/FIREFLY-2 study:
https://www.clinicaltrials.gov/study/NCT05566795

Who is conducting the LOGGIC/FIREFLY-2 study?
Day One is conducting the study in collaboration with the Low-Grade Glioma in Children (LOGGIC) consortium, a group of internationally recognized experts in pLGG research, with an extensive network of pediatric oncology centers across Europe

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)
- There are three different *RAF* genes (*ARAF, BRAF,* and *CRAF*) and up to 75% of pLGGs have changes in one of these genes and therefore, the RAF protein, which may cause tumors to grow
  - **~70%** of pLGGs have changes in the *BRAF* gene
  - ***BRAF* fusions** are very common in pLGG

- Depending on where the tumor is located in the brain, pLGGs may cause people to feel tired, have headaches, and have difficulties with concentration, thinking, walking or balance, and sometimes, with vision

Types of gene changes

Mutation: is a spontaneous change in a specific part of a gene that makes it work incorrectly (example: BRAF V600E-mutation)

Fusion: is when part of a gene rearranges and fuses to part of a different gene and makes it work incorrectly (example: *KIAA1549*::*BRAF* fusions)

Abbreviations: **AYAs**, adolescents and young adults; **pLGG**, pediatric low-grade glioma; **SoC**, standard of care

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

How is pLGG treated?

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

When surgery is not possible or incomplete, systemic* 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 growing children

"Targeted therapies" are a newer type of systemic treatment which may be taken as a pill or a liquid. Many target a key cancer pathway called the MAPK pathway and block proteins responsible for tumors, such as MEK and RAF

Targeted therapies are sometimes combined (**"combination therapy"**) as they can block, or inhibit, specific proteins in the MAPK pathway

- Some targeted therapies (**"MAPK inhibitors"**) target proteins that come from BRAF mutations only, others may target proteins that come from *BRAF* fusions and mutations

pLGG is considered a chronic disease, so often multiple courses of therapies are needed over time to prevent tumors 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, a protein made by one of the *RAF* genes, *BRAF*
- It is in a class of molecules known as "type II RAF inhibitors"
- FIREFLY-1 (NCT04775485) is an ongoing phase 2 study of tovorafenib in children and AYAs with relapsed/recurrent pLGG (Arms 1 & 2) with changes in the *BRAF* gene who have previously received systemic anticancer treatment
  - A recent analysis using a June 5, 2023 study data cutoff was published in *Nature Medicine* in November 2023
- The FIREFLY-1 analysis found that tumors decreased in size in approximately 1 out of 2 participants with pLGG in the Efficacy Group (Arm 1)
  - In the Safety Group (Arms 1 and 2), most of the common side effects were mild to moderate in severity and did not significantly impact participants from continuing treatment

Click here to view the FIREFLY-1 publication

What is the LOGGIC/FIREFLY-2 study?

- An ongoing two-arm, randomized, open-label phase 3† study being conducted at ~100 sites‡ in children and AYAs younger than 25 years of age with newly diagnosed pLGG with a change in the *RAF* gene requiring systemic therapy
- It is comparing once-weekly tovorafenib (Arm 1) with chemotherapy§ (Arm 2)

*Systemic treatments are any type of drug therapy that spreads throughout the entire body. They can be given as an injection, infusion, or as a pill. For example, chemotherapy moves through the blood to help tumors shrink or disappear.

†Phase 3 studies compare how well a new treatment works and how safe it is compared with a treatment that is considered the current standard of care.

‡In Europe, the Asia Pacific region (Singapore, South Korea, Australia, and New Zealand), and North America (US and Canada).

§Doctor's choice from a defined selection of chemotherapy options considered current standard of care.

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

Pronounciations: **MAPK**, map-kay

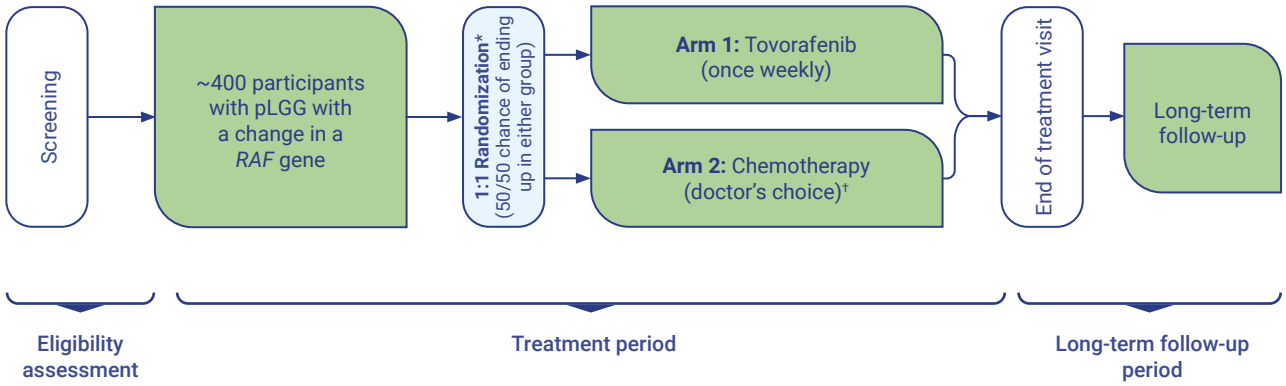
LOGGIC/FIREFLY-2 study design

Who is eligible to participate?

A detailed list of criteria as to what makes someone eligible or ineligible to participant in this study is available online and a participating doctor would determine eligibility; generally, eligible participants should:

- Be younger than 25 years of age and newly diagnosed with pLGG
- Have changes in the *RAF* gene and have a tumor that is growing based on a type of brain imaging called magnetic resonance imaging (MRI)
- Have not received any prior systemic anticancer treatment for pLGG

What treatments will participants receive?



*Randomization will factor in certain participant characteristics, such as **tumor location** and **type of change in the *RAF* gene**, in order to ensure balanced groups

†The doctor's choice of chemotherapy will be chosen prior to randomization.

Options are one of the following current standard of care treatments for pLGG: 1) Children's Oncology Group - Vincristine/Carboplatin, 2) International Society for Paediatric Oncology - Low-Grade Glioma Vincristine/Carboplatin, or 3) Vinblastine

How long will participants receive treatment for?

Arm 1 tovorafenib

Up to 5 years, including long-term follow-up

- Option to continue tovorafenib if their tumor worsens or their doctor thinks they are benefiting from continuing

Arm 2 chemotherapy

1 – 1.5 years (depending on the chemotherapy selected), and then long-term follow-up (up to 5 years)

- Option to receive tovorafenib if their tumor worsens while on chemotherapy or after finishing chemotherapy

Treatment will continue until completion or any of the following occurs: the tumor worsens, unacceptable toxicity, study withdrawal, or end of study

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

What is LOGGIC/FIREFLY-2 evaluating?

The goal of the study is to determine how tovorafenib compares with chemotherapy*, as a safe and effective treatment, in children and AYAs with newly diagnosed pLGG with a change in the *RAF* gene who require systemic anticancer treatment.

- The primary objective, to assess the impact of tovorafenib on tumors and in comparison with chemotherapy, will be determined by the **objective response rate**, which is the sum of the **complete response** (proportion whose tumor disappeared) and the **partial response** (proportion whose tumor significantly decreased)
- Other important key secondary objectives will further assess the impact after the start of treatment and will compare tovorafenib and chemotherapy:

Progression-free survival (PFS)
Average length of time a participant's cancer does not grow or spread during their lifetime

Duration of response (DOR)
Average length of time (while on treatment) that a tumor does not grow or spread

Overall survival (OS)
Average length of time participants live

- Other secondary and exploratory objectives will utilize other measures to compare outcomes of participants in the 2 treatment arms

What else will LOGGIC/FIREFLY-2 evaluate?

Other select assessments†

What is measured and when are they measured?	These measures assess changes in:
MRI scan Every 12 weeks	Tumor size
Visual acuity (eye) test At every MRI visit (if needed)	Ability to see
Neurological functioning and adaptive behaviors 1, 2, and 5 years after the start of treatment	Brain function such as memory and thinking
Quality of life‡ 1, 2, and 5 years after the start of treatment	Ability to participate in and enjoy daily activities
Safety monitoring§ Throughout the study (various timepoints)	How someone feels or if certain chemicals in their blood (or other tests) are changing, indicating side effects
Pharmacokinetics‖,¶ Day 1 of cycles 1, 2, and 4: before each dose and 2 hours after Day 1 of cycles 7, 10, and 13: before each dose When there is a serious side effect: any time	Ability to detect, monitor, and treat tumors

*Doctor's choice from a defined selection of chemotherapy options considered current standard of care. †All measures will be assessed at baseline before the start of study treatment. ‡In participants over 2 years of age. For children under 4 years of age, caregiver(s)/parent(s) will complete the proxy-reporting quality of life assessment. For children above 5 years of age, both the child and parent will complete a self-report and parent proxy report version of the assessment, if applicable. Quality of life assessments will only be conducted if local language translation is available. §Includes assessments of vital signs, skin and bone health. ‖Study of how a drug acts in the body over a period of time, including how it is absorbed, distributed, metabolized, and excreted. ¶For cycles 2, 4, 7, 10, and 13, blood can be collected on Day 1 or up to 3 days before or after. Samples taken before a dose will be collected 0–1 hours before. Samples taken 2 hours after a dose will be collected between 1–3 hours afterwards.

When will the LOGGIC/FIREFLY-2 study be completed?

March 2030 (estimated); however, some early results may be available earlier as the estimated completion of the primary endpoint portion (assessment of the impact of tovorafenib on tumors and in comparison with chemotherapy) is February 2026.

Conclusions from this publication

The results from the LOGGIC/FIREFLY-2 study aim to:

- Inform if tovorafenib shrinks tumors in participants and by how much, how many participants' tumors shrink, and how it compares with chemotherapy*
- Provide information on the side effects of tovorafenib, how severe they may be, and if they impact participants from continuing treatment
- Provide additional support for the evaluation of tovorafenib as a potential treatment in children and AYAs newly diagnosed with pLGG with a change in a *RAF* gene

Overall summary

The ongoing LOGGIC/FIREFLY-2 study, is trying to find out whether an investigational anticancer treatment, tovorafenib, is safe and effective in treating children and AYAs under 25 years of age who have been diagnosed with pLGG and have not yet received treatment.

- The type of pLGG of interest includes changes in a *RAF* gene
- Once-weekly tovorafenib (pill or liquid form) is being compared with chemotherapy*
- Participants must not have already received chemotherapy or systemic anticancer treatments for pLGG
- Results aim to support the evaluation of tovorafenib as a potential treatment in children and AYAs newly diagnosed with pLGG with a change in a *RAF* gene
- The trial is currently enrolling participants

*Doctor's choice from a defined selection of chemotherapy options considered current standard of care.

Abbreviations: **AYAs**, adolescents and young adults; **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 LOGGIC/FIREFLY-2 study.

Click here to view more information on the LOGGIC/FIREFLY-2 study

Click here to view more information on clinical trials in general

Click here to view more information on clinical trials childhood cancer

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