A Phase 3, Randomized, International Multicenter Trial of DAY101 Monotherapy Versus Standard of Care Chemotherapy in Patients with Pediatric Low-Grade Glioma Harboring an Activating RAF Alteration Requiring First-Line Systemic Therapy

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This study has been transitioned to CTIS with ID 2024-510742-13-00 check the CTIS register for the current data. The primary objective is to compare the objective response rate (ORR) assessed per Response Assessment in Neuro Oncology for low-grade...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON53920

Source
ToetsingOnline

Brief title
LOGGIC/FIREFLY-2

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain tumor, malignant glioma

Research involving
Human

Sponsors and support

Primary sponsor: Day One Biopharmaceuticals, Inc.
Source(s) of monetary or material Support: the sponsor;Day One Biopharmaceuticals;Inc.

Intervention

Keyword: activating RAF alteration, DAY101, pediatric low-grade glioma

Outcome measures

Primary outcome

The primary objective is to compare the objective response rate (ORR) assessed per Response Assessment in Neuro Oncology for low-grade gliomas (RANO-LGG) criteria by Independent Review Committee (IRC) of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in patients with pediatric low-grade glioma harboring an activating rapidly accelerated fibrosarcoma gene (RAF) alteration requiring first line systemic therapy.

Secondary outcome

Key Secondary Objectives:

• To compare the progression-free survival (PFS) assessed by IRC of tovorafenib monotherapy versus SoC chemotherapy per RANO LGG criteria.

• To compare the duration of response (DOR) assessed by IRC of tovorafenib monotherapy versus SoC chemotherapy per RANO-LGG criteria.

• To compare the overall survival (OS) of tovorafenib monotherapy versus SoC chemotherapy.

Secondary Objectives:

• To compare the safety and tolerability of tovorafenib monotherapy versus SoC chemotherapy.

• To evaluate changes in neurological function and adaptive behavior in the following domains between tovorafenib versus SoC chemotherapy using Vineland Adaptive Behavior Scale (VABS).

• To compare changes in visual function outcomes of tovorafenib monotherapy versus SoC chemotherapy in patients with optic pathway glioma (OPG).

• To compare the ORR of tovorafenib monotherapy versus SoC chemotherapy as assessed by IRC per Response Assessment in Pediatric Neuro-Oncology for high-grade glioma (RANO-HGG) and Response Assessment in Pediatric Neuro-Oncology for low-grade glioma (RAPNO LGG) criteria.

• To compare the clinical benefit rate (CBR) of tovorafenib monotherapy versus SoC chemotherapy as assessed by IRC per RANO-LGG, RANO-HGG, and RAPNO-LGG criteria.

• To compare time to response (TTR) of tovorafenib monotherapy versus SoC chemotherapy as assessed by IRC per RANO-LGG, RANO-HGG, and RAPNO-LGG criteria.

• To compare the PFS of tovorafenib monotherapy versus SoC chemotherapy as assessed by IRC per RANO HGG and RAPNO-LGG criteria.

• To compare the DOR of tovorafenib monotherapy versus SoC chemotherapy as assessed by IRC per RANO-HGG and RAPNO-LGG criteria.

• To evaluate health-related quality of life (HRQoL) in tovorafenib versus SoC chemotherapy using Patient-Reported Outcomes Measurement Information System (PROMIS®) test battery.

Exploratory Objectives:

• To compare the ORR of tovorafenib monotherapy versus SoC chemotherapy as assessed by Investigator per RANO-LGG criteria.

• To compare the CBR of tovorafenib monotherapy versus SoC chemotherapy as assessed by Investigator per RANO-LGG criteria.

• To compare TTR of tovorafenib monotherapy versus SoC chemotherapy as assessed by Investigator per RANO-LGG criteria.

• To compare the PFS of tovorafenib monotherapy versus SoC chemotherapy as assessed by Investigator per RANO-LGG criteria.

• To compare the DOR of tovorafenib monotherapy versus SoC chemotherapy as assessed by Investigator per RANO-LGG criteria.

• To compare changes in growth and development between tovorafenib monotherapy versus SoC chemotherapy.

• To compare chemotherapy-induced peripheral neuropathy (CIPN) outcomes of tovorafenib monotherapy versus SoC chemotherapy in patients >= 5 years of age.

• To compare the neuroendocrine morbidity between tovorafenib monotherapy versus SoC chemotherapy.

• To characterize changes in total tumor volume [including cysts] following treatment with tovorafenib and SoC chemotherapy by magnetic resonance imaging (MRI) volumetric image analysis.

• To characterize changes in apparent diffusion coefficients following treatment with tovorafenib and SoC chemotherapy using diffusion-weighted imaging analysis.

• To evaluate changes in HRQoL with tovorafenib versus SoC chemotherapy using

the Pediatrics Quality of Life* Core Module (PedsQL Core) and Pediatrics Quality of Life* Cancer (PedsQL-Cancer), collectively referred as PedsQL.

• To determine the ORR of patients who are initiated on tovorafenib after discontinuing SoC chemotherapy due to radiographic progression as assessed by (1) IRC per RANO-LGG, RANO HGG, and RAPNO LGG criteria, and (2) Investigator per RANO-LGG criteria.

• To evaluate time to initiation of next treatment following discontinuation of primary therapy.

• To determine the CBR of patients who are treated with tovorafenib after discontinuing SoC chemotherapy due to radiographic progression as assessed (1) IRC per RANO LGG, RANO-HGG, and RAPNO-LGG criteria, and (2) Investigator per RANO-LGG criteria.

• To compare cystic involution between the study arms.

• To compare the efficacy and safety of individual SoC chemotherapy regimens versus tovorafenib.

• To evaluate the concordance of prior local laboratory rapidly accelerated fibrosarcoma (RAF) molecular profiling with a central RAF alteration assay being evaluated by the Sponsor.

• To explore whether early response in infant chiasmatic-hypothalamic glioma (CHG) at 6 and 12 weeks correlates with response after 24 weeks of treatment.

• To assess the pharmacokinetics of tovorafenib.

• To evaluate preliminary information on the palatability and acceptability of tovorafenib tablets and powder for oral suspension (PfOS) formulations.

Study description

Background summary

See protocol section 1 - introduction

Study objective

This study has been transitioned to CTIS with ID 2024-510742-13-00 check the CTIS register for the current data.

The primary objective is to compare the objective response rate (ORR) assessed per Response Assessment in Neuro Oncology for low-grade gliomas (RANO-LGG) criteria by Independent Review Committee (IRC) of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in patients with pediatric low-grade glioma harboring an activating rapidly accelerated fibrosarcoma gene (RAF) alteration requiring first line systemic therapy.

Study design

This is a 2-arm, randomized, open-label, multicenter, global, Phase 3 study to evaluate the efficacy, safety, and tolerability of tovorafenib monotherapy versus SoC chemotherapy in patients with pediatric low-grade glioma harboring an activating RAF alteration requiring first-line systemic therapy. Patients with RAF alterations will be identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments (CLIA) of 1988 or other similarly certified laboratories. Approximately 400 treatment naïve low-grade glioma patients will be randomized 1:1 to either tovorafenib (Arm 1) or an Investigator*s choice of SoC chemotherapy (Arm 2). Randomization will be stratified by primary location of the tumor (supratentorial midline vs. other), type of genomic alteration (fusion vs. mutation), CDKN2A status (deletion vs. wild type/unknown), and infant CHG diagnosis (yes vs. no).
This study consists of a Screening phase, a treatment phase, an End of Treatment (EOT) Visit, a 30-Day Safety Follow-Up (SFU) visit, and a long-term follow-up (LTFU) period. Upon completion of study treatment, ongoing safety, disease stability/progression, survival status, and subsequent anticancer therapies will be assessed in the LTFU period. For each patient, study participation is up to 5 years, inclusive of the treatment phase and a LTFU period.
Arm 1 (tovorafenib): Treatment cycles will repeat every 28 days in the absence of disease progression. Patients will continue tovorafenib until any of the following occurs: disease progression based on RANO LGG criteria, unacceptable toxicity, withdrawal of consent to treatment, or end of study.
Arm 2 (Investigator*s Choice of SoC Chemotherapy): Patients will receive 1 of 3 SoC chemotherapy options selected by the treating Investigator: Children*s

Oncology Group - Vincristine/Carboplatin (COG-V/C) regimen, International Society for Paediatric Oncology - Low-Grade Glioma Vincristine/Carboplatin (SIOPe-LGG-V/C) regimen, or vinblastine (VBL) regimen. The choice of SoC chemotherapy regimen will be selected prior to patient randomization. Treatment will continue until completion of therapy or until any of the following occurs: disease progression based on RANO-LGG criteria, unacceptable toxicity, withdrawal of consent to treatment, or end of study.
Patients who discontinue treatment due to disease progression will have (1) radiographic evidence of progressive disease based on RANO-LGG, as determined by the Investigator and confirmed by the IRC, or (2) clinical progression based on RANO-LGG criteria determined by the Investigator. Investigators are encouraged to discuss cases of clinical progression and early radiographic progression without clinical symptom with the Sponsor Medical Monitor prior to treatment discontinuation or initiation of a different form of treatment for the malignancy. Patients may continue therapy beyond progressive disease per Section 5.3 (of the protocol).

Intervention

DAY101 is provided as both oral tablet and powder for reconstitution formulations.
Vincristine is provided as a solution for injection, carboplatin is provided as a concentrate for solution for infusion, and VBL is provided as a solution for injection.

Patients will be initiated on study treatment of DAY101 or SoC chemotherapy after randomization. The choice of SoC chemotherapy regimen the patient would receive in this study (COG-V/C, SIOPe-LGG-V/C, or VBL) will be selected prior to patient randomization.
Arm 1 (DAY101): Patients enrolled in Arm 1 will be initiated on once weekly dosing of DAY101 at 420 mg/m2 (not to exceed 600 mg) starting C1D1 according to the patient*s baseline body surface area (BSA). Treatment cycles will repeat every 28 days and DAY101 will be administered on Days 1, 8, 15, and 22 of each 28-day cycle (4 week cycle).
Arm 2 (COG-V/C): During induction (first 12 weeks), vincristine is given weekly during Week 1 to Week 10. Carboplatin is given on Weeks 1, 2, 3, 4, 7, 8, 9, and 10. Patient will not receive treatment for the last 2 weeks of induction. During maintenance, vincristine and carboplatin are given in repeating cycles until completion of 60 weeks of therapy (8 maintenance cycles): vincristine on Weeks 1, 2, and 3 and carboplatin on Weeks 1, 2, 3, and 4. Note: Each cycle during maintenance is 6 weeks (42 days).
Arm 2 (SIOPe-LGG-V/C): During induction (first 24 weeks, first 7 cycles), vincristine is given weekly during Week 1 to Week 10, and on Weeks 13, 17, and 21. Carboplatin is given on Weeks 1, 4, 7, 10, 13, 17, and 21. During consolidation, vincristine and carboplatin are given in repeating cycles until completion of 81 weeks of therapy: vincristine on Weeks 1, 2, and 3 8, and 15 and carboplatin on Week 1. Note: Each cycle during consolidation is 6 weeks (42

days).
Arm 2 (VBL): Vinblastine is given weekly, and treatment will continue until completion of 70 weeks of therapy, radiographic progression, or unacceptable toxicity. One cycle is defined as 28 days (4 weeks).

Tumors will be assessed by radiographic tumor measurements using MRI of the brain and/or spine.
Adaptive behaviors will be evaluated using the Vineland III Adaptive Behavior Scale (VABS).
Standard monitoring for safety is outlined in the protocol and will include physical examination, neurological examination, dermatology examination, bone assessment (Tanner stage < 4-5), Karnofsky/Lansky score, cardiac function, clinical adverse events (AEs), laboratory variables (eg, hematology and serum chemistries), and vital signs.
Patients with an underlying visual function deficit related to the primary malignancy or OPG will have a visual acuity examination at Screening, every radiographic response assessment, EOT Visit, and continue every 6 months during LTFU (Arm 1 and Arm 2).
In patients 2 years of age or older, Health-Related Quality of Life will be assessed using the Pediatrics Quality of Life**Core (PedsQL Core), Pediatrics Quality of Life**Cancer (PedsQL-Cancer), and PROMIS® assessment for the patient or parent/caregiver.

Study burden and risks

Risks associated with study drug administration as explained above in Section E9. What risks does participation involve for human subjects?

Risks and discomforts associated with study procedures are as follows:
Many of the tests in this study, such as an MRI, are regularly done as a part of standard treatment for this type of tumor. However, these tests may be done more frequently during this study.
- Biopsy: Only in patients for whom an archival tumor tissue sample is not available. A biopsy involves the removal of a small amount of tissue from the tumor so that it can be examined. The sample may be removed from the tumor by a needle biopsy, which involves the insertion of a needle into the precise area of the tumor, usually using x-ray guidance. Although both surgical biopsy or needle biopsy are usually safe, there are some potential risks: swelling or bleeding, infection, blood clots, reaction to anesthesia.
- MRI: MRI scans use powerful magnets, and some MRI scanners are very narrow. With a certain type of dye used for MRI scans, some patients with kidney disease may have a severe reaction of skin thickening, joint pain and/or swelling, and in rare cases, lung, and heart problems and even death. Sedation or anesthesia may be required for a MRI, which have their own side effects.
- X-ray: This test uses a machine to allow light to pass through the body to create a picture inside for the investigator to see. This test will be done to check the patient's bones in the wrist/hand. The patient should stay very still

while the test is being done, which may feel uncomfortable.
- Blood Samples: Side effects of having blood taken may include pain, redness, swelling, and/or bruising where the needle enters the body. Rare instances of fainting, excess bleeding, blood clotting, or infection have occurred.
- Electrocardiograms: To perform the test, sticky patches (electrodes) will be placed on the skin to record the patient's heart*s activity. the patient may feel some discomfort when the technician removes the adhesive patches after the procedure, similar to pulling off an adhesive bandage. The adhesive patches can also cause skin irritation or rash in some patients.
- Echocardiogram (ECHO): There are no risks expected from ECHO.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Newborns

Inclusion criteria

- Less than 25 years of age with a low-grade glioma harboring a documented known activating RAF alteration
- Histopathologic diagnosis of glioma or glioneuronal tumor
- At least one measurable lesion as defined by Response Assessment in Pediatric Neuro-Oncology (RANO) criteria
- Meet indication for first-line systemic therapy

Exclusion criteria

- Patient has any of the following tumor-histological findings:
a) Schwannoma
b) Subependymal giant cell astrocytoma (Tuberous Sclerosis)
c) Diffuse intrinsic pontine glioma, even if histologically diagnosed as WHO Grade I-II
- Patient*s tumor has additional pathogenic molecular alterations
- Known or suspected diagnosis of neurofibromatosis Type 1 or 2 (NF-1/NF-2)
- Prior or ongoing nonsurgical anticancer therapy for this indication (eg, chemotherapy, oral/IV targeted therapy) including radiation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	27-02-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Cellcristin
Generic name:	Vincristine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	n/a
Generic name:	DAY101 (tovorafenib)
Product type:	Medicine
Brand name:	Ribocarbo-L
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vinblastine STADA
Generic name:	Vinblastine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-05-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-05-2024

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-06-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510742-13-00
EudraCT	EUCTR2022-001363-27-NL
ClinicalTrials.gov	NCT05566795
CCMO	NL82554.041.22