Essai Clinique

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Titre	A Phase 3 Randomized Study of Selumetinib Versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) Associated Low-Grade Glioma (LGG)
Protocole ID	COG-ACNS1831
ClinicalTrials.gov ID	NCT03871257
Type(s) de cancer	Cerveau (SNC)
Phase	Phase III
Type étude	Clinique
Médicament	Selumetinib versus Carboplatine/Vincristine
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Statut	Actif en recrutement
Date d'activation	21-06-2022
But étude	This phase III trial studies if selumetinib works just as well as the standard treatment with carboplatin/vincristine (CV) for subjects with NF1-associated low grade glioma (LGG), and to see if selumetinib is better than CV in improving vision in subjects with LGG of the optic pathway (vision nerves). Selumetinib is a drug that works by blocking some enzymes that low-grade glioma tumor cells need for their growth. This results in killing tumor cells. Drugs used as chemotherapy, such as carboplatin and vincristine, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. It is not yet known whether selumetinib works better in treating patients with NF1-associated low-grade glioma compared to standard therapy with carboplatin and vincristine.

Critères d'éligibilité	• Patients must have a body surface area (BSA) of >= 0.5 m^2 at enrollment
	• Patients must have neurofibromatosis type 1 (NF1) based on clinical criteria and/or germline genetic testing
	• Patients must be newly diagnosed or have previously diagnosed NF-1 associated LGG that has not been treated with any modality other than surgery
	• For patients with optic pathway gliomas (OPGs):
	  • Newly-diagnosed patients with OPG are eligible if there are neurologic symptoms (including visual dysfunction, as defined below) or other exam findings associated with the tumor
	  • Previously-diagnosed patients with OPG are eligible if they have new or worsening neurologic symptoms (including visual dysfunction, as defined below) or have tumor growth
	  • For both newly-diagnosed and previously-diagnosed OPG, the patient may be eligible, irrespective of whether there has been tumor growth or other neurological symptoms or worsening, if they meet at least one of the following visual criteria:
	  • Visual worsening, defined as worsening of visual acuity (VA) or visual fields (VF) documented within the past year (by examination or history); OR
	  • Significant visual dysfunction (defined as VA worse than normal for age by 0.6 logMAR [20/80, 6/24, or 2.5/10] or more in one or both eyes)

- For patients with LGG in other locations (i.e., not OPGs):
    - Newly-diagnosed patients with LGG are eligible if there are neurologic symptoms or other exam findings associated with the tumor
        - NOTE: Newly-diagnosed patients with LGG without associated neurologic symptoms or exam findings are not eligible
    - Previously-diagnosed patients with LGG are eligible if they have new or worsening neurologic symptoms or have tumor growth
- Although not required, if a biopsy/tumor resection is performed, eligible histologies will include all tumors considered LGG or low-grade astrocytoma (World Health Organization [WHO] grade I and II) by 5th edition WHO classification of central nervous system (CNS) tumors with the exception of subependymal giant cell astrocytoma
- Patients must have two-dimensional measurable tumor >= 1 cm^2
- Patients with metastatic disease or multiple independent primary LGGs are allowed on study
- Creatinine clearance or radioisotope glomerular filtration Rate (GFR) >= 70 mL/min/1.73 m^2 OR a serum creatinine based on age/gender within 7 days prior to enrollment as follows:
    - Age; maximum serum creatinine (mg/dL)
    - 2 to < 6 years; 0.8 (male) and 0.8 (female)
    - 6 to < 10 years; 1 (male) and 1 (female)
    - 10 to < 13 years; 1.2 (male) and 1.2 (female)
    - 13 to < 16 years; 1.5 (male) and 1.4 (female)
    - >= 16 years; 1.7 (male) and 1.4 (female)
- Total bilirubin =< 1.5 x upper limit of normal (ULN) for age within 7 days prior to enrollment (children with a diagnosis of Gilbert's syndrome will be allowed on study regardless of their total and indirect [unconjugated] bilirubin levels as long as their direct [conjugated] bilirubin is < 3.1 mg/dL)
- Serum glutamate pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) =< 3 x upper limit of normal (ULN) = 135 U/L within 7 days prior to enrollment. For the purpose of this study, the ULN for SGPT is 45 U/L
- Albumin >= 2 g/dL within 7 days prior to enrollment
- Left ventricular ejection fraction (LVEF) >= 53% (or institutional normal; if the LVEF result is given as a range of values, then the upper value of the range will be used) by echocardiogram within 7 days prior to enrollment
- Corrected QT (QTc) interval =< 450 msec by electrocardiography (EKG) within 7 days prior to enrollment
- Absolute neutrophil count >= 1,000/uL (unsupported) within 7 days prior to enrollment
- Platelets >= 100,000/uL (unsupported) within 7 days prior to enrollment
- Hemoglobin >= 8 g/dL (may be supported) within 7 days prior to enrollment
- Patients with a known seizure disorder should be stable and should have not experienced a significant increase in seizure frequency within 2 weeks prior to enrollment
- Patients 2-17 years of age must have a blood pressure that is =< 95th percentile for age, height, and gender at the time of enrollment. Patients >= 18 years of age must have a blood pressure =< 130/80 mmHg at the time of enrollment (with or without the use of antihypertensive medications).
    - Note: Adequate blood pressure can be achieved using medication for the treatment of hypertension
- All patients must have ophthalmology toxicity assessments performed within 4 weeks prior to enrollment
- For all patients, an MRI of the brain (with orbital cuts for optic pathway tumors) and/or spine (depending on the site(s) of primary disease) with and without contrast must be performed within 4 weeks prior to enrollment
- For patients who undergo a surgery on the target tumor (not required), a pre- and post-operative* MRI of the brain (with orbital cuts for optic pathway tumors) or spine (depending on the site(s) of primary disease) with and without contrast must also be performed within 4 weeks prior to enrollment
    - The post-operative MRIs should be performed ideally within 48 hours after surgery if possible
- Patients must have a performance status corresponding to Eastern Cooperative Oncology Group (ECOG) scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients =< 16 years of age
- Patients must have the ability to swallow whole capsules
- Patients must have receptive and expressive language skills in English or Spanish to complete the quality of life (QOL) and neurocognitive assessments
- All patients and/or their parents or legal guardians must sign a written informed consent.
- All institutional, Food and Drug Administration (FDA), and National Cancer Institute (NCI) requirements for human studies must be met.

Critères d'exclusion

- Patients must not have received any prior tumor-directed therapy including chemotherapy, radiation therapy, immunotherapy, or bone marrow transplant. Prior surgical intervention is permitted
- Patients with a concurrent malignancy or history of treatment (other than surgery) for another tumor within the last year are ineligible
- Patients may not be receiving any other investigational agents
- Patients with any serious medical or psychiatric illness/ condition, including substance use disorders likely in the judgement of the investigator to interfere or limit compliance with study requirements/treatment are not eligible

- Patients who, in the opinion of the investigator, are not able to comply with the study procedures are not eligible
- Female patients who are pregnant are not eligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential
- Lactating females who plan to breastfeed their infants are not eligible
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 12 weeks after stopping study therapy are not eligible
    - Note: Women of child-bearing potential and males with sexual partners who are pregnant or who could become pregnant (i.e., women of child-bearing potential) should use effective methods of contraception for the duration of the study and for 12 weeks after stopping study therapy to avoid pregnancy and/or potential adverse effects on the developing embryo
- Cardiac conditions:
    - Known genetic disorder that increases risk for coronary artery disease. Note: The presence of dyslipidemia in a family with a history of myocardial infarction is not in itself an exclusion unless there is a known genetic disorder documented
    - Symptomatic heart failure
    - New York Heart Association (NYHA) class II-IV prior or current cardiomyopathy
    - Severe valvular heart disease
    - History of atrial fibrillation
- Ophthalmologic conditions:
    - Current or past history of central serous retinopathy
    - Current or past history of retinal vein occlusion or retinal detachment
    - Patients with uncontrolled glaucoma
        - If checking pressure is clinically indicated, patients with intraocular pressure (IOP) > 22 mmHg or ULN adjusted by age are not eligible
    - Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor, or strabismus) or longstanding orbito-temporal plexiform neurofibroma (PN, such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study
- Treatments and/or medications patient is receiving that would make her/him ineligible, such as:
    - Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to study enrollment even if less than 100% of the daily recommended dosing for vitamin E
    - Surgery within 2 weeks prior to enrollment, with the exception of surgical placement for vascular access or cerebrospinal fluid (CSF) diverting procedures such as endoscopic third ventriculostomy (ETV) and ventriculo-peritoneal (VP) shunt.
        - Note: Patients must have healed from any prior surgery prior to enrollment
- Patients who have an uncontrolled infection are not eligible