diffuse intrinsic pontine glioma (DIPG), whose long-term survival is virtually non-existent. In the case of DIPG, the only treatment option that has shown an increase in survival has been radiotherapy, improving symptoms and reducing tumour size in 80% of cases. However, this treatment remains merely palliative and survival rates are still very low. On the other hand, medulloblastoma has experienced a significant improvement in cure rates thanks to the latest advances, but the sequels in patients are significant and almost 40% experience relapse or progression. Thus, there is a need to develop therapeutic alternatives aimed to get a more effective and less toxic treatment, especially for a disease such as DIPG, which is currently incurable. dCELYVIR is a new therapeutic strategy composed by patient's own stem cells carrying an oncolytic adenovirus, which has shown an adequate safety profile, as well as significant penetration of the blood-brain barrier in preclinical studies. However, information in the clinic is limited and more research is needed to further develop this therapy. The aim of this study is to evaluate the safety, tolerability and efficacy of AloCELYVIR, based on stem cells from healthy donors, in monotherapy in patients with relapsed/progressing medulloblastoma or in combination with radiotherapy in patients with DIPG.

Main Objective

1. To evaluate the safety of the combination of AloCelyvir and radiotherapy in patients with newly diagnosed DIPG.
2. To evaluate the safety of AloCelyvir in monotherapy in patients with progression/relapse in medulloblastoma.

Primary Endpoints

1. Dose-Limiting Toxicities rate (DLTs)

Temporary moments of secondary assessment

1. Every week during 4 weeks.

Secondary Objective

1. Measurement of antitumor activity (measured as objective response rate [complete response and partial response] of the combination/monotherapy) 2. Feasibility of the combination/monotherapy
3. Safety (expansion phase)
4. Estimation of progression-free survival (PFS)
5. Estimation of overall survival (OS)
6. To compare the progression-free survival and overall survival of cohort A and B with a historical cohort of newly diagnosed DIPG patients and with a historical cohort of patients with relapse medulloblastoma.
7. To study the antiadenoviral immune response in patients
8. To Study the replication kinetics of Icovir-5

Secondary Endpoints

1. Objective response rate 2. Rate of patients meeting selection criteria who can receive at least one cycle of Alo-Celyvir
3. Progression-free survival (PFS)
4. Overall survival
5. To compare the progression-free survival and overall survival of cohort A and B with a historical cohort of newly

diagnosed DIPG patients and with a historical cohort of patients with relapse medulloblastoma
6. Adverse Events Rate
7. Kinetics of anti-Adenovirus serotype 5 antibody titers
8. Kinetics of the number of CD8 antiadenovirus T-lymphocytes
9. Kinetics of circulating adenoviral particles

Temporary moments of secondary assessment

1. Every 12 weeks since the start of treatment until disease progression.
2. Since the start of recruitment until the first dose of AloCelyvir. 3. Every 12 weeks since the start of treatment until disease progression.
4. Every 12 weeks since the start of treatment until death.
5. Every 12 weeks since the start of treatment until disease progression.
6. Every week during 8 weeks and at week 10 of study treatment. 7. Every week during 8 weeks and at week 10 of study treatment.
8. Every week during 8 weeks and at week 10 of study treatment.
9. Every week during 8 weeks and at week 10 of study treatment.

Inclusion criteria

INCLUSION CRITERIA COMMON TO THE TWO COHORTS 1. Patients aged 1 to 21 years. 2. Written informed consent signed by the patient's legal representative and, if applicable, the minor (informed consent in patients 12 years of age or older). 3. Measurable or evaluable disease according to RANO criteria. 4. Appropriate functional status, organic function (renal, hepatic) and hematological values: o Lanksy and karnofsky functional status >=50%. Patients who use a wheelchair due of tumor-associated paralysis will be considered as outpatients for functional status evaluation. o Haematology function: • Platelet count >=75.000/µL (without support for 3 days) • Absolute neutrophil count (ANC) >=500/ µL (without growth factor for 3 days) • Hemoglobin >= 8 g/dL (Transfusion allowed) o Liver and renal function • Glomerular filtration rate (GFR) (estimated by Schwartz) >60 mL/min/1.73 m2 • Total bilirubin <= 1.5 × the upper limit of normal (ULN) • Transaminases (GOT and GPT) <=3 × the upper limit of normal (ULN). <= 5 times ULN for patients with hepatic metastasis. 5. Patient able to comply with treatment and schedule of visits and assessments 6. Life expectancy of >=8 weeks. 7. Highly effective contraceptive methods (Pearl rate <1) for sexually active males and females of childbearing age (CTFG, Reccomendations related to contraception and pregnancy in clinical trials V 1.1 2020--15). A woman is considered to have reproductive potential, i.e., childbearing, when she has reached menarche through menopause, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy 8. Highly sensitive negative pregnancy test in blood or urine for childbearing females. INCLUSION CRITERIA COMMON TO THE COHORT A 1. Patient with new DIPG diagnosis (clinical, radiological, or histological in case a biopsy was performed before being included in the study). 2. Not having received previous treatment with radiotherapy or chemotherapy. 3. Patient able to receive radiotherapy INCLUSION CRITERIA COMMON TO THE COHORT B 1. Patient diagnosed with relapsed and/or refractory medulloblastoma. Patients must have received at least surgery, radiation therapy and chemotherapy as part of standard treatment and have failed these treatments before they can participate in this study. 2. To be recovered to <= G1 from the toxic effects according to CTCAE derived from the previous treatments, excluding ototoxicity, alopecia and peripheral neurotoxicity.

Exclusion criteria

EXCLUSION CRITERIA COMMON TO THE TWO COHORTS
1. Previous treatment with Celyvir or AloCelyvir.
2. Known active bacterial, viral, fungal or parasitic infection not controlled

3. Known active Hepatitis B or C virus or VIH infection.
4. If patients are treated with corticosteroids, they should be clinically stable and on stable or tapering doses of steroids for at least one week.
5. To be receiving another anti-cancer treatment not foreseen in this protocol or to anticipate receiving it during the patient's participation in the same concomitant with the experimental treatment
6. Clinically significant or uncontrolled serious active and past systemic diseases that may pose an added risk to the patient
EXCLUSION CRITERIA COMMON TO THE COHORT A
1. Spontaneous massive intratumoral bleeding. Patients with post-operative bleeding (in case of biopsy or surgery) may be included in the study provided that the bleeding is controlled. The same rule applies for other postoperative complications (infection, loss of cerebrospinal fluid, absence of wound closure, subdural collection ...)
2. Patients who have previously received radiotherapy to the brain stem for another malignancy
EXCLUSION CRITERIA COMMON TO THE COHORT B
1. Washout period respect to previous treatments:
- At least two weeks since the last dose of chemotherapy. For patients receiving low-dose metronomic oral chemotherapy, this period is at least one week.
- At least four weeks since the autologous hematopoietic stem cell transplant
- At least two weeks since the last focal radiotherapy or six weeks in case of cranio-spinal radiotherapy.
- At least 2 weeks or 5 half-lifes (whichever occurs first) since the last dose of a biological or investigational treatment.

Calendar

(Last Update: 13/07/2021)

Authorization	Start of Trial	First patient inclusion	Halted	Restarted
19/04/2021	Not aported	Not aported	Not aported	Not aported

End of recruitment	Premature end (Spain)	Premature End (Global)	Trial end (Spain)	Trial end (Global)
Not aported	Not aported	Not aported	Not aported	Not aported

Sponsor

Fundación de Investigación Biomédica Hospital Niño Jesús España

Avenida Menéndez Pelayo, 65 28009 Madrid

Contact Person

APICES SOLUCIONES S.L - Clinical Operations Department

+34 91 8166804 100

ana.moreno@apices.es

Monetary support: Asociacion Unidos contra el DIPG / Fundación el Sueño de Vicky / Fundación Cris Contra el Cáncer|

Ceim

CEIm Hospital Infantil Universitario del Niño Jesús

Avda. Menéndez Pelayo, 65 28009 Madrid

ceic.hnjs@salud.madrid.org

Sites

Active (12/07/2021)

HOSPITAL INFANTIL UNIVERSITARIO NIÑO JESUS

Madrid

MADRID

Servicio de Oncohematología

Medication

ALOCELYVIR

Solución para perfusión

-

Active Principles: Alogenic bone marrow stem adult mesenchymal cells expanded Infected with Icovir-5|

Experimental

No results