# ACT001 for the Treatment of Diffuse Intrinsic Pontine Gliomas and H3K27-altered High Grade Gliomas

Status: RECRUITING

## Eligibility Criteria

Sex: ALL
Age: 12 months to 39 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

1. Patients must be ≥ 12 months and ≤ 39 years of age at the time of study enrollment.
2. Diagnosis:

- Cohort A: Newly Diagnosed DIPG
    - Patients with newly-diagnosed DIPG with typical MRI findings (tumors with a pontine epicenter and diffuse involvement of at least 2/3 of the pons) with or without biopsy and have completed radiation therapy (RT) within 28 to 35 calendar day prior to start of therapy.
    - Patients must have started RT <42 calendar days from radiographic diagnosis (for non-biopsied DIPG patients only) or definitive surgery, whichever is later.
        - If a biopsy was performed, the date of surgical biopsy will be considered the date of definitive diagnostic surgery; if a patient underwent two upfront surgeries [e.g., biopsy then debulking], this is the date of the second surgery)
- Cohort B: progressive/recurrent DIPG or H3K27-altered HGG OR refractory disease
    - Patients with DIPG (no biopsy required), pathologically-confirmed (at diagnosis or recurrence) H3K27-altered DIPG, or extra-pontine H3K27-alteredHGG who have progressive/recurrent or refractory disease
    - Progressive/recurrent: patients who have progressive or recurrent disease following frontline treatment must have included at least focal RT. New lesions since completion of frontline RT qualify as progressive disease.
    - Refractory disease is defined as: Presence of persistent, measurable, abnormality on conventional MRI that is further distinguished by histology or advanced imaging, OR as determined by the treating physician and discussed with the Study Chair(s) prior to enrollment.
    - Patients with H3K27-altered spinal HGG are eligible.
    - Patients with metastatic disease are eligible.
        1. Disease Status
- Cohort A: patients may have any disease status but must have completed initial radiation therapy (RT) before enrollment.
- Cohort B: Patients must have measurable disease assessable by MRI. Patients may have extra neuronal disease.
    1. Performance Level: Karnofsky Performance Scale score ≥ 50% for patients > 16 years of age and Lansky Performance Scale score > 50% for patients ≤ 16 years of age (applies to all patients) Note: Patients who are unable to walk because of paralysis, but who are capable of using a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
    2. Prior anti-cancer therapy:
- For Cohort A ONLY:
- Surgery, radiation (focal to disease) and/or steroids (dexamethasone with goal to wean dexamethasone throughout protocol therapy) are permissible. Temozolomide administered concurrently with RT is permissible. Bevacizumab use is permitted given the last dose was administered >/= 21 days prior to enrollment. No other prior anticancer therapy for DIPG will be allowed.
- Patients must enroll and start treatment on study between 28 and 35 calendar days post-completion of RT.
- Patients must have started RT <42 calendar days of initial diagnosis (defined as the date of diagnostic biopsy or resection; if a patient underwent two upfront surgeries [e.g., biopsy then resection or debulking], this is the date of the second surgery).
- Radiotherapy must have been administered at standard dose of 54 Gy for DIPG patients. Any variances in the radiotherapy dose within 10% of the standard doses outlined above will be discussed with the Study Chair to confirm eligibility prior to study enrollment.
- For Cohort B ONLY: Patients must have fully recovered from the acute treatment related toxicities (defined as </= Grade 1 if not defined in eligibility criteria) of all prior chemotherapy, immunotherapy, radiotherapy, or any other treatment modality prior to entering on this study, with the exception of alopecia.

Notes to the above for Cohort B: Patients with chronic Grade 2 toxicities may be eligible per discretion of the Investigator and Sponsor (e.g., Grade 2 chemotherapy-induced neuropathy). Grade 2 or 3 toxicities from prior anti-tumor therapy that are considered irreversible - defined as having been present and stable for > 6 months (such as ifosfamide-related proteinuria) may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the Investigator and Sponsor.)

The wash out period between the prior anti-cancer chemotherapy, and enrollment must be:
1. Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
2. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor.
3. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of

beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
4. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
5. Monoclonal antibodies: > 21 days must have elapsed from the infusion of last dose of antibody
6. Radiation therapy:

* All Cohort B patients: Patients must have received their last fraction of focal irradiation to new sites of progressive disease \> 14 days prior to enrollment.

* Patients who received CSI must have received their last fraction \> 3 months prior to enrollment.
* Progressive/recurrent disease: Patients who received re-irradiation to primary disease must have received their last fraction \> 3 months prior to study enrollment.
* Refractory Disease:

* Patients must have completed frontline RT \> 6 months prior to enrollment.
* Patients who received re-irradiation to primary disease must have received their last fraction \> 3 months prior to study enrollment.

1. Stem Cell Transplant: Patients must be ≥ 3 months since autologous stem cell transplant. Patients who received allogenic stem cell transplant or solid organ transplant are not eligible for study

    1. Organ Function Requirements (applies to all patients)
2. Adequate bone marrow function defined as:

* Peripheral absolute neutrophil count (ANC) \> 1000/mm³
* Platelet count \> 100,000/mm³ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

1. Adequate renal function defined as:

* Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² or
* A serum creatinine based on age/gender as follows (Schwartz et al. J. Peds, 106:522, 1985): Age Maximum Serum Creatinine (mg/dL) Male Female 1 to \< 2 years 0.6 0.6 2 to \< 6 years 0.8 0.8 6 to \< 10 years 1.0 1.0 10 to \< 13 years 1.2 1.2 13 to \< 16 years 1.5 1.4 ≥ 16 years 1.7 1.4

1. Adequate liver function defined as:

* total bilirubin must be \</=1.5X institutional ULN for age
* AST (serum glutamic-oxaloacetic transaminase \[SGOT\]) / ALT (serum glutamic-oxaloacetic transaminase \[SGPT\]) ≤ 2.5 × institutional upper limit of normal
* Serum albumin ≥ 2 g/dL

1. Adequate cardiac function defined as:

* Ejection fraction of ≥ 50% by echocardiogram
* QTc ≤ 450 msec (by Bazett formula)

1. For Cohort B: Adequate neurologic function defined as:

* Patients with seizure disorders may be enrolled if seizures are well- controlled. Well controlled is defined by no increase in seizure frequency in the 7 days prior to enrollment.
* Patients with neurological deficits should have deficits that are stable for at least the 7 days prior to enrollment.

1. Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.
2. Absence of other clinically significant concomitant active medical disorder, based on the investigator's judgement.

Exclusion Criteria:

A patient who meets any of the following exclusion criteria will not be eligible in the study (Applies to both cohorts except where noted below):

1. Cohort A only: Patients with metastatic disease.
2. Concomitant medications:

- Corticosteroids:
    - Cohort A - Patients receiving corticosteroids are eligible regardless of dosing
    - Cohort B - Patients receiving corticosteroids who have been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are eligible
- Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible (Refer study inclusion criteria relating to anti-cancer therapies)
    - Cohort A - Patients that have received any anti-cancer treatment other than surgery, RT, temozolomide concurrent with RT, and/or previous bevacizumab with appropriate washout period are not eligible.
- Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
- Anticonvulsants should be used as clinically indicated. The use of enzyme inducing anticonvulsants is not permitted
- LHRH agonist / antagonists are not permitted
- High Dose Biotin (B7) supplements are not permitted

    1. Concomitant medications used with caution: selective serotonin reuptake inhibitor (SSRI) such as Lexapro, Fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram should be used with caution.
    2. Infection: Patients who currently have an uncontrolled infection (in the opinion of the PI) are not eligible.
    3. Patients who have received a prior solid organ transplantation are not eligible.
    4. Pregnant or breast-feeding women will not be entered on this study due to unknown risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are postmenarchal. Males or females of reproductive

potential may not participate unless they have agreed to use an effective contraceptive method.

5. Patients of childbearing or child fathering potential must agree to use adequate contraceptive methods (hormonal or barrier method of birth control; abstinence) while being treated on this study and for 3 months after completing therapy. Note: The definition of effective contraception will be based on the judgement of the principal investigator or a designated associate.
6. Patients who are in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
7. Patients who have previously received either ACT001 or parthenolide are not eligible.

## Conditions & Interventions

Interventions:
DRUG: ACT001
Conditions:
Diffuse Intrinsic Pontine Gliomas (DIPG), Progressive DIPG, Refractory DIPG, Recurrent DIPG, H3K27-altered High Grade Glioma
Keywords:
High Grade Glioma, Diffuse Intrinsic Pontine Glioma

## More Information

Description:
This is a Phase II open-label study to investigate the safety and efficacy of ACT001 in patients with DIPG and H3K27-altered HGG.

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