A Phase I study examining the feasibility of intermittent convection-enhanced delivery (CED) of MTX110 for the treatment of children with newly diagnosed diffuse midline gliomas

https://clinicaltrials.gov/ct2/show/NCT04264143

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Convection Enhanced Delivery (CED)  
Basic Principles

The infusion of drugs under controlled pressure to the brain parenchyma via targeted micro-catheters

• CED utilizes bulk flow rather than diffusion
• Diffuse flow: Fick’s law, \( J = -D \nabla C \),
• Bulk flow pressure gradient: Darcy’s law: \( v = -K \nabla p \)
• Few cms vs few mms

• infusion rates typically range from 0.1 to 10 μl/min
• Diffuse Intrinsic Pontine Glioma
• 10-20 new patients per year per million population
• Median survival: 9 months
• Radiation therapy is the only standard treatment
• providing benefit in 2/3 patients
• for extra 3-6 months..

El-Khury et al J Neurooncol. 2019 Oct;145(1):177-184.
HDACis and DIPG (Panobinostat, VPA)

Grasso et al Nat Med. 2015 Jun;21(6):555-9. doi
Convection Enhanced Delivery (CED)
Current Status DIPG
MTX110 preclinical work for CED

- Gills lab investigated the toxicity, distribution, and clearance of a water-soluble formulation of Panobinostat (MTX110) in Juvenile male Wistar rats ($n = 24$)
- Large-animal toxicity was investigated using a clinically relevant MRI-guided translational porcine model of CED in which a drug delivery system designed for humans was used.
- Panobinostat was administered at 30 mM to the ventral pons of 2 juvenile Large White–Landrace cross pigs.
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Singleton et al./J Neurosurg Pediatr. 2018 Sep;22(3):288-296
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| Trial Title |
|-------------|
| CED of MTX110 |

**Clinical Phase**: I

**Trial Design**: Prospective non-randomized single arm study historically controlled

**Trial Participants**: Children above the age of 3 years with newly diagnosed diffuse midline glioma

**Planned Sample Size**: Maximum 9 patients

**Treatment duration**: Maximum 2 cycles

**Planned Trial Period**: 2 years

**Follow-up duration**: Until death

**Investigational Medicinal Product**: Objectives

**Primary Endpoint**: To evaluate the safety and Maximum Tolerated Dose (MTD) of chronic MTX110 CED in children with diffuse midline gliomas

**Secondary Endpoints**: To determine the Objective Response Rate with MTX110 via CED in this population, Documentation of PFS and OS post-treatment with IMP, To determine Progression Free Survival (PFS) and Overall Survival (OS), To determine the steady state volume of drug distribution, Assessment of volumetric and metabolic changes with contrast enhancement intensity on MRI and MR spectroscopy, To evaluate the quality of life of the family and the patient that is being treated with CED

**Quality of life assessments**
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### Study Objectives

| Objectives                                                                 | Outcome measures                                                                 |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| **Primary Endpoint**                                                      |                                                                                  |
| A phase I study to evaluate the safety and Maximum Tolerated Dose (MTD) of chronic MTX110 CED in children with diffuse midline gliomas | Common Terminology Criteria for Adverse Events (CTCAE) v5.0                      |
| To determine the Objective Response Rate with MTX110 via CED in this population | Documentation of response based on Pediatric RANO criteria                        |
| To determine Progression Free Survival (PFS) and Overall Survival (OS)    | Documentation of PFS and OS post treatment with IMP                              |
| To determine the steady state volume of drug distribution                 | Assessment of volumetric and metabolic changes with contrast enhancement intensity on MRI and MR spectroscopy |
| To evaluate the quality of life of the family and the patient that is being treated with CED | QoL assessment tool: PedsQL™ 4.0 Brain Tumor Module                              |

**Secondary Endpoints**
Eligibility- Inclusion Criteria

Diagnostic criteria
- Age more than 3 years up to the 18th birthday
- Radiological diagnosis of DIPG with tumor confined to the region of the pons or bilateral thalami without cystic changes or hematoma obstructing the planned catheter trajectories
- Radiological diagnosis of bithalamic glioma tumor confined to bilateral thalami without cystic changes or hematoma obstructing the planned catheter trajectories
- Radiological features of DIPG: intrinsic, pontine based infiltrative lesion; hypointense in T1 weighted images (T1WIs) and hyperintense in T2 sequences, with mass effect on the adjacent structures and occupying at least 50% of the pons

Prior and concomitant therapy
- No prior therapy is allowed other than involved field radiotherapy (54Gy) and CSF diversion for hydrocephalus, including endoscopic third ventriculostomy (ETV) or a ventriculo-peritoneal shunt.
- No concomitant medicine or therapies for treatment are permitted while the patient is enrolled in this study.

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Eligibility- Inclusion Criteria

Subject characteristics
- Subjects must be healthy enough to tolerate surgery and general anesthesia 14 days or fewer from registration, based on the opinion of the principal investigator. This includes, but is not limited to:
  - **Performance status:**
    - Karnofsky performance status or Lansky play score of ≥70 assessed at diagnosis
  - **Hepatic:**
    - Total bilirubin: within normal institutional limits
    - AST(SGOT)/ALT(SGPT): \( \leq 2.5 \times \) institutional upper limit of normal
  - **Renal:**
    - Creatinine: within normal institutional limits
    - Creatinine clearance: ≥ 60 mL/min/1.73m² for patients with creatinine levels above institutional normal
  - **Hematopoietic:**
    - Absolute neutrophil count: ≥ 1,500/μL
    - Platelet count: ≥ 100,000/μL – no transfusion within 7 days
    - Hemoglobin level: ≥ 10g/dL – no transfusion within 7 days
    - PT and APTT: within normal institutional limits
- No documented current bleeding disorder

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**Study Schema**

- **Surgery:** Planning MRI, Drug delivery device implantation, Stereotactic biopsy
- **First pulse infusion:** Infusion with MTX110+Gd via pump for 48 hours
- **Rest:** Decrease infusion to basal rate for 5-7 days
- **Repeat Pulse Infusion:** Infusion with MTX110+Gd via pump for 48 hours
- **Pump and catheter removal:** (Day 10-14)
- **Follow up:** At weeks 1-2 and 4-6 post infusion, MRI every 3 months for 2 years as per primary treating physician

This is a phase I open label non-randomized trial.
## Infusion Pulse #1 PINE score monitoring

| Symptom | Grade | Symptom | Grade |
|---------|-------|---------|-------|
| **General** | | **Cranial Nerves** | |
| Headache | | Visual failure | |
| Nausea | | Difficulty moving right eye | |
| Vomiting | | Difficulty moving left eye | |
| Mobility | | Facial sensory changes | |
| Behavioural change | | Facial Weakness | |
| Mood | | Hearing change | |
| Incontinence | | Communication issues | |
| Seizures | | Dysphagia | |
| Constipation/ Diarrhoea | | | |
| Fever | | Body/limb sensation | |
| Breathing problems | | R Arm Weakness | |
| Hiccoughs | | L Arm Weakness | |
| | | R Leg Weakness | |
| | | L Leg Weakness | |

Hollingworth and Zacharoulis  
J Neurooncol 2020 Sep;149(2):263-272
CONVECTION-ENHANCED DELIVERY of MTX110

- 3 patients treated so far at 30 microM
- NO SAEs
- Toxicity: Grade II diplopia (1) Grade I sensation (n=1), headache Grade II (n=2)

- 1 patient progressed 8 months post treatment

![Tumor prior to infusion](image1)
![After infusion](image2)

Drug (MTX110) filling up the tumor
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