

PNOC015: An Open Label Single Arm Study of MTX110 Delivered by Convection-enhanced Delivery (CED) in Patients with Diffuse Intrinsic Pontine Glioma (DIPG) Previously Treated with External Beam Radiation Therapy

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Disclosures

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Rationale for Trial Design

- Children with diffuse intrinsic pontine glioma (DIPG) continue to have a dismal prognosis with median survival rates of about 9 months
- No standard therapy besides radiation therapy has been established
- Potentially effective therapeutic agents may fail due to poor blood-brain barrier penetration
- Direct intraparenchymal drug delivery such as CED can overcome these barriers and ensure adequate drug exposure to tumor cells
- Panobinostat has been shown to be an effective cytotoxic agent across different DIPG model systems
- MTX110, a soluble form of panobinostat, has favorable convection properties in prior large animal (pig) studies

PNOC 015 Trial Design

Newly diagnosed patient with DIPG after completion of standard of care radiation



Enrollment on PNOC015



Assignment to appropriate dose level with potential to dose escalated based on tolerability



Repeat CED with co-infusion of Prohance every 4 to 6 weeks pending tolerability and feasibility of ongoing disease control

Dose level	Concentration MTX110 (μM)	Total Volume (mL)	Day of therapy
1	30	3	Day 1
2	30	6 (3 mL each day)	Day 1, 2
3	30	8 (4 mL each day)	Day 1, 2
4	30	10 (5 mL each day)	Day 1, 2
5	30	12 (6 mL each day)	Day 1, 2
5 ^a	45	12 (6 mL each day)	Day 1, 2
6	60	12 (6 mL each day)	Day 1, 2
6 ^a	75	12 (6 mL each day)	Day 1, 2
7	90	12 (6 mL each day)	Day 1, 2

Demographics

7 eligible participants were enrolled between May 2018 – March 2020

- Median age: 8 years (range 5-20)
- Median number of CED cycles: 4 (range 2-8)
- Median follow-up time from study enrollment: 418 days (range 137-614)

Sex	Age at diagnosis	Pathology at diagnosis	Total treatment cycles (CED)	Progression free survival (months)	Overall survival (months)
F	5	Diffuse midline glioma H3K27M-mutant	2	4	14
M	9	Diffuse midline glioma H3K27M-mutant	4	7	17
M	7	Diffuse midline glioma H3K27M-mutant	8	14	26
M	11	NA – no biopsy done	4	8	21
M	20	Diffuse midline glioma H3K27M-mutant	2	9	21
M	5	Diffuse midline glioma H3K27M-mutant	2	3	11
M	8	Diffuse midline glioma H3K27M-mutant	4	5	11

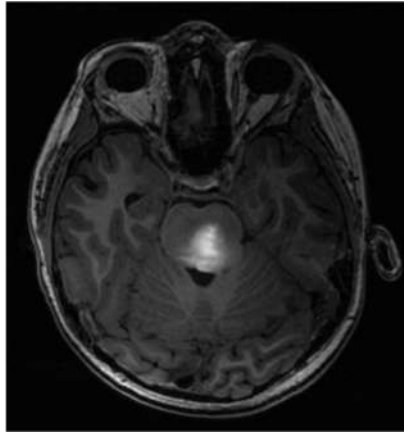
PNOC 015 Adverse Events

- Predominantly grade 1 toxicities
- Five (5) grade 3 events
- No grade 4 events

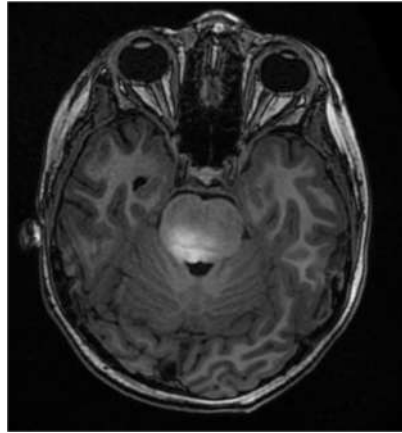
	Any Grade	Grade 3
	N (%) of Subjects	
Any Adverse Event	6 (86)	
General disorders and administration site conditions	6 (86)	-
Fatigue	3 (43)	-
Gait disturbance	3 (43)	1 (14)
Investigations	5 (71)	-
Electrocardiogram QT interval prolonged	3 (43)	-
Lymphocyte count decreased	2 (29)	-
Neutrophil count decreased	-	1 (14)
Musculoskeletal and connective tissue disorders	3 (43)	-
Muscle weakness R-sided	3 (43)	-
Nervous system disorders	6 (86)	-
Ataxia	2 (29)	-
Dizziness	3 (43)	-
Dysarthria	2 (29)	-
Facial nerve disorder	2 (29)	-
Headache	3 (43)	-
Paresthesia	2 (29)	-
Muscle weakness R-sided	-	1 (14)
Vagus nerve disorder	-	1 (14)
Stridor	-	1 (14)

CED of MTX110 leads to effective convection in DIPGs

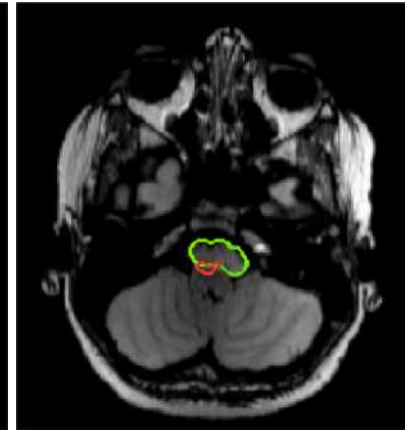
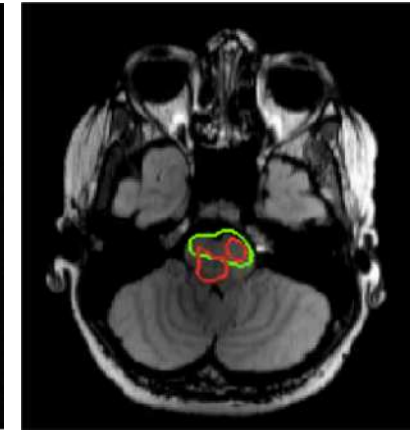
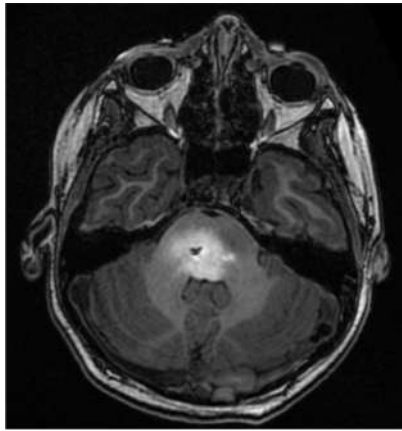
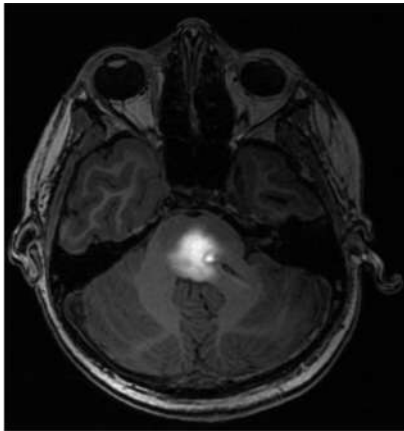
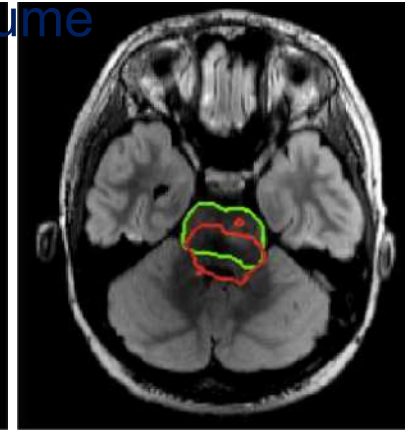
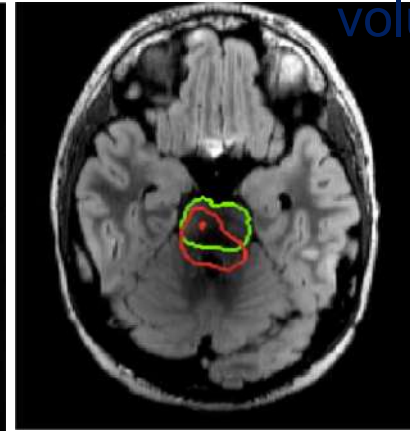
Treatment #1
Left Entry



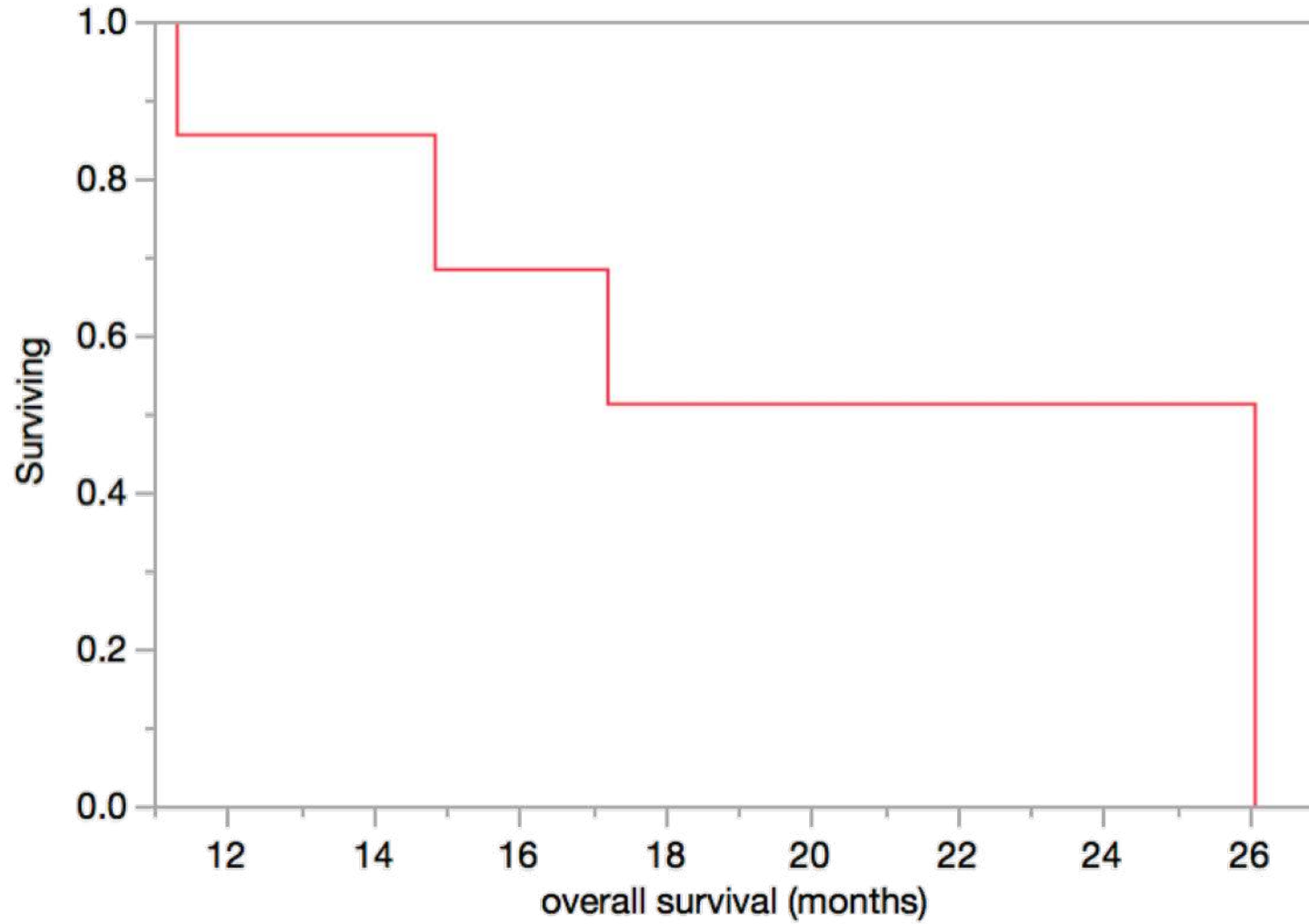
Treatment #2
Right Entry



Green: Baseline lesion volume
Red: Combined treatment



PNOC015: Overall survival outcome



PNOC015 Summary

- CED with MTX-110 in patients with DIPG is feasible, tolerable, and may lead to prolonged survival
- Co-infusion with Prohance can be used to determine ratio of Volume(infusion): Volume(distribution) – ranges between 1:3 to 1:3.5
- OS is promising but remains to be reviewed in the context of available molecular data for each patient and also in the setting that some patients may have undergone re-irradiation
- Several patients progressed outside the treatment field, suggesting that either larger infusion volumes or combination with systemic therapy should be considered in future trials
- Ongoing assessment of imaging parameters as well as QOL assessments

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Families and Patients

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