ISPNO 2020

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

Research support from:

Novartis
Bristol Meyers Squibb
Pfizer
Midatech
Regeneron
Oncoceutics
Del Mar

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Rationale for Trial Design

- Children with diffuse intrinsic pontine glioma (DIPG) conintue 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

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Enrollment on PNOC015

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

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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

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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

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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)

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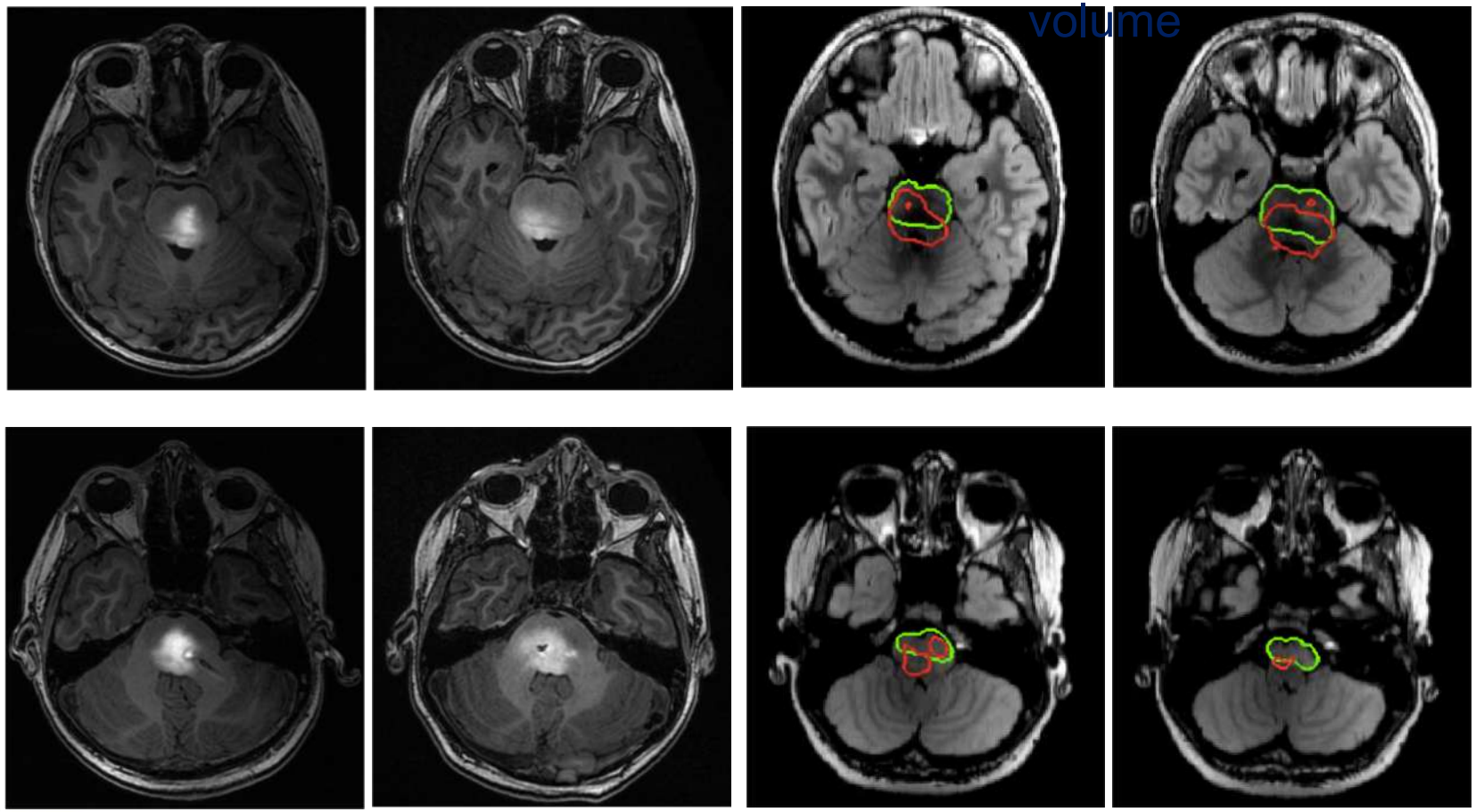
CED of MTX110 leads to effective convection in DIPGs

Treatment #1
Left Entry

Treatment #2
Right Entry

Green: Baseline lesion volume
Red: Combined treatment volume



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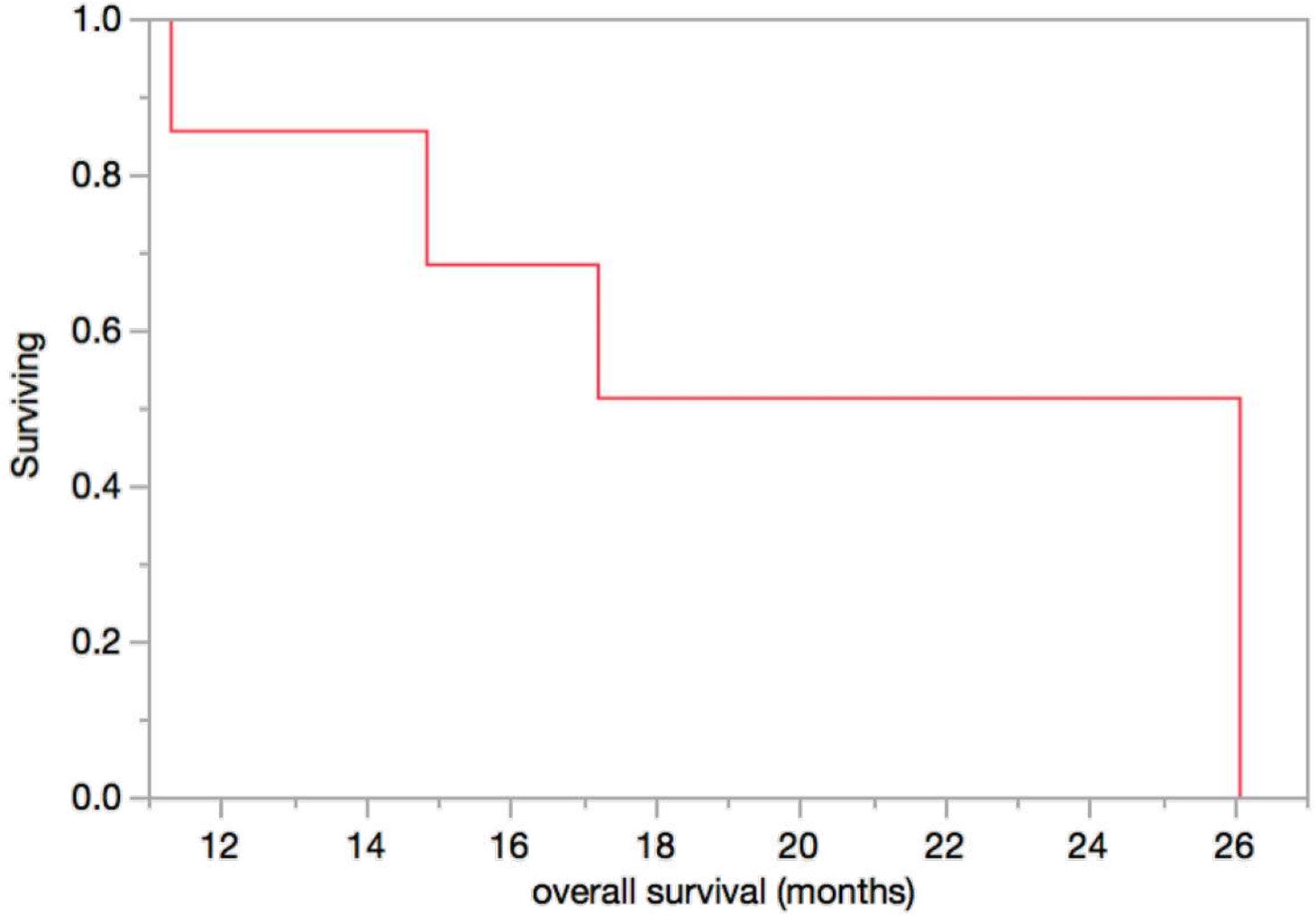
PNOC015: Overall survival outcome



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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

Acknowledgement

- Nalin Gupta
- Cassie Kline
- Carly Hoffmann
- Javier Villanueva-Meyer
- Annette Molinaro
- Shannon Raber
- Erin Bonner
- Javad Nazarian
- Mariella Filbin
- Michael Prados

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Families and Patients

Funding sources:

- The Pediatric Brain Tumor Foundation, DIPG Collaborative; Midatech Inc.

- Midatech as a sponsor had no involvement in study analysis

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