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Intratumoral Delivery of MDNA55, an Interleukin-4 Receptor Targeted Immunotherapy, by MRI-Guided Convective Delivery for the Treatment of Recurrent Glioblastoma

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BACKGROUND

- Treatment options for patients with recurrent GBM are very limited and positive outcomes remain very rare.[1,2]
- Tumor-targeted therapies for recurrent GBM has been limited by suboptimal delivery of therapeutic agents.
- Intratumoral delivery of MDNA55 using MRI-guided convection enhanced delivery (CED) is currently being tested in a Phase 2 open label study in patients with recurrent GBM (NCT02858895).
- MDNA55 is co-infused with Gadolinium-based contrast agent (GdDTPA) to allow real-time monitoring of drug distribution and to optimize intratumoral catheter placement.

MDNA55: TARGETING THE INTERLEUKIN-4 RECEPTOR

- MDNA55 consists of a bioengineered circularly permuted IL-4 (cpIL-4) fused to the catalytic domain of *Pseudomonas* exotoxin A (PE).[3]
- MDNA55 binds to IL-4 receptor (IL-4R) overexpressed by GBM and immunosuppressive cells of the tumor microenvironment.[4-7]
- This results in internalization of MDNA55 in the target cells where protease-mediated cleavage of the pro-apoptotic domain of MDNA55 (i.e. PE) results in cell death by arresting protein synthesis.[8]

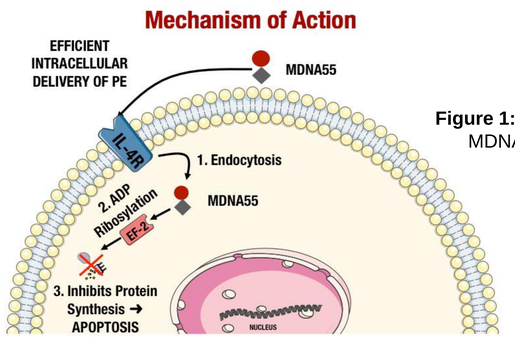


Figure 1: Schematic representation of MDNA55 mechanism of action

MDNA55: A Molecular Trojan Horse

MDNA55-05 PHASE 2 STUDY DESIGN

An open-label, non-randomized, Phase 2, multicenter study of Convection-Enhanced Delivery (CED) of MDNA55 in adults with recurrent or progressive Glioblastoma (n=52) ClinicalTrials.gov ID#: NCT02858895

DIAGNOSIS	PLANNING	SINGLE TREATMENT	FOLLOW-UP
• GBM at 1st or 2nd relapse • KPS ≥ 70 • Tumor Diameter ≥ 1 cm, ≤ 4 cm	• MRI - Tumor Size and Location • Optimal Catheter Trajectory(ies)	• Surgical Placement of 1-4 Catheters • Real-Time Monitoring of MDNA55 Distribution (GdDTPA)	• Patient Safety • Tumor Response Assessment by RANO-based criteria **Primary Endpoint:** - ORR **Secondary Endpoints:** - OS - PFS

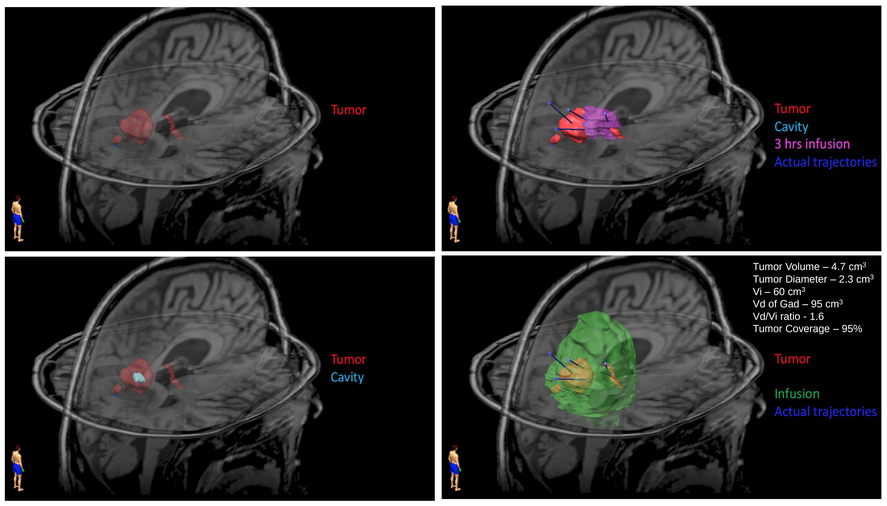
METHODS:

Table 1. Key CED Parameters

Parameters	Group 1	Group 2
Drug Conc.	1.5 µg/mL	1.5 - 3.0 µg/mL
Vol of Infusion	Based on tumor size	Fixed (60 mL)
Tracer / conc.	Gadolinium; 7mmol	Gadolinium; 7mmol (then 2mmol*)
Flow rate	Up to 50 µL/min/catheter	Total flow rate of all catheters does not exceed 50 µL/min
# Catheters / Placement	1 - 4 catheters in tumor region	4 catheters, if possible (min of 2 catheters in tumor region and remaining catheters within 2 cm of peritumoral margin)
Real-Time Infusion Monitoring	First 3 - 6 hours of infusion	
Total Infusion Time	Up to 48 hours	

*Concentration of gadolinium was reduced to 2 mmol in later versions of the protocol due to FDA and EMA recommendation to minimize exposure in humans.

Catheter trajectory planning and infusate distribution was performed using Brainlab iPlan® Flow software. Percent coverage was calculated based on the fraction of the target volumes covered by the determined gadolinium distribution at end of infusion (example shown below).



RESULTS:

To date, 39 subjects have been enrolled in this clinical trial. Preliminary results of MDNA55 distribution are available for 23 subjects. Total volume of MDNA55 was initially administered to subjects based on tumor size (Table 1, Group 1).

Table 2. Subjects receiving adaptive infusion volumes based on tumor size (n=12)

	Vol of enhancing mass (cm3)	Vol of infusion (mL)	Vol of distribution (mL)	% Coverage Enhancing lesion
Mean (stdev)	8.2 (7.5)	32.7 (18.3)	66.4 (29.8)	74.7% (16.9)
Median (range)	5.3 (1.6 – 25.5)	27.0 (12.0 – 66.0)	58.9 (30.4 – 130.2)	77.2 (46.0 – 94.3)

Evaluation of drug distribution patterns and safety data suggested that improvements to drug distribution could be further enhanced by moving to a fixed volume of 60 mL administered via 4 catheters and allowing placement outside the peritumoral area. (Table 1, Group 2).

Table 3. Subjects receiving fixed infusion volume of 60 mL (n=11)

	Vol of enhancing mass (cm3)	Vol of infusion (mL)	Vol of distribution (mL)	% Coverage Enhancing lesion
Mean (stdev)	8.3 (4.5)	59.6 (0.9)	103.1 (43.6)	59.9% (23.1)
Median (range)	6.8 (4.0 – 16.9)	60.0 (57.6 – 60.3)	76.3 (58.4 – 175.3)	63.1% (21.9 – 97.2)

Although increased infusion volumes (exceeding 40 mL) led to increased mean volume of distribution, it did not improve the target percentage coverage of the enhancing lesion (Table 3, Fig 2).

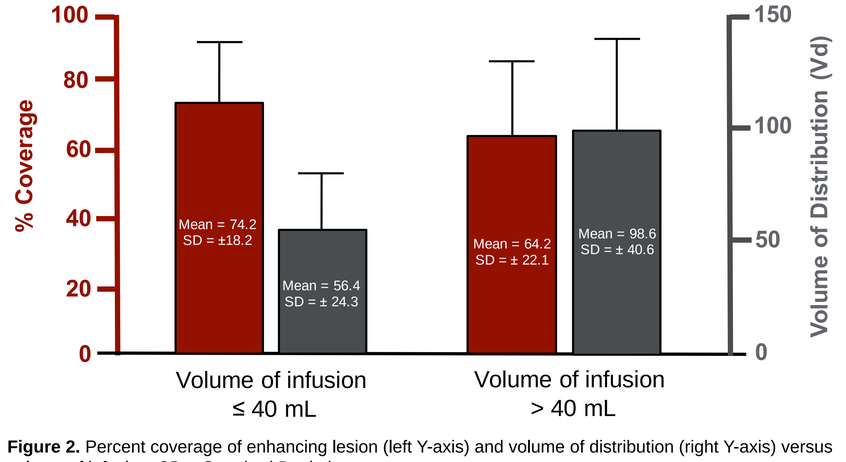


Figure 2. Percent coverage of enhancing lesion (left Y-axis) and volume of distribution (right Y-axis) versus volume of infusion; SD = Standard Deviation

SAFETY OF MDNA55

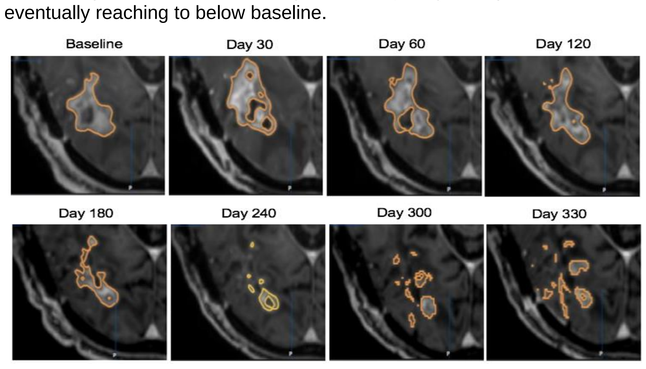
- No systemic toxicity following doses of 18 – 240 µg of MDNA55.
- No clinically significant laboratory abnormalities.
- Drug-related adverse events were primarily neurological/aggravation of pre-existing neurological deficits characteristic with GBM.

AEs ≥ Grade 3	Worst CTCAE Grade (n)		Relatedness[a]	SAE
	Grade 4	Grade 3	I = Infusion D = Drug	Y = Yes N = No
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Peritumoral edema	1		I	Y
Nervous System Disorders				
Seizure		2	D / D	Y / N
Hemiparesis		2	D, I / D, I	N / N
Hydrocephalus[b]		1	D, I	Y
Hemiplegia		1	D	Y
Stroke		1	I	Y
Psychiatric Disorders				
Depression		1	D, I	N

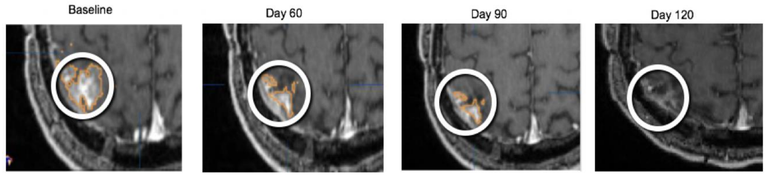
SAE = Serious Adverse Event
[a] As per Investigator or Sponsor
[b] The SAE of Hydrocephalus was assessed to be unrelated to study drug and the infusion procedure by the sponsor due to temporal gap.

EFFICACY OF MDNA55: PATTERNS OF RESPONSE

Case 1: Subject experienced increase in contrast enhancement lasting over 120 days, due to pseudo-progresssion, the result of local tissue reaction to inflammatory infiltration seen with immunotherapies. Over the following 8 months, subject experienced continual tumor decline eventually reaching to below baseline.



Case 2: Early onset response. Subject with a partial response (PR); tumor continued to decline significantly after MDNA55 treatment in the absence of any pseudo-progression. Subject is still ongoing on trial.



CONCLUSIONS

- Realtime imaging with co-infused GdDTPA distribution enables optimization of catheter placement and infusion parameters.
- Infusion volumes exceeding 40 mL and placement of catheters outside the enhancing tumor did not improve the target percentage coverage of the tumor and may contribute to increased safety events.
- Under the current protocol version, all subjects are receiving individualized volume of MDNA55 (according to tumor size), but not exceeding 40 mL to minimize risks of target effects.
- There is early evidence of sustained disease control and biologic activity of MDNA55.
- Further refinement of MDNA55 regime can enhance patient benefits.

REFERENCES

1. Keles GE *et al.* J Neurosurg, 2004.
2. Weller M *et al.* Neuro-Oncology, 2013.
3. Kreitman RJ *et al.* Proc Natl Acad Sci USA, 1994.
4. Puri RK *et al.* Int J Cancer, 1994.
5. Puri S. *et al.* Cancer, 2005.
6. Joshi BH *et al.* Cancer Res, 2001.
7. Joshi BH *et al.* British J of Cancer, 2002.
8. Wedekind JE *et al.* J. Mol. Biol., 2001.

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