Understanding Biological Activity, Tumor Response and Pseudo-progression in a Phase-2b Study of MDNA55 in Adults with Recurrent or Progressive Glioblastoma

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BACKGROUND

- MDNA55 is an experimental agent in clinical development for intra-tumoral treatment of recurrent glioblastoma (GBM) and other central nervous system tumors by convection-enhanced delivery (CED).
- Pseudo-progression (PsP) in GBM:
  - is characterized by increased contrast enhancement on MRI, indistinct from underlying tumor (true) progression.
  - commonly occurs following radiotherapy with temozolomide[1] and immunotherapies.
  - is the result of local tissue reaction resulting from extensive inflammatory infiltration, increased vascular permeability, tumor necrosis and oedema.
  - begins to appear in serial neuroimaging within 3 months of causative exposure, can have delayed presentation after 6 months.[2,3]
  - creates a significant confounder in evaluating response to immunotherapies.[4]
  - is difficult to distinguish from true progression using routine clinical MRI.
  - requires pathological confirmation or use of advanced MRI techniques.
- Natural history of PsP can differ according to causative agent
  - PsP has been described in clinical trials with MDNA55.[5,6]
  - Unmasking of underlying responses can take several months.[5,6]
- PsP can lead to premature discontinuation of effective therapies if not recognized.
- In this study, we explore the use of supportive diagnostic modalities to aid in accurate response assessments and argue the importance of refining overall response tools according to treatment type.

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).[7]
- MDNA55 binds to IL-4 receptor (IL-4R) overexpressed by GBM and immunosuppressive cells of the tumor microenvironment.[8-11]
- 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.[12]

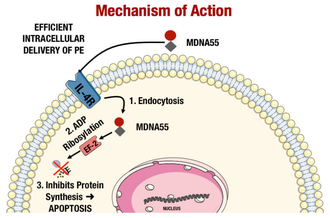


Figure 1: Schematic representation of MDNA55 mechanism of action

MDNA55-05: PHASE 2b 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

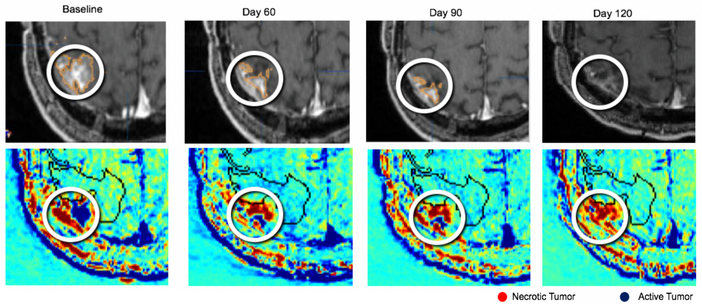
DIAGNOSIS	PLANNING	SINGLE TREATMENT	FOLLOW-UP
• GBM at 1st or 2nd relapse • KPS ≥ 70 • Tumor Diameter ≥ 1 cm, ≤ 4 cm	• MRI - Tumor Size and Location • Optimal Catheter Trajectory(ies)	• Surgical Placement of 1-4 Catheters • Real-Time Monitoring of MDNA55 Distribution (GdDTPA)	• Patient Safety • Tumor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

RESPONSE PATTERNS SEEN AFTER MDNA55 TREATMENT

To date, 34 subjects have been enrolled in this clinical trial. Male subjects comprise 65% of the population and median age was 55 (range 35-77). Prior treatments include surgery (n=34), radiation (n=34) and temozolomide (n=33).

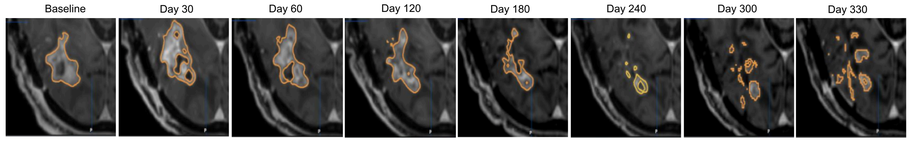
Review of some early post-treatment MRIs show extensive changes to enhancement which show increases lasting several months after treatment and then take another several months to resolve. Multi-modal MRI helps differentiate changes due to progression from local tissue reactions (pseudo-progression). Response patterns seen after MDNA55 include early progression, early onset response and delayed onset response.

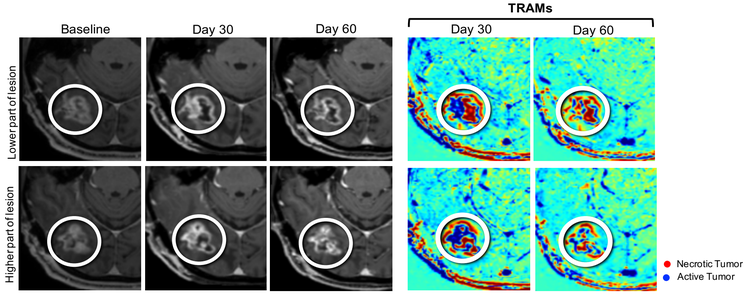
CASE 1: SUBJECT SHOWING EARLY ONSET RESPONSE



Subject with a partial response (PR): tumor continued to decline significantly after MDNA55 treatment in the absence of any pseudo-progression. Treatment Response Assessment Maps (TRAMs, **lower panels**), a novel imaging modality to distinguish pseudo-progression from progression[13], taken at Days 60, 90 and 120 show a gradual decline in the size of active tumor (blue) and an increase in necrotic tumor (red) when compared to baseline.

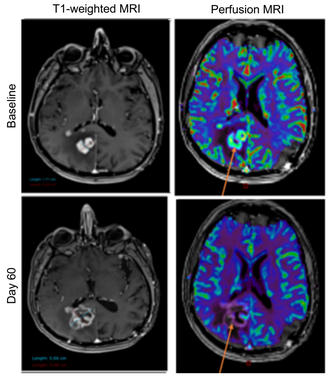
CASE 2: SUBJECT SHOWING DELAYED ONSET RESPONSE

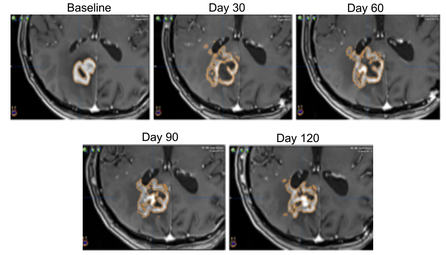




Subject experienced increase in contrast enhancement lasting over 120 days, however TRAMs show improvement occurring between Day 30 and Day 60 in the lesion area, showing mostly red (necrotic) regions at Day 60. Over the following 8 months, subject experienced continual tumor decline eventually reaching to below baseline; however, it took until Day 180 to see resolution of pseudo-progression. This subject has since received a 2nd infusion of MDNA55.

CASE 3: SUBJECT SHOWING DELAYED ONSET RESPONSE





Perfusion-MRI measures the amount of blood uptake in tissue. Increase in contrast enhancement in T1-weighted MRI at Day 60 is suggestive of progression, however decrease blood uptake by perfusion MRI (**arrows**) indicate decreased active tumor and suggesting pseudo-progression. This shows the diagnostic difference between perfusion and conventional post contrast imaging, and further supports the requirement for multi-modal MRI in determining the underlying tumor response to MDNA55.

SAFETY

- 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.
- Study recruitment is ongoing with treatment doses up to the established MTD of 240 µg.

DISCUSSION

- Tumor response assessment tools (e.g. RANO, iRANO, mRANO) can be compromised by presence of PsP
  - Cases 2 and 3 may have been considered progressive disease (PD)
  - Natural history of PsP varies by tumor type and by experimental agent
  - Limitations / discontinuations with one-off treatments (as opposed to ongoing cyclical treatments with ongoing toxicities)
- Next generation of RANO-based assessments for immuno-active therapies need:
  - Use of supportive diagnostic modalities (biopsy, advanced imaging)
  - Alignment with current thinking in other solid tumours (imRECIST)[14]
  - Consideration of best overall response occurring after apparent initial progressive disease

CONCLUSIONS

- Demonstrated biologic activity of MDNA55 in recurrent GBM
  - Imaging suggestive of disease control in some subjects
- PsP greatly confounds interpretation of study imaging
  - Agent specific
  - Causes premature withdrawals. Precludes ability to fully assess therapeutic effects
  - Impacts on clinical trial response assessments
- The use of multimodality MRI +/- biopsy aids determination of pseudo-progression, unmasks underlying tumor response. Enables subject retention during this critical period for evaluation of benefits of MDNA55

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