

Real time, image guided high flow CED in recurrent glioblastoma (rGBM); initial experience from phase 2 study of a targeted immunotherapy, MDNA55 (cpIL-4PE)

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Introduction: MDNA55 is a targeted immunotherapeutic agent comprising a circularly permuted interleukin-4 (cpIL-4) fused to a truncated version of *Pseudomonas* exotoxin A (PE). MDNA55 binds to the interleukin-4 receptor (IL-4R), over-expressed by GBM cells and immunosuppressive cells of the tumor microenvironment (TME), and is endocytosed with the cleaved PE domain inducing tumor cell death via ADP-ribosylation of the Elongation Factor-2.

Methods: MDNA55-05 is a multi-center, single-arm, Phase 2b study of intratumoral infusion of MDNA55 in rGBM using a stepped catheter, infusion modelling (for catheter placement) and intra-operative real-time imaging of drug distribution. Infusions are started at 3µL/min/catheter then progressively increased under real-time MRI imaging according to the observed pattern of drug distribution and proximity of key structures.

An interim evaluation of CED success, tolerability and safety was completed.

Results: 10 rGBM subjects at 1st or 2nd recurrence with tumors 1.8 – 4.3 cm in diameter received 12-66ml of MDNA55 delivered at a concentration of 1.5 µg/mL via 1-3 catheters at flow-rates of up to 15µL/min/catheter.

Table 1: Summary of safety

Subjects (n) with AE Gd ≥3	SAE (n)	Related AE [Grade 1&2] (n)	Related AE [Grade 3&4] (n)	Related AE during infusion [all grades] (n)
2	1 (not related)	2	0	2 (all grade 1)

No SUSARs have been reported and no reports suggestive of acutely raised ICP, cerebral irritation or volume-related effects. AEs are generally consistent with the underlying disease.

Some remarkable distributions have been observed. Tumor coverage ranged from 43% to 100%, with 70% and 40% coverage of 1cm and 2cm penumbra respectively. Ratio of volume of distribution (Vd) to the volume infusion (Vi) ranged from 2.2 to 0.6. Reasons for lower Vd/Vi ratios will be detailed.

When catheter placement was inaccurate, realtime imaging of GdDTPA distribution enabled adjustments to catheter depth which dramatically improved tumor coverage.

Conclusions: Step-up of infusion rates under real-time MRI guidance enables delivery of MDNA55 by CED in rGBM at infusion rates of up to 15µL/min/catheter. MRI guidance is therefore critical for optimal drug distribution in brain tumors. Reassuring initial safety review enabled ongoing recruitment in the study.