#99LBA MDNA55, a Locally Administered IL4 Guided Toxin for Targeted Treatment of Recurrent Glioblastoma Shows Long Term Survival Benefit

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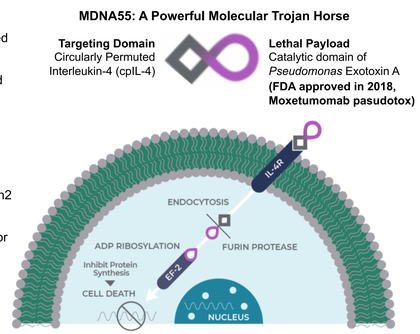
Background:

- GBM is an aggressive, universally fatal disease; all patients recur.
- Worse prognosis is associated with:
  - *De novo* GBM[1]
  - Unmethylated *MGMT* promoter[3]
  - No resection at recurrence[5]
  - *IDH* wild-type status[2]
  - High steroid use[4]
  - IL4R receptor (IL4R) over-expression[6-8]
- IL4R is over-expressed in GBM and the tumor microenvironment.
- MDNA55 is an IL4R-targeted immunotoxin administered using convection-enhanced delivery (CED) to bypass the blood brain barrier.
- A Phase 2b trial of MDNA55 was completed in subjects with recurrent GBM (rGBM); long-term survival data was available as of 15 Sep 2020 and are presented here.

- **MDNA55:** Targets the IL4R expressed in CNS tumors but not healthy brain
- **Localized Delivery:** Bypasses Blood Brain Barrier (BBB)
- **Highly Selective:** Avoids collateral damage to healthy brain
- **Disrupts the Tumor Microenvironment (TME):** Targets IL4R positive MDSCs and disrupts Th2 bias
- **Immunogenic Cell Death:** Anti-tumor immunity is initiated and remains active after MDNA55 is cleared

MDNA55: A Powerful Molecular Trojan Horse



MDNA55-05 Phase 2b Open-Label Single Arm Study in rGBM (NCT02858895)

DIAGNOSIS	PLANNING	TREATMENT	FOLLOW UP
• Adults ≥ 18 yrs • *De novo* GBM at initial diagnosis • 1st or 2nd relapse • No resection • KPS ≥ 70 • *IDH* wild-type only • Retrospective IL4R analysis from initial Dx	• MRI - tumor size and location • Optimal catheter trajectory	• Image-guided catheter placement • Monitor MDNA55 distribution in real-time with co-infusion of Magnevist ® • Single infusion (median 26.5 hrs.) • Conc. range: 1.5-9.0 µg/mL • Volume range: 12-66 mL • Total Dose range: 18-240µg • Transient low-dose BEV allowed for symptom control and/or steroid sparing • (6 and 9 µg/mL cohorts only)	1º **Endpoint** • OS 2º **Endpoint** • ORR • PFS • OS vs. IL4R expression • Safety

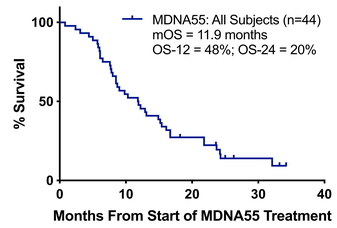
Patient Demographics	N=44
Age	56 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS: 70, 80	22 / 44 (50%)
90, 100	22 / 44 (50%)
***De novo* GBM**	44 / 44 (100%)
No resection at recurrence	44 / 44 (100%)
***IDH* WT**	37 / 37 (100%)
Unmethylated *MGMT*	23 / 40 (58%)
IL4R over-expression	21 / 40 (53%)
Steroid use > 4mg/day	23 / 44 (52%)
Max Tumor Diameter	29.6 mm (8 – 59)
# Prior Relapse: 1 , 2	35 (79%) , 9 (21%)

MDNA55-05 Safety Profile

- No systemic toxicities
- No clinically significant laboratory abnormalities
- Drug-related adverse events were primarily neurological/aggravation of pre-existing neurological deficits characteristic with GBM; manageable with standard measures.

Related AEs ≥ Grade 3 Occurring in ≥ 5% Subjects (SOC / Preferred Term)	Total N=47 [n (%)]
# of Subjects	**10 (21.3)**
Nervous system disorders	**10 (21.3)**
Brain Edema / Hydrocephalus	4 (8.5)
Hemiparesis	3 (6.3)
Seizure	3 (6.3)

Long-Term Survival Seen with Single Treatment of MDNA55 (All Subjects, N=44)

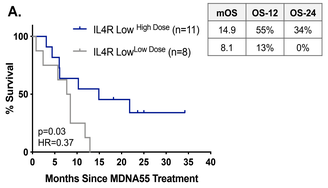


2-year survival rate (OS-24) = 20%

Long-Term Survival Seen in Subpopulation of IL4R High Subjects + IL4R Low Subjects Receiving High Dose MDNA55 (N=32)

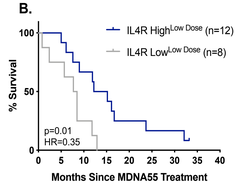
Examination of MDNA55 dose together with IL4R expression indicated an apparent dose-effect relationship on survival. **(A)** Subjects in the IL4R Low group showed improved survival when treated with high dose MDNA55 (median 180 µg; range 180-240 µg). **(B)** Within the low dose group, impact of IL4R expression (High vs. Low) was significant on survival outcome. **(C)** In the IL4R High group, survival was favorable irrespective of MDNA55 dose. **(D)** When IL4R High subjects (irrespective of dose) were pooled with IL4R Low subjects receiving high dose (IL4RHigh + IL4RLow^{HighDose}), this combined population (n=32) had a mOS of 14.0 months and OS-24 of 20%. Survival data from the combined population indicates that most patients, irrespective of their IL4R status, could potentially benefit from a single high dose of MDNA55.

A.



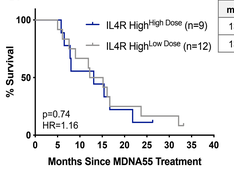
mOS	OS-12	OS-24
14.9	55%	34%
8.1	13%	0%

B.



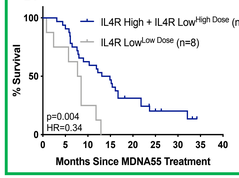
mOS	OS-12	OS-24
13.7	58%	17%
8.1	13%	0%

C.



mOS	OS-12	OS-24
13.1	56%	11%
13.7	58%	17%

D.



mOS	OS-12	OS-24
14.0	56%	20%
8.1	13%	0%

2-yr Survival Rate After MDNA55 Treatment Demonstrates Increase of ~100% Compared to FDA-Approved Therapies

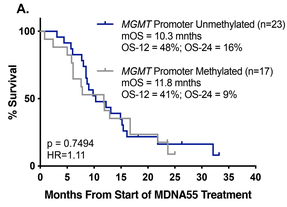
Therapy	rGBM Population sample size, N	mOS (months)	OS-12	OS-24
MDNA55 (All Subjects)	(n=44)	11.9	48%	20%
MDNA55 Subpopulation (IL4R High + IL4R Low$^{High Dose}$)	(n=32)	14.0	56%	20%
Approved Therapies				
Bevacizumab[1]	(n=85)	9.2	22%*	NA
Bevacizumab[2]	(n=48)	7.8	28%*	NA
Bevacizumab + Lomustine[3]	(n=288)	9.1	31.5%	5%*
Lomustine[3]	(n=149)	8.6	34.1%	10%*
Temozolomide[4]	(n=138)	5.4	18%*	NA
Carmustine implant[5]	(n=72)	6.5	12%*	5%*
Tumor Treating Fields[6]	(n=120)	6.6	20%	10%*

* Approximations based on Kaplan-Meier curve; NA: Not available
References: 1=Friedman et al., 2009; 2=Kreisl et al. 2008, 3=Wick et al., 2017; 4=Brada et al., 2001; 5=Gliadel Prescribing Information; 6=Stupp et al., 2012

Long-Term Survival Also Seen in rGBM Subjects with Unmethylated *MGMT* Promoter

- Unmethylated *MGMT* promoter is associated with resistance to temozolomide and poor survival outcomes; subjects with unmethylated *MGMT* promoter comprise approximately 50% of the GBM population.[3,9,10]
- No difference in mOS was observed between subjects with unmethylated and methylated *MGMT* promoters in **(A)** all subjects, or **(B)** in IL4R High + IL4R Low$^{High Dose}$ subjects after MDNA55 treatment.
- Two-year survival rate was 16-22% in unmethylated *MGMT* subjects treated with MDNA55; an increase of up to 100% compared to standard therapies.

A.



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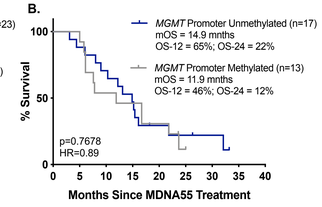


Comparison of Survival in *MGMT* Unmethylated Groups

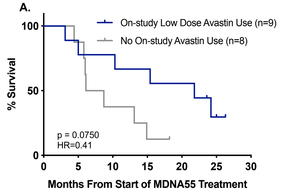
Product	rGBM Population sample size, N	mOS (months)	OS-12	OS-24
MDNA55 - *MGMT* Unmethylated Group				
All Subjects	(n=23)	10.3	48%	16%
IL4R High + IL4R Low$^{High Dose}$	(n=17)	14.9	65%	22%
Approved Therapies – *MGMT* Unmethylated Groups				
Lomustine[1]	(n=44)	7.2	22.2%	< 10%
Bevacizumab + Lomustine[1]	(n=102)	8.0	22.4%	< 5%
Bevacizumab[2]	(n=67)	9.7	30%*	10%*

* Approximations based on Kaplan-Meier curve
References: 1=Wick et al., 2017; 2=Reardon et al., 2020

Transient Low-Dose Bevacizumab Following MDNA55 Treatment Improves Survival

- In the higher concentration cohorts (6 and 9 µg/mL; n=17), transient use of low-dose bevacizumab (Avastin®), at doses typically used to control radiation induced necrosis (5 mg/kg q2w or 7.5 mg/kg q3w)[11], was allowed for management of symptom control and/or steroid sparing.
- In subjects receiving transient low-dose bevacizumab: **(A)** mOS was 21.8 months in all subjects, OS-24 was 44%; **(B)** mOS was 18.6 months in the sub-population of IL4R High subjects and IL4R Low subjects receiving high dose MDNA55, OS-24 was 38%. Median number of cycles of bevacizumab was 3 cycles in both groups.

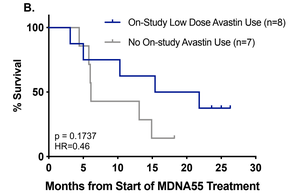
A.



Group	N	mOS (months)	OS-12	OS-18	OS-24
On-study Low dose Avastin use	9	21.8	67%	56%	44%
No On-study Avastin Use	8	7.4	38%	13%	NE

NE = Not evaluable due to limited data for this time point

B.

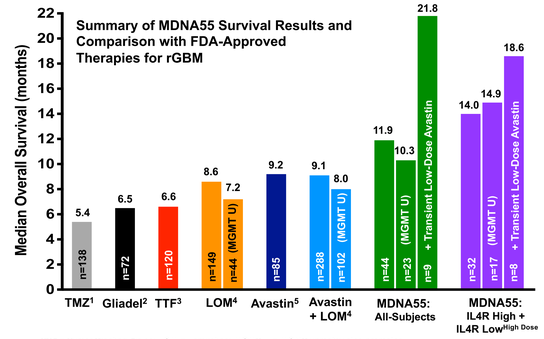


Group	N	mOS (months)	OS-12	OS-18	OS-24
On-study Low dose Avastin use	8	18.6	63%	50%	38%
No On-study Avastin Use	7	6.1	43%	14%	NE

Prolonged Progression-Free Survival After MDNA55 Treatment

Therapy	N	mPFS	PFS-12
MDNA55 Groups			
All Subjects	41	3.6*	27%
IL4R High + IL4R Low$^{High Dose}$	32	3.0*	24%
Approved Therapies			
Avastin[1]	85	4.2	10%**
Avastin[2]	48	4.0	10%**
Lomustine[3]	149	1.5	2%**
Avastin + Lomustine[3]	288	4.2	10%**

* Assessed by mRANO criteria using radiologic data only; ** Approximations based on Kaplan-Meier curve.
References: 1=Friedman et al., 2009; 2=Kreisl et al. 2008; 3=Wick 2017



TTF = Tumor Treating Fields; LOM = Lomustine; MGMT U = MGMT unmethylated promoter
Refences: 1=Brada et al., 2001; 2=Gliadel FDA Label 2018; 3=Stupp et al., 2012; 4=Wick et al., 2017; 5=Friedman et al., 2009

Summary and Conclusions:

- The MDNA55-05 study enrolled rGBM patients with limited treatment options and poor prognostic factors with an expected mOS of only 6-9 months, OS-24 of 0-10% and PFS-12 of 0-10%.
- Single treatment with MDNA55 demonstrated a ~50% increase in mOS and a ~100% increase in 2-year survival compared to FDA-approved therapies:
  - Median OS was 11.9 months in all subjects and 14.0 months in sub-population of IL4R High subjects and IL4R Low subjects receiving high dose MDNA55.
  - OS-24 was 20% in both groups.
- PFS at 12 months was 24-27% in subjects treated with MDNA55, an increase of > 100% compared to standard therapies.
- An increase of up to 100% in 2-year survival was also seen in subjects with unmethylated *MGMT* promoter, indicating that MDNA55 may provide benefit to GBM patients resistant to temozolomide.
- Transient low dose bevacizumab further improved survival: mOS was 21.8 months with OS-24 of 44% in all subjects and 18.6 months with OS-24 of 38% in IL4R High + IL4R Low$^{High Dose}$ subjects.
- Findings demonstrate that by combining precise drug delivery and targeting the IL4R, single treatment with MDNA55 has potential to present a superior treatment option for improved survival and tumor control in rGBM patients who otherwise rapidly succumb to this disease.

REFERENCES: 1) Mineo et al., Acta Neurochir. 2005; 2) Yan et al., NEJM 2009; 3) Hegi et al., NEJM 2005; 4) Wong et al. BJC 2015; 5) Van Linde et al. J. Neurooncol. 2017; 6) Kohanbash et al. Cancer Res. 2013; 7) Han and Pun. J of Neuro-Oncology, 2018; 8) D'Alessandro et al., Cancers (Basel). 2019; 9) Smrdel et al., Radiol Oncol. 2016; 10) Wick et al. Nature Rev Neurology, 2014; 11) Delishaj et al., J Clin Med Res. 2017

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