Clinical efficacy of MDNA55, an Interleukin-4 Receptor Targeted Immunotherapy, in Recurrent GBM Delivered by Convection Enhanced Delivery (CED)

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SNO 25th Anniversary Society for NeuroOncology

Duke University School of Medicine

MEDICENNA

Disclosures

Dr. John H. Sampson is a consultant/advisor for Medicenna Therapeutics.

MDNA55, an Interleukin-4 Receptor Targeted Immunotherapy

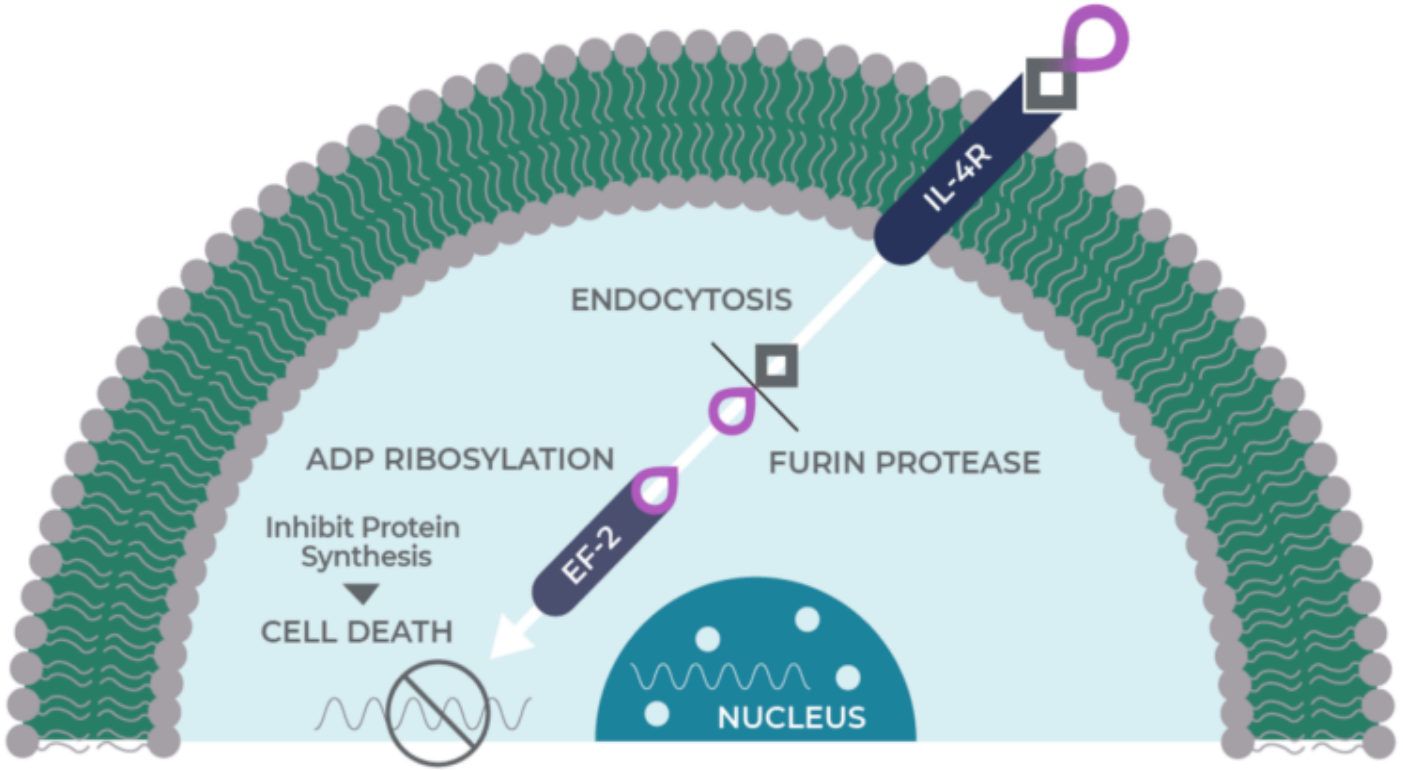
- GBM is an aggressive, universally fatal disease; all patients recur.
- Worse prognosis is associated with:
  - *De novo* GBM[1]
  - *IDH* wild-type status[2]
  - Unmethylated *MGMT* promoter[3]
  - No resection at recurrence[4]
  - IL4R over-expression[5-7]
- IL4R is over-expressed in GBM and the tumor microenvironment.
- MDNA55 is an IL4R-targeted immunotoxin administered using CED to bypass the blood brain barrier.

MDNA55, A Molecular Trojan Horse

Targeting Domain
Circularly Permuted Interleukin-4 (cpIL-4)

Lethal Payload
Catalytic domain of *Pseudomonas* Exotoxin A

(FDA approved in 2018, Moxetumomab pasudotox)



1) Mineo et al., Acta Neurochir. 2005; 2) Yan et al., NEJM 2009; 3) Hegi et al., NEJM 2005; 4) Van Linde et al. J. Neurooncol. 2017; 5) Kohanbash et al. Cancer Res. 2013; 6) Han and Puri. J of Neuro-Oncology, 2018; 7) D'Alessandro et al., Cancers (Basel). 2019

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

DIAGNOSIS

- 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

PLANNING

- MRI - tumor size and location
- Optimal catheter trajectory

TREATMENT

- 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)

FOLLOW UP

1º Endpoint

- OS

2º Endpoint

- ORR
- PFS
- OS vs. IL4R expression
- Safety

MDNA55-05 Patient Demographics and Safety

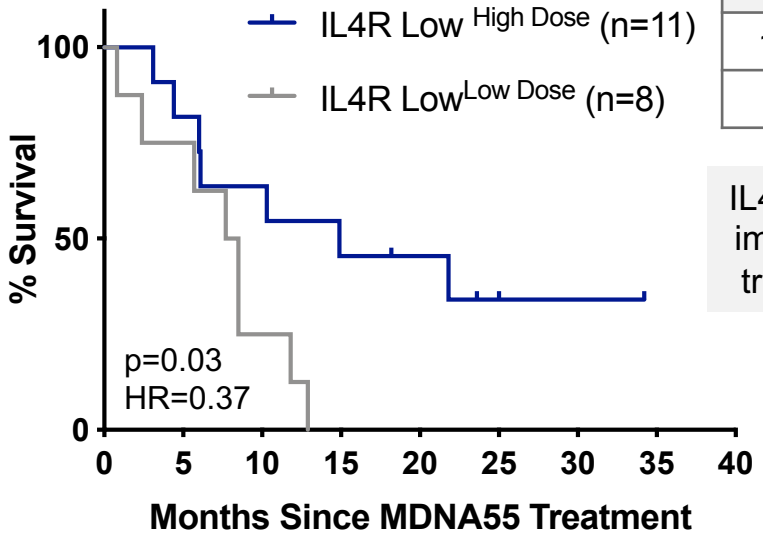
Patient Demographics	N=44
Age	56 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS: 70, 80	22 / 44 (50%)
90, 100	22 / 44 (50%)
***De novo* GBM**	44 / 44 (100%)
No resection at recurrence	44 / 44 (100%)
***IDH* WT**	37 / 37 (100%)
Unmethylated *MGMT*	23 / 40 (58%)
IL4R over-expression	21 / 40 (53%)
Steroid 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 AEs were primarily neurological/aggravation of pre-existing neurological deficits characteristic with GBM; manageable with standard measures.

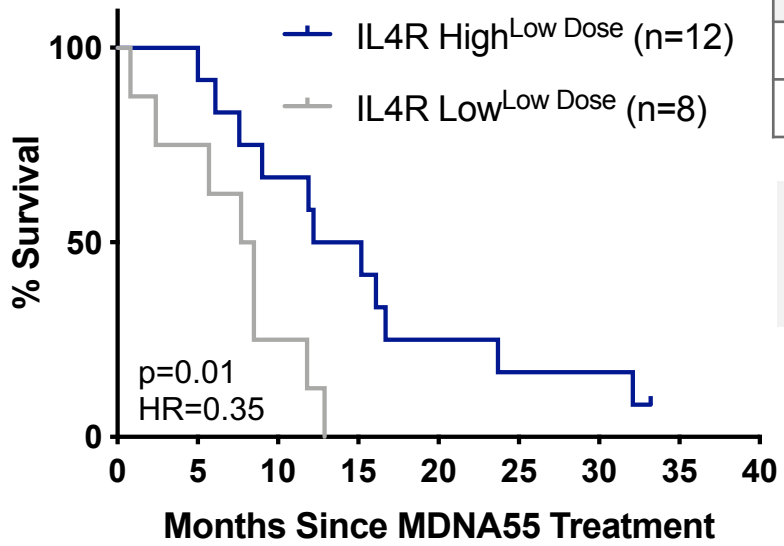
Related AEs ≥ Grade 3 Occurring in ≥ 5% Subjects	Total N=47 [n (%)]
# of Subjects	**10 (21.3)**
Nervous system disorders	**10 (21.3)**
Brain Edema / Hydrocephalus	4 (8.5)
Hemiparesis	3 (6.3)
Seizure	3 (6.3)

Effect of MDNA55 Dose and IL4R Expression on Survival



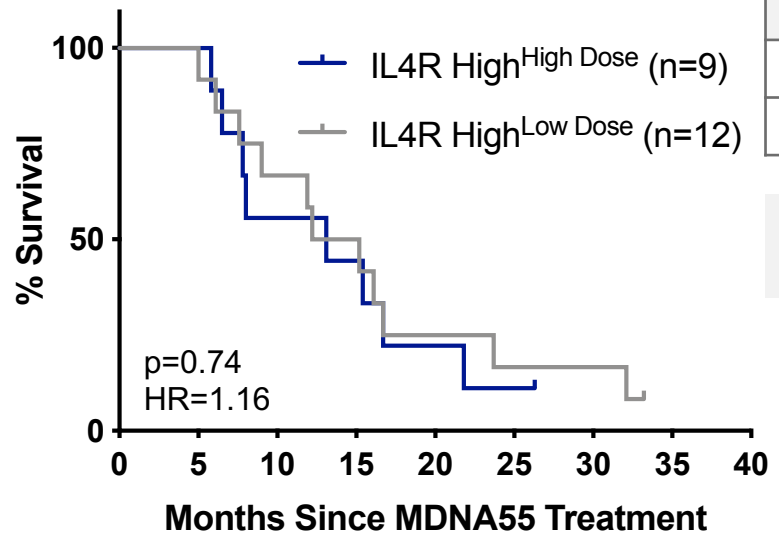
mOS	OS-12	OS-24
14.9	55%	34%
8.1	13%	0%

IL4R Low group showed improved survival when treated with high dose.



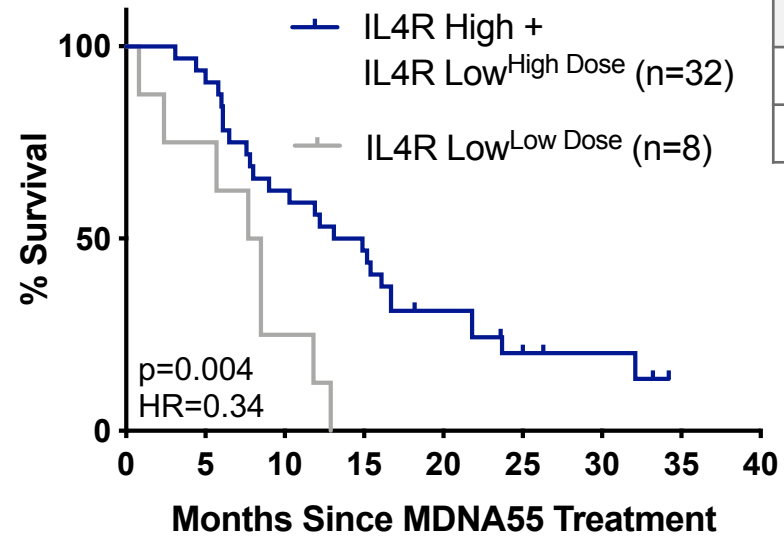
mOS	OS-12	OS-24
13.7	58%	17%
8.1	13%	0%

At low dose, only High IL4R expression improved survival.



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

No effect of dose seen in IL4R High group.

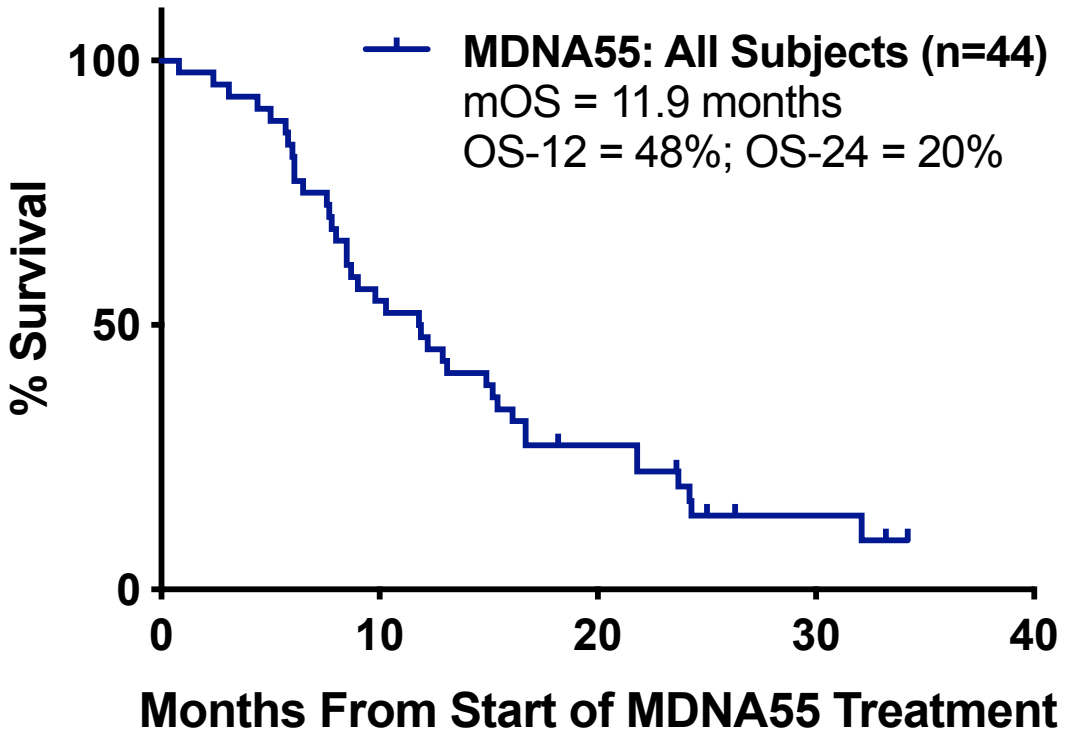


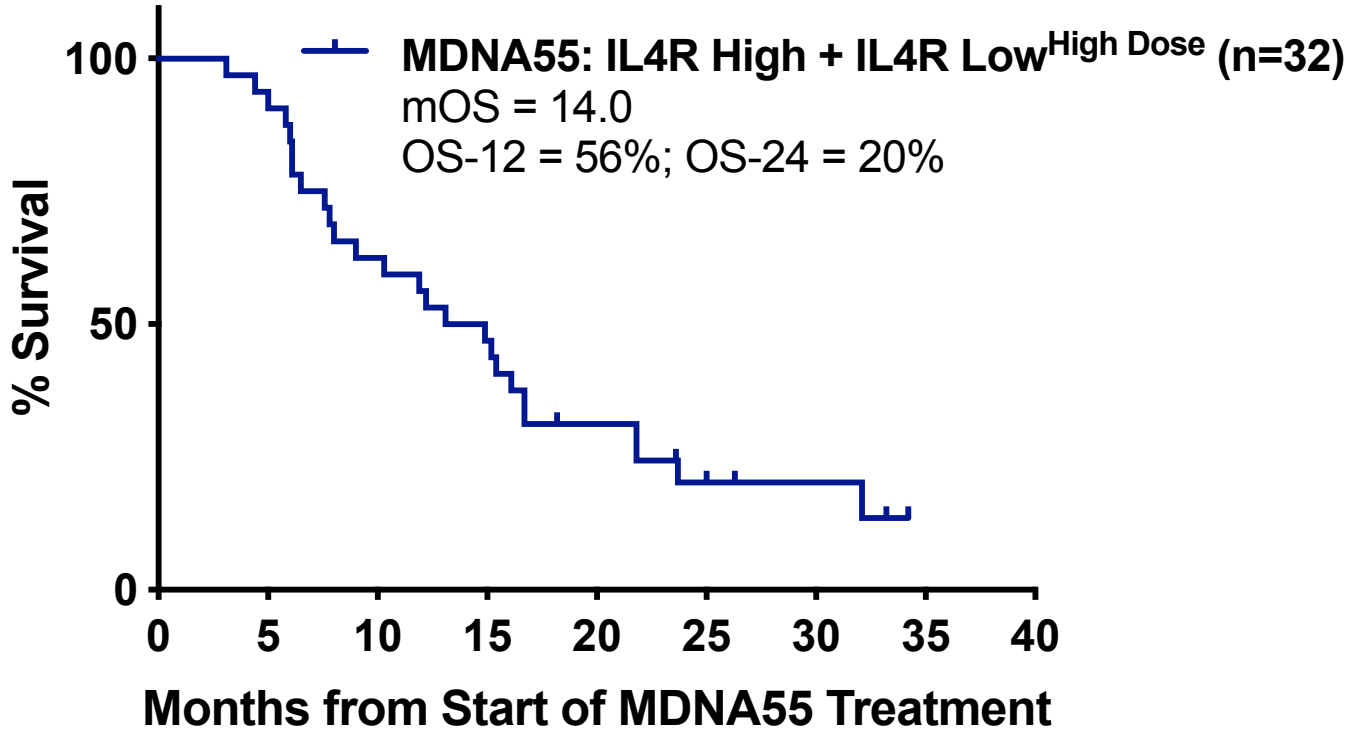
mOS	OS-12	OS-24
14.0	56%	20%
8.1	13%	0%

IL4R High (irrespective of dose) and IL4R Low patients receiving high dose were identified to benefit most from single treatment of MDNA55.

Improved Survival Seen with MDNA55 Treatment

2-Year Survival Rate of 20%

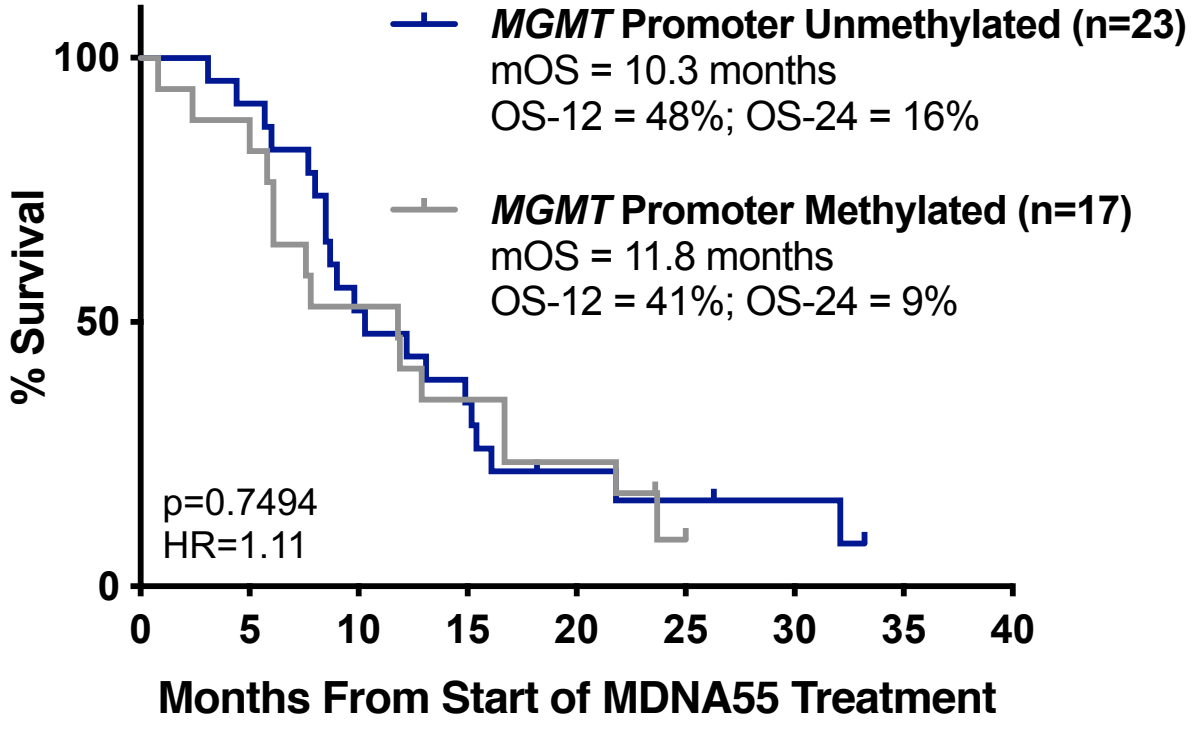




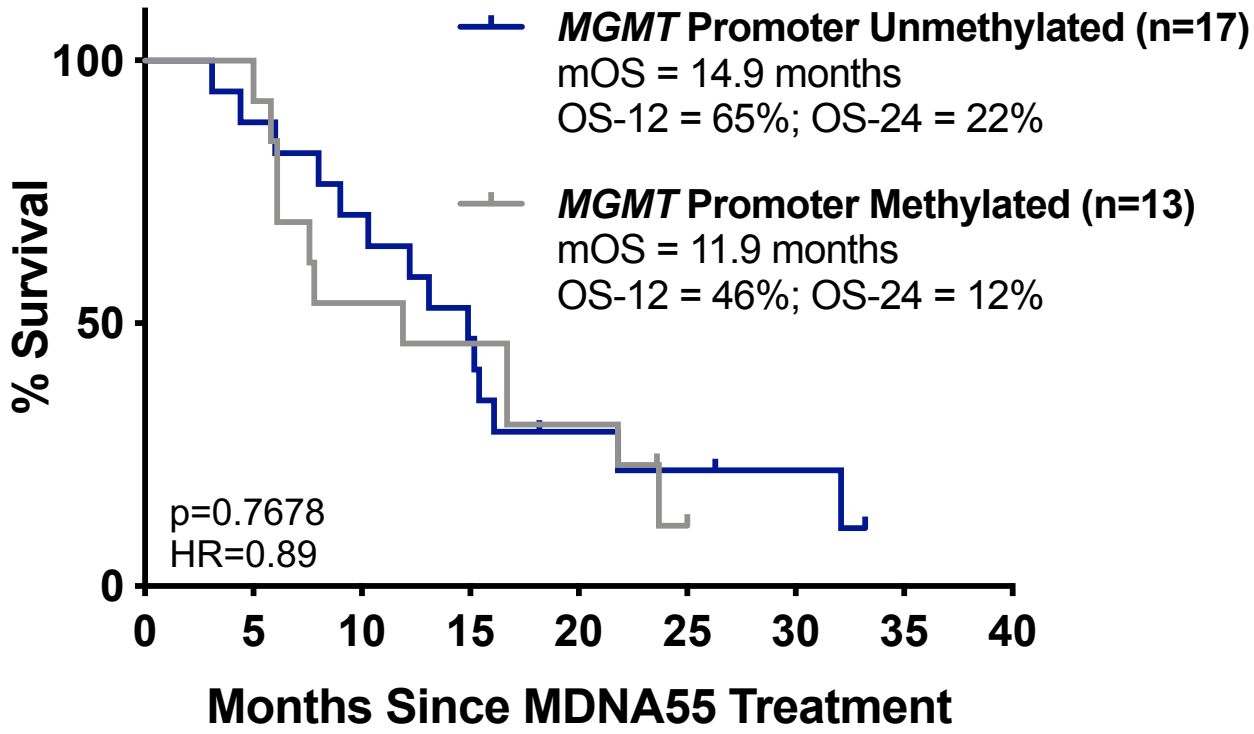
MDNA55 is Effective in *MGMT* Promoter Unmethylated rGBM

MDNA55 is Potent in a Temozolomide-Resistant Population

All-Comers

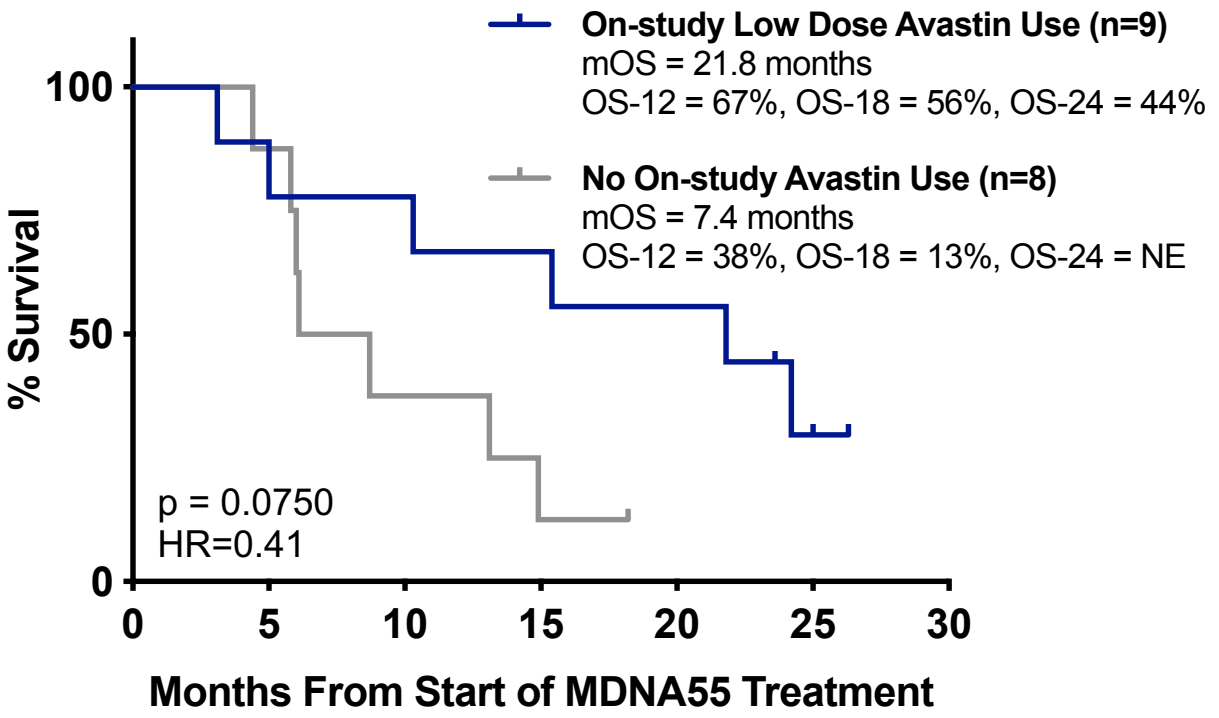


IL4R High + IL4R Low High Dose

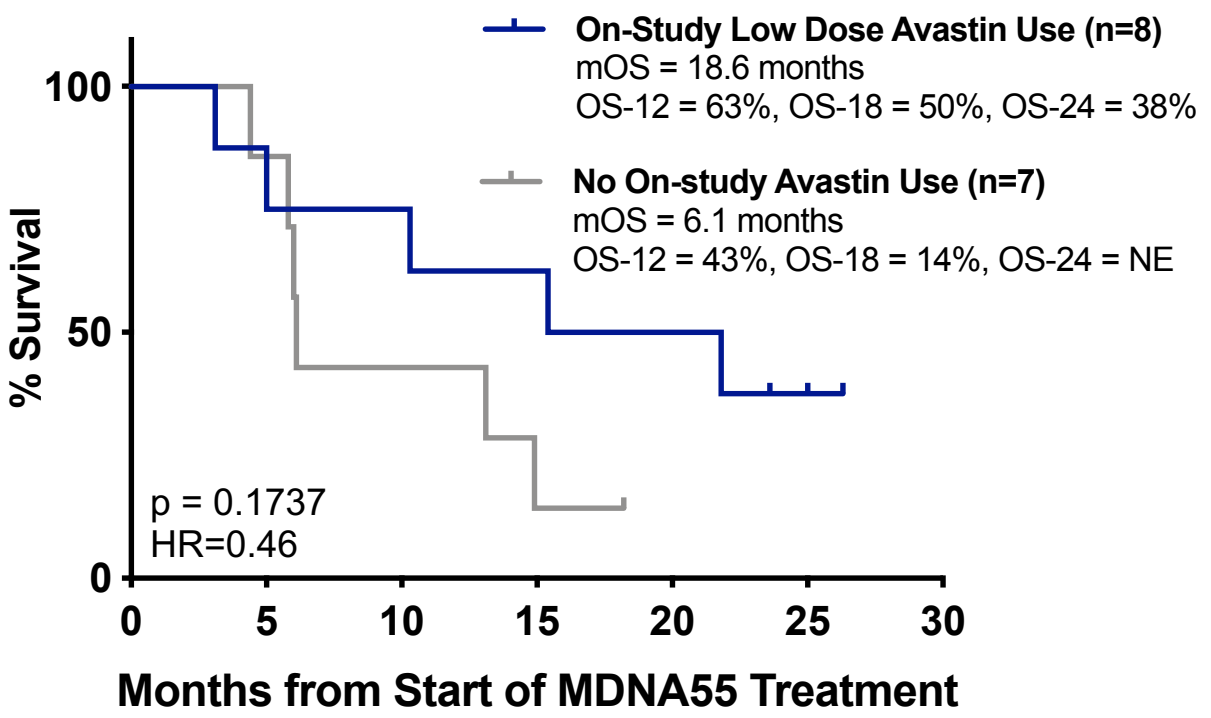


Transient Low-Dose Bevacizumab Following MDNA55 Treatment Improves Survival

All-Comers



IL4R High + IL4R Low High Dose



- In the higher concentration cohorts (6 and 9 µg/mL; n=17), transient use of low-dose bevacizumab (5 mg/kg q2w or 7.5 mg/kg q3w) was allowed for management of symptom control and/or steroid sparing.
- Median number of cycles of bevacizumab was 3 cycles in both groups.
- In the higher concentration cohorts, 10 patients had Low IL4R, 5 patients had High IL4R, and 2 patients were unknown.

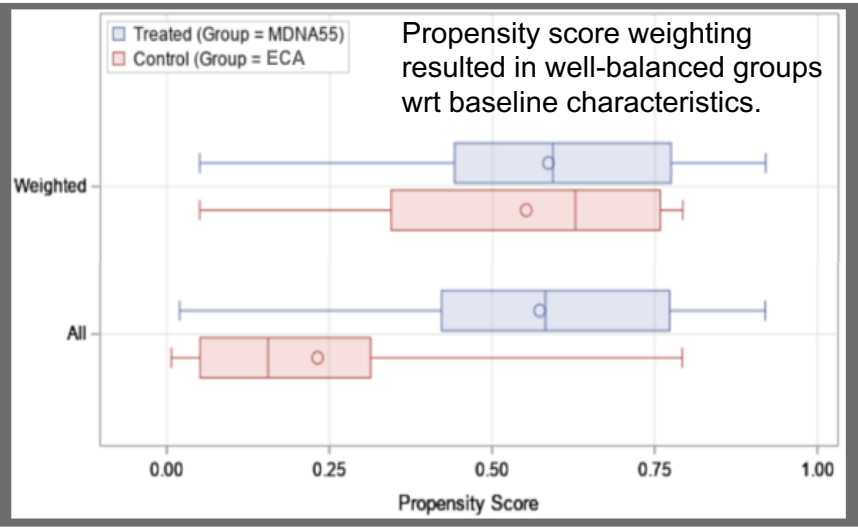
MDNA55 Shows Improvement of ~ 100% in mOS Compared to External Control Arm (ECA)

Comparison with External Control Arm:

- Conducted separate study to identify contemporaneous rGBM patients matched on eligibility and prognostic characteristics as MDNA55 patients:
  - *de novo* GBM, IDH wild-type, not candidates for re-resection
- Objective was to compare survival outcome of MDNA55 and matched ECA.

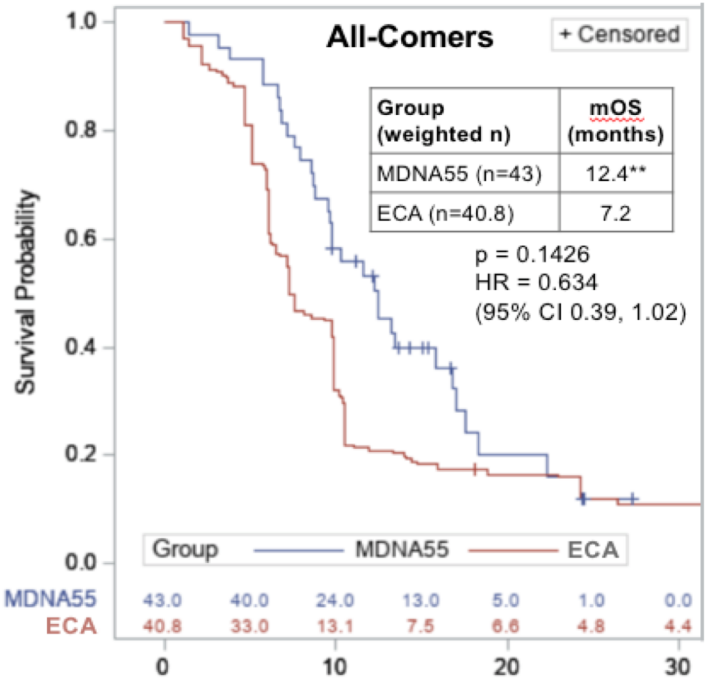
Propensity Score Methods:

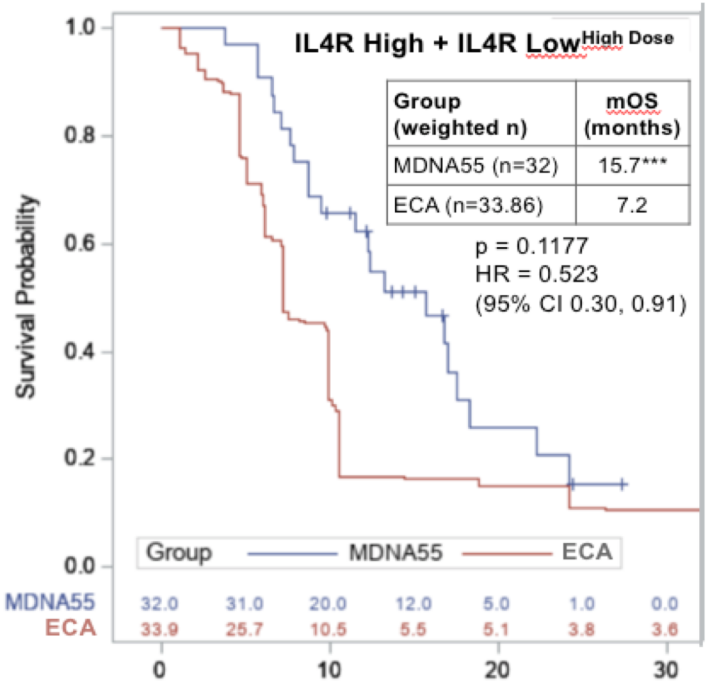
- Propensity score weighting was used to balance baseline characteristics b/w MDNA55 and ECA:
  - Age
  - Sex
  - KPS
  - IL4R status
  - MGMT status
  - Time to relapse
  - # prior relapse
  - Extent of resection at initial Dx
  - Tumor size
  - Tumor Location
  - Steroid Use



Results*:

- Weighted All-comers (n=43): mOS is 12.4 months vs. 7.2 months in ECA.
- Weighted IL4R High + IL4R Low$^{\text{High Dose}}$ (n=32): mOS is 15.7 months vs 7.2 months in ECA.
- Survival time more than doubled in the IL4R High + IL4R Low$^{\text{High Dose}}$ group compared to ECA.





*Survival was calculated from time of relapse
**mOS is 12.4 months as of 15Sep2020
***mOS is 14.5 months as of 15Sept 2020

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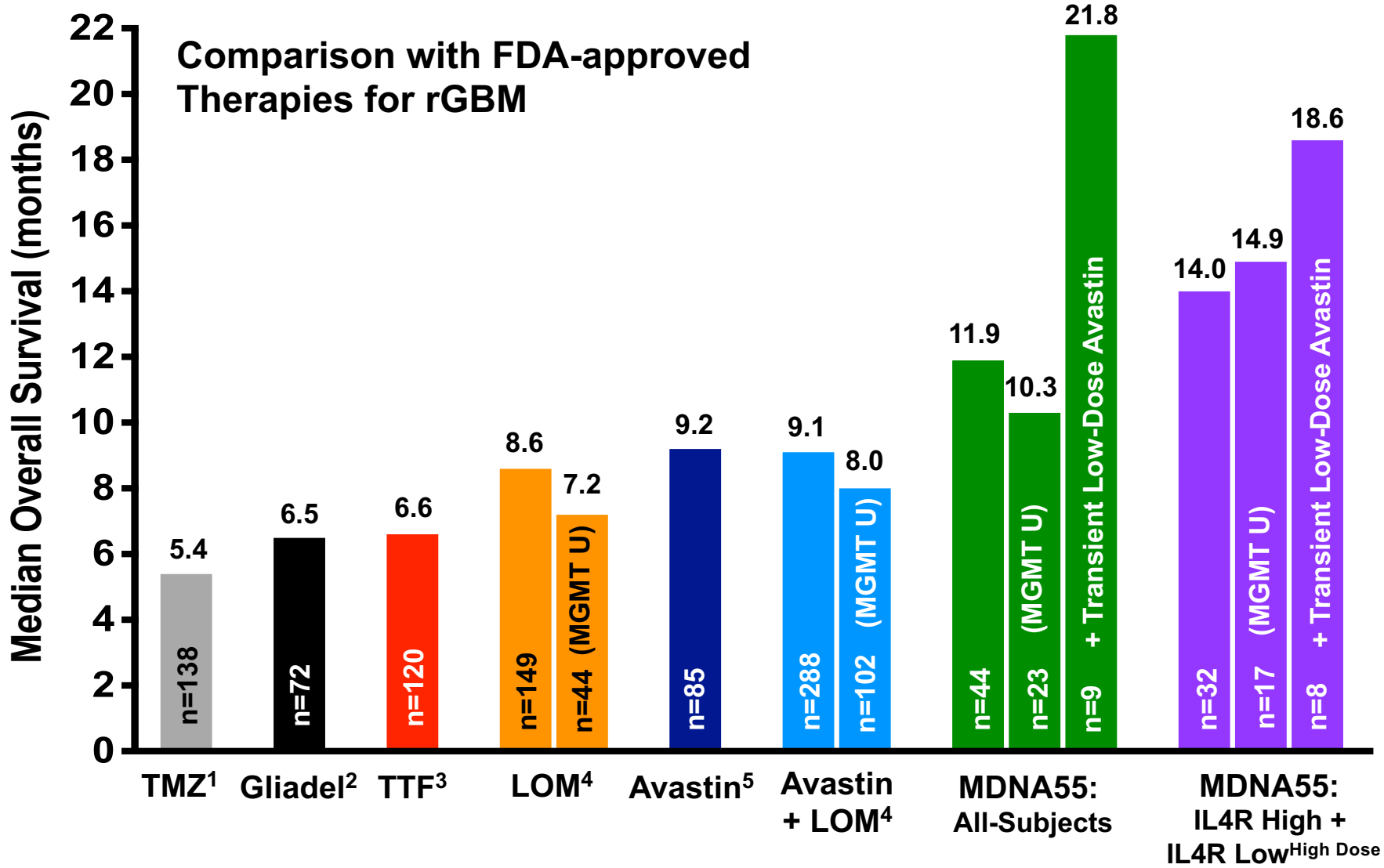
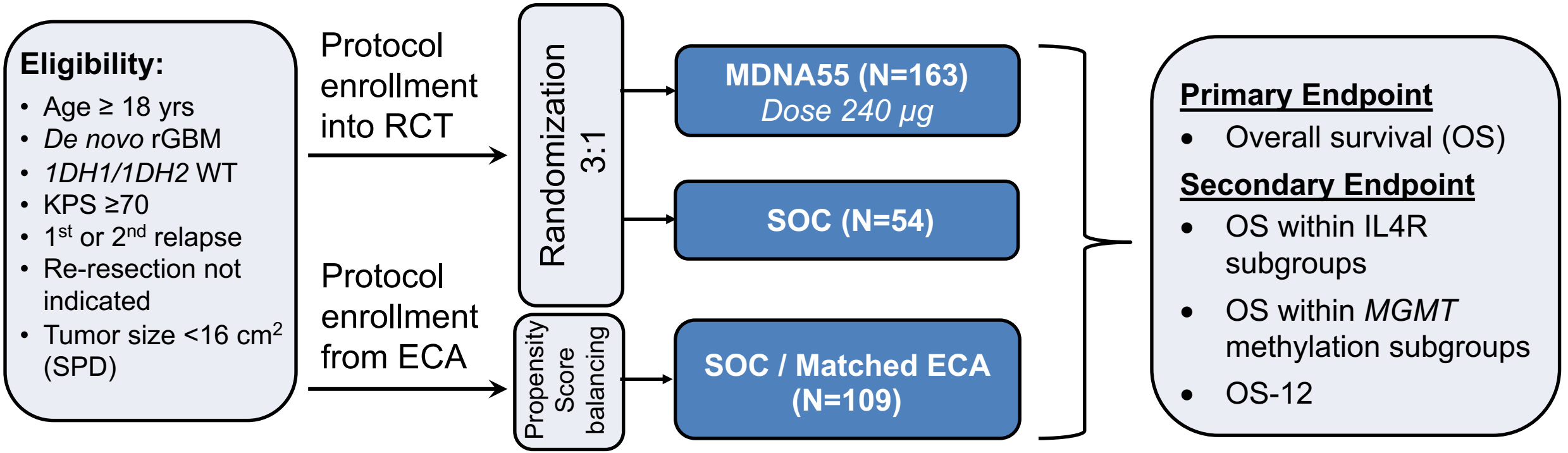
Summary of MDNA55 Survival Results



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

Planned Phase 3 Trial – Hybrid Design with External Control



SOC therapies allowed:

- Bevacizumab (Avastin®)
- Lomustine (CCNU, CeeNU®, Gleostine™)
- Temozolomide (Temodar®)
- Tumor Treating Fields (Optune®)
- Radiation Therapy

Assumptions:

- 90% power
- HR of MDNA55 vs. pooled control = 0.65
- 2-sided alpha = 0.05
- Effect size = 4.6 months in mOS time
- Drop-out rate = approximately 5%

Hybrid Design Offers Streamlined Approach to Provide Active Treatment and Reduce Assignment to SOC

Failed Phase 3 Trials in rGBM with OS as Primary Endpoint (conducted between 2003 – 2019)

Agent (Sponsor)	Target/Class	Study Design	Control Arm	Total Subjects Enrolled
Edotecarin (Pfizer)	Topoisomerase I inhibitor	1:1 randomization	TMZ, Camustine, or LOM	118 (59 in SOC)
IL13-PE38QQR (INSYS Therapeutics)	IL13R-targeted toxin	2:1 randomization	Gliadel	296 (104 in SOC)
Bevacizumab (EORTC)	VEGF inhibitor	2:1 randomization	LOM	437 (149 in SOC)
Tumor Treating Fields (Novocure)	Device	1:1 randomization	Best active chemotherapy	237 (117 in SOC)
Toca 511 + Toca FC (Tocagen)	Retroviral vector	1:1 randomization	TMZ, LOM, or BEV	403 (202 in SOC)
VB-111 (VBL Therapeutics)	Angiogenesis inhibitor	1:1 randomization	BEV	256 (128 in SOC)
Nivolumab (BMS)	PD-1 inhibitor	1:1 randomization	BEV	369 (185 in SOC)
MDNA55 (Medicenna)	**IL4R-targeted toxin**	**3:1 randomization**	**BEV, LOM, TMZ, TTF, RT**	**217 (54 in SOC)**

Summary & Conclusions

- MDNA55-05 enrolled rGBM patients with limited treatment options and poor prognostic factors; expected mOS is only 6-9 months with OS-24 of 0-10%.
- Single treatment with MDNA55 demonstrated ~50% increase in mOS and ~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.
- When tested against a propensity-matched ECA, improvement of ~100% in mOS was seen in MDNA55 populations over the control group.
- Increase of up to 100% in 2-year survival rate also seen in subjects with unmethylated *MGMT* promoter; 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$^{\text{High Dose}}$ subjects.
- Findings demonstrate that by combining precise drug delivery and targeting IL4R, MDNA55 presents superior treatment option for rGBM patients who otherwise rapidly succumb to this disease.
- A Phase 3 trial of MDNA55 in rGBM utilizing a hybrid design consisting of a matched external control arm will allow robust OS analysis while significantly reducing the number of participants randomized to SOC.

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…..And most of all, to the patients & their families

CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS