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MDNA55, an IL4-Guided Toxin in Recurrent GBM: Phase 2b Results and Use of an External Control Arm in a Registration Trial

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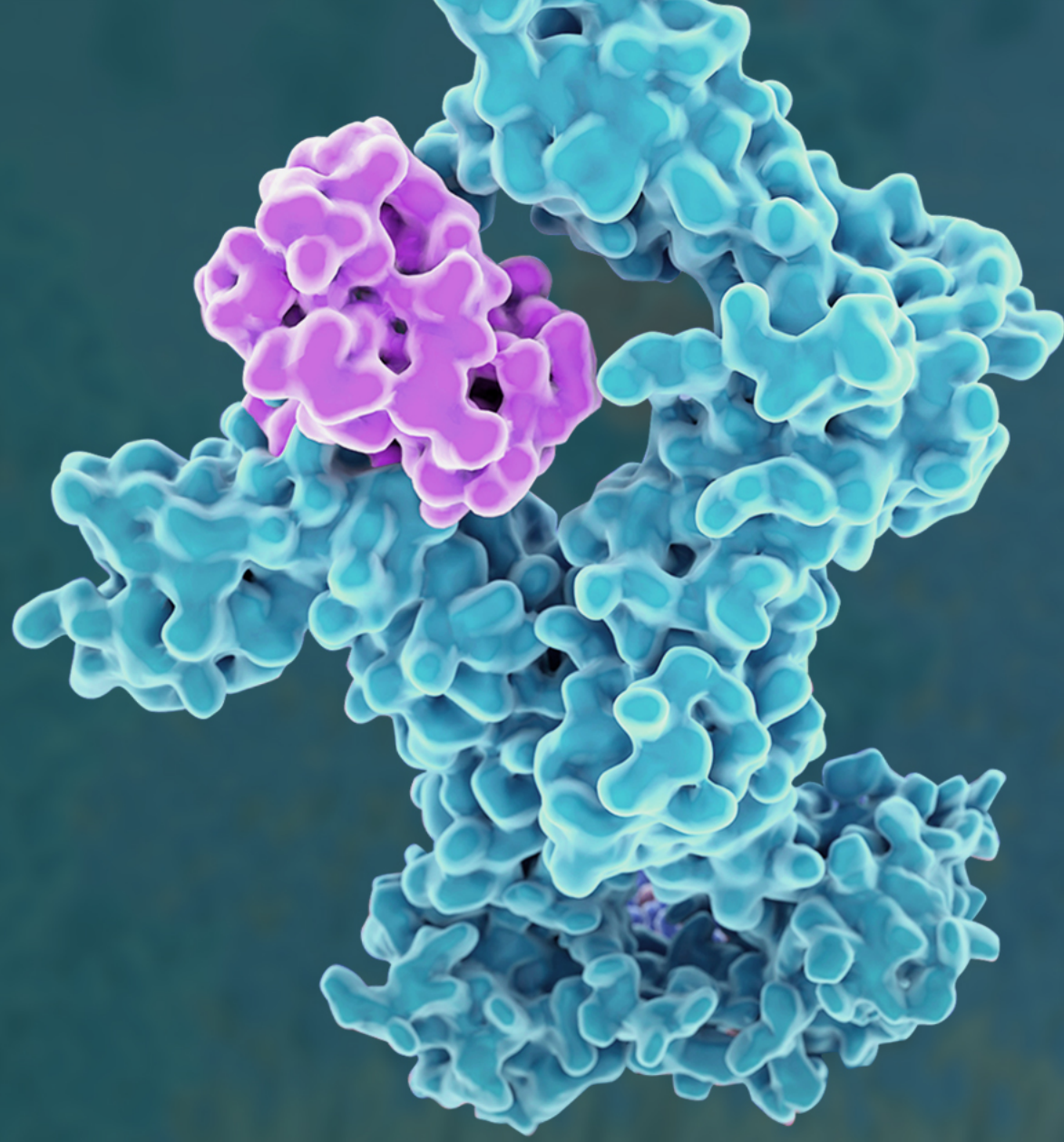

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Discussion Points

- Present updated results from the Phase 2b clinical trial: results show improved 2-year survival rate and long-term tumor control (progression-free survival).
- Present use of a propensity matched External Control Arm (ECA) to demonstrate utility for go/no go decisions and reduce risk in a registration trial.
- Present a novel hybrid design incorporating an ECA in a planned recurrent GBM registration trial.

MDNA55: A Targeted Immunotherapy for GBM

MDNA55

Targets the IL4R, which is expressed in brain tumors and in the tumor microenvironment (TME), but not the healthy brain

Highly Selective

Avoids off-target toxicity

Disrupts the TME

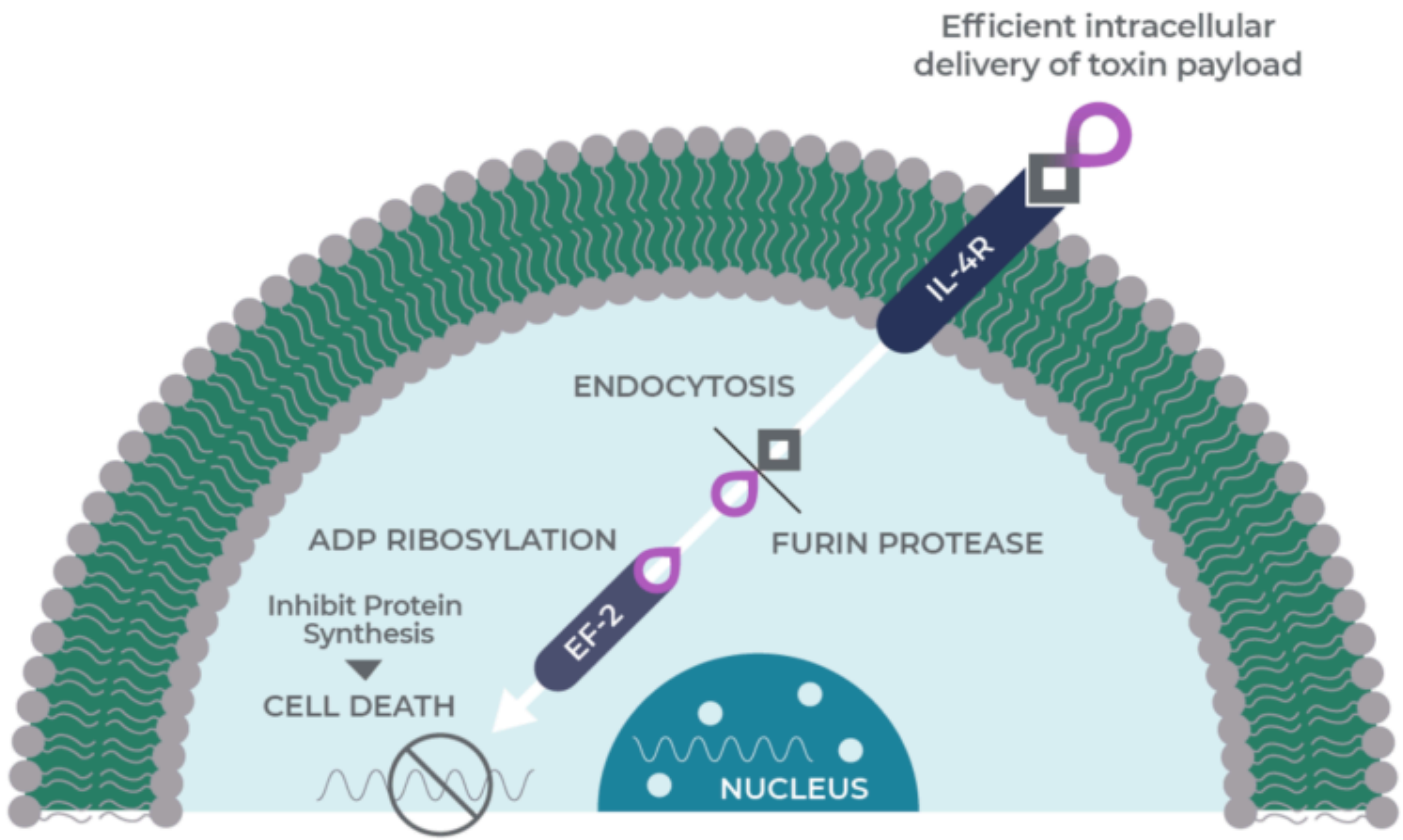
By targeting IL4R positive cells found throughout the TME, MDNA55 unblinds the tumor to the body's immune system

Sustained Immune Memory Response

Anti-tumor immunity is initiated and remains active after MDNA55 is cleared

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

Lethal Payload
Catalytic domain of *Pseudomonas* Exotoxin A (FDA approved Moxetumomab pasudotox)



Updated results from MDNA55-05 Phase 2b Clinical Trial

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MDNA55-05 Phase 2b Study Design

Open-Label Single Arm Study in Recurrent GBM Patients (n=47) (NCT02858895)

ELIGIBILITY

- Adults ≥ 18 yrs
- De novo GBM
- 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 real-time drug distribution 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)

ENDPOINTS

1º Endpoint

- OS

2º Endpoint

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

MDNA55-05 Demographics and Safety

Patient Demographics	N=44
Age (median, range)	55 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS at Enrolment: 70, 80 90, 100	22 / 44 (50%) 22 / 44 (50%)
De novo GBM	44 / 44 (100%)
Poor candidates for repeat surgery	44 / 44 (100%)
IDH Wild-type	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 (80%) , 9 (20%)

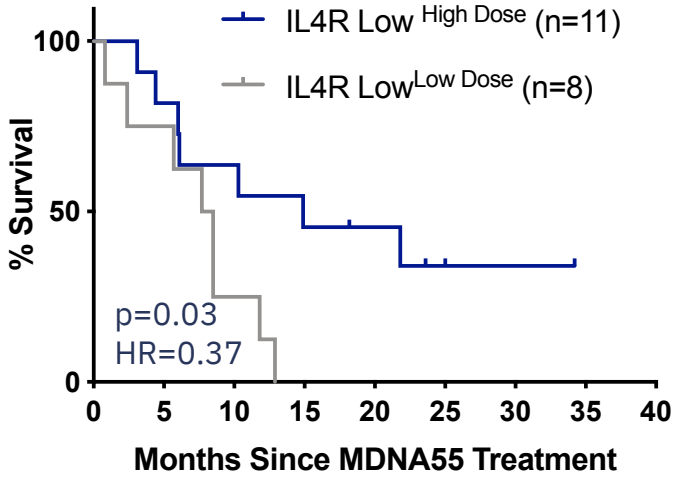
*Based on central tumor assessments

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.

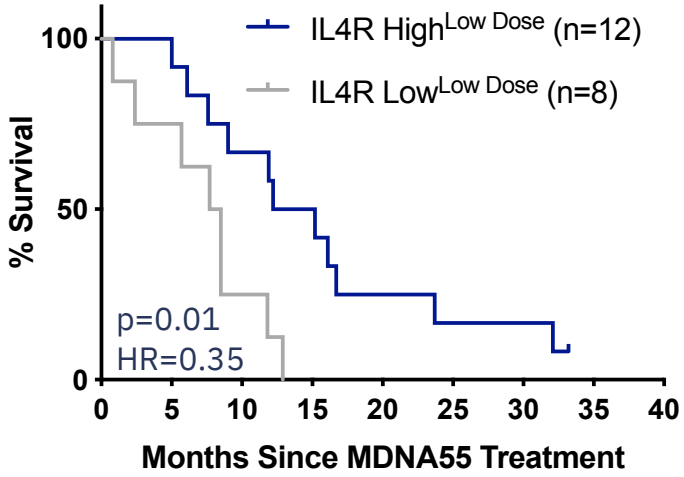
Related AEs ≥ Grade 3 Occurring in ≥ 5% Subjects	Total N=47 [n (%)]
# of Subjects	10 (21.3)
Nervous system disorders	10 (21.3)
Brain Edema / Hydrocephalus	4 (8.5)
Hemiparesis	3 (6.3)
Seizure	3 (6.3)

Effect of MDNA55 Dose and IL4R Expression on Survival



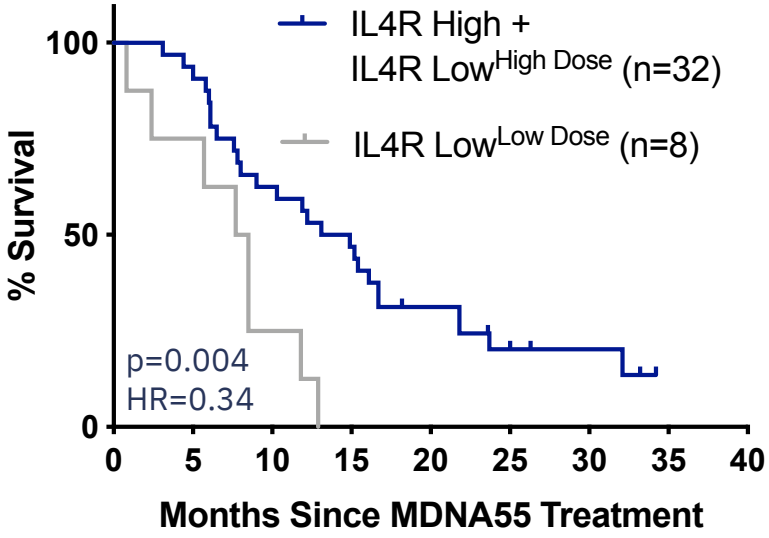
mOS	OS-12	OS-24
14.9	55%	34%
8.1	13%	0%

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.



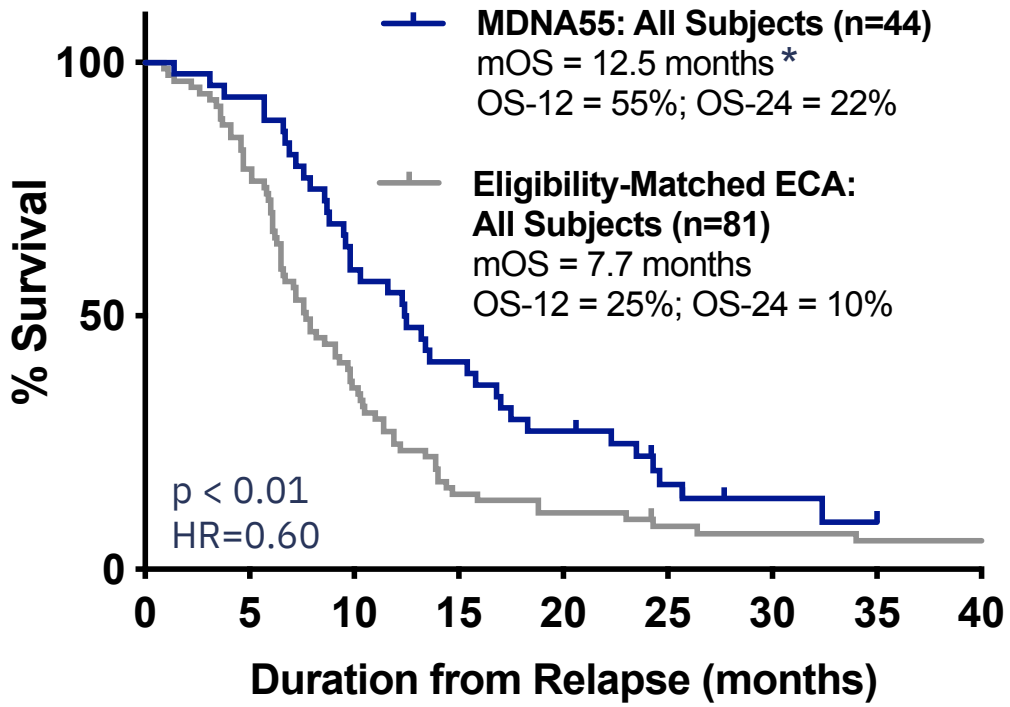
mOS	OS-12	OS-24
14.0	56%	20%
8.1	13%	0%

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

Prolonged Survival Observed After MDNA55 Treatment

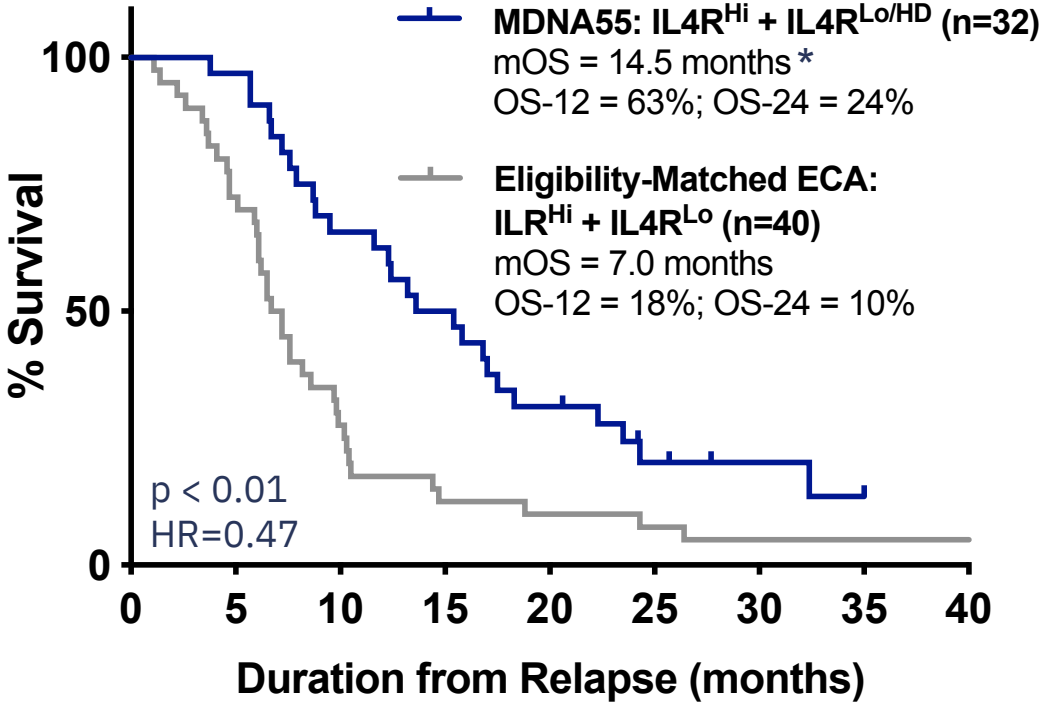
2-Year Survival Rate > 20% in MDNA55 Subjects

All-Comers



*Survival calculated from date of relapse.
Median OS from time of MDNA55 treatment is 11.9 months;
OS-12 = 48%; OS-24 = 20%

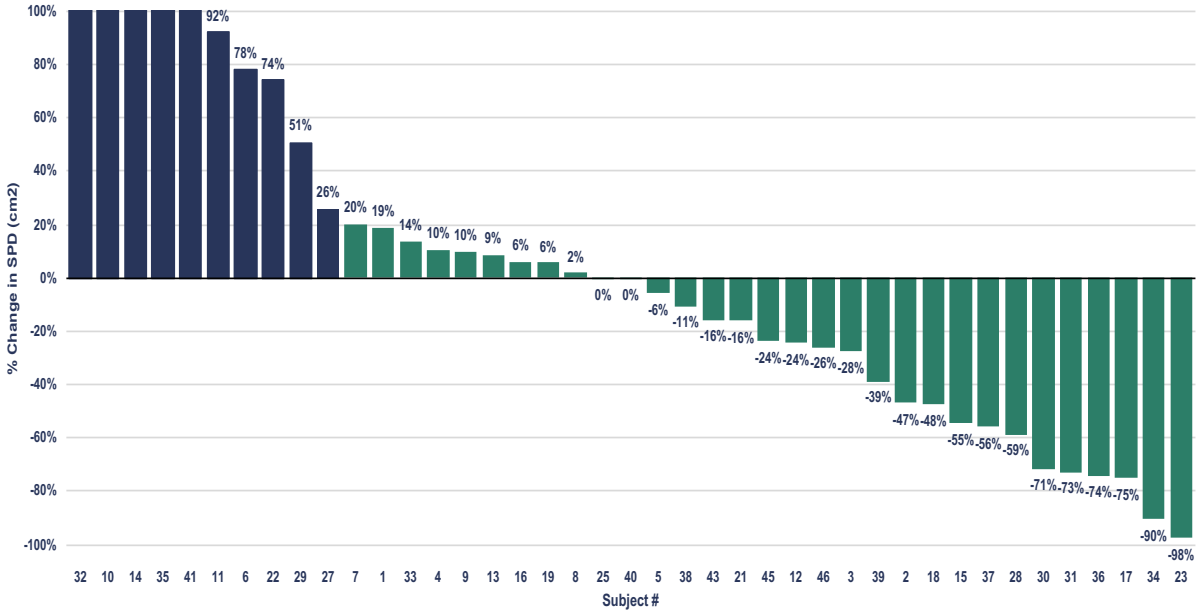
IL4R^{Hi} + IL4R$^{Lo/HD}$



*Survival calculated from date of relapse.
Median OS from time of MDNA55 treatment is 14.0 months;
OS-12 = 56%; OS-24 = 20%

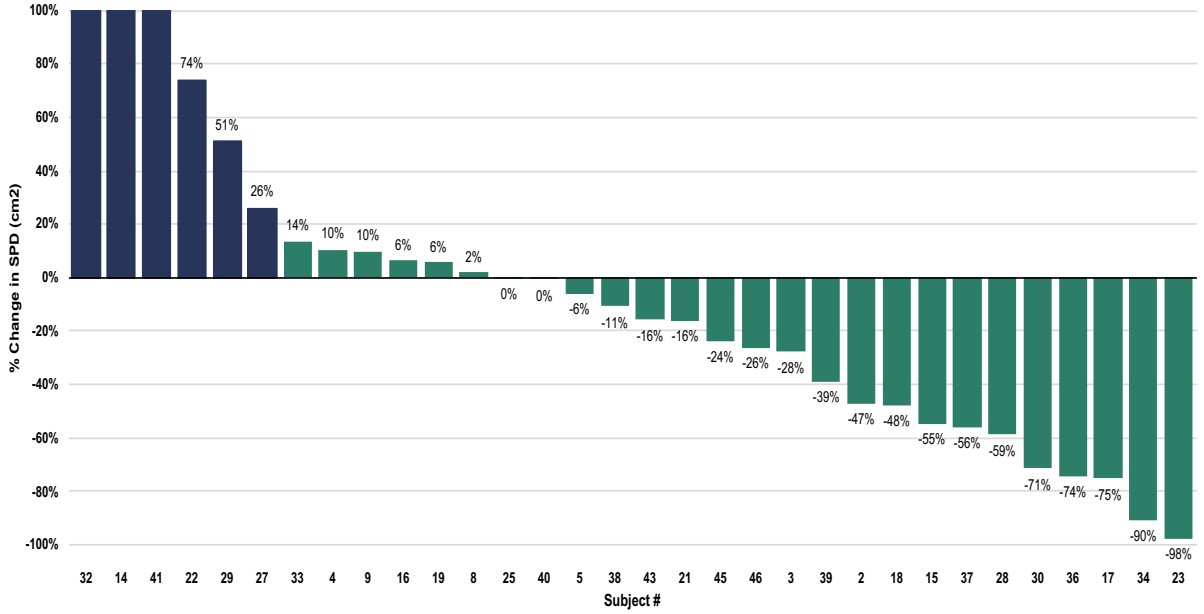
Tumor Control Observed in a Majority of Patients

All-Comers



Tumor control rate = 76%
(31/41 evaluable subjects)

IL4R^{Hi} + IL4R$^{Lo/HD}$



Tumor control rate = 81%
(26/32 evaluable subjects)

Shown are tumor responses assessed from nadir based on radiologic imaging only

Prolonged Progression-Free Survival After MDNA55 Treatment

Increase of > 100% in PFS-12 Compared to Standard Therapies

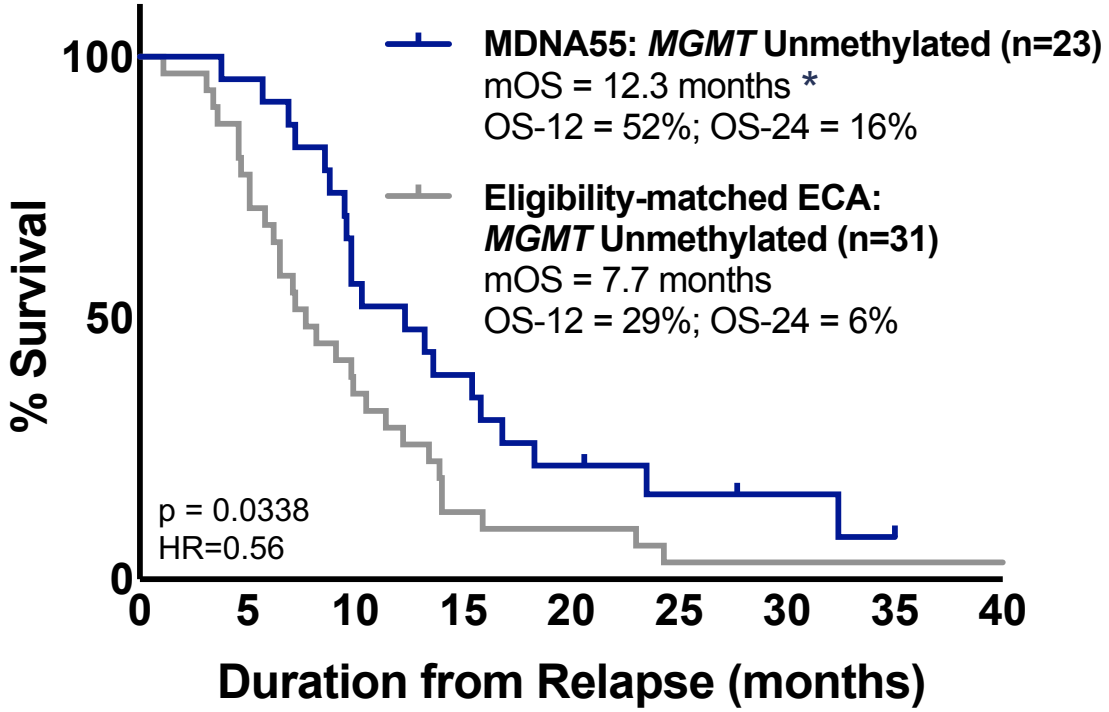
Therapy	N	mPFS	PFS-12
MDNA55 Groups			
All Subjects	41	3.6*	27%
$IL4R^{Hi}$ + $IL4R^{Lo/HD}$	32	3.0*	24%
Approved Therapies			
Avastin[1]	85	4.2	10%**
Avastin[2]	48	4.0	10%**
Lomustine[3]	149	1.5	2%**
Avastin + Lomustine[3]	288	4.2	10%**

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

MDNA55 is Effective in MGMT Promoter Unmethylated rGBM

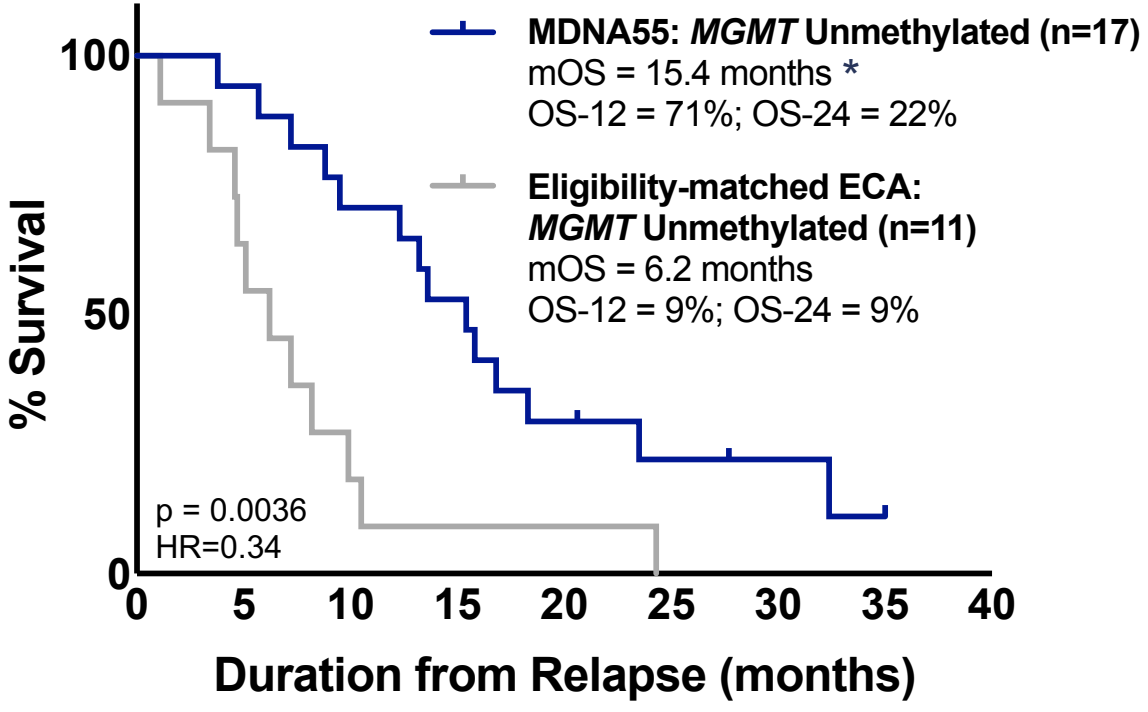
MDNA55 is Potent in a Temozolomide-Resistant Population

All-Comers



*Survival calculated from date of relapse.
Median OS from time of MDNA55 treatment is 10.3 months;
OS-12 = 48%; OS-24 = 16%

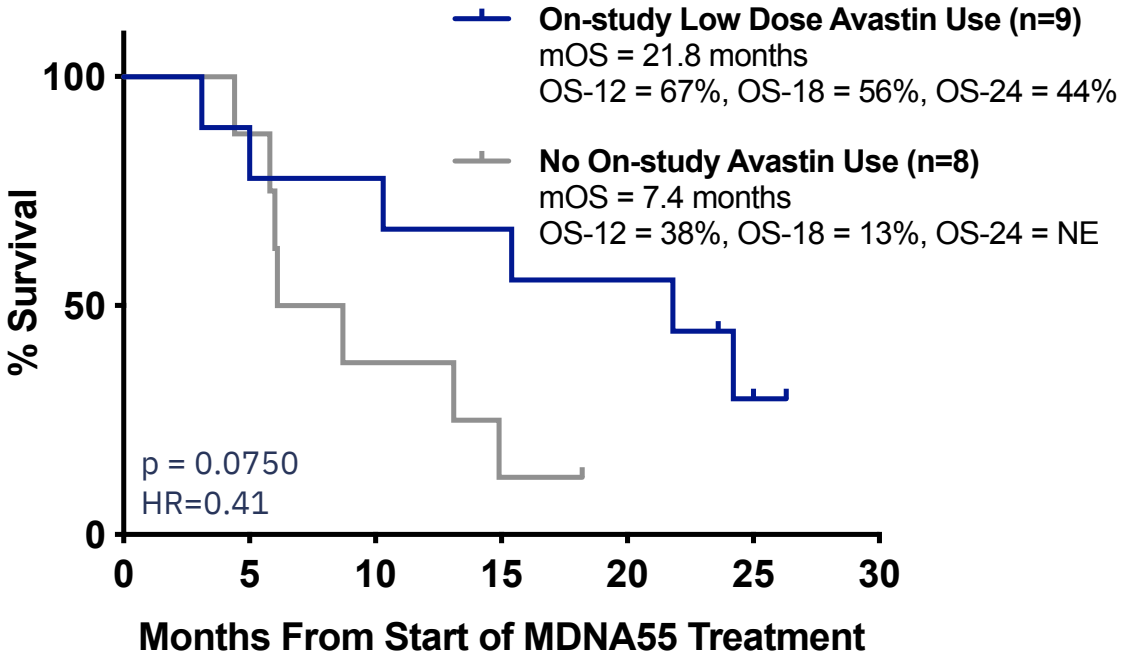
IL4R^{Hi} + IL4R$^{Lo/HD}$



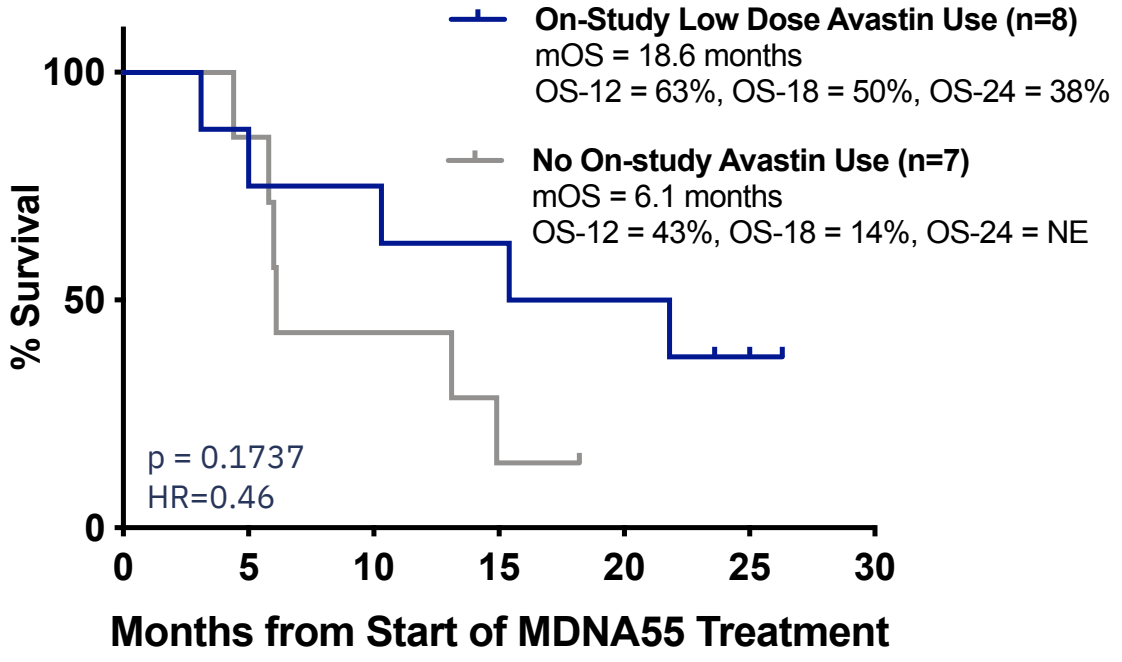
*Survival calculated from date of relapse.
Median OS from time of MDNA55 treatment is 14.9 months;
OS-12 = 65%; OS-24 = 22%

Low-Dose Transient Avastin Post-MDNA55 Improves Survival

All-Comers

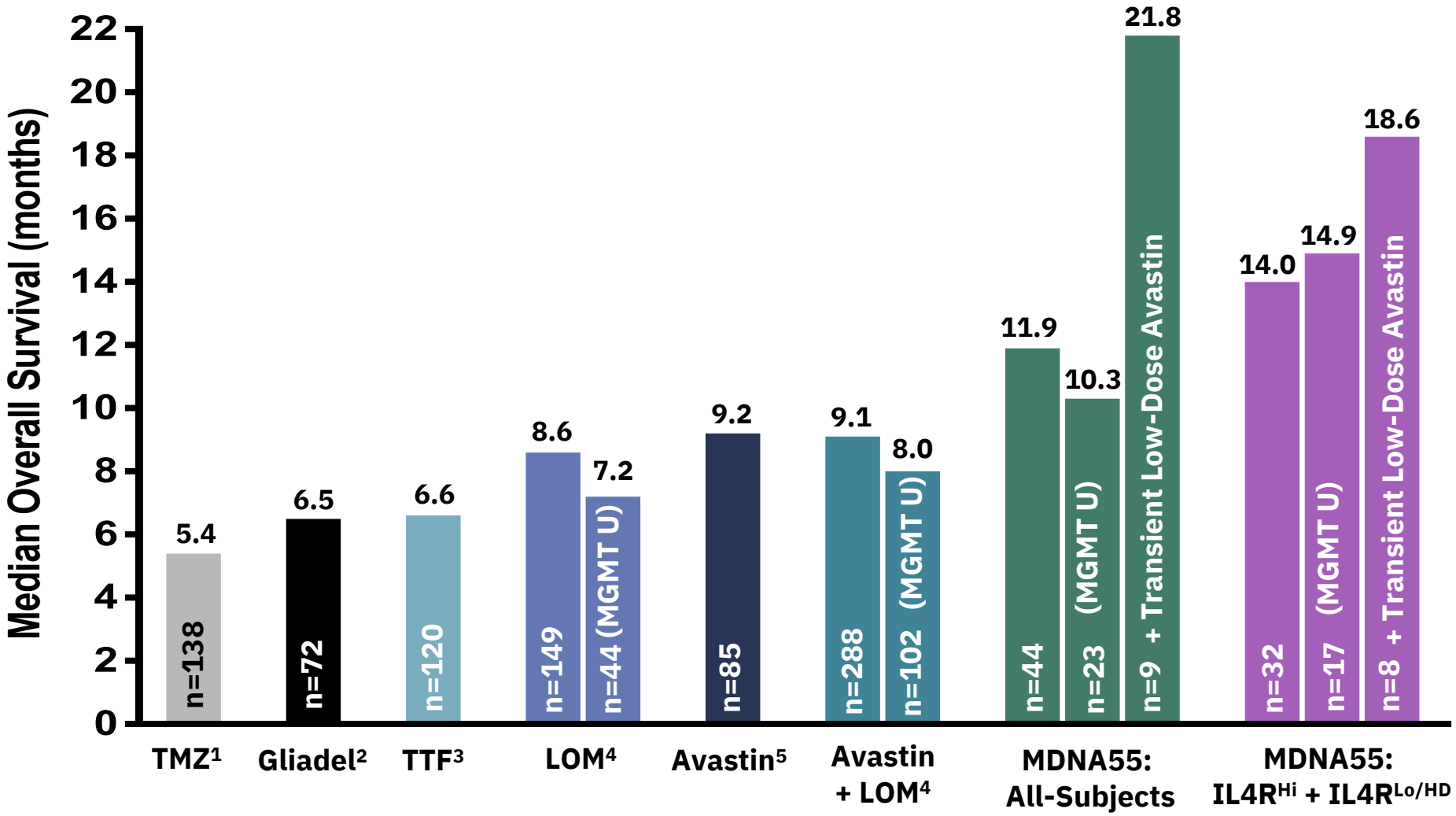


IL4R^{Hi} + IL4R$^{Lo/HD}$



- In the higher concentration cohorts (6 and 9 µg/mL; n=17), transient use of low-dose Avastin (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 Avastin 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.

Improved Survival Compared to Approved Therapies



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

Use of Propensity Matched External Control Arm (ECA) to Demonstrate Utility for Go/No-Go Decisions

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Retrospective Matched-External Control Arm Study

For Comparison of Survival Against MDNA55-05 Study

ELIGIBILITY

- Adults ≥ 18 yrs
- De novo GBM
- 1st or 2nd relapse
- Not candidates for resection
- KPS ≥ 70
- IDH wild-type only
- Tumor size ≥1cm x ≤ 4cm
- Archive tissue from initial Dx if available

SOURCE

- Patient registries at:
  - University of California, San Francisco (UCSF)
  - St. Michael's Hospital (Toronto, Canada)
- Study conducted under IRB-approved protocols
- Investigators and Medicenna blinded to survival outcome
- IL4R analysis used same IHC assay as MDNA55-05 study

TREATMENT

Types of therapies received in the ECA (n=81):

- Avastin (26%)
- Lomustine (25%)
- Temozolmide (14%)
- Experimental Therapy (20%)
- Irinotecan (7%)
- Avastin + Lomustine (5%)
- Radiotherapy (2%)
- Avastin + Radiotherapy (1%)

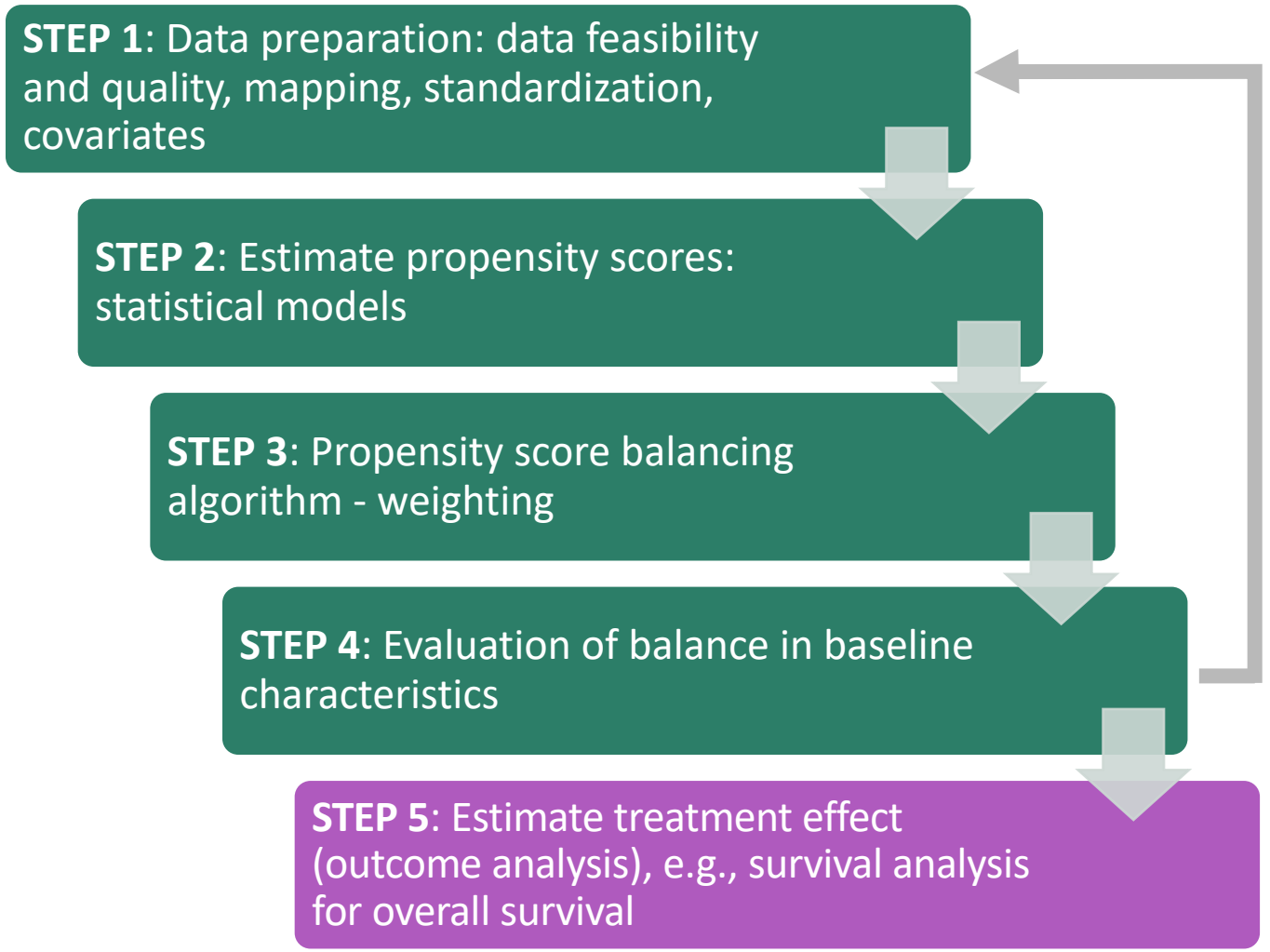
ANALYSIS

- Propensity score methodology was used to balance groups on key prognostic factors; performed prior to unblinding survival data
- Survival time was computed using a common index date (i.e., date of relapse)
- KM curves and HRs were calculated accounting for propensity score weights

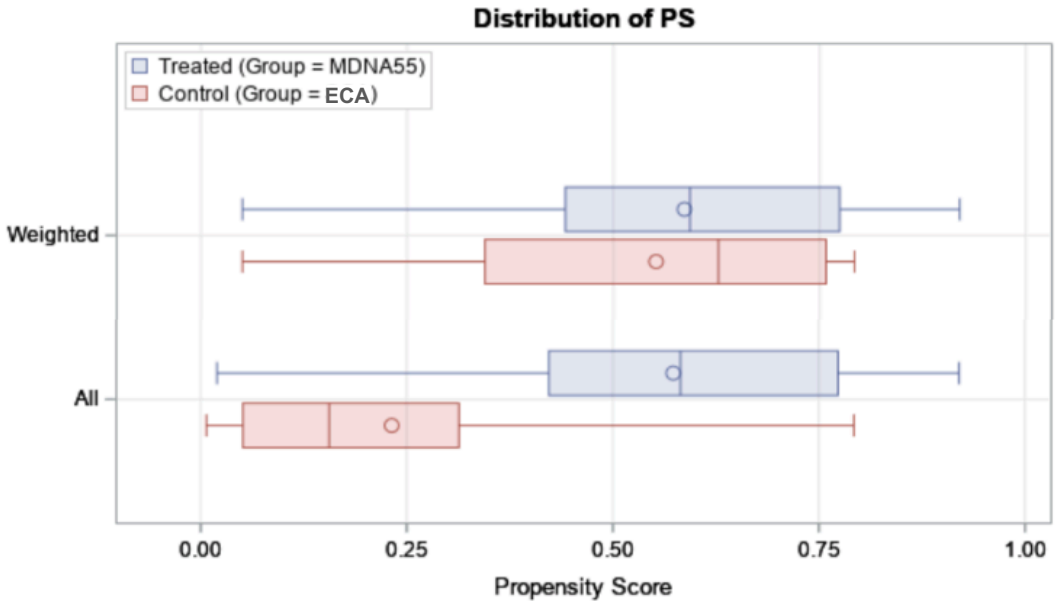
Construction of the External Control Arm

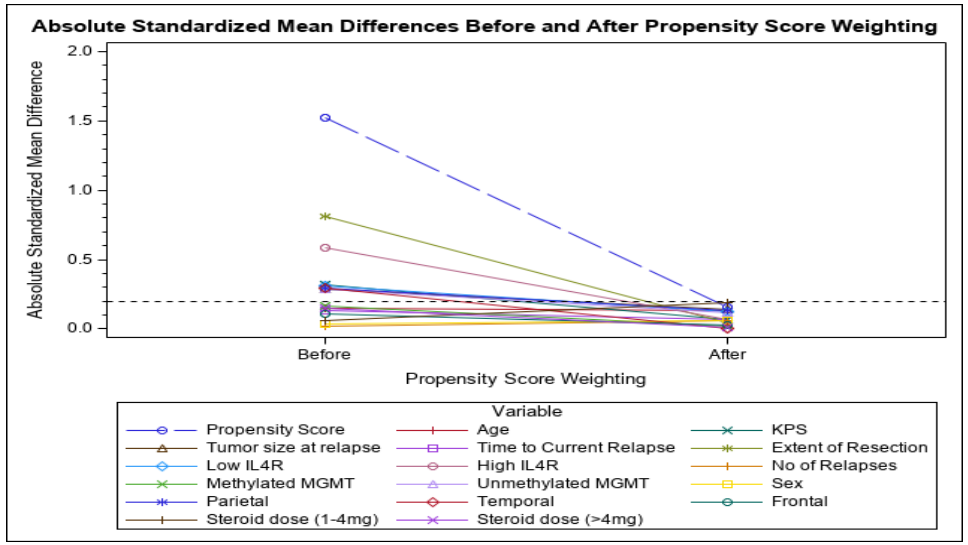
Baseline Characteristics used for Propensity Matching

- Age
- Sex
- KPS
- MGMT methylation status
- IL4R expression level
- Time from initial diagnosis to relapse
- Number of prior relapses
- Extent of resection at initial diagnosis
- Tumor size at relapse
- Tumor location at relapse
- Steroid use prior to treatment

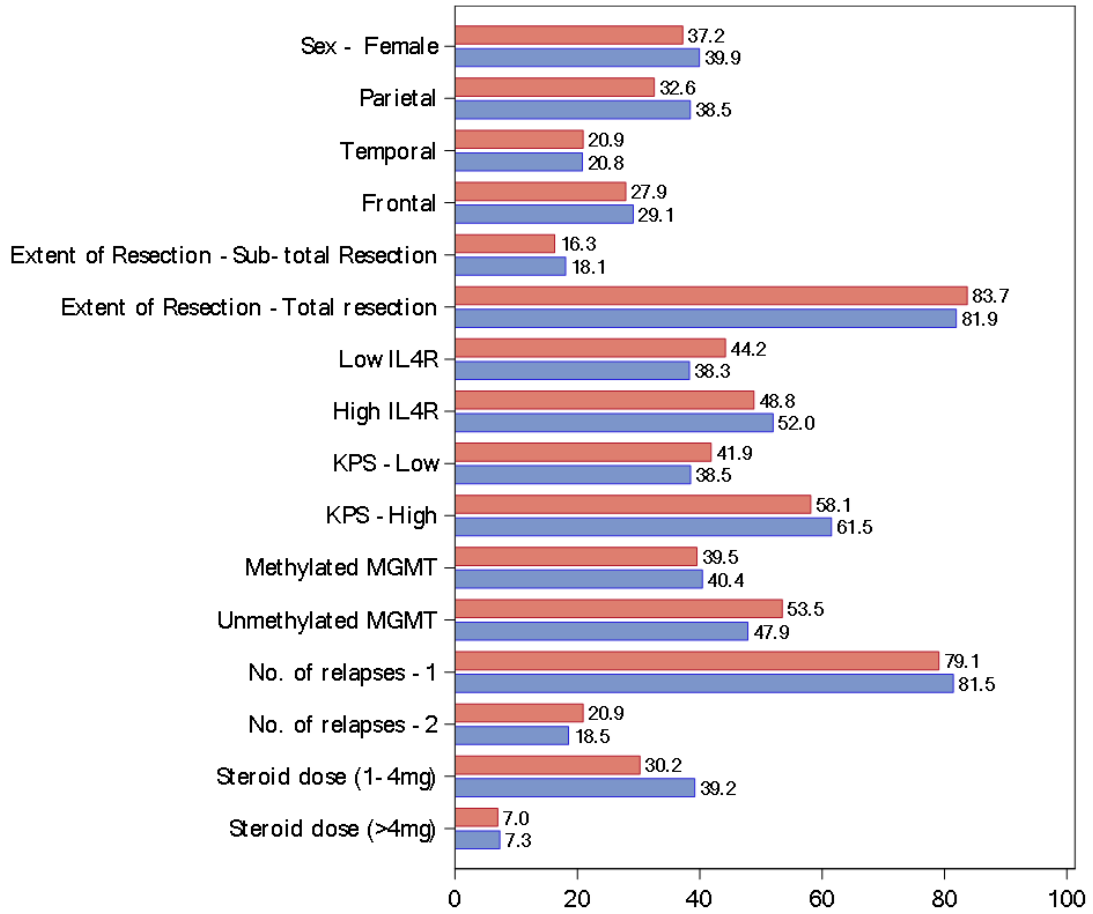


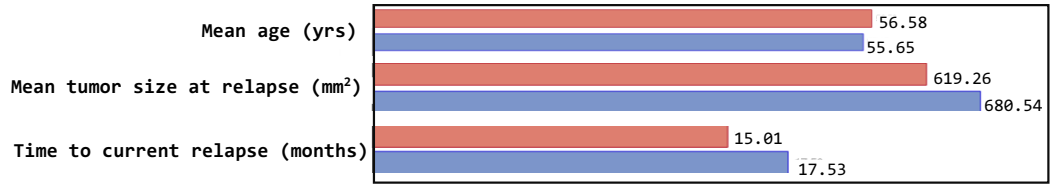
Weighted Baseline Characteristics are Well Matched



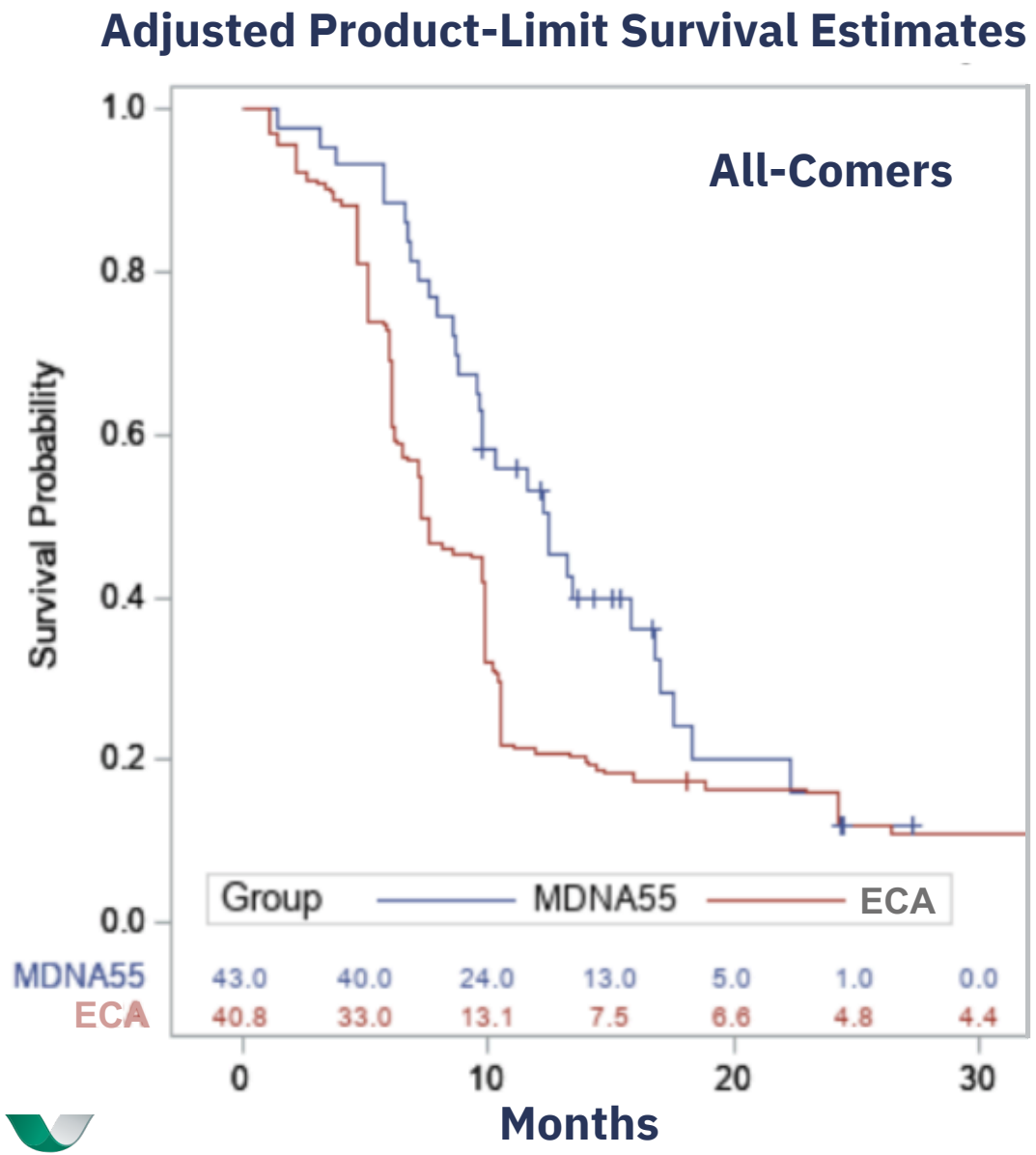


Baseline Demographic and Disease Characteristics





Weighted Survival Analysis: All-Comers

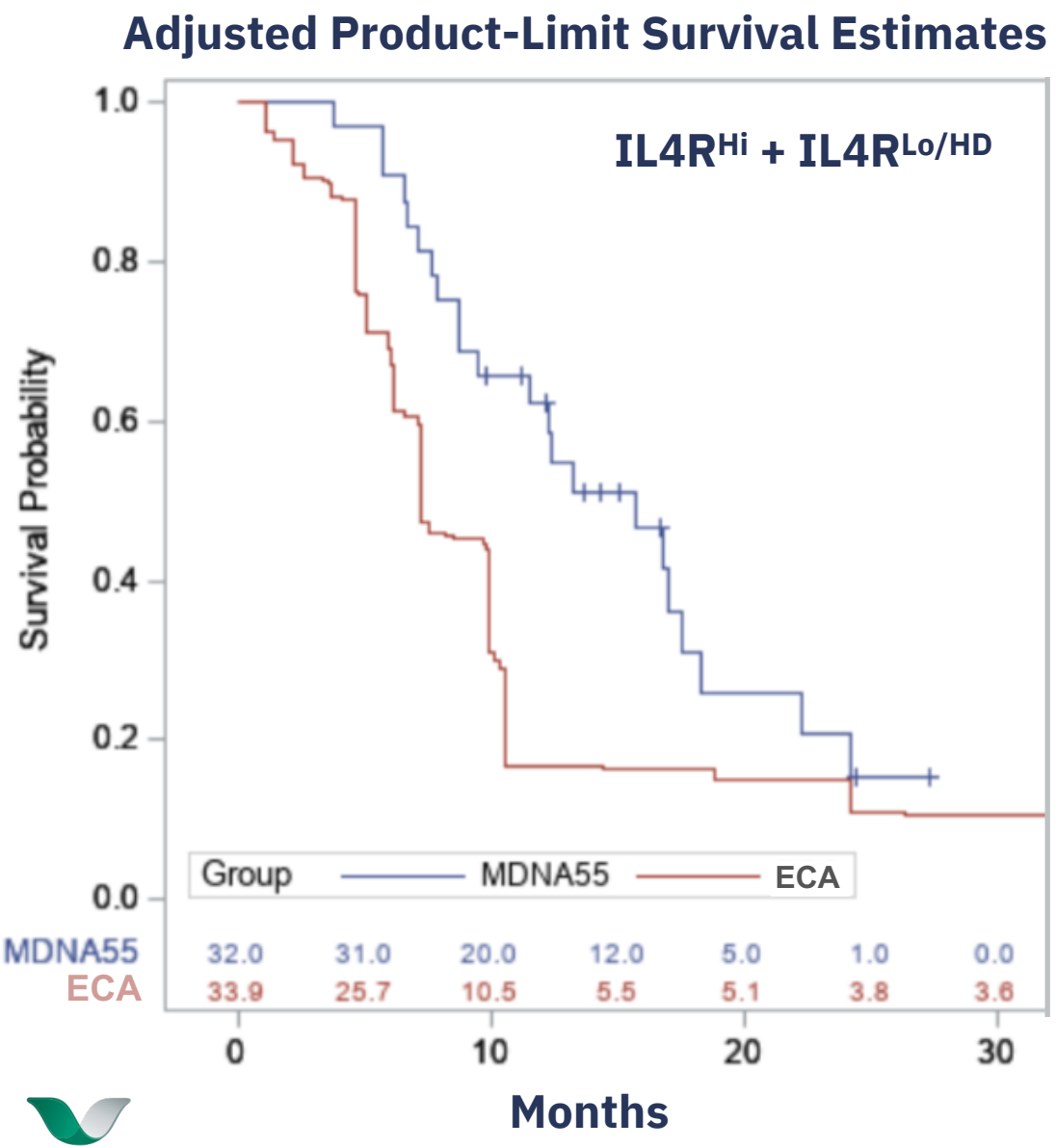


Propensity score weighted estimates:

Group	Median (months)	Log-rank test p-value
MDNA55 (n=43)	12.4	0.1426
ECA (n=40.8)	7.2	

Comparison	Hazard Ratio	95% Confidence Limits	
MDNA55 vs ECA	0.634	0.392	1.026

Weighted Survival Analysis: IL4R^{Hi} + IL4R$^{Lo/HD}$ Subgroup



Propensity score weighted estimates:

Group	Median (months)	Log-rank test p-value
MDNA55 (n=32)	15.7	0.1177
ECA (n=33.86)	7.2	

Comparison	Hazard Ratio	95% Confidence Limits	
MDNA55 vs ECA	0.523	0.300	0.913

Incorporating an ECA in a Phase 3 Registration Trial:

Localized **I**nfusion by CED in Recurrent **G**lioblastoma With **H**igh-Dose MDNA55 **T**herapy (**LIGHT**)

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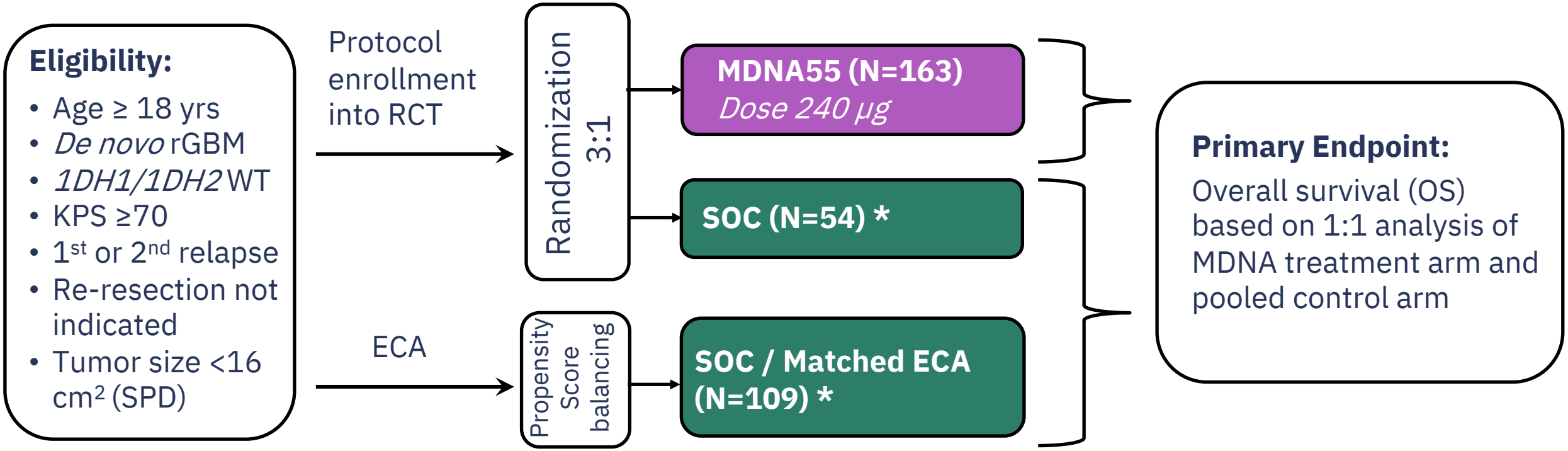
Challenges Associated with a Traditional RCT in rGBM

- Current NCCN guidelines specify “efficacy of SOC for rGBM is suboptimal and consideration of clinical trials is highly encouraged”
- Very high unmet need and dismal prognosis result in patients seeking experimental therapy in a trial where there is no risk of randomization to a control SOC arm
- Blinding may be unfeasible (i.e. due to method of administration) – inability to blind undermines the purpose of randomization
- Withdrawal prior to study therapy initiation of a significant percentage of participants randomized to the control arm may jeopardize the validity of the control arm experience and thereby undermine the value of a randomized trial design for the trial in question.
- Disproportionate discontinuation from SOC arm has been reported as a cause of study failure in GBM studies

Planned MDNA55 Phase 3 Trial – Hybrid Design with ECA



** Pooled control arm*

SOC therapies allowed:

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

- Study powered at 90% to detect a HR of MDNA55 versus Pooled Control Arm = 0.65, at the 2-sided 0.05 overall level of significance.
- Effect size is 4.6 months in mOS time (i.e., mOS time of 13.1 months in the MDNA55 arm versus 8.5 months in the control arm.

Summary

- First randomized hybrid control arm with an ECA component for a registration trial in oncology
- Trial design retains many elements preferred by FDA for a registration trial
  - Large proportion of patients randomized
  - OS endpoint
  - All data elements required for ECA
- Keys to FDA's acceptance of trial design
  - Significant unmet medical need
  - No substantive change in SOC for rGBM over the time period covered in the ECA
  - Near-contemporaneous ECA by limiting to last 5 years
  - Large effect size demonstrated in Phase 2b study
  - Buy-in and, in fact, encouragement from FDA statistical review group

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Thank you

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