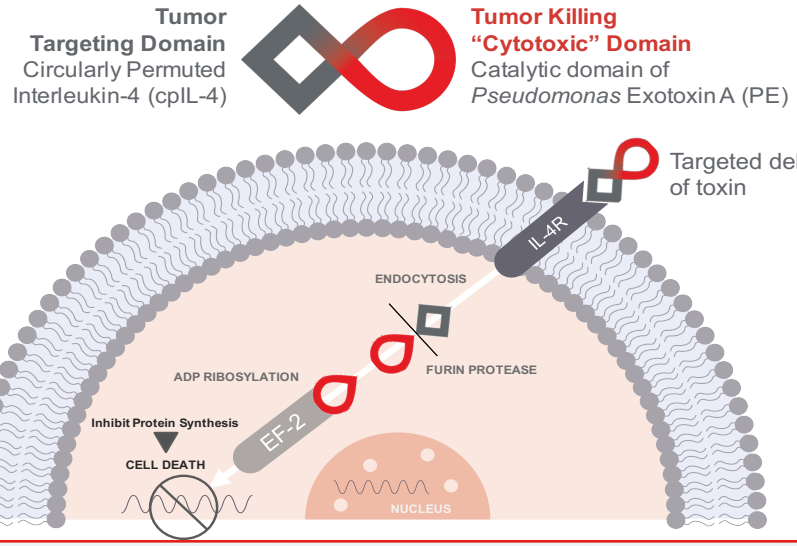
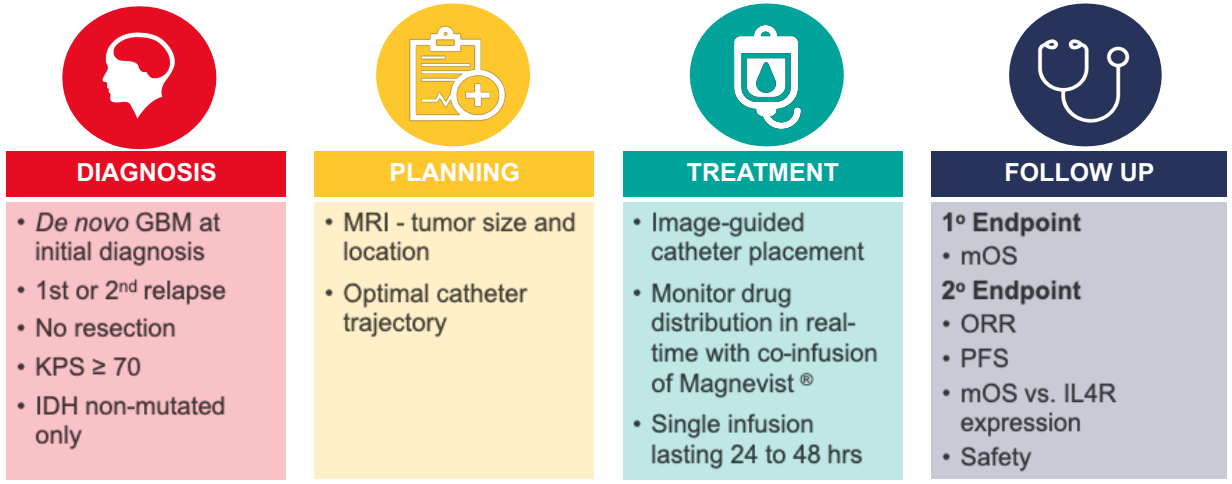
MDNA55 Survival in Recurrent Glioblastoma (rGBM) Patients Expressing the Interleukin-4 Receptor (IL4R) as Compared to a Matched Synthetic Control

BACKGROUND:

- GBM is an aggressive, universally fatal disease; all patients recur.
- IL4R receptor (IL4R) is over-expressed in GBM and tumor microenvironment.
- Worse prognosis associated with:
  - *de novo* GBM[1]
  - IDH WT[2]
  - MGMT promoter unmethylated[3]
  - High steroid use[4]
  - No resection at recurrence[5]
  - IL4R over-expression[6-8]
- MDNA55 is an IL4R targeted immunotoxin studied in a Ph 2b trial in rGBM using convection-enhanced delivery to bypass the BBB.



MDNA55-05 Ph 2b Open-Label Single Arm Study in Recurrent GBM Patients (NCT02858895)



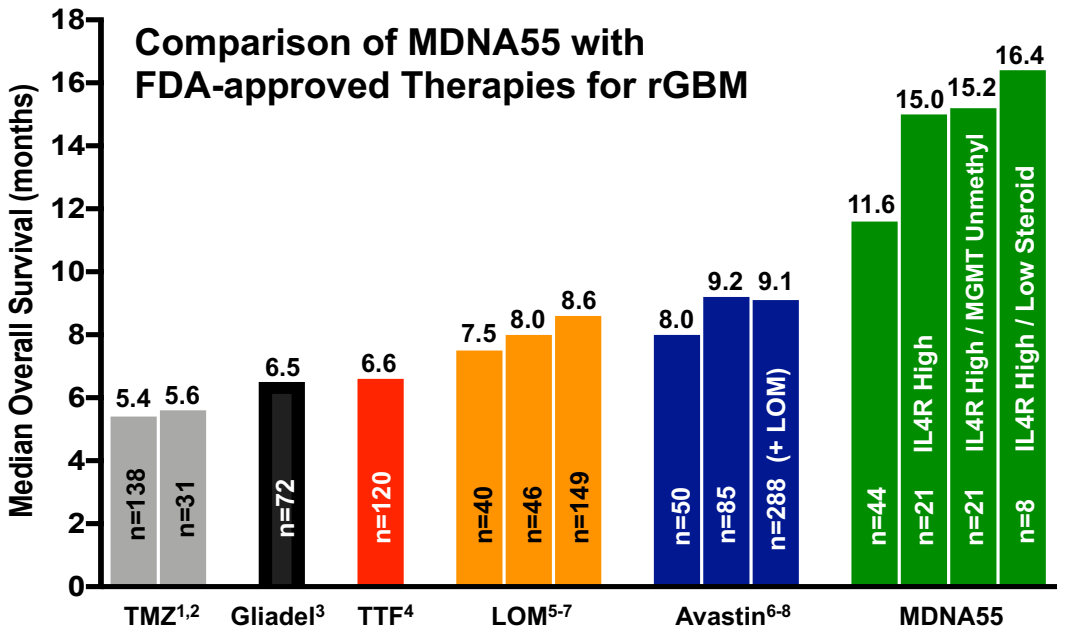
Patient Demographics	N=44
Age	56 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS: 70, 80	22 / 44 (50%)
90, 100	22 / 44 (50%)
De novo GBM	44 / 44 (100%)
No resection at recurrence	44 / 44 (100%)
IDH WT	37 / 37 (100%)
Unmethylated MGMT	23 / 40 (58%)
IL4R over-expression	21 / 40 (53%)
Steroid use > 4mg/day	23 / 44 (52%)
Max Tumor Diameter	30 mm (12 – 65)
# Prior Relapse: 1 , 2	35 (80%) , 9 (20%)

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)

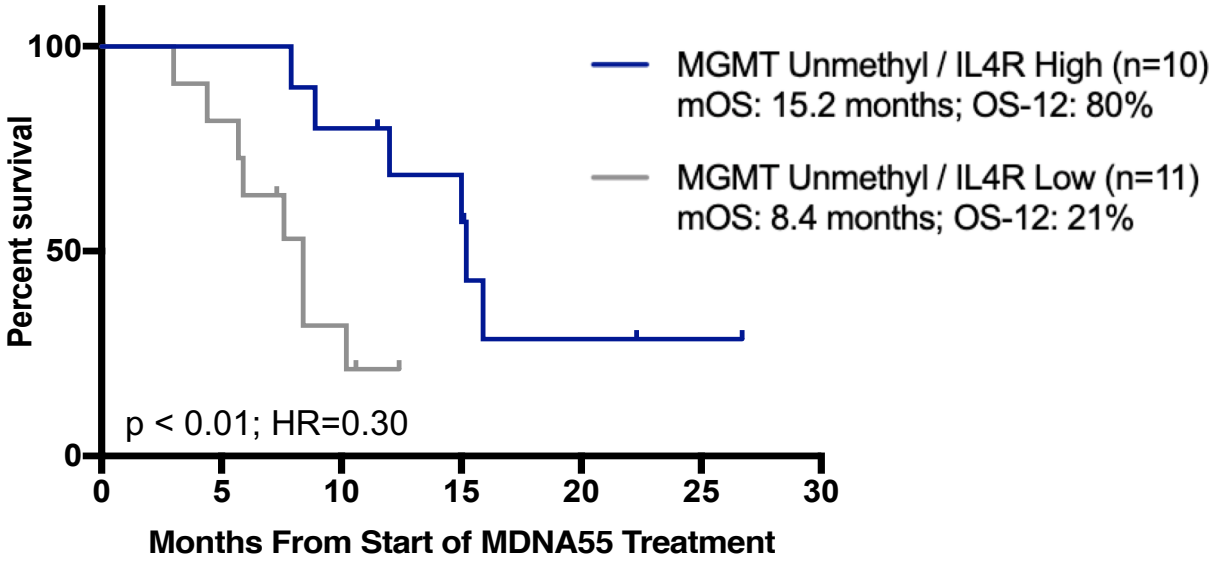
J Sampson, AS Achrol, MK Aghi, K Bankiewicz, M Bexon, S Brem, A Brenner, C Chandhasin, S Chowdhary, M Coello, S Das, JR Floyd, S Han, S Kesari, F Merchant, N Merchant, D Randazzo, M Vogelbaum, F Vrionis, M Zabek, and N Butowski

Improved Survival Seen with MDNA55, Particularly in IL4R High Subjects

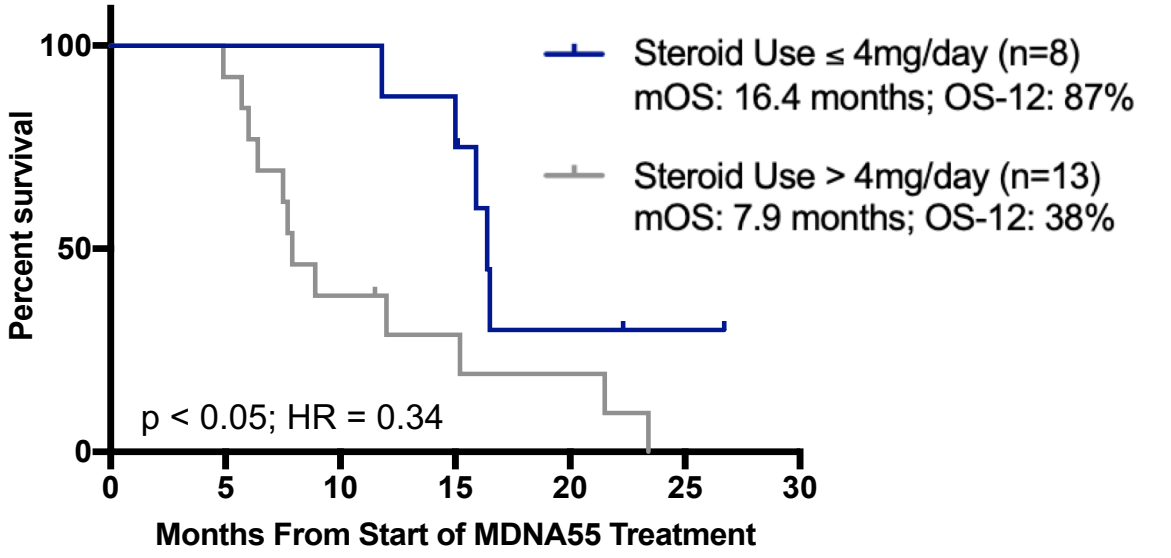
- All subjects (n=44): mOS is 11.6 months; ~ 50% increase compared to null hypothesis of 8.0 months based on FDA-approved therapies. OS-12 is 46%.
- IL4R High Group (n=21): mOS is 15 months vs 8.4 months in IL4R Low group (data not shown); p=0.2175; HR= 0.65
  OS-12 is 57% vs. 33%, respectively.
- IL4R High Subgroups: Improved outcomes also seen in unmethylated MGMT (n=21), low steroid use (n=8) (**see panels below**).



Improved Survival in IL4R High Subjects Despite MGMT Unmethylated Status



Improved Survival in IL4R High Subjects with Low Steroid Use



1) Brada et al., 2001; 2) Kim et al., 2015; 3) Gliadel FDA Label 2018; 4) Stupp et al., 2012; 5) Brandes et al., 2016; 6) Taal et al., 2014; 7) Wick et al., 2017; 8) Friedman et al., 2009

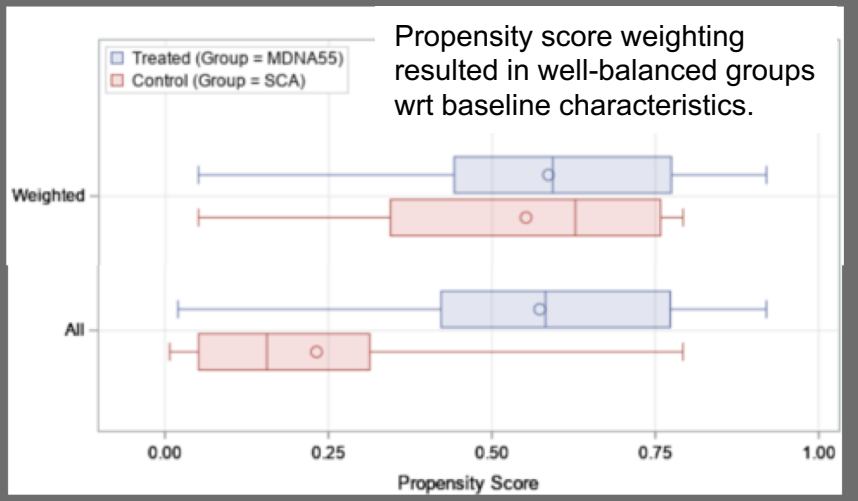
Improvement in mOS of Over 100% Seen in MDNA55 IL4R High Subjects Compared to a Synthetic Control Arm (SCA)

Comparison with a Synthetic 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 SCA.

Propensity Score Methods:

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



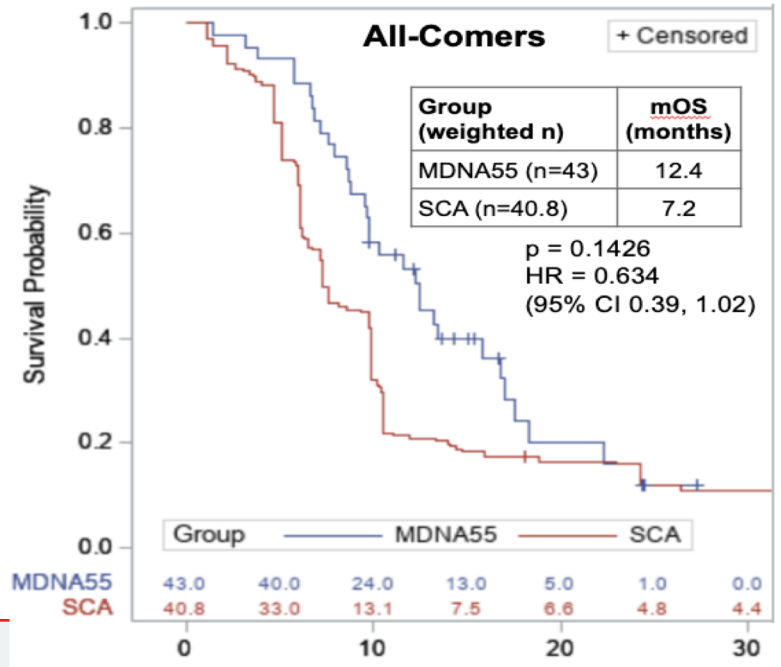
Propensity score weighting resulted in well-balanced groups wrt baseline characteristics.

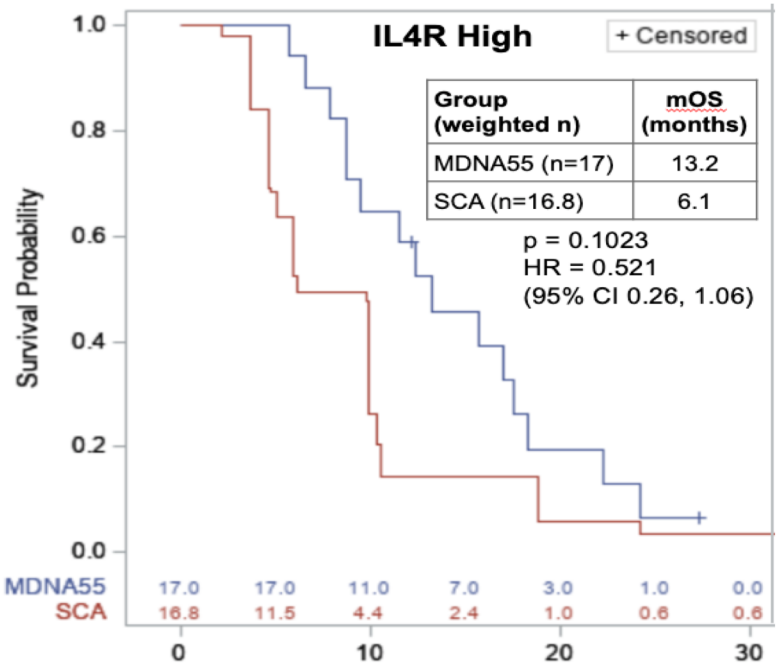
Results*:

- Weighted All-comers (n=43): mOS is 12.4 months vs. 7.2 months in SCA.
- Weighted IL4R High group (n=17): mOS is 13.2 months vs 6.1 months in SCA.
- Survival time more than doubled in the MDNA55 IL4R High group; this is an unprecedented outcome particularly when high IL4R expression is associated with poor outcomes in GBM.

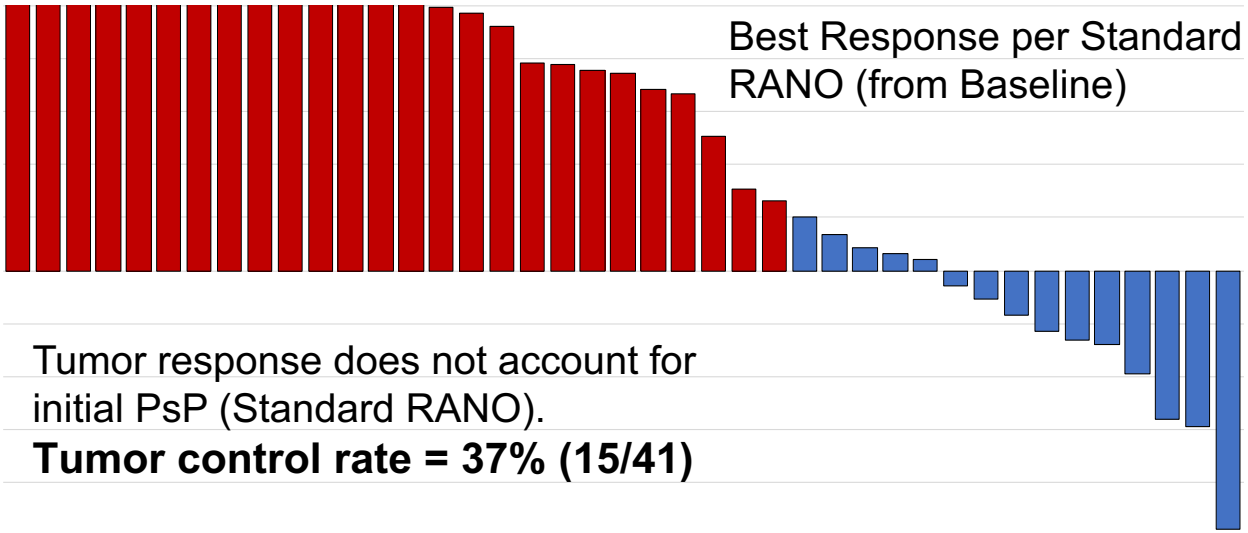
*Survival was calculated from time of relapse

Adjusted Product-Limit Survival Estimates (With Number of Subjects at Risk)

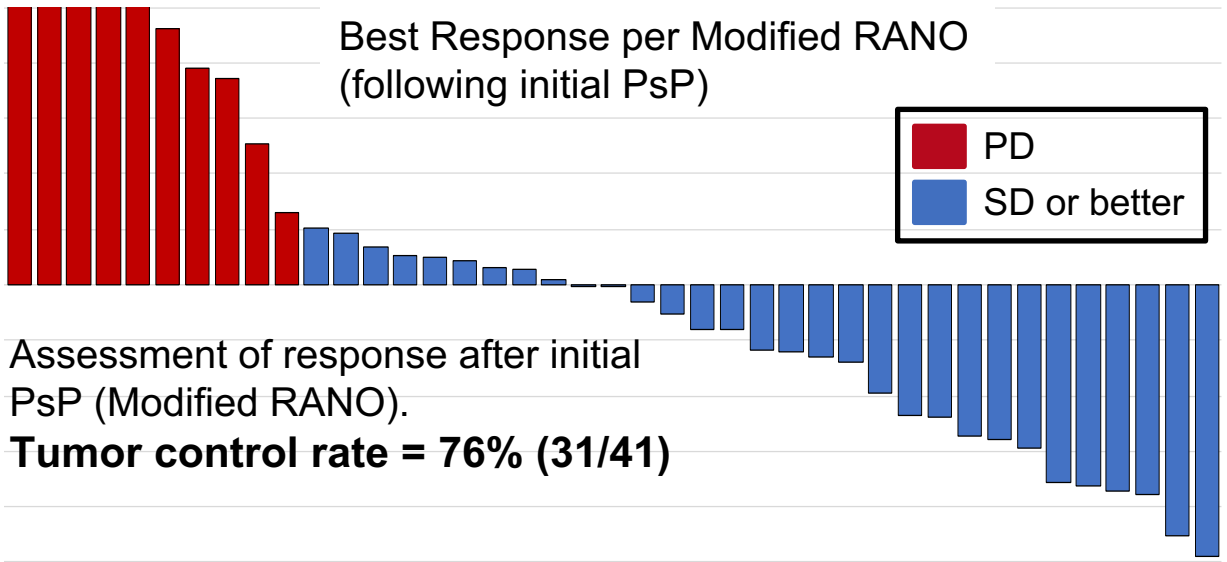




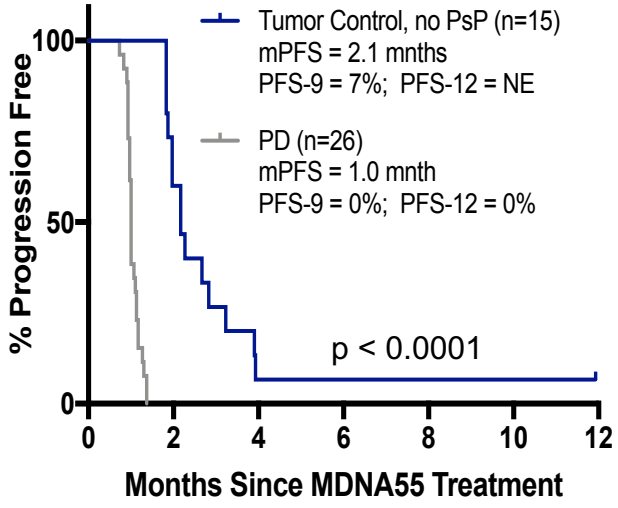
Tumor Control Following Pseudo-Progression (PsP) is Associated with Longer PFS and OS

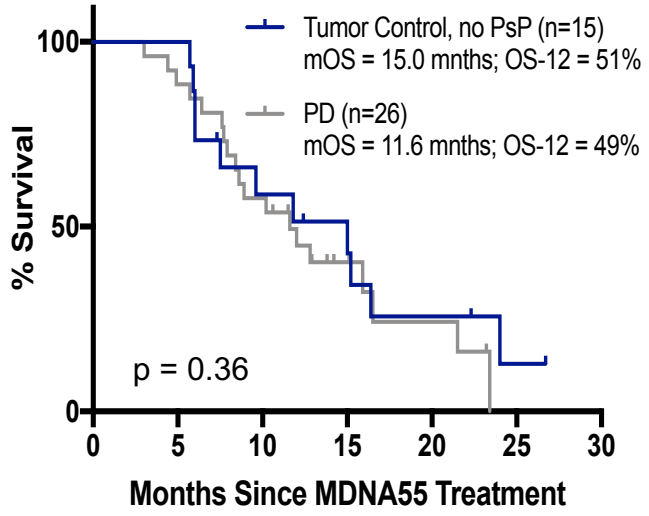


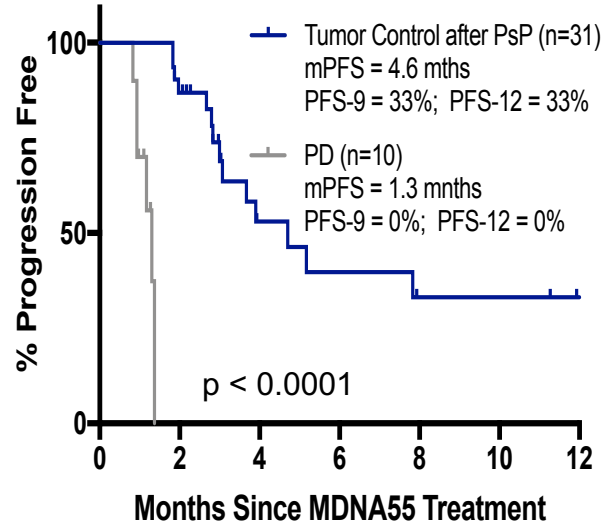
Tumor response does not account for initial PsP (Standard RANO).
Tumor control rate = 37% (15/41)

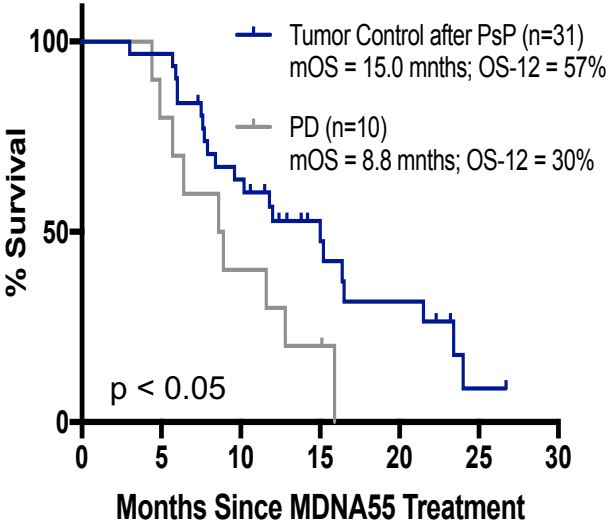


Assessment of response after initial PsP (Modified RANO).
Tumor control rate = 76% (31/41)









*Based on radiologic assessments only

Summary & Conclusions

Phase 2b Study Results:

Group	Efficacy Parameter	Results (95% CI)
Survival Parameters		
All (n=44)	mOS (months)	11.6 (7.90, 15.15)
	OS-12	46% (31, 60%)
IL4R High (n=21)	mOS (months)	15.0 (7.70, 16.43) HR=0.65
	OS-12	57% (33, 75%)
Responders (n=31)	mOS (months)	15.0 (8.36, 21.48) HR=0.45
	OS-12	57% (37, 72%)
Response Parameters*		
All (n=41)	Tumor Control Rate	31 (76%)
All (n=41)	mPFS (months)	3.6 (2.62, 7.70)
	PFS-12	27% (11, 46%)
Responders (n=31)	mPFS (months)	4.6 (2.95, 12.13) HR=0.11
	PFS-12	33% (0.13, 0.55)

- Subjects treated with MDNA55 represent a difficult to treat population (*de novo* GBM, IDH wild-type, not eligible for surgery at recurrence).
- Targeted therapies such as MDNA55 directed to IL4R may improve patient outcomes and help guide patient selection for future clinical studies.
- MDNA55 is potent in unmethylated MGMT setting; survival increased by ~ 7 months in IL4R High vs. IL4R Low subjects; MDNA55 may be beneficial in patients resistant to temozolomide.
- Response based on pseudo-progression provides more reliable surrogate for survival with immunotherapy agents.
- Single treatment with MDNA55 increases survival >100% in subjects expressing high levels of IL4R when compared to a matched SCA; provides an unprecedented outcome for this highly lethal disease.

Duke University · Penn · Cleveland Clinic · UT Medicine CTRC Health Science Center San Antonio · Oregon Health & Science University · UCSF University of California San Francisco · John Wayne Cancer Institute · Boca Raton Regional Hospital · Mazowiecki Szpital Brodnowski · Cancer Prevention & Research Institute of Texas

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 G et al. Cancer Res, 2013; 7 Han J. and Puri R. J of Neuro-Oncology, 2018; 8 D'Alessandro G, et al. Cancers (Basel) 2019

*Based on independent radiographic assessment per mRANO

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Additional Data

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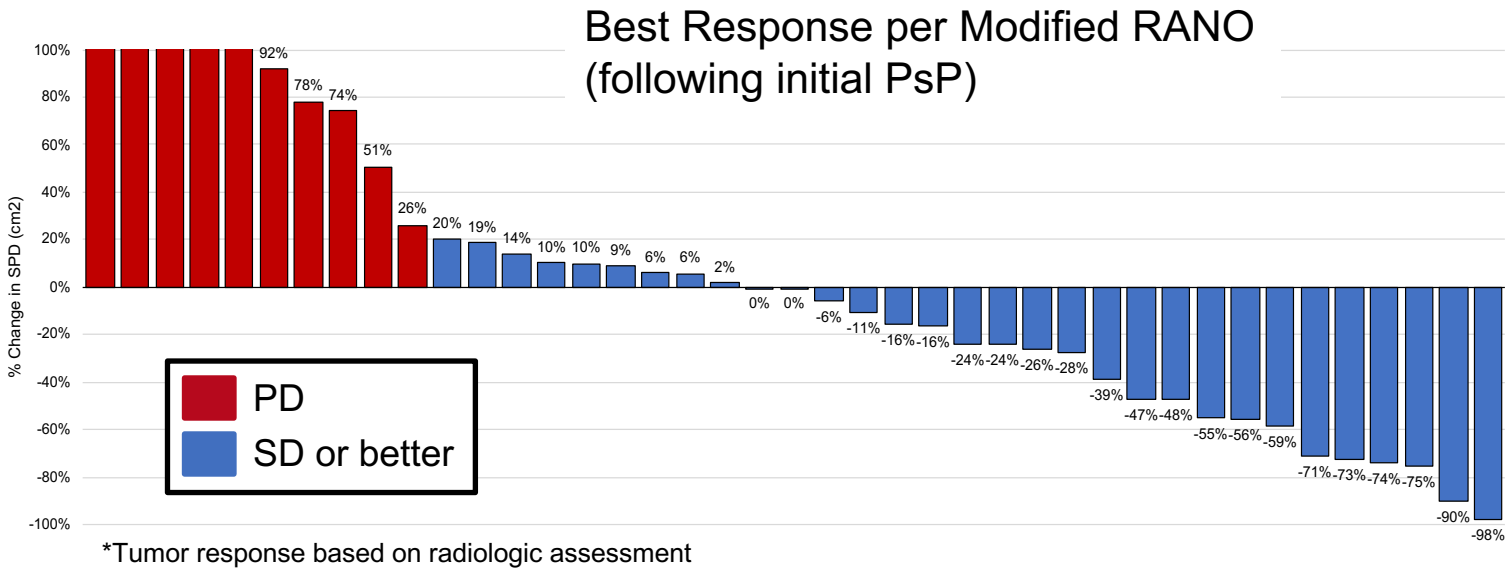
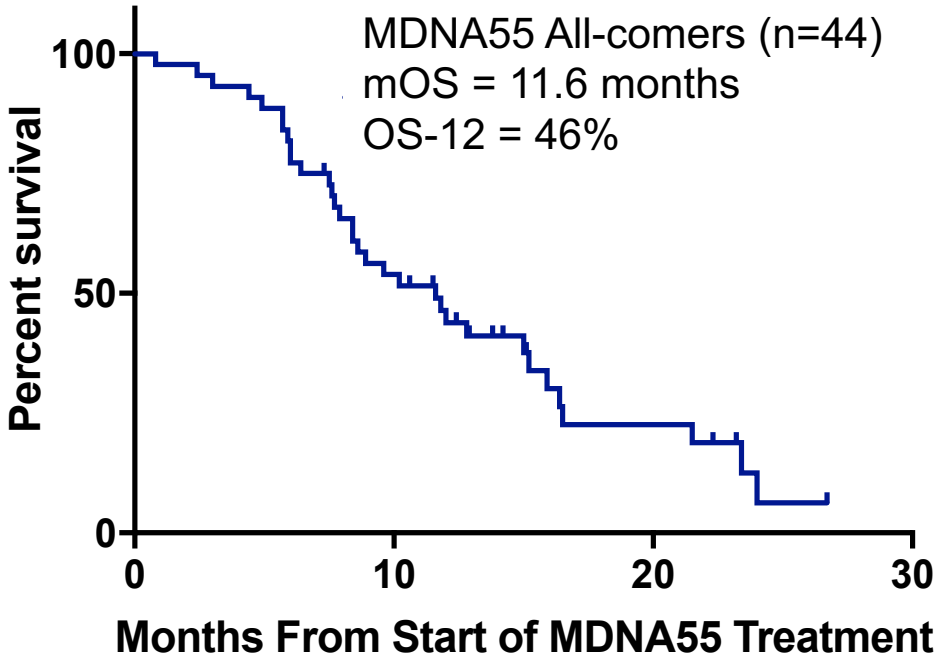
MDNA55 ALL-EVALUABLE: TUMOR CONTROL RATE & SURVIVAL



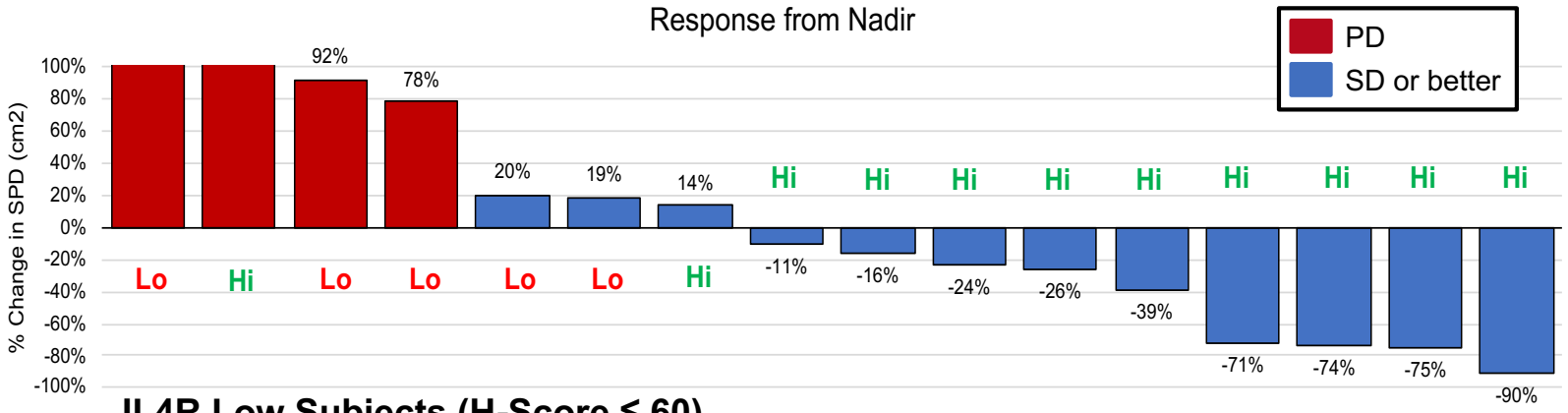
*Tumor response based on radiologic assessment



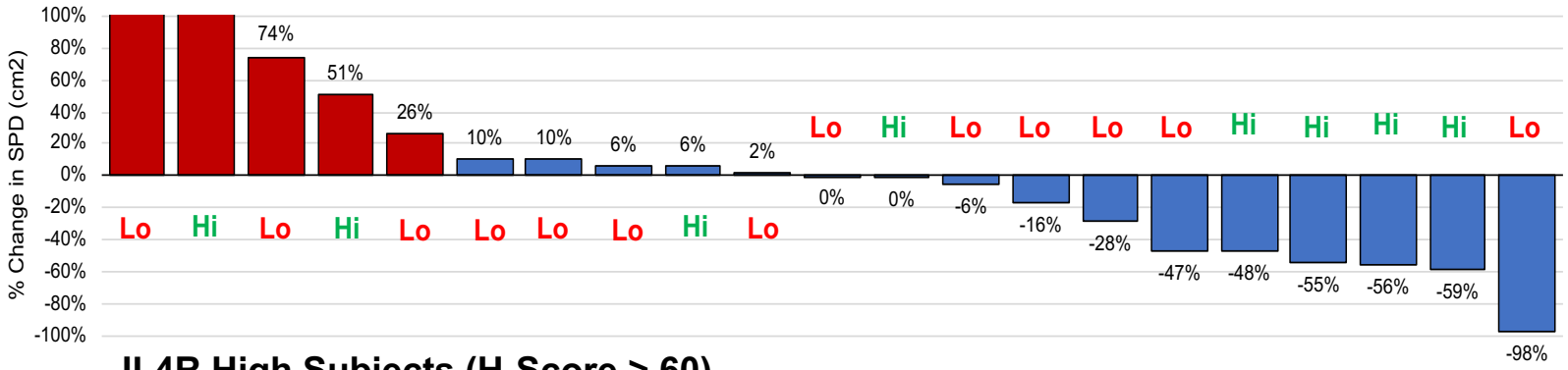
Tumor Control Rate = 76% (31/41)

IL4R HIGH & LOW GROUPS: TUMOR CONTROL RATE & SURVIVAL

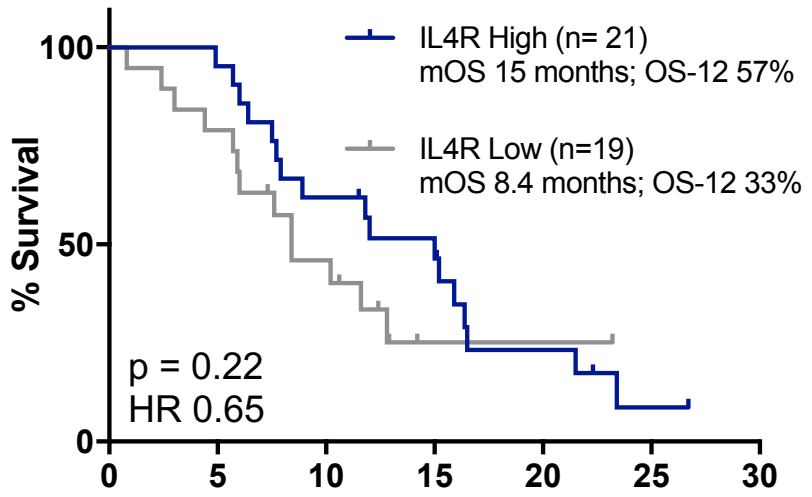
Tumor control and longer survival in IL4R Low subjects attributed to high MDNA55 dose

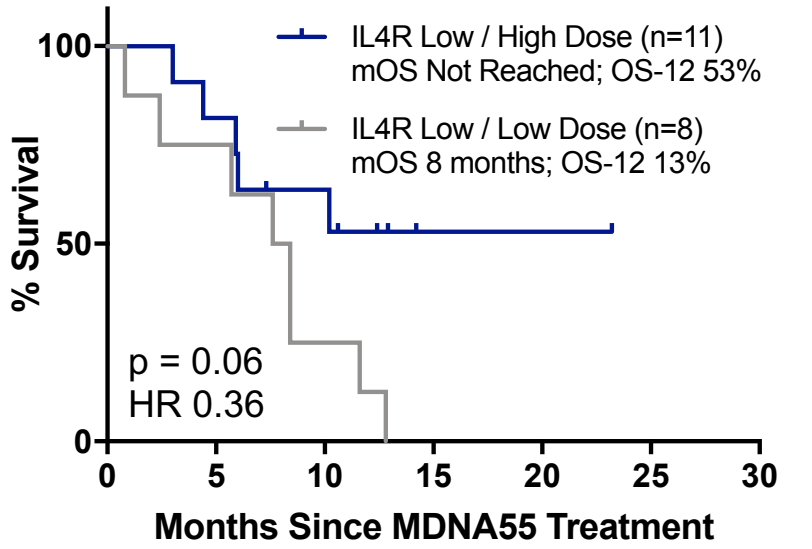


IL4R Low Subjects (H-Score ≤ 60)
% High Dose: 69% (11/16)
TCR = 75% (12/16): High Dose 83% (10/12), Low Dose: 17% (2/12)



IL4R High Subjects (H-Score > 60)
% High Dose: 38% (8/21)
TCR = 76% (16/21): High Dose: 38% (6/16), Low Dose: 62% (10/16)



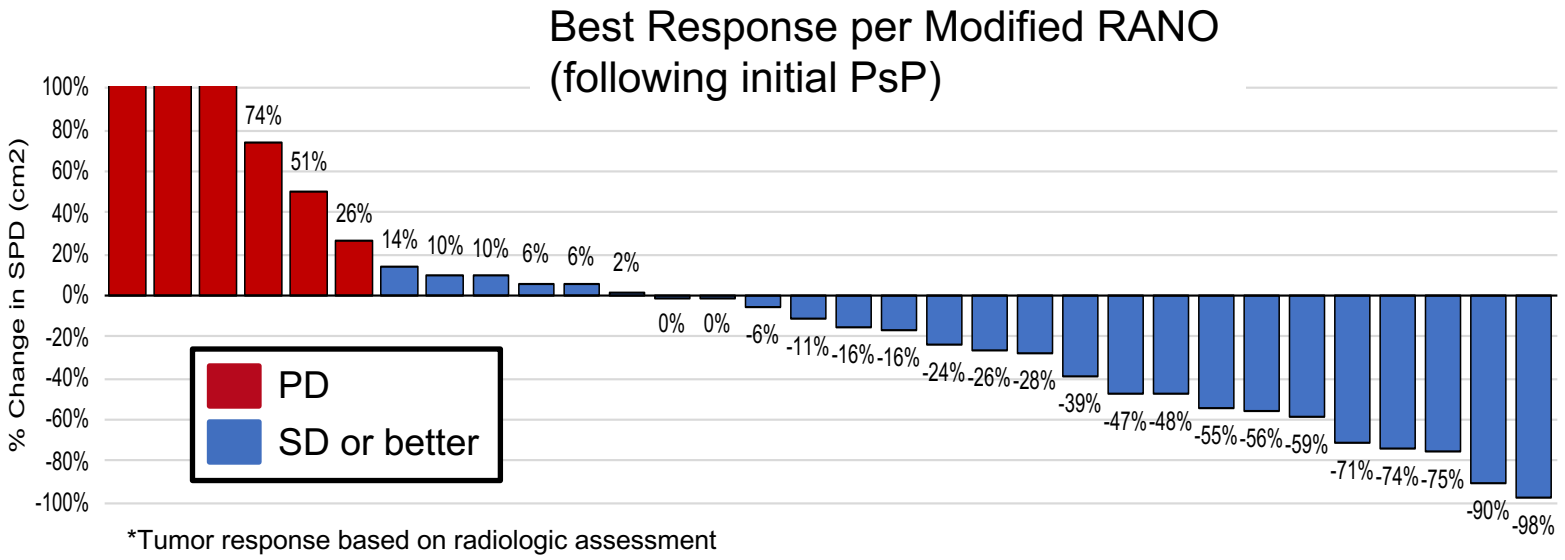


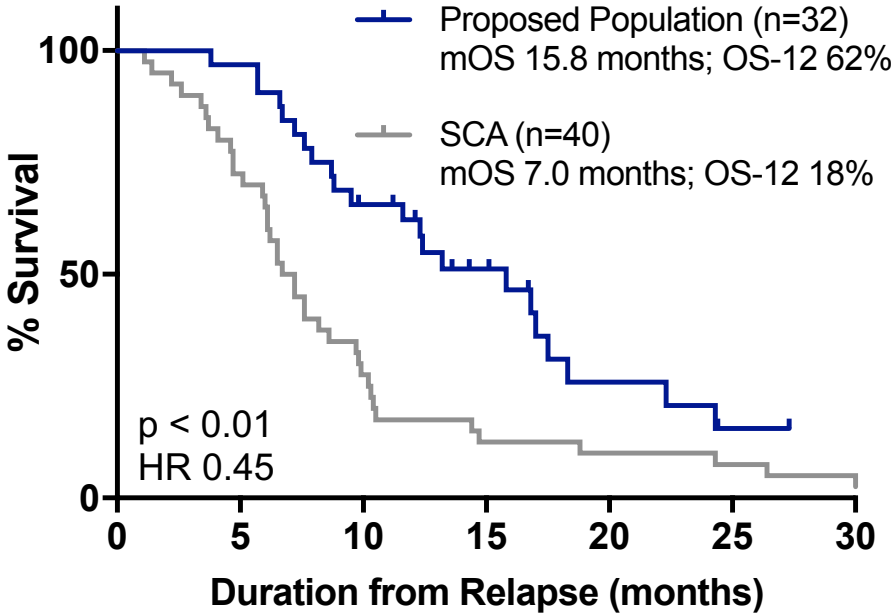
*Tumor response based on radiologic assessment by 2D mRANO

MDNA55 PROPOSED POPULATION: TUMOR CONTROL RATE & SURVIVAL

Proposed Population shows > 100% improvement in survival when compared to SCA

A Proposed Population (n=32) comprised of all IL4R High (irrespective of dose) as well as IL4R Low patients receiving the high dose





Tumor Control Rate = 81% (26/32)

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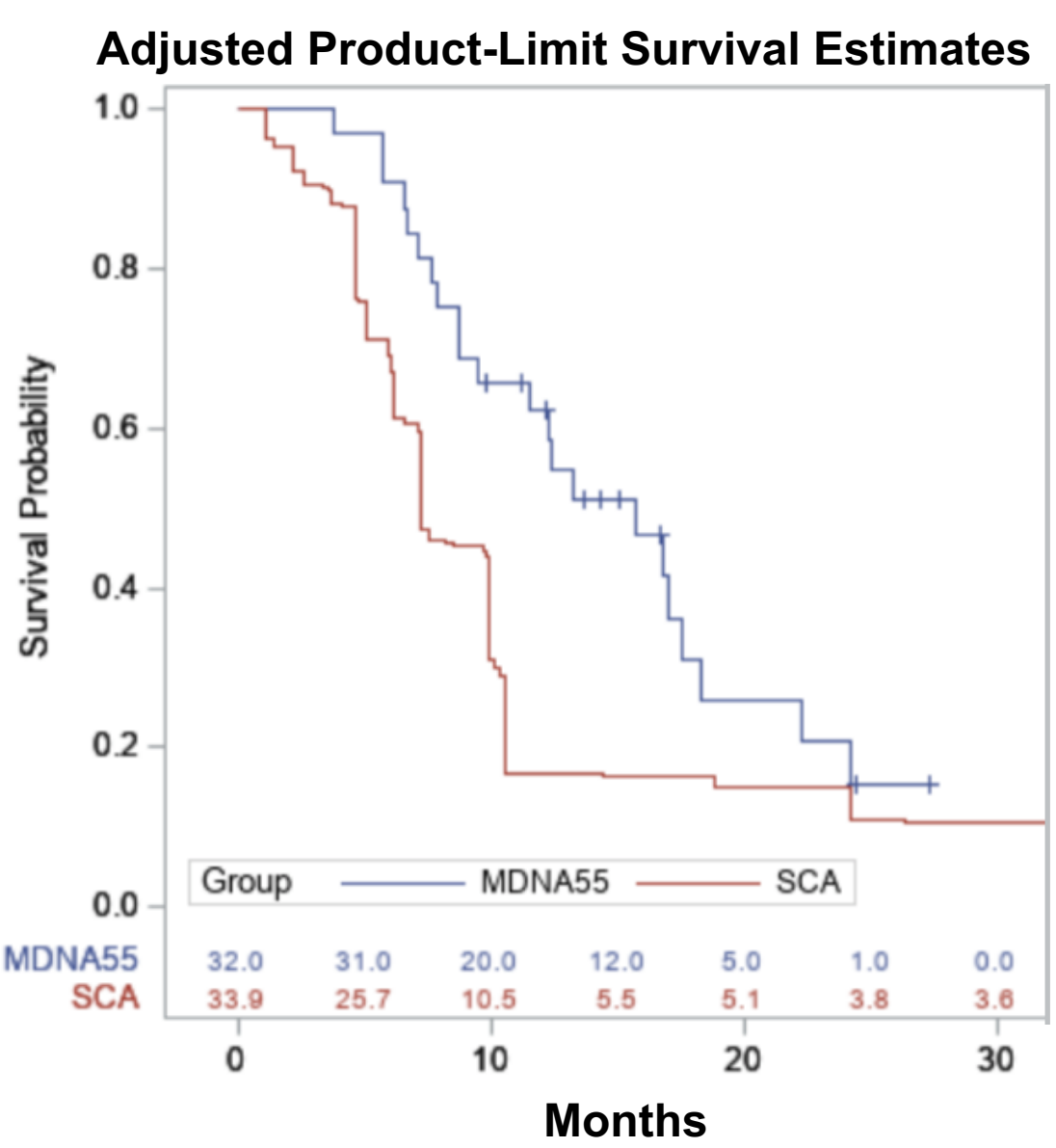
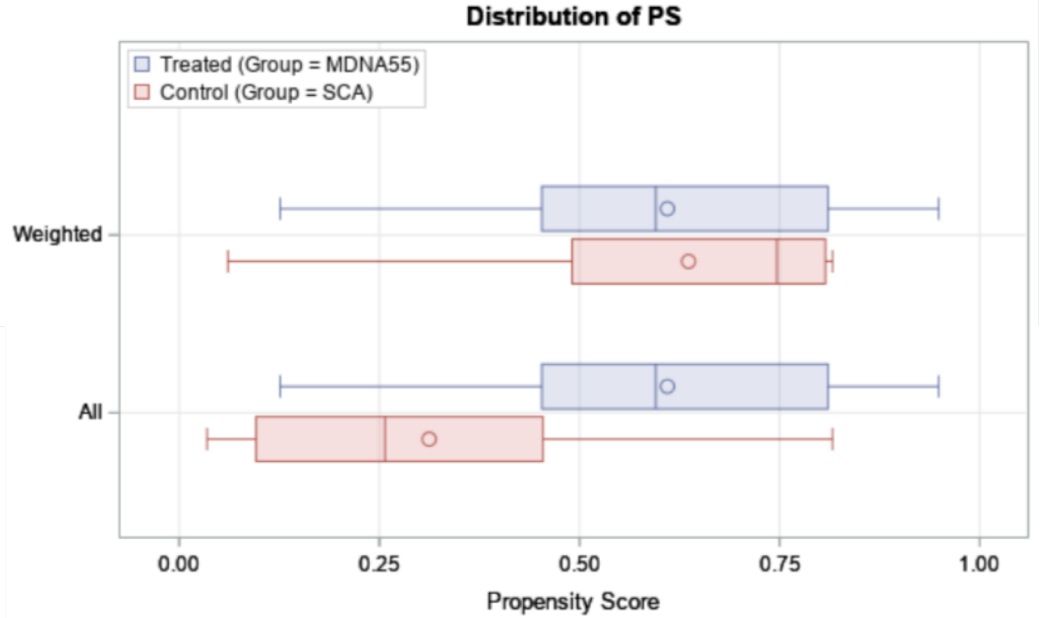
MDNA55 PROPOSED POPULATION: IMPROVED SURVIVAL COMPARED TO SCA (WEIGHTED ANALYSIS)





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

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

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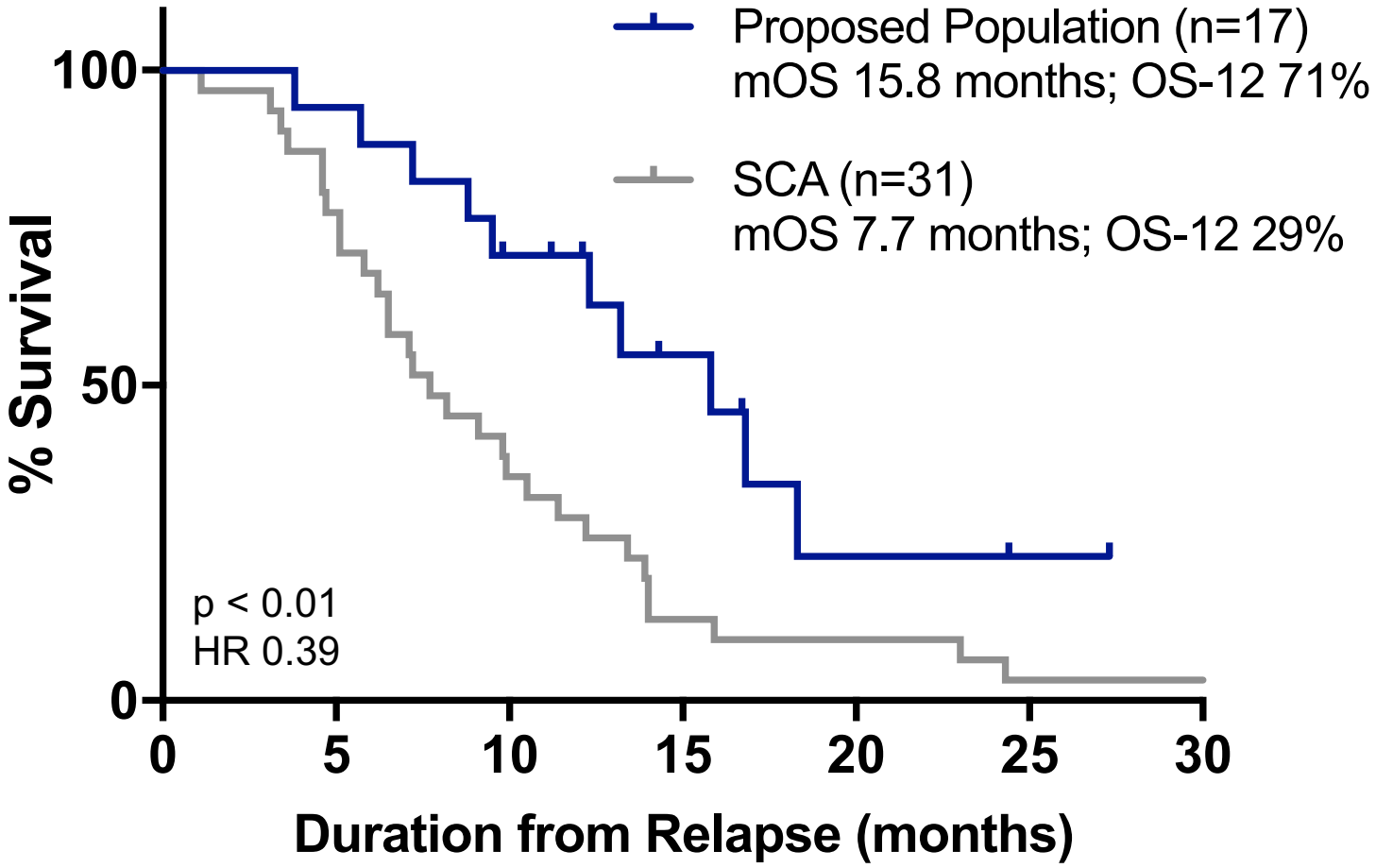
MDNA55 PROPOSED POPULATION: IMPROVED SURVIVAL IN MGMT UNMETHYLATED GROUP



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SUMMARY

- Similar tumor control rates (TCR) were seen in patients with Low IL4R expression (H-Score ≤ 60) and High IL4R expression (H-Score > 60); TCR of 75% vs. 76%, respectively.
- However, the majority of IL4R Low patients (11 of 16) received high doses of MDNA55 (180 - 240 μg; median 180 μg) whereas only 8 of 21 IL4R High patients received the high dose of MDNA55.
- The IL4R Low group receiving high dose also showed improved survival (mOS Not Reached, OS-12 of 53%) when compared to the low dose group (mOS = 8 months, OS-12 = 13%).
- A Proposed Population (n=32) comprised of all IL4R High (irrespective of dose) as well as IL4R Low patients receiving the high dose were identified to benefit the most from a single treatment of MDNA55.
- Median survival and OS-12 in this population was 15.8 months and 62% vs 7.0 months and 18%, respectively, when compared to the eligibility matched SCA; improvement in survival was also seen with MDNA55 in MGMT unmethylated patients.
- TCR in the Proposed Population was 81% based on radiologic assessment by mRANO criteria.
- These data indicate MDNA55 has potential to benefit all rGBM patients treated at the high dose (180 μg) irrespective of IL4R expression.

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

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