Validation of Modified RANO (mRANO) determined PFS as a Strong Predictor of OS in Recurrent GBM Treated with a Targeted Immunotoxin

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Disclosures

Ellingson: Advisor for Hoffman La-Roche; Siemens; Medicenna; MedQIA; Bristol Meyers Squibb; Imaging Endpoints; VBL; and Agios Pharmaceuticals. Paid Consultant for MedQIA; Siemens; Hoffman La-Roche; Imaging Endpoints; Medicenna; and Agios.

Chandhasin, Coello, Merchant N., Merchant F.: Employees of Medicenna.

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Study Background

- Radiographic response assessment is critical for identifying therapeutic benefit of new treatments.

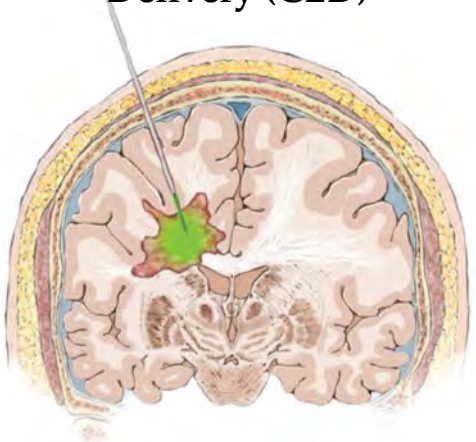
- Standard RANO (**sRANO**), **iRANO**, and modified RANO (**mRANO**) were all developed as improvements or modifications to previous criteria but haven't been evaluated side-by-side nor correlated with OS in a prospective trial.

Objective: Comparison of **sRANO, iRANO**, and **mRANO** response, PFS, and association between PFS and OS in a novel immunotoxin trial in recurrent GBM.

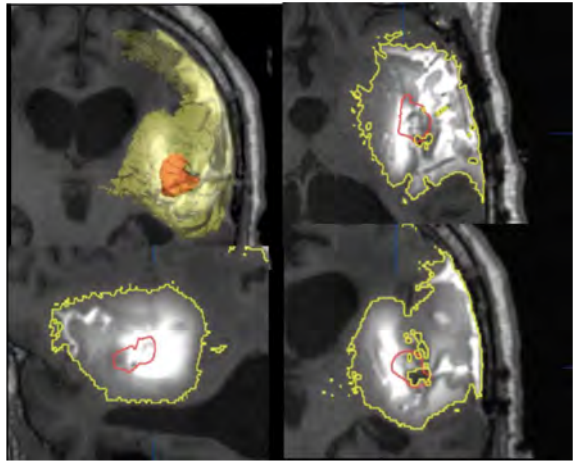
Methods

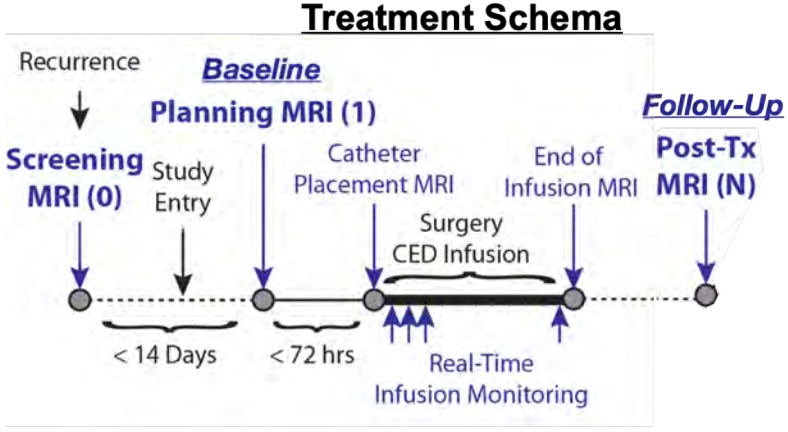
- A total of 42 of 47 patients with rGBM were enrolled in a phase II convection-enhanced delivery of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) and had measurable disease at baseline and adequate imaging.

Convection-Enhanced Delivery (CED)



Jahangiri et al., *J Neurosurg* 2017; 126: 191-200.





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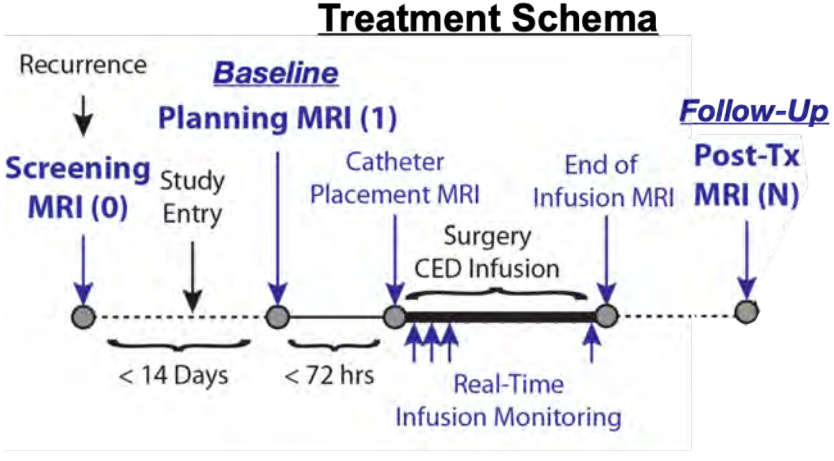
Methods

- A total of 42 of 47 patients with rGBM were enrolled in a phase II convection-enhanced delivery of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) and had measurable disease at baseline and adequate imaging.

- Patients we kept on trial *past the first initial progressive disease event* to purposefully validate **iRANO** and **mRANO**

- Bidirectional tumor measurements were created by local sites and independent radiologic facility (IRF)

- These measurements were consolidated and **sRANO, iRANO**, and **mRANO** were applied



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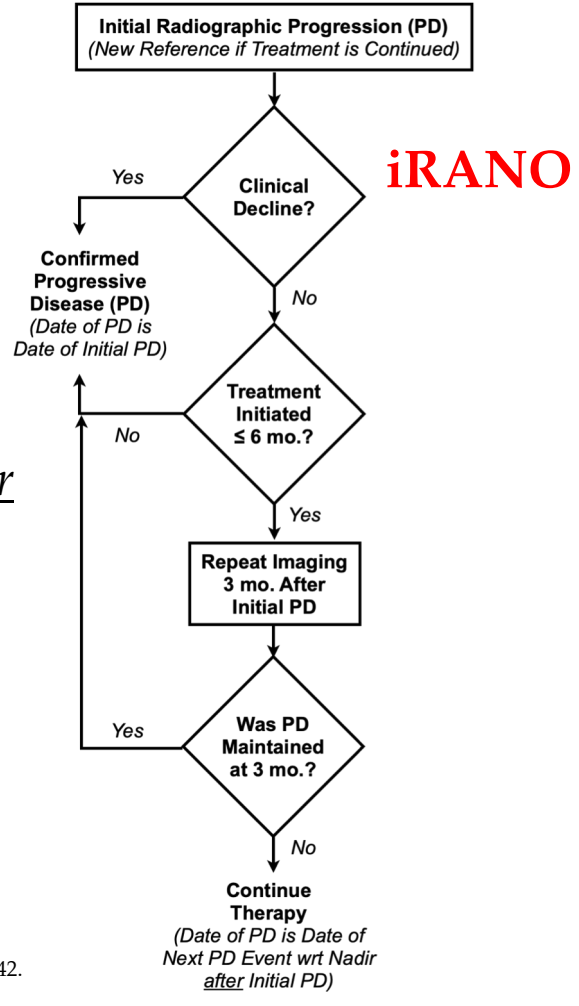
Methods – sRANO, iRANO & mRANO

- **sRANO** – 1st evidence of progressive enhancement → PD
- **iRANO** – 1st evidence of progressive enhancement → Prelim PD (if w/in 6 months)
  - Repeat Imaging after 3 months (continue treatment)
  - If PD was maintained 3 months later → Backdate PD
  - If not, continue treatment until next PD event (wrt nadir *after* initial PD event)
- **Clinical/Neurological Decline → PD**

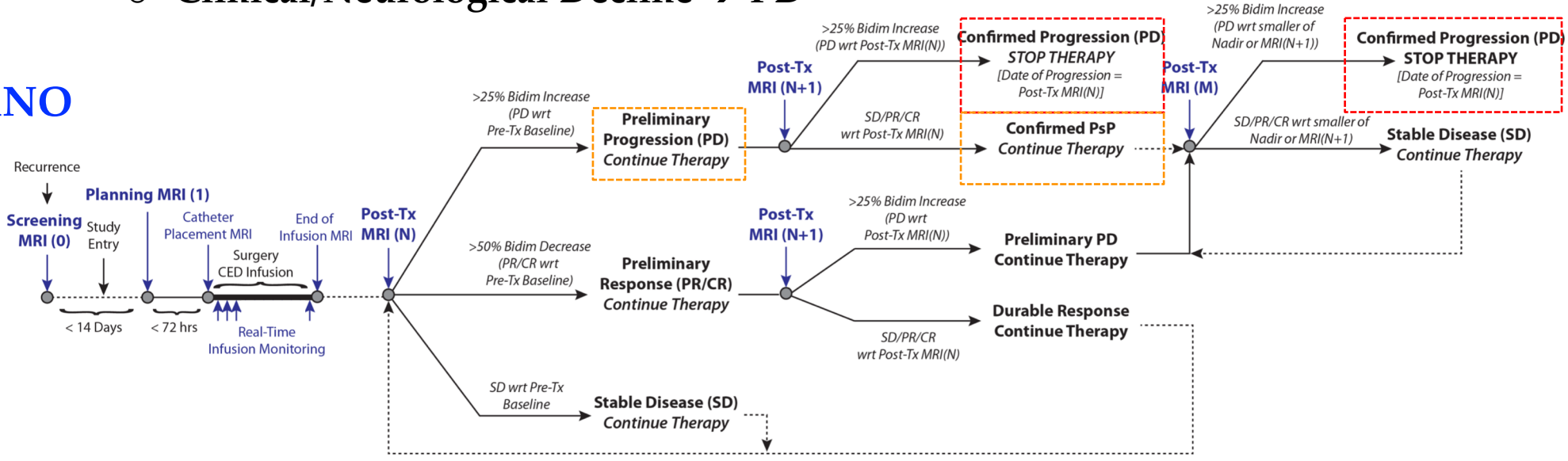


Okada H et al., *Lancet Oncol* 2015; 16(15): e534-e542.

Methods – sRANO, iRANO & mRANO

- **mRANO** – 1st evidence of progressive enhancement → **Prelim PD**
  - Repeat Imaging at next schedule time point (continue treatment)
  - If tumor *continues* to grow (subsequent PD) → **Confirmation of PD** (backdated to date of prelim PD)
  - If tumor is *stable or shrinking* → **Confirmation of PsP** (continue treatment)
  - Next confirmed PD with respect to PsP scan or nadir → **Confirmed PD (date of PD)**
- **Clinical/Neurological Decline → PD**

mRANO



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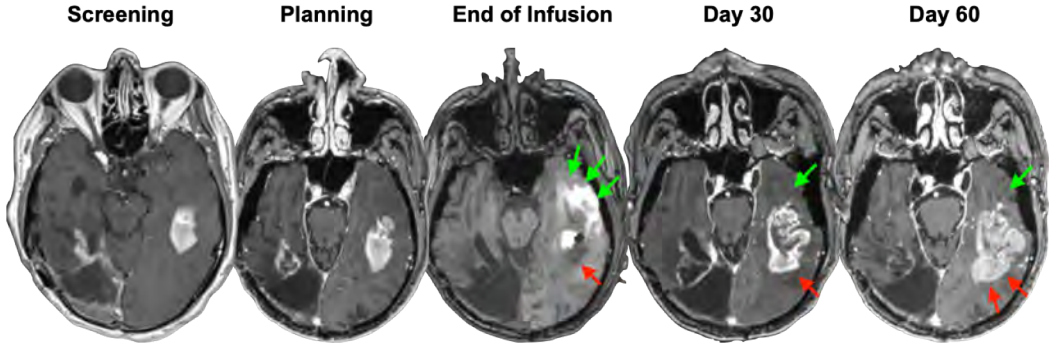
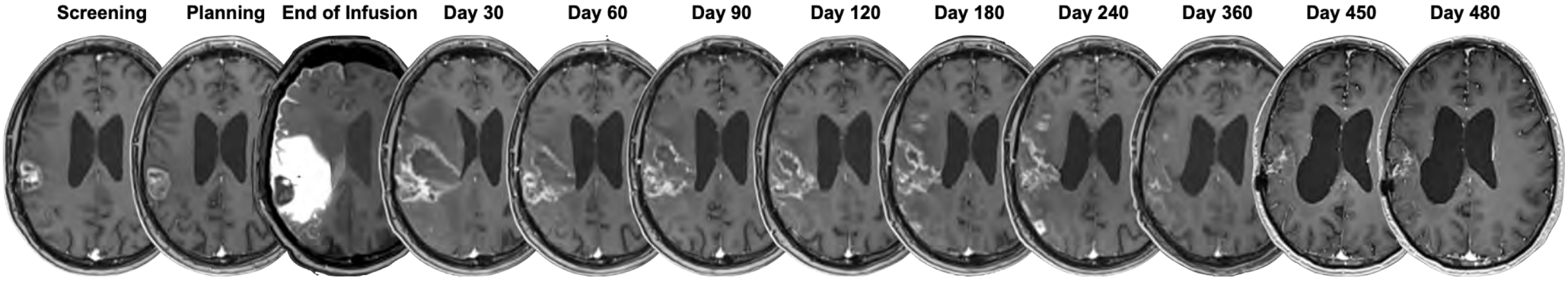
Ellingson BM, Wen PY, Cloughesy TF, *Neurotherapeutics* 2017; 14(2): 307-320.

Results – Early Failure vs. PsP





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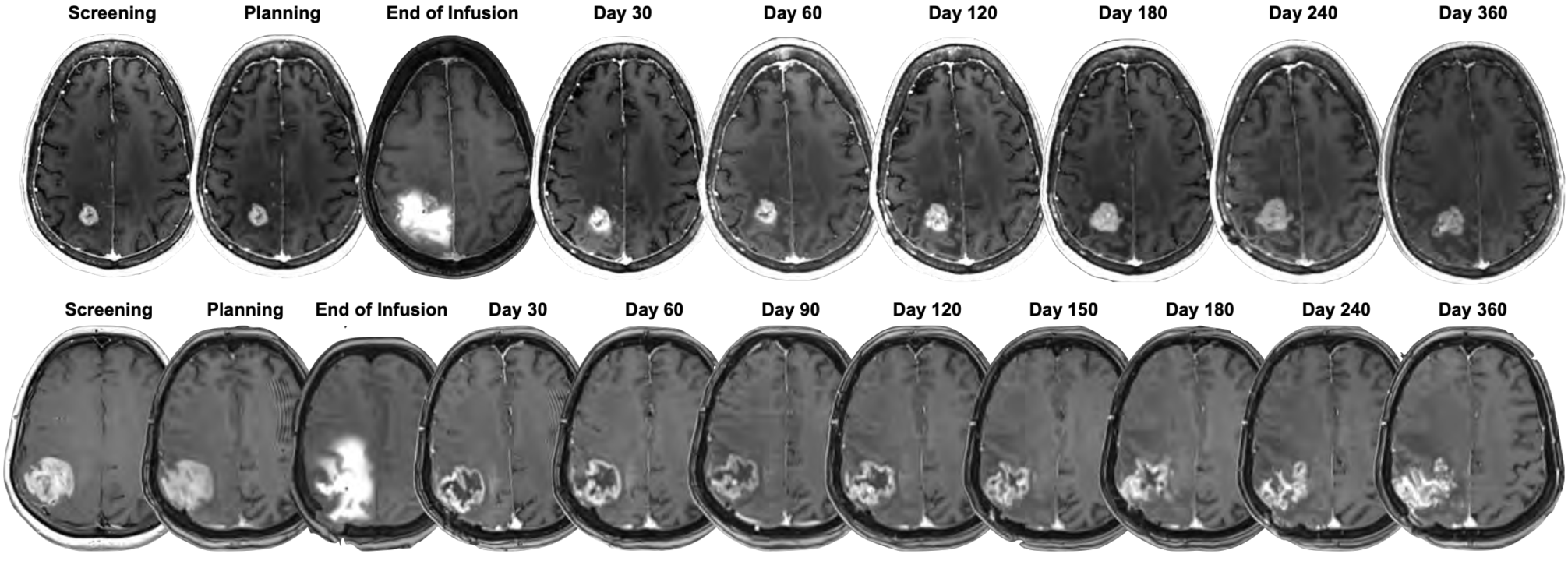
Results – Long Term Control



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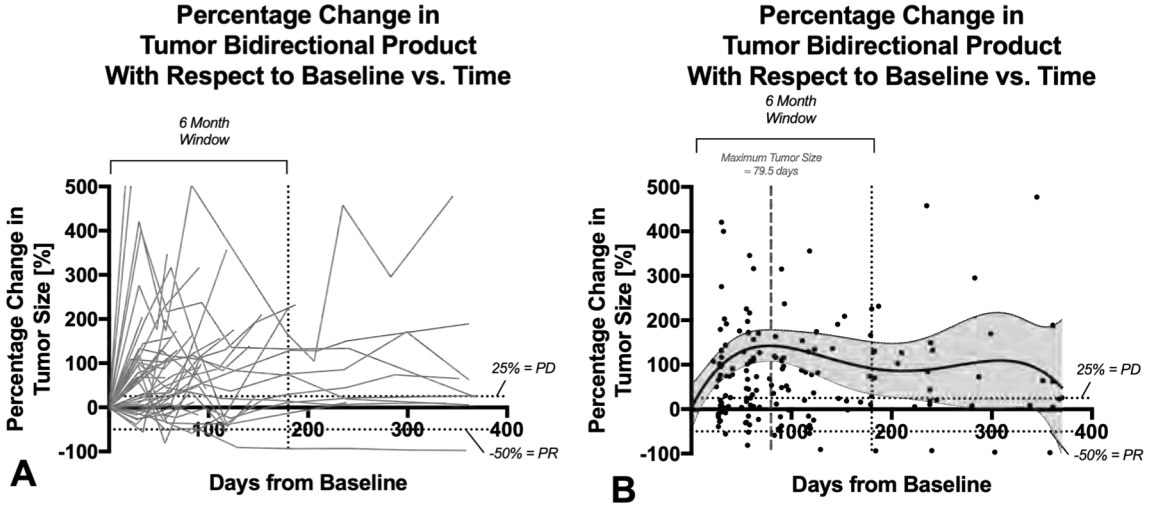
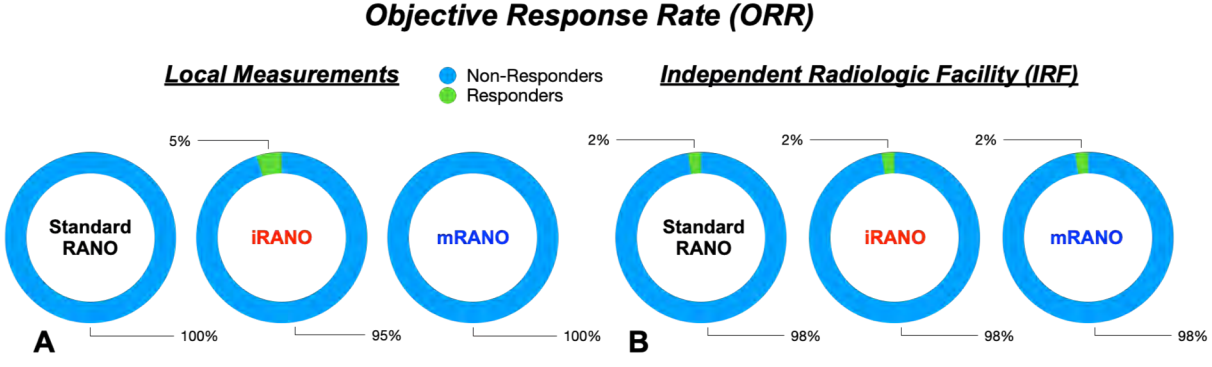
Results – Temporal Trends & ORR

- **OS** – 11.8 months (median)
- **Temporal Trends:** Average +130% increase by ~80 days
- **ORR** – 2% (1 of 42) using IRF



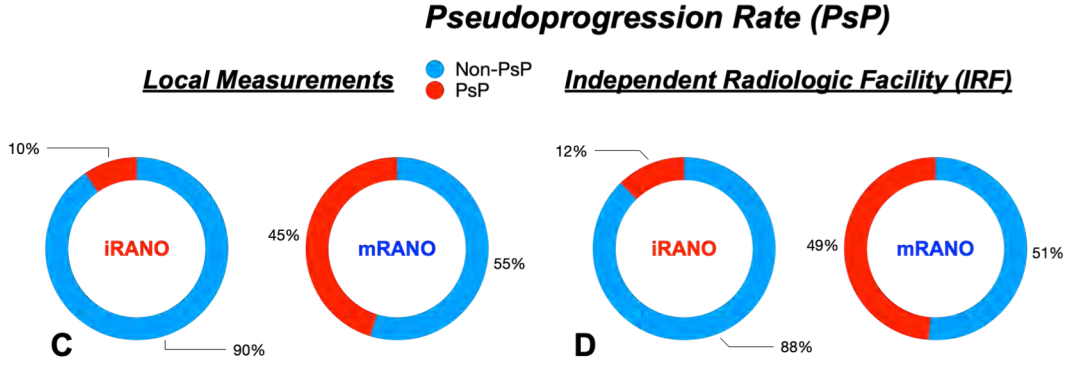


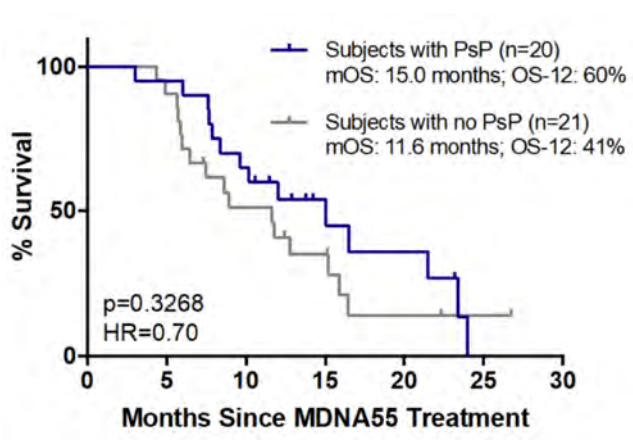
Results – Pseudoprogression (PsP)

- **PsP** – 10-12% iRANO*
  45-49% mRANO

- Many did not have confirmation @ 3 mo follow-up (~60%)

- **Patients with PsP had slightly better OS**





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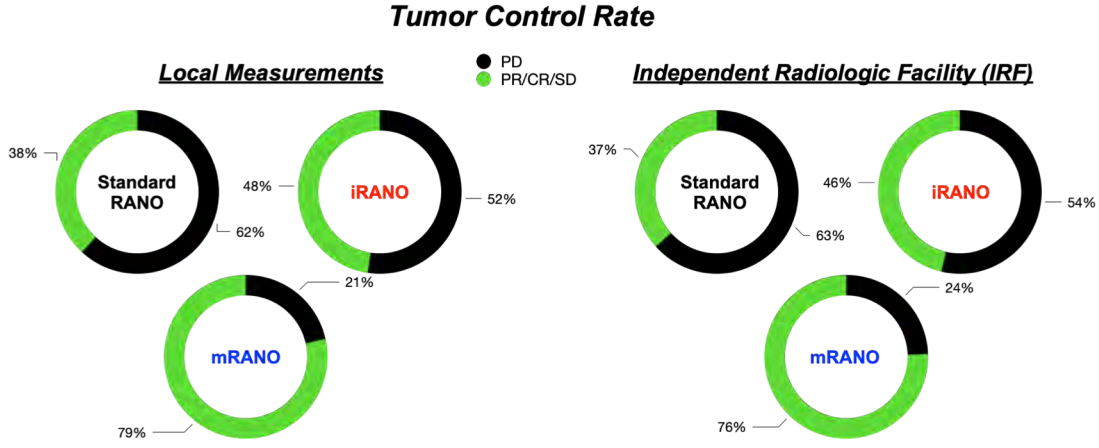
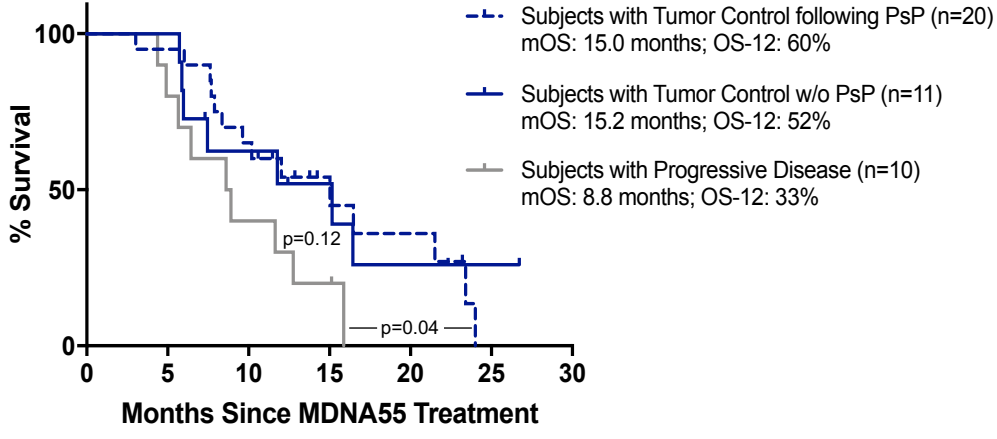
Results – Rate of Tumor Control

- **Rate of Tumor Control (SD or Better):**
  - **sRANO** - 37-38%
  - **iRANO** – 46-48%
  - **mRANO** – 76-79%

- **Tumor Control (w/ PsP) → longer OS**



mRANO: Control vs. No Control



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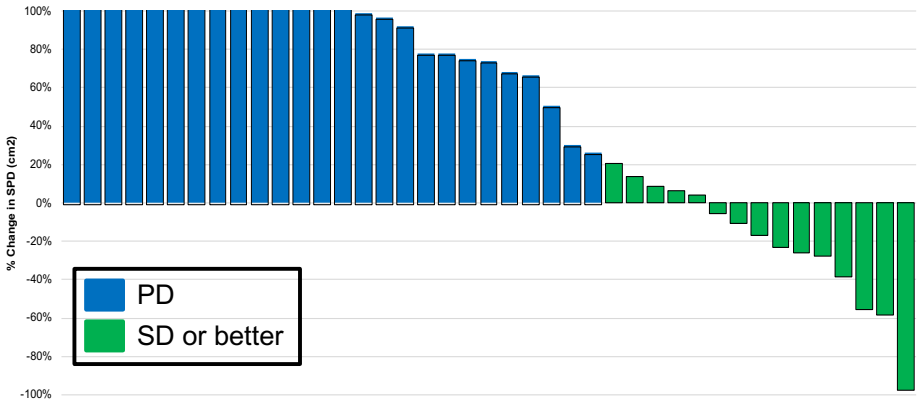
Results – Rate of Tumor Control

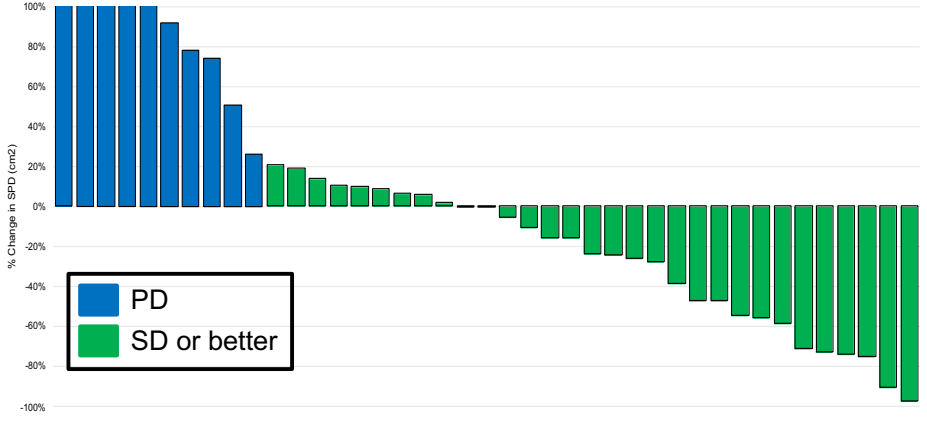
Best Response Assessed per Standard RANO (from Baseline)



Tumor response does not account for initial PsP (Standard RANO).

Tumor control rate = 37%
(15/41 evaluable subjects)

Best Response per mRANO (following initial PsP)



Assessment of response after initial PsP (Modified RANO).

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

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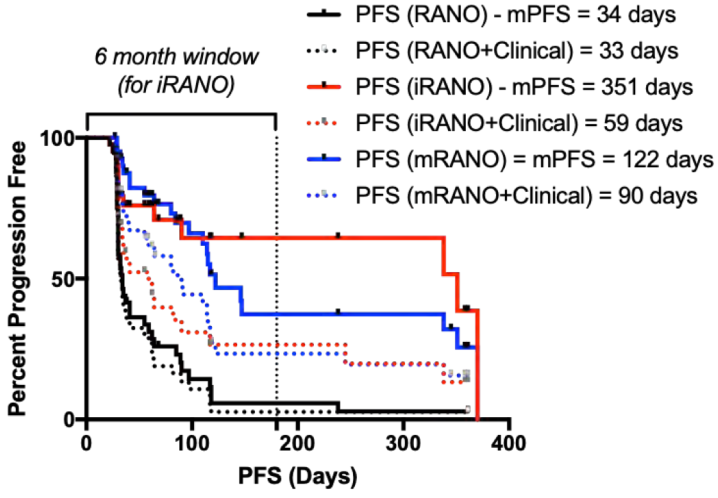
Results – Progression-Free Survival (PFS)

- **sRANO PFS < iRANO & mRANO** (*P<0.0001*)
- **iRANO PFS ≈ mRANO PFS**
- **PFS6 Rates:**
  - **sRANO** - 2.4-5.8%
  - **iRANO** – 43-64%
  - **mRANO** – 33-37%

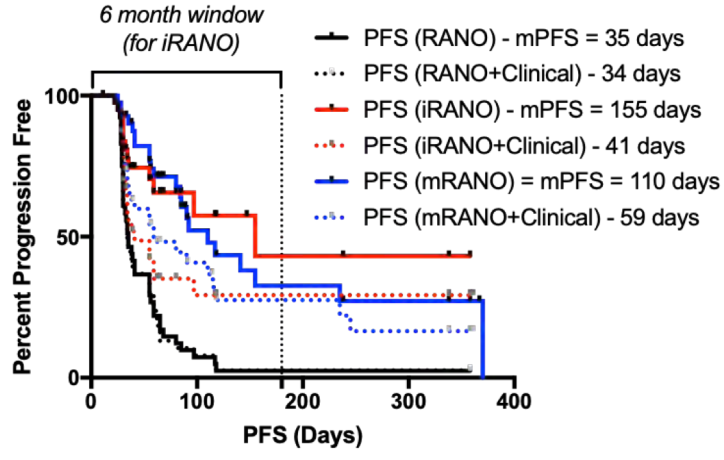
Local Measurements

Comparison of PFS Between RANO Criteria



Independent Radiologic Facility (IRF)

Comparison of PFS Between RANO Criteria



- ~60% of patients had unconfirmed PD according to iRANO
- Inclusion of Clinical/Neurological data *shortened* iRANO PFS (P = 0.0094), but did not change mRANO or sRANO (radiographic came first)
  - 20% of patients had neurological deterioration prior to iRANO progression

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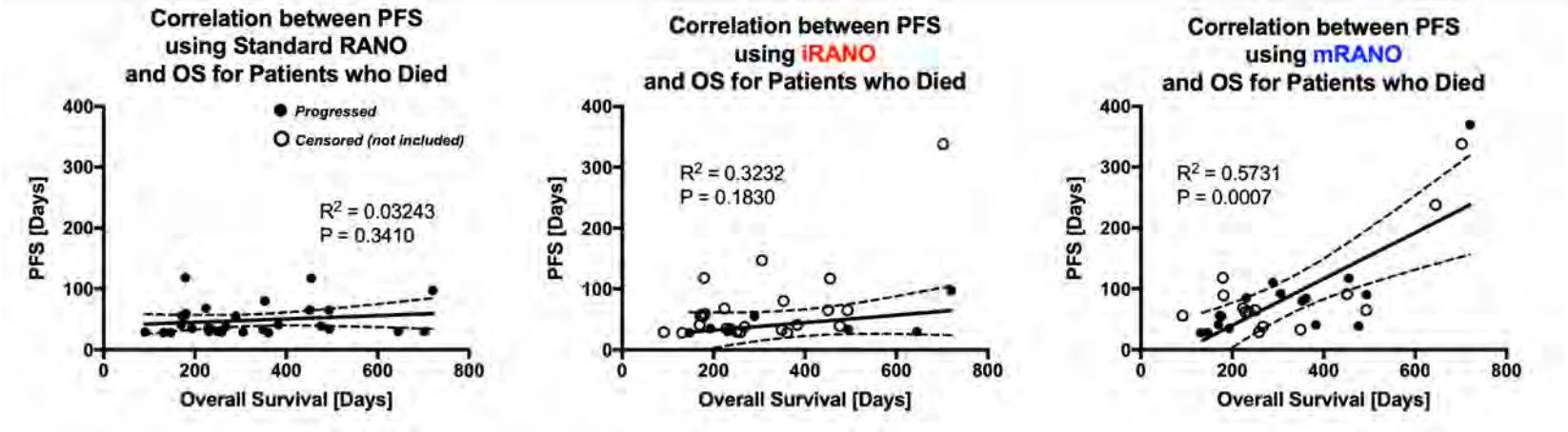
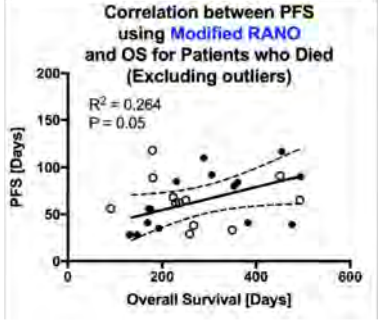
Results – Correlation between PFS and OS

Independent Radiologic Facility (IRF)



- **sRANO** - No correlation between PFS and OS (*IRF: R^2=0.03, P=0.34*)
- **iRANO** – No correlation between PFS and OS (*IRF: R^2 = 0.32, P=0.18*)
- **mRANO** – Significant correlation between PFS and OS (*IRF: R^2=0.57, P=0.007*)

Independent Radiologic Facility (IRF)



Note: ~60% of patients were censored via iRANO

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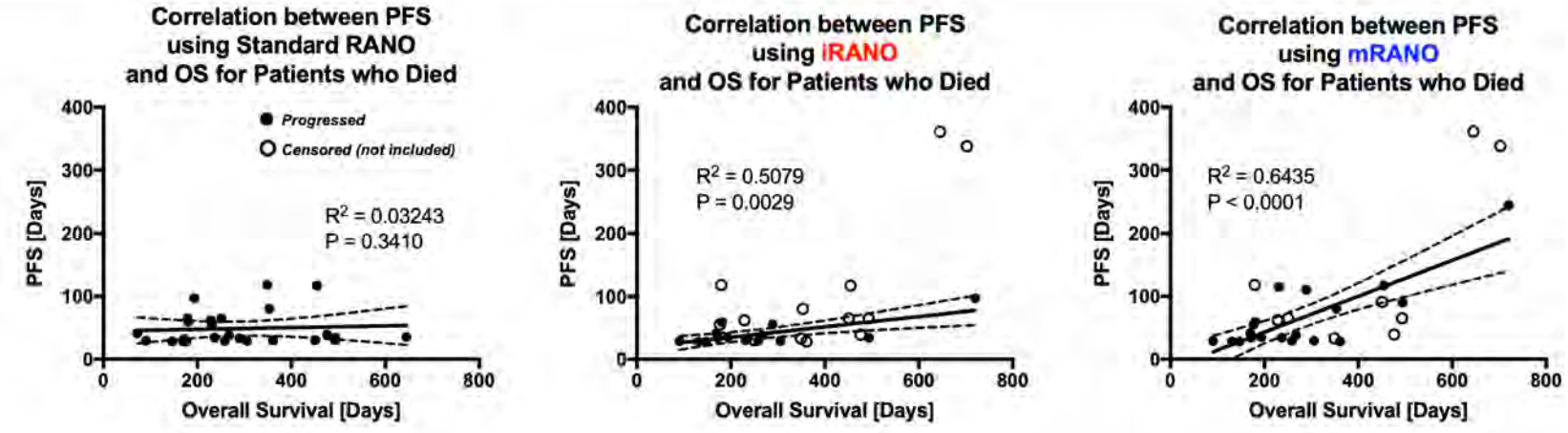
Results –PFS vs. OS (w/ Clinical)

Independent Radiologic Facility (IRF) + Clinical Status



- **sRANO** - No correlation between PFS and OS (*IRF: R^2=0.03, P=0.34*)
- **iRANO** – Significant correlation between PFS and OS (*IRF: R^2 = 0.51, P=0.0029*)
- **mRANO** – Significant correlation between PFS and OS (*IRF: R^2=0.64, P<0.0001*)

Conclusions

- **sRANO** and **iRANO**-defined PFS do not correlate with OS in recurrent GBM treated with the IL4 receptor targeted immunotoxin (MDNA55)
- A large proportion of patients (~60%) were censored due to lack of 3 mo. Follow-up according to **iRANO** guidelines
- Locally and IRF-determined PFS using **mRANO** strongly correlated with OS in recurrent GBM treated with MDNA55
- Patients with PsP + evidence of subsequent tumor control on mRANO had a longer OS compared with patients not showing disease control
- Together, this suggests **mRANO** may be superior to **sRANO** and **iRANO** for immunotherapy trials in recurrent GBM

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