iRANO (and mRANO) for Immunotherapy
In Brain Tumors

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Radiology
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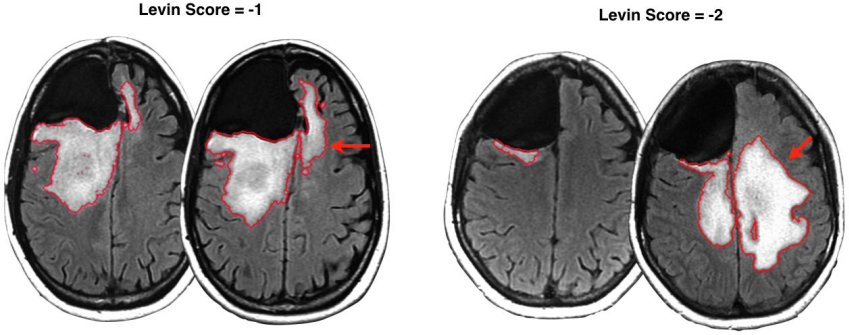
Brief History of Response Assessment in Neuro Oncology

Levin Criteria (Levin, J Neurosurg, 1977)

- Malignant gliomas are "explosive" tumors
- Doubling time ~ 21 days for treatment naïve GBM (Ellingson, *Cancer*, 2016)
- **Qualitative Visual Assessment by an Expert** can be used to identify time of failure or response

Victor Levin, MD



Modified Levin Criteria for Evaluating Anaplastic Astrocytoma

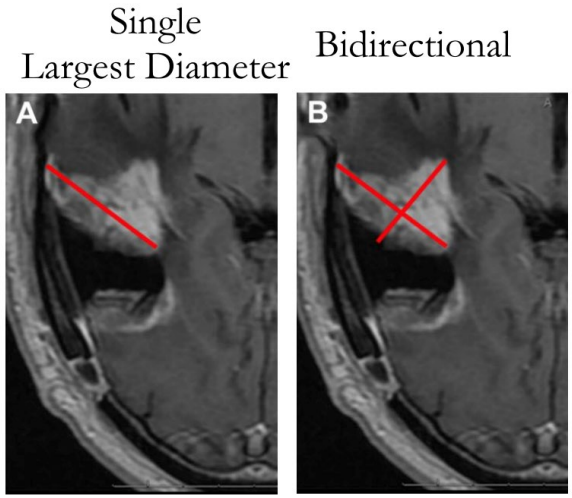
Levin Score (Analog Visual Assessment)	*Radiographic Response*	*Description*
+3	CR	Complete disappearance of all T2/FLAIR hyperintensity
+2	PR	Definite shrinkage / improvement in T2/FLAIR lesion
+1	SD	Possible shrinkage / improvement in T2/FLAIR lesion
0	SD	Unchanged T2/FLAIR lesion size
-1	SD	Possibly worse / growing T2/FLAIR lesion
-2	PD	Definitely worse / growing T2/FLAIR lesion
-3	PD	New T2/FLAIR lesion and/or growing/emerging contrast enhancement

Brief History of Response Assessment in Neuro Oncology

Macdonald Criteria (Macdonald, J Clin Oncol, 1990)

- Improvements to the Levin Criteria (Levin, J Neurosurg, 1977) and WHO Systemic Oncology Response Criteria (single direction)
- Examines changes in **contrast enhancement** after therapy
- % Change in **Bidirectional measurements**
  - Unidirectional measurements are not appropriate
- Maintained as the standard response assessment criteria for > 20 years

David Macdonald, MD, FRCPC



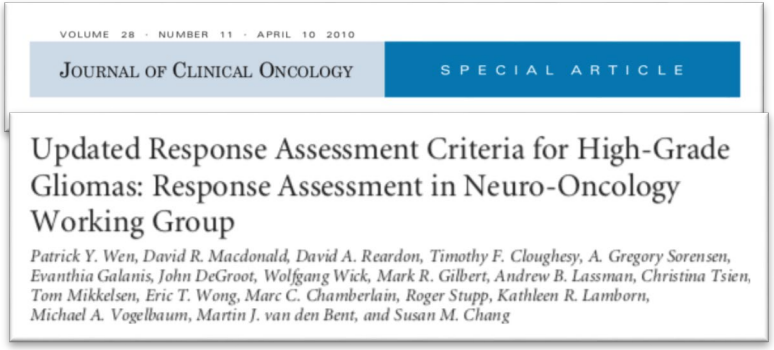
Jain RK, MedScape.org

Brief History of Response Assessment in Neuro Oncology

RANO – Response Assessment in Neuro Oncology (Wen, J Clin Oncol, 2010)

- "Extended" Macdonald criteria
- Includes qualitative assessment of T2/FLAIR hyperintensity
  - Difficult to quantitatively assess
  - T2/FLAIR hyperintensity may be due to edema, non-enhancing tumor, etc.
- Includes numerous other improvements
  - Measurable vs. non-measurable disease
  - Inclusion/exclusion criteria
  - Requirement of confirmatory scans
  - Recommendations for dealing with patients with equivocal imaging changes
  - Criteria for non-enhancing tumor progression

Patrick Wen, MD



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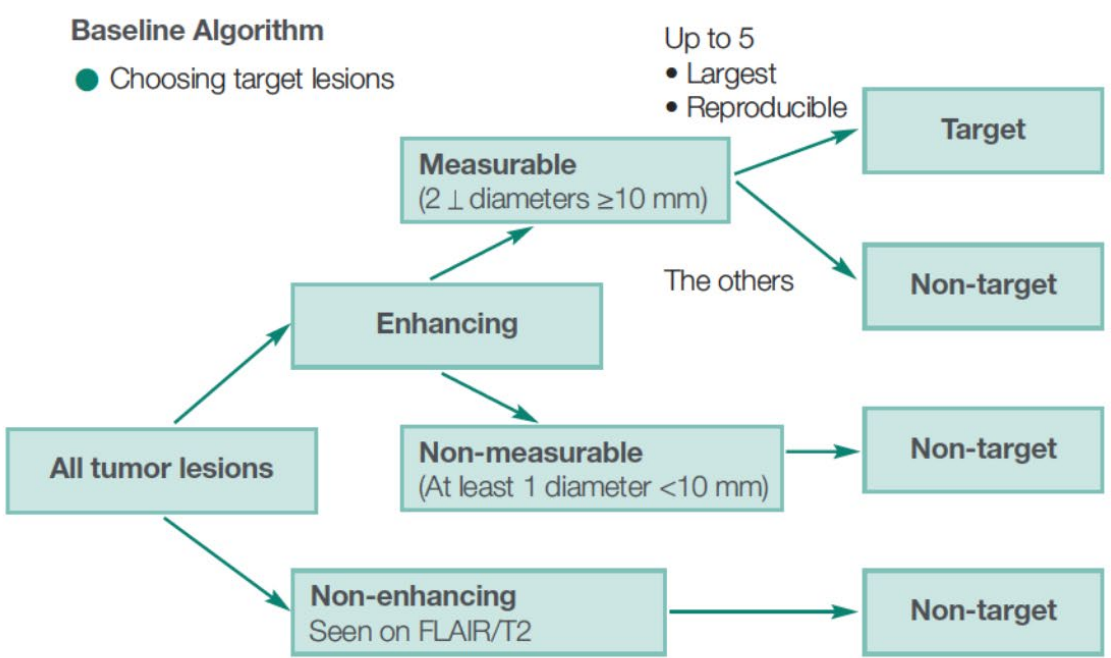
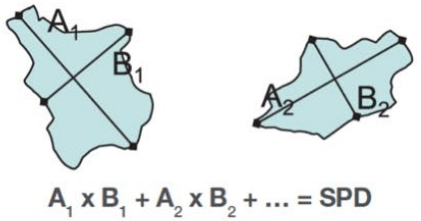
Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

Patrick Y. Wen, David R. Macdonald, David A. Reardon, Timothy F. Cloughesy, A. Gregory Sorensen, Evanthia Galanis, John DeGroot, Wolfgang Wick, Mark R. Gilbert, Andrew B. Lassman, Christina Tsien, Tom Mikkelsen, Eric T. Wong, Marc C. Chamberlain, Roger Stupp, Kathleen R. Lamborn, Michael A. Vogelbaum, Martin J. van den Bent, and Susan M. Chang

Brief History of Response Assessment in Neuro Oncology

RANO – Response Assessment in Neuro Oncology (Wen, J Clin Oncol, 2010)





Brief History of Response Assessment in Neuro Oncology

RANO – Response Assessment in Neuro Oncology (Wen, J Clin Oncol, 2010)

Response	Definition
Complete Response (CR)	All target lesions have disappeared (look out for pseudoresponse†)
Partial Response (PR)	SPD decreased by ≥50% from baseline value (look out for pseudoresponse†)
Stable Disease (SD)	SPD <50% decrease to <25% increase
Progressive Disease (PD)	SPD increased by ≥25% from nadir value (look out for pseudoprogression‡)
Unable to Assess (UA)	Some target lesions cannot be evaluated because of technical factors

† - CR and PR have to be confirmed ≥4 wks later. If not confirmed, response is SD.

‡ - Apparent PD within 12 weeks of radiation

Brief History of Response Assessment in Neuro Oncology

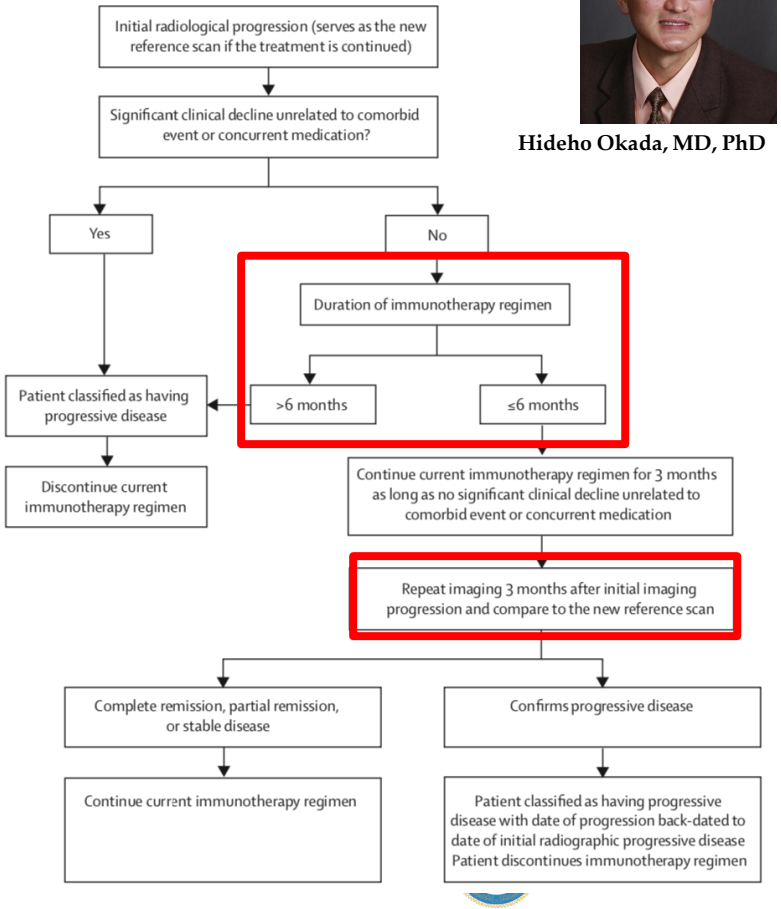
iRANO – "Immune" Response Assessment in Neuro Oncology

(Okado et al., Lancet Oncol 2015)

Hideho Okada, MD, PhD

- Goal is to allow patients to weather transient changes that might occur within the initial treatment (e.g. inflammation - Pseudoprogression)
- iRANO includes a "6 month window" of observation to "confirm progression" 3 months later.

- U.S. FDA considers this "exploratory" and needs to be "validated" against RANO
- The FDA has expressed concerns with using iRANO with single-arm studies because of the observation window requirement



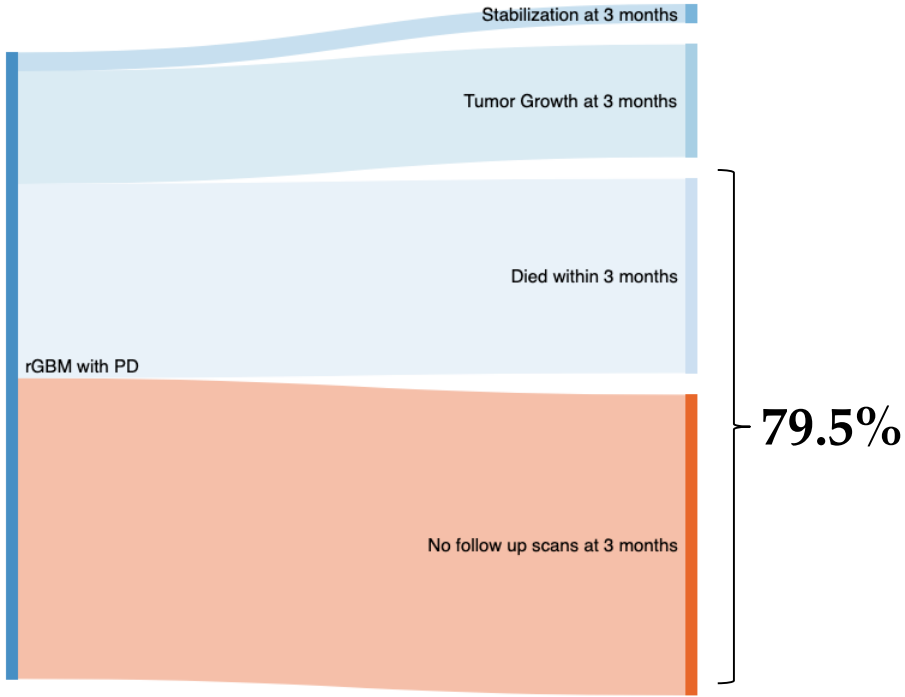
iRANO – "Immune" Response Assessment in Neuro Oncology

- **Primary issue is with this arbitrary 3-month window to "confirm PD"**

iRANO Study of PD1 Inhibitors in Clinical Practice (ASCO 2020)

Of 70 patients who progressed within 6 mos and had documented death, 2.9% had disease stabilization, **31.4% died before the 3-month confirmation**, **48.1% had no follow-up confirmatory imaging exams** and 17.6% had documented tumor growth.

This means ~80% of rGBM die or change treatment before they confirm PD via iRANO

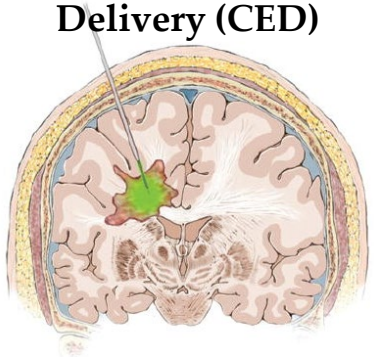


Ellingson BM, Huang RY, et al., ASCO 2020

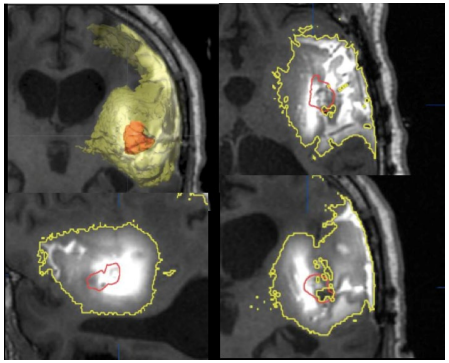
iRANO – "Immune" Response Assessment in Neuro Oncology

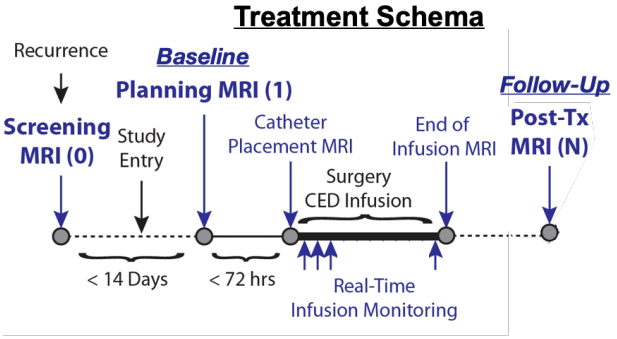
- **Primary issue is with this arbitrary 3-month window to "confirm PD"**
  - A total of 42 of 47 patients with rGBM were enrolled in a phase II convection-enhanced delivery of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) and had measurable disease at baseline and adequate imaging.

Convection-Enhanced Delivery (CED)



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





~60% of patients were censored for PFS via iRANO due to no 3 month follow up exam after PD (died or no longer on study)

Brief History of Response Assessment in Neuro Oncology

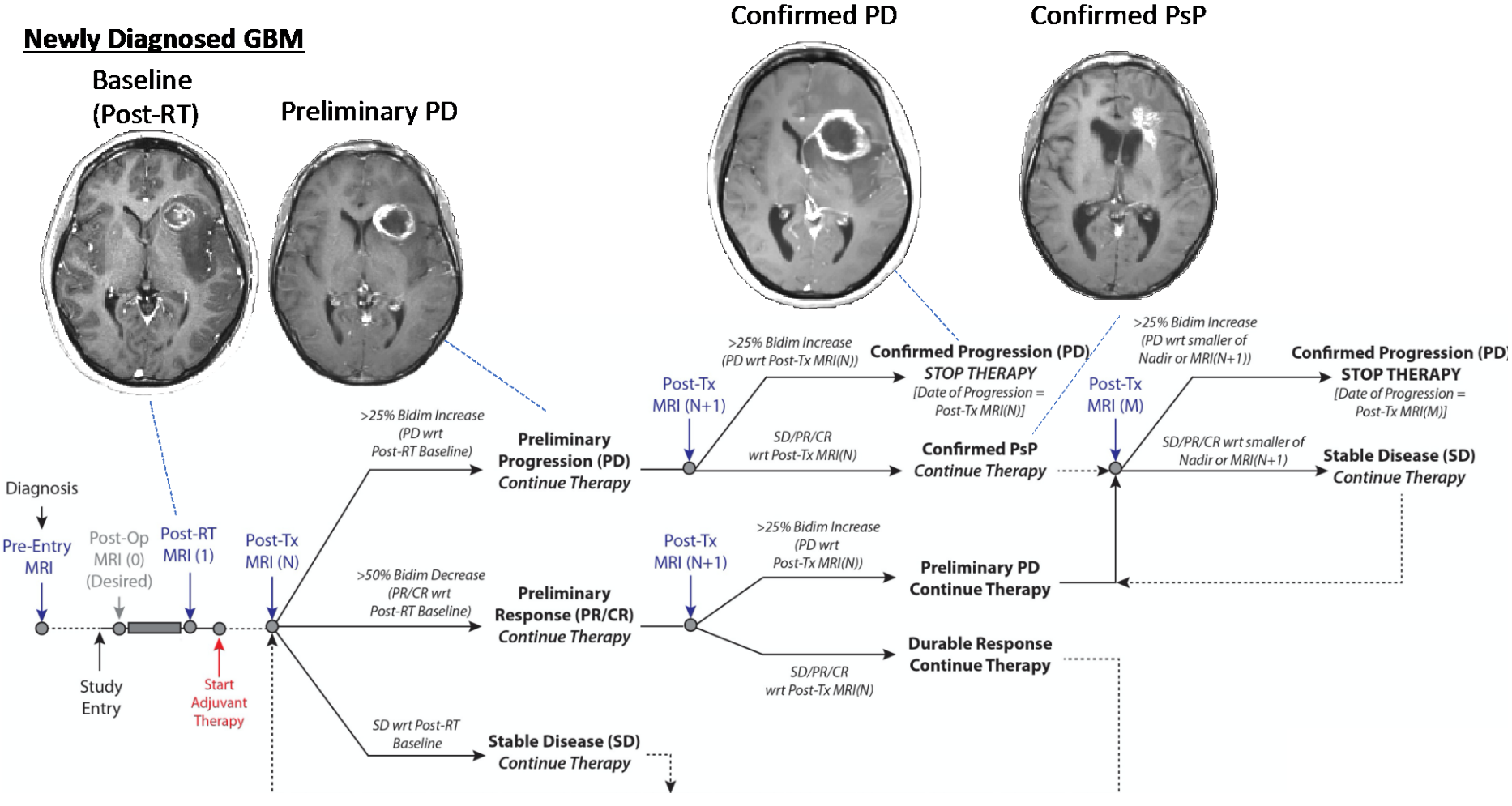
mRANO – "Modified" Response Assessment in Neuro Oncology

(Ellingson, Wen, Cloughesy, *Neurotherapeutics*, 2017)

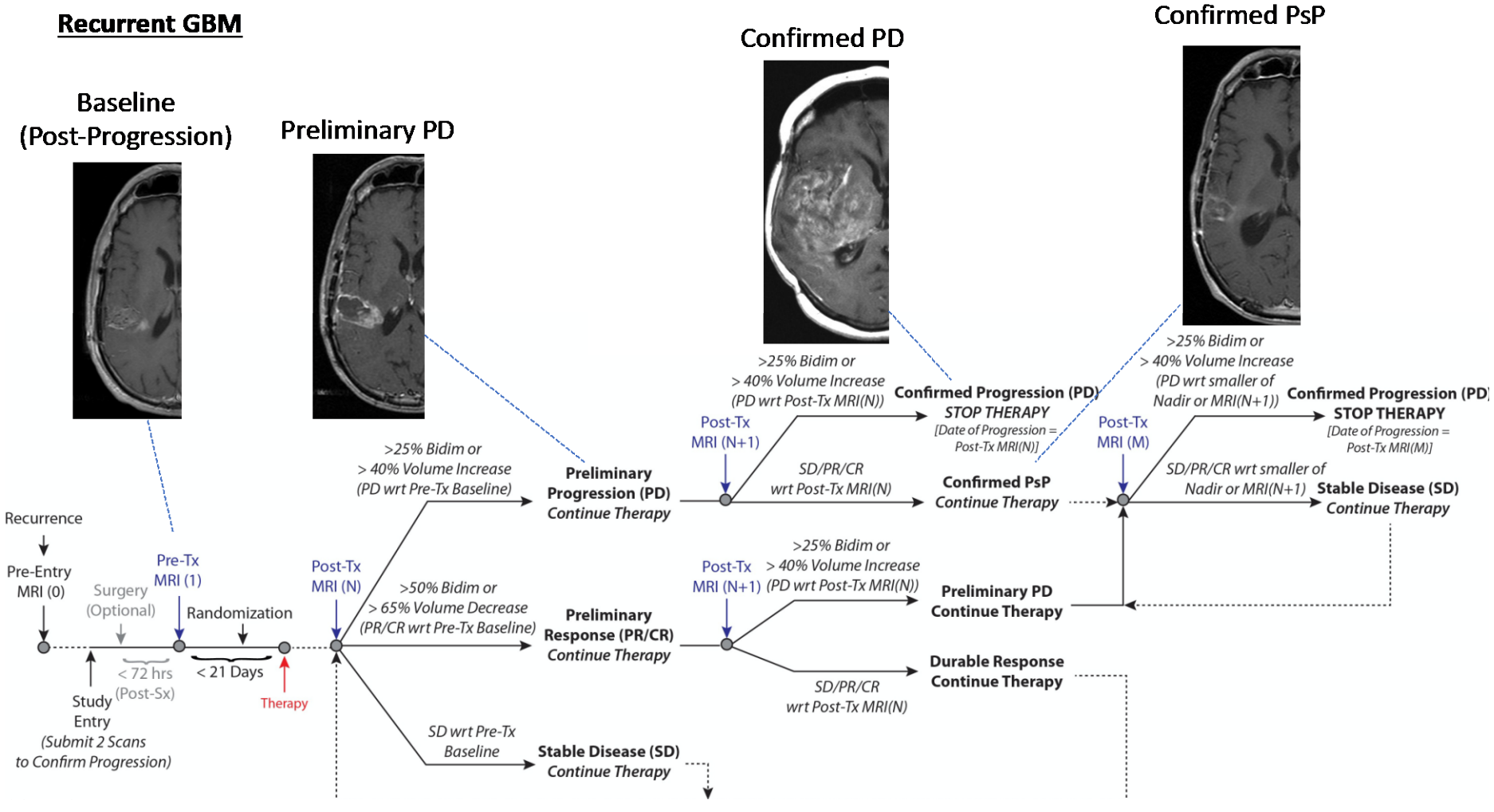
- Designed for adaptive or "bucket" trials with many types of therapeutics (e.g. GBM AGILE)
- Allows patients to safely stay on drug so we can more thoroughly study efficacy
- Compatible with current clinical practice, easy to implement, practical logistics, etc.
- Recommendations are *evidence based*
- Compatible with RANO paradigms for validation *and* historic comparison (ORR, etc.)

- **Improvements to RANO and iRANO**
  - **No FLAIR evaluation** – *data suggests it adds complexity, subjectivity, and cost with questionable gain in clinical value* *(Boxerman, Neuro Oncol, 2013; Huang, Clin Cancer Res, 2016; Howosielski, Neurology 2014; Neuro Oncol 2017)*
  - **Baseline in Newly Diagnosed GBM = Post-Radiation Scan** – *Post-op scan is often off protocol for trials, corrupted by blood products, and data shows changes from the post-RT scan predict OS* *(Ellingson ASCO 2016; Neuro Oncol 2017)*
  - **Confirmation of Progression** – *Uses next follow up scan to check for continued growth (PD backdated) or check for pseudoprogression (PsP – PD occurs at the next follow up)*

mRANO – "Modified" Response Assessment in Neuro Oncology

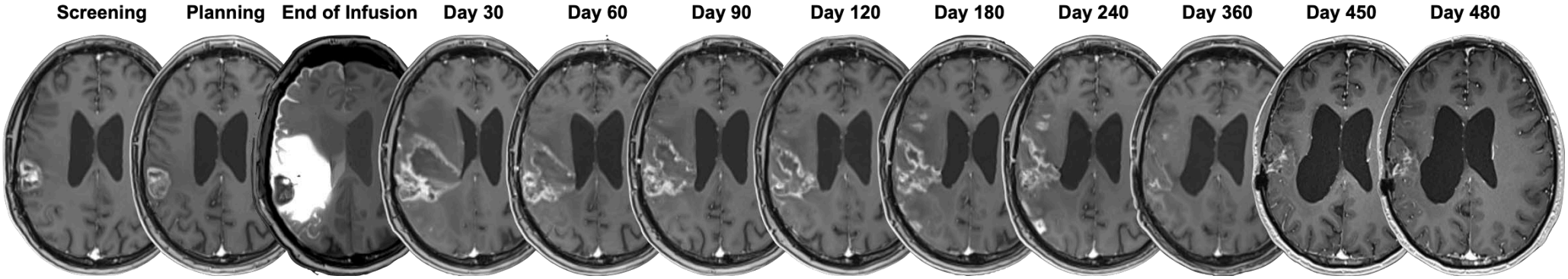


mRANO – "Modified" Response Assessment in Neuro Oncology



iRANO vs. mRANO for Immunotherapies – Example

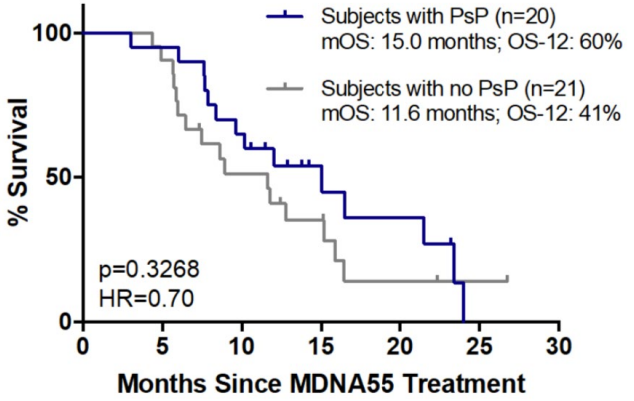
- **Phase II CED trial of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) in rGBM**



- **Pseudoprogression (PsP)**
  12% iRANO*
  49% mRANO

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

mRANO: PsP vs. No PsP

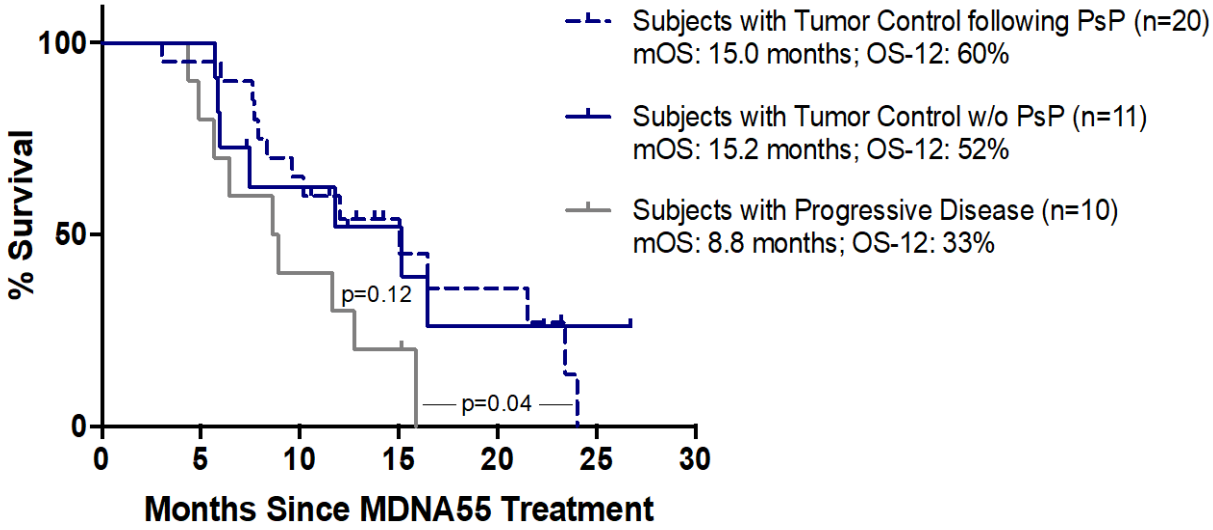


Ellingson BM, Chandhasin C, et al., SNO 2020
Ellingson BM, Sampson J, et al., *Clin Cancer Res* 2021 (Submitted)

iRANO vs. mRANO for Immunotherapies – Example

- **Phase II CED trial of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) in rGBM**
  - **Rate of Tumor Control (SD or Better):**
    - **sRANO** - 37%
    - **iRANO** – 46%
    - **mRANO** – 76%
    - **Tumor Control (w/ PsP) → longer OS**

mRANO: Control vs. No Control



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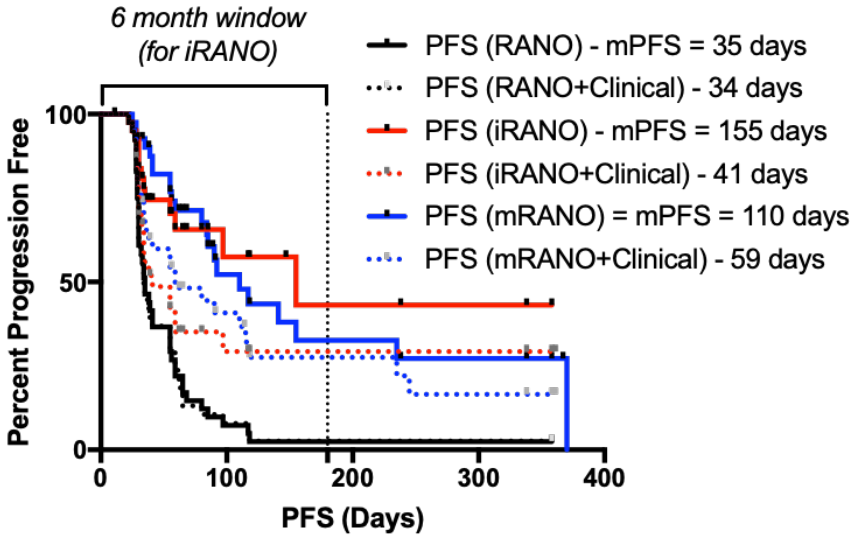
iRANO vs. mRANO for Immunotherapies – Example

- **Phase II CED trial of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) in rGBM**

  - **PFS6 Rates (local and central reads):**
    - **sRANO** - 2.4-5.8%
    - **iRANO** – 43-64%
    - **mRANO** – 33-37%

Independent Radiologic Facility (IRF)

Comparison of PFS Between RANO Criteria



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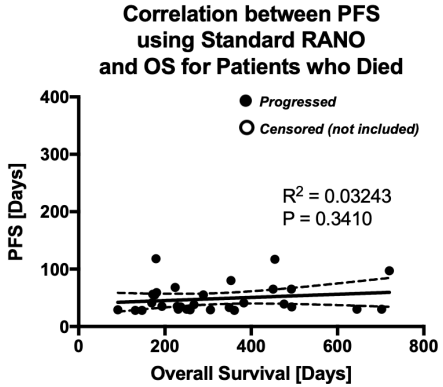
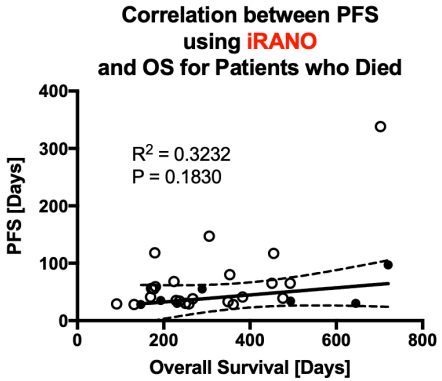
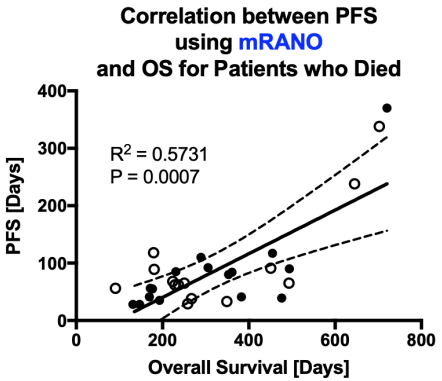
iRANO vs. mRANO for Immunotherapies – Example

- **Phase II CED trial of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895) in rGBM**

Independent Radiologic Facility (IRF)

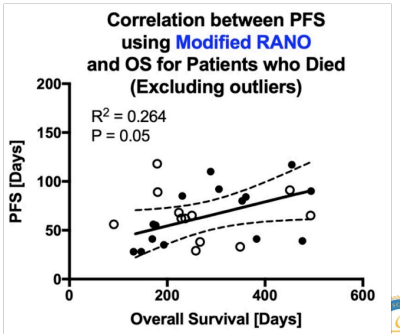






- **sRANO** - No correlation between PFS and OS (*IRF: R^2=0.03, P=0.34*)
- **iRANO** – No correlation between PFS and OS (*IRF: R^2 = 0.32, P=0.18*)
- **mRANO** – Significant correlation between PFS and OS (*IRF: R^2=0.57, P=0.007*)

Independent Radiologic Facility (IRF)



Note: ~60% of patients were censored via iRANO

Ellingson BM, Chandhasin C, et al., SNO 2020
Ellingson BM, Sampson J, et al., *Clin Cancer Res* 2021 (Submitted)

Current Status of RANO for Immunotherapies…

- **RANO** (Wen et al., **J Clin Oncol** 2010)
  - U.S. FDA still considers conventional RANO the “gold standard” for response assessment
  - Worried about “historic” comparisons, so RANO is always performed on top of other assessments
- **iRANO** (Okado et al., **Lancet Oncol** 2015)
  - U.S. FDA considers this “exploratory” and needs to be “validated” against RANO
  - In recurrent GBM trials, high rates of censorship and utility is limited for patient management
  - Updated criteria (v2.0) based on new data to come out soon
- **mRANO** (Ellingson et al., **Neurotherapeutics** 2017)
  - U.S. FDA allows use of mRANO for patient management and secondary/exploratory endpoints (with comparison arms)
  - Used in dozens of trials currently for immunotherapy and other therapeutics in GBM

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ABC2 Brain Cancer Breakthroughs