

Research Roundtable

“Update of the Response Assessment in Neuro-Oncology (RANO) Criteria & Discussion of Overall Response Rate (ORR)”

April 1, 2022

RANO 2.0 Consensus Positions

The group reviewed recommended consensus positions for RANO 2.0 developed through analysis of the available data and an iterative process of discussion among stakeholder groups and experts.

Group Discussion

- Continued consideration is needed in deciding how to evaluate evidence of change to confirm progression (e.g., at least 25% change over prior 6 months) for trial eligibility. There is a need to address the rate of growth in comparison with a time frame for review.
- Small tumors (1-2 cm diameter) tend to have early progression and early response. Accounting for baseline tumor size in evaluating therapies for these tumors is still an active debate.
- With the new World Health Organization criteria, as traditionally lower-grade histology tumors are now considered glioblastoma (GBM), there will be challenges assessing responses as some of these tumors are non-enhancing.
- There are ethical issues in evaluating pseudo-progression within a randomized trial for recurrent GBM, where pseudo-progression is unlikely in the control arm such as lomustine, which is toxic, but likely within the experimental arm. It may not be best for patients in the control arm to stay on study for the extra period needed to confirm progression within the experimental arm.
- There is an assumption that patients in clinical trials receive better care and have better outcomes. However, there is published data that there is not necessarily benefit overall among patients on trials vs. those receiving standard of care.
- Patients would like to understand these issues and be brought to the table for discussions about progression and evaluation of benefit from therapies. In addition to tumor size and growth, patients are focused on measures of quality of life.
- From the patient perspective, there is also concern about access, accuracy, and consistency among imaging technology across institutions. It would be a benefit to the field overall if there could be a standard that all institutions and centers must meet.
- Industry sees a need to develop additional approaches for identifying trial progress using non-survival endpoints to evaluate promising drugs that might have some effect or benefit but not enough to push survival. Industry is seeking more consistency in its approach to these issues.
- Issues involving assessment criteria are different in pediatric brain tumors (RAPNO). Where the adult community is moving toward a single unified set of response criteria, in pediatrics there are multiple criteria based on tumor types.

Use of Overall Response Rate (ORR) in Neuro-Oncology Trials

Neuro-oncology differs from other cancers and has unique challenges that should be considered in determining appropriate endpoints. NBTS's goal in raising the discussion during this Research Roundtable was to kick off a process by which a multi-stakeholder working group can develop additional clarity on this topic.

Based on the importance of imaging, the neuro-oncology field has been working to improve the standardization of image acquisition, evaluate central reads, and address manual, automated, and hybrid approaches to image evaluation. Movement toward volumetric measurements may eventually provide the most reproducible evaluations. The field is also working to understand attribution of a change on the MRI scan and how that change impacts tumor burden and the effect of treatment. Additionally, RANO 2.0 variability relating to baseline scans, confirmatory scans, and calling progression is being addressed with streamlined criteria.

All of this provides the foundation upon which to increase confidence in the use of imaging to identify ORR and then connect that response to clinical benefit that has meaning for the patient to allow us to use ORR as a surrogate for overall survival (OS). There has been progress in defining the concept of a rate of change outcome measure, with additional work underway to evaluate that concept retrospectively and prospectively.

Regulators note challenges for use of ORR in assessing brain tumors, as patients are often treated with multiple therapies simultaneously (including radiation), and changes in tumors can be very difficult to measure based on current imaging techniques. As a result, FDA has not typically recommended using ORR as the primary endpoint for brain tumor trials and, instead, recommends OS. This can be problematic because OS cannot be interpreted in the context of a single-arm trial, and it may be challenging to enroll patients in a study when the control arm therapy is not known to improve survival.

Group Discussion

- There is continuing need to discuss and develop clarity about the type of data that would be helpful to regulators in improving confidence in imaging assessments for brain tumors.
- Integrated benefit measurements that consider cognition and movement could also be helpful in correlating response rate with survival. Retrospective evaluation of past trials may help to develop this type of framework and create categories of clinical benefit from which to draw conclusions. Examples of these factors include pain control, seizure, or quality of life measures.
- The field needs to tackle questions about how to develop endpoints that are uniquely appropriate for neuro-oncology trials, including developing an approach for using ORR as a stand-alone measure of clinical benefit or part of a composite assessment. It may be helpful to develop an algorithm that reflects the magnitude of benefit, durability, and confidence in imaging to ensure that standards are appropriately high, but therapies that can bring benefit are not rejected.