



Research Roundtable

Conducting Clinical Trials in Certain Front-Line Settings

December 16, 2022

On December 16, 2022, a multi-stakeholder, multi-disciplinary group of distinguished brain tumor experts, industry leaders, regulatory officials, and patient/caregiver representatives (see Appendix A) convened for a half-day virtual Roundtable meeting focused on the topic of Conducting Clinical Trials in Certain Front-Line Settings.

This NBTS Research Roundtable focused on re-thinking neuro-oncology clinical trial models as participants explored the current trial paradigms and considered the risk and benefits of conducting studies in ***newly diagnosed patients, including prior to, or in combination with, standard of care.*** Unlike previous Roundtable meetings that have been focused on driving to an outcome of a defined next step, the agenda for this session was designed to encourage participants to express varying points of view through open discussion among clinicians, drug and device developers, patients, and regulators.

Key Takeaways

The Current Scenario

- The current paradigm for drug development for brain tumors is to conduct clinical trials of novel agents in patients with recurrent/refractory disease. Standard of care can lead to alterations in the mutation profile of the tumor, which makes understanding responders/non-responders in the recurrent setting very difficult.
- Although there are some patients for whom standard of care chemotherapy (temozolomide [TMZ]) shows modest benefit, in general, the current standards of care (including radiation) offer patients with high-grade gliomas little chance for long-term survival.
- Unlike other solid tumors, confirmed diagnosis of brain tumors is generally made after surgical resection.
- Regulators are open to discussions with sponsors seeking to evaluate novel agents in newly diagnosed patients prior to the administration of chemotherapy (temozolomide) and/or radiation where an appropriate rationale exists.

Opportunities & Considerations for Disrupting the Paradigm

- There are opportunities, in appropriate instances, to disrupt the current paradigm by evaluating novel agents “up front” in newly diagnosed patients (either in conjunction with or prior to administration of standard of care chemotherapy and/or radiation).
- While clinicians, regulators, industry officials, and patients are interested in this type of disruption, these efforts must be based on a strong scientific rationale and clear communication with patients about their options.
- There is some support for moving to a paradigm like what has occurred in pediatric cancers generally, where clinical trial enrollment could be considered standard of care for newly diagnosed patients.
- The field could benefit from increased opportunities to evaluate tumor tissue (from biopsies) before and after administration of novel drugs to better understand the therapeutic impact.
- While biopsy before resection is not currently the standard approach with brain tumors, there is opportunity to consider disrupting the paradigm and moving toward a staged biopsy-novel treatment-surgery approach in some instances where delaying resection and/or standard of care would not create undue risk for the patient.
- Ethical considerations and concerns from institutional review boards (IRBs) about deferring radiation and potentially delaying surgery to allow for an upfront evaluation of a novel agent must be addressed.
- The neuro-oncology field could benefit from developing patient criteria or characteristics (e.g., biomarker, tumor size, tumor location, rate of change in imaging, steroid dose) that would indicate low likelihood of risk among newly diagnosed patients to undergo a biopsy-treat-resection approach.

Patient Perspective

- Newly diagnosed patients are often at one of the most vulnerable stages of their lives, feeling like they must make major, life-and-death decisions in a short period of time.
- Patients need to have agency and feel some control over their decisions. They need to feel they are partners in their care decisions and have trust in their clinicians.
- Each patient will have a different approach to shared decision-making based on their situation and values.
- Clinicians need to have strong communication skills, especially when dealing with a newly diagnosed high-grade glioma patient.
- In general, in the community setting, there is much more to be done to provide information, awareness, and education to patients and caregivers about clinical trials (including those that may be designed for newly diagnosed patients).

Clinician Perspective

- There should be a strong rationale for decisions, and trial designs must ensure patient safety.
- Testing novel therapies among newly diagnosed patients could enable opportunities to find more effective doses, both within a study and within individual patients within a study.
- There might be rational consideration of other approaches delaying the use of radiation and chemotherapy, but there needs to be careful consideration and rationale regarding what approaches would benefit most from this type of paradigm shift.
- A key aspect to determining when and how to disrupt the paradigm includes a robust partnership among basic science, clinical science, regulators, physicians, and patients and asking: “What do we need to learn about this drug?” and “What's the setting in which we need to learn about it?”
- This initial disruption of the existing paradigm will require training and education.

Regulator Perspective

- Regulators are open to the idea of introducing novel therapies in the newly diagnosed setting but expect to see appropriate rationale for trial design. Additionally, the informed consent needs to clearly describe any potential benefits patients may be forgoing or delaying by enrolling in a study that is different from standard of care.
- In considering disrupting the paradigm, trial sponsors should meet with FDA early to review all the key factors, including prior experience with the drug, the target, how much is known about the target of the drug, and any experience that can be borrowed from other disease settings to support the potential use of the drug in this setting.

Industry Perspective

- A key reason to disrupt the current paradigm is that the current approach — in place for decades — has not yielded success. Improving treatments for GBM remains a significant need.
- Industry shares the perspective that improving patient outcomes is a top priority. For industry, this is ultimately achieved by obtaining FDA approval for new therapies.
- Within industry, one of the challenges is limited resources.
- Partnerships across industry, academia, and the regulatory community are critical to moving forward and ensuring that any new paradigm will have the maximum opportunities to succeed.