



December 17, 2021

**“2021 WHO Classification of Tumors of the Central Nervous System:
Implications for Clinical Trials”**

The eighth Research Roundtable meeting convened on December 17, 2021, engaging a multi-stakeholder, multi-disciplinary group of distinguished brain tumor experts, industry leaders, regulatory officials, and patient/caregiver representatives for a half-day virtual session focused on implications of the fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS). This reclassification emphasizes the use of molecular characterization in CNS tumor identification, diagnosis, and treatment. The Roundtable meeting provided the opportunity for a timely multi-stakeholder discussion—including patient perspectives—to identify and address topics and issues raised by the implementation of the new classification.

Through a condensed, interactive program agenda Roundtable participants discussed key considerations, challenges, and resource needs for the brain tumor clinical trial community in implementing the updated WHO classification. Participants focused on ways to incorporate the new classification system while evaluating data from ongoing studies and planning future studies.

Major themes included:

Implementation for Current Studies

- In the near term, it will be important for the brain tumor community, including sponsors, clinicians, and regulators to understand the landscape of ongoing and recently completed trials that are impacted by the changing classifications.

Trial Design

- As additional tumor sub-types are identified, creating smaller cohorts of patients, there is a need to ensure that eligibility criteria are as flexible as possible to avoid making it harder for patients to access clinical trials. This need is especially true for pediatric brain tumors.
- As FDA reviews trial data during this transition period, regulators will want to clearly understand from sponsors what population has been under study, for whom the study drug

is indicated, and that the patient population in the comparator is representative, not just based on molecular subtype, but also the known clinical prognostic variables, treatment location, etc.

- There is consensus that, during the period of transition (“buffer period”), newly classified groups of patients should be included in clinical trials so they can receive state-of-the-art care, as separate cohorts, and for secondary analyses as necessary to help develop evidence needed for eventual use of the 2021 classification independently within a clinical trial setting.
- As the new classification system is implemented, it may be more difficult to rely on historical controls/external datasets, especially in the adult population.
- In the pediatric brain tumor arena, where there are few randomized controlled studies given rare tumor types and small numbers of patients, it is important to be able to use external datasets (as discussed during the NBTS Research Roundtable in July 2021).
- For small subgroups and rare tumors, it may be productive to archive genetic and genomic data/samples for future use when the field has new information with which to analyze them and develop informed conclusions.

Developing Consensus on Clinical Criteria and Definitions

- It is important to develop consistent terminology and definitions to ensure that datasets can be harmonized and pooled to support pre-clinical studies that can help build the knowledge base for the entire field.
- Since the traditional approach has been to include all IDH-mutant and IDH-wildtype patients in the GBM category, it becomes important under the new system for the community to align on consensus criteria for deciding which IDH-wildtype patients will continue to be considered GBM patients based on similar expected outcomes. This will support efforts to appropriately define inclusion criteria for ongoing studies and identify relevant analyses or the need for separate cohorts in future trials.

Education & Access

- The new classification system further underscores the need for education aimed at patients, healthcare providers, and industry colleagues about the importance of biomarker testing, while advocating for policy changes that ensure appropriate testing with timely results is available and adequately covered/reimbursed for all patients.
- Many patients want to understand more about their tumors, including what type of brain tumor they have (specific diagnosis and characteristics). Patients seek reassurance that they are on the right treatment plan.

Action Steps stemming from the Roundtable included:

- The need for development of resources and tools to support the field in making as seamless a transition as possible to the updated WHO classification system, including

educational materials for patients, providers, policymakers, and payers, along with consensus template materials for clinical trial investigators and sponsors.

- Policy efforts are needed to promote widespread availability and payer coverage of biomarker testing.
- Members of the brain tumor academic clinical and investigator community have agreed to collaborate in pooling existing datasets for a research project that can help to align the field regarding most appropriate approaches.
- Industry colleagues have expressed willingness to collaborate in a pre-competitive environment to support needed pre-clinical efforts and leverage data to advance the field.