Research Roundtable

Dose Optimization in Early Neuro-Oncology Clinical Development

On February 9, 2024, a multi-disciplinary group of distinguished brain tumor experts, industry leaders, regulatory officials, and patient/caregiver representatives convened for a half-day virtual Roundtable meeting focused on the topic of **Dose Optimization in Early Neuro-Oncology Clinical Development.** The goal of this NBTS Research Roundtable was to understand how dose optimization studies can be implemented in early phase clinical trials to maximize the benefit/risk profile of brain tumor therapies.

Key Takeaways

- Drug development must move away from the traditional approach of identifying a maximum tolerated dose and toward more innovative approaches to define optimal dose throughout the drug development process.
- Project Optimus is an FDA program that focuses on dosage optimization for oncology products, with the goal of ensuring that cancer drug dosages are optimized for maximum efficacy and safety using the totality of available data.
- There is a distinction between "optimized dosage" and "optimal dose." The focus on dosage takes into account not just the amount of drug but also factors like regimen, schedule, interval, and times of day for administration.
- The FDA emphasizes population analysis, striving to make the general population in trials as realistic as possible. This approach involves looking at factors such as race, expanding eligibility criteria as appropriate, and incorporating patients with varying degrees of renal and hepatic impairment based on the latest understanding of drug clearance.
- The FDA does not expect dose optimization in adults before moving into pediatrics. Flexibility is crucial, and a one-size-fits-all approach is not appropriate.
- Dose selection can create a dilemma when a higher dose might be necessary to observe efficacy, but the potential for toxicity, especially in refractory or recurrent cases, is a concern. The challenge is to find a balance and to not exclude a potentially effective dosage due to concerns about toxicity.
- There are unique challenges for dose optimization in neuro-oncology clinical development, including issues related to poor prognosis, the blood-brain barrier, difficulty in gathering serial biopsies, differences among and within the adult and pediatric populations, and lack of standardization of patient-reported outcome (PRO) measures to capture real-time or retrospective insights about how patients feel and function.

- Preclinical data, biomarker pharmacokinetic/pharmacodynamic (PK/PD) metrics, and modeling are important for guiding trial design and supporting clinical dose optimization. There may also be a unique opportunity to use imaging in early studies.
- PRO data are a valuable complement to traditional safety data in dose optimization, as tolerability measures, such as overall symptom burden, are assessed. There are opportunities to advance greater standardization among PRO data by leveraging digital platforms to provide real-time insights into how patients feel and function.
- Clinicians must engage patients in a discussion about benefit-risk perceptions and help to set appropriate expectations about side effects from treatments and dosing considerations.
- Addressing dose optimization requires employing various trial designs (e.g., window of opportunity studies), safety considerations, and the integration of different data types and endpoints.

Future Implementation and Path Forward

While there is general alignment around the value of identifying dosage as early as possible within brain tumor drug development, there is a need for the neuro-oncology field to advance concrete steps toward making that standard practice in the near term. Several important concepts were discussed during the Roundtable for achieving this goal, including:

- Innovating clinical trial design by moving beyond traditional safety-focused approaches and exploring new endpoints for safety and efficacy
- Including statistical/mathematical modeling and a focus on quantitative approaches that allow for evaluating dosage throughout the development program
- Advancing more standardized PRO tools and digital tools to allow for real-time data collection from patients relating to side effects, tolerability, and "bother"

One specific recommendation was for the neuro-oncology field to advance effective modeling strategies by focusing on a distinct development program, perhaps for BRAF-positive tumors. This effort could help the field align on the best approaches that could then be adopted more broadly. Another specific activity suggested was to create a blog or paper to share lessons learned from dose-finding studies, with a focus on optimizing dosages and providing insights to the entire neuro-oncology community.

The FDA has advanced multiple additional processes to help sponsors and investigators design studies for dose optimization, including providing guidance and additional resources on their website and offering additional meeting opportunities to discuss dose-related questions and advance novel modeling approaches. NBTS can help to solve the "engineering problem" associated with optimizing doses for brain tumor clinical development by convening experts in the field and disseminating lessons learned from successful dose-finding efforts.