Workshop on Product Development for Central Nervous System (CNS) Metastases
March 22, 2019, Silver Spring MD

Co-sponsors: U.S. Food and Drug Administration and National Brain Tumor Society

Draft Executive Summary

Background:
There is a paucity of effective treatments for patients with central nervous system (CNS) metastases. Moreover, there are few clinical trials and a need for more attention to this high unmet medical need. One impediment to product development for CNS metastases is uncertainty on the optimal clinical trial endpoints and study designs for evaluating products. This unique workshop brought key stakeholders together to evaluate what is needed to advance development of effective products and consider optimal endpoints and clinical trial designs related to this topic.

Workshop Goals and Objectives:

● To provide a forum for open discussion among FDA, clinicians, researchers, patient advocates, and industry on clinical trials for patients with CNS metastases
● To discuss and work toward identifying endpoints for clinical trials for patients with brain metastases
● To educate researchers and product developers about relevant regulatory science and policy issues important to CNS metastases product development
● To accelerate the development of products for the treatment of CNS metastases
● Facilitate open discussions among major stakeholders in the field of CNS metastases

Pre-Workshop Videos:

● Non-Small Cell Lung Cancer and Brain Metastases - https://vimeo.com/321238545/d8e4285af1 Dr. Ross Camidge, Director of Thoracic Oncology at the University of Colorado Cancer Center, provides a primer on Non-small cell lung cancer and brain metastases.

● CNS Metastases from Melanoma: The Role of Systemic Therapy - https://vimeo.com/321238550/cb003eb745 Dr. Michael Davies, Deputy Chairman of MD Anderson Cancer Center for Melanoma Medical Oncology on the role of systemic therapy for CNS metastases from melanoma.

● Radiotherapy in the Management of Brain Metastases - https://vimeo.com/321234317/33959e4ee9 Dr. Paul Brown, Professor of Radiation Oncology at the Mayo Clinic, discusses radiotherapy in the current management of brain metastases.

● Systemic Therapy for Breast Cancer Brain Metastases - https://vimeo.com/321238559/2e386b8fda Dr. Nancy U. Lin, Associate Chief of Dana-Farber
Cancer Institute Breast Oncology Division, presents on the current treatments of breast cancer brain metastases and where the science currently stands to find a systemic therapy.

- **Leptomeningeal Metastasis** - [https://vimeo.com/321233589/90c96c6991](https://vimeo.com/321233589/90c96c6991) Dr. Emilie Le Rhun, Physician in Neurology & Neurosurgery, at the Centre Hospitalier Régional et Universitaire (CHRU) de Lille, presents the latest findings, standard of care, and the main challenges in treating Leptomeningeal Metastasis.

**Key Takeaways:**

- There is enthusiasm for including patients with CNS metastases broadly in clinical trials. Patients and advocates voiced that having such opportunities is a major source of hope for them.
- There is general consensus that patients with CNS metastases can be more broadly included in trials without compromising safety or trial design, and many past assumptions need to be challenged.
- New guidance is also needed [note: new draft guidance from the FDA (Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm633132.pdf) has already been published as of the time of this summary] to clarify recommendations for eligibility criteria. Additional FDA guidance from this Workshop is being considered.
- There is recognition that more needs to be done to include patients with leptomeningeal disease in clinical trials.
- There may be key differences in CNS metastases biology compared with the primary tumor and other (extracranial) metastases and there is a need to develop trials and drugs that specifically target CNS metastases.
- Developing innovative endpoints and selection of endpoints for CNS metastases trials remains a major challenge, and ultimately might depend on the trial, drug, cohort of patients, and other specific factors. Appropriate endpoints may differ between early and late clinical development.
- Imaging is one area where additional work may help make radiographic endpoints more feasible in trials evaluating CNS metastases. This will include refinement and adoption of RANO brain metastases guidelines, as well as the development of standards for acquiring imaging data in trials using new and advanced imaging methods.

**Opening Remarks by Dr. Richard Pazdur, U.S. Food and Drug Administration:**

- CNS metastases is a very challenging area and it is commendable that so many groups have come together to focus on these issues.
- The FDA is eager to hear from all stakeholders and to discuss ways to stimulate product development for CNS metastases.

**Presenting the Challenge: Drs. Joohee Sul (FDA) and Patrick Wen (Dana-Farber Cancer Institute)**

- In evaluating products related to CNS metastases, context matters. There can be differences in outcomes related to the type of cancer, the trial design, the drug or drug combination, imaging techniques, and the patient characteristics. All these factors should be considered.
This is an opportune time to bring stakeholders together to identify the optimal conduct of CNS metastases trials. There is strong interest in clarifying how and when to include brain metastases patients in trials, the endpoints to use, the standards to improve data collection, and appropriate response criteria.

Workshop Sessions Overview:

I. Defining the Problem of CNS Metastases

II. Key Issues for Clinical Development for Brain Metastases
   ○ Identifying Targets for Brain Metastases Clinical Studies
   ○ Selecting Drugs Candidates for Brain Metastases
   ○ Issues with Conducting Brain Metastases Clinical Trials
   ○ Standardizing Brain Metastases Response Assessment

III. Clinical Benefit in Patients with Brain Metastases
   ○ Regulatory Definition of “Clinical Benefit”
   ○ Defining Endpoints Framework for CNS Metastases
   ○ Regulatory Challenges for CNS Metastases
   ○ Re-thinking Trial Designs for Stimulating Product Development for CNS Metastases

IV. Therapy Development: Challenges and Opportunities
   ○ Defining Strategies to Advance Product Development

Workshop Sessions Highlights:

Session I: Defining the Problem of CNS Metastases
- Each year, approximately 70,000-170,000 cancer patients are diagnosed with brain metastases, while ~100,000 will die every year as the result of brain metastases. The incidence of brain metastases appears to be increasing.
- These patients are consistently underrepresented in clinical trials/early therapeutic development, which is frustrating for patients.
- Radiation remains the primary treatment modality for brain metastases, with stereotactic radiosurgery (SRS) applied in manageable cases; however whole brain radiation therapy (WBRT) is still the standard approach for patients with diffuse brain metastases, despite concerns related to toxicity.
- It is increasingly important to understand how to best incorporate radiation, in terms of timing, sequence, combination with other treatments like chemotherapy or immunotherapy, and how to assess response and impact on cognitive function.
- There is a growing list of molecular targets for brain metastases that can lead to new therapeutic options; however better preclinical models are needed for translational research.
- Leptomeningeal disease (LMD) is a major unmet medical need. The disease will affect 10% of patients with solid tumors and is extremely aggressive with poor median survival (2-3 months), no clear diagnostic standards, and a lack of trials available for these patients.
Challenges for treating patients with CNS metastases include:
  ○ Heterogeneity of the patient population (e.g., different tumor types and treatment histories)
  ○ Lack of integration of care teams (need multidisciplinary teams)
Assumptions may interfere with the ability to enroll patients on clinical trials:
  ○ Many trials exclude patients with brain metastases due to concerns that the drugs may not penetrate the blood-brain barrier (BBB).
  ○ There is a belief that immunotherapy would cause unacceptable neurotoxicity.
  ○ There is a belief that these patients will have poor outcomes and will not live long enough to successfully participate in trials.
It is important to include patients with CNS metastases in a thoughtful manner, as early as possible in the drug development/clinical trials, particularly those patients who have progressed on therapy.
The field is learning that BBB penetration may not be as preclusive as previously thought (i.e., drugs may not need to cross the BBB to have effect) and the BBB can also be intentionally disrupted if needed.
LMD is the “last frontier”; if a product demonstrates activity in LMD, this would be important to note. Specific models and translational studies are needed as well.
Patients with LMD are willing to participate in clinical trials and will come from all over the country if a trial is available for them. It is important to get these patients on trials quickly.
Patients with LMD might need to be included in a separate cohort in clinical trials.

Session II: Key Issues for Clinical Development for Brain Metastases
Studies dating back to 2010 have demonstrated that CNS metastases may be molecularly different than their corresponding primary tumor or other sites of metastases, with de novo genetic changes and divergent patterns of evolution. These discoveries are important because they raise the question of whether a biopsy from a primary tissue or other sites of metastases -- can be used to make treatment decisions about CNS metastases and optimum targets.
  ○ Intriguingly, spatial heterogeneity for brain metastases is relatively low; different lesions within the brain seem to share driver alterations. These mutations, such as CDK losses, and mutations of PI3K/AKT/mTOR, HER2/EGFR may be clinically actionable because they are fairly common (found in 50% of patients in the study).
  ○ Better preclinical models for CNS metastases that incorporate common mutational drivers found in patients are urgently needed to speed up drug development process as well as to gain understanding whether BBB penetration is required for efficacy across the board, and how the microenvironment matters.
  ○ For potential drug selection, mechanism of action should be prioritized before debating whether there is BBB penetration.
  ○ Disease presentations for CNS metastases should be considered when designing cohorts (symptomatic/asymptomatic; active extracranial disease/stable disease).
  ○ Building standards for these trial-related aspects -- especially imaging related endpoints -- will be critical and the following should be considered:
    ○ Thin, high-resolution 3D imaging to accurately assess the extent of the disease and consensus around a RANO brain metastases imaging guidelines.
    ○ Guidelines for assess/verifying progression/pseudo-progression
● Advanced imaging could be beneficial (DSC perfusion imaging; MR spectroscopy; PET imaging, including FDG-PET).
● For patients, trials represent hope that options still exist.

Session III: Clinical Benefit in Patients with Brain Metastases

Part I (Pre-lunch)
● The regulatory definition of “clinical benefit” is different for traditional approval based on efficacy endpoints vs. accelerated approval where surrogate endpoints may be used, and clinical benefit is confirmed in post-marketing studies.
● It is important to consider the strength of efficacy endpoints - what is being measured, is it being accurately measured, the magnitude of the effect, etc.
● The more interpretation that is needed, the less reliable the endpoint is - there is a continuum with different endpoints related to the risk of bias.
  ○ Tumor endpoints have advantages because it is a direct measure of the disease
    ■ Lesion(s) location is important in terms of response - there could be some areas where the lesion/tumor response may not be particularly meaningful for overall disease control or survival (activity vs. benefit).
  ○ Patient-reported outcomes (PROs) have some subjectivity and variability but do measure what a patient is feeling.
● The totality of evidence demonstrating a response can represent clinical benefit.
  ○ It is important to think about this prior to the trial, however, so all available data (location, depth of response, duration, survival, function, radiographic response, etc.) can be collected to determine clinical benefit.
● It is important, however, when considering multiple, parallel endpoints to carefully develop a statistical hierarchy prioritizing meaningful endpoints, that can be measured, at the top. This is most important in later-stage trials.
● Another argument to include patients with CNS metastases in trials early on is to evaluate the drug activity in early phase trials so that secondary endpoints can be considered in later development.
● Endpoints can also differ depending on the type of intervention.
  ○ In addition to including patients with CNS metastases in trials, these patients may not require discontinuation from trials if their disease progresses. Local therapies such as SRS could be used to control the disease and keep patients on trial.
● Patients often think QoL is equally as important as OS, and may want to avoid WBRT, and maintain neurocognitive function.

Part II (Post-lunch)
● Challenges of evaluating therapies for CNS metastases include defining brain metastasis-specific efficacy endpoints and eligibility criteria, CNS imaging, response assessment criteria, study design, and sample size.
  ○ Efficacy endpoints require measurement of both magnitude of effect and the durability of the response.
  ○ Typically, patients with untreated asymptomatic disease have been included in clinical trials, which may bias the data.
● Baseline imaging assessment of the CNS rarely occurs when screening patients for trials

● An important is how to interpret an intracranial response in the setting of systemic disease.

● Sponsors often recycle clinical trial protocols and are not thoughtfully considering eligibility criteria; therefore, patients may be excluded for irrelevant reasons. Sponsors need to be less “academically lazy” in this regard.

● Currently, fewer than 1% of patients with CNS metastases are represented in clinical trials. Patients may need to be enrolled in in a separate cohort, especially in later-phase trials.

● If patients are enrolled and treated earlier in the course of their disease, it could also prevent new lesions from developing.

● From an Industry perspective, there is a need to distinguish between trials looking for CNS activity and those that are not. There is a big difference in what the label would look like if you’re developing a drug specifically for CNS metastases, or including patients with CNS metastases in the study; drugs would be developed differently for these two scenarios.
  ○ There is a need to develop studies specifically for CNS metastases against novel targets.
  ○ For those trials that aren’t looking for CNS activity, it could be beneficial to include patients with CNS metastases on early-phase trials because if you see activity in the CNS that likely represents real activity. In phase III trials, Industry worries about endpoints, patient heterogeneity, lines of therapy, disease state and burden.
  ○ Additionally, the lack of good preclinical models makes it tough to incentivize Industry to conduct CNS metastases-specific trials, since companies use preclinical data to make decisions on the direction of future development.

Session IV: Therapy Development: Challenges and Opportunities

● The RANO brain metastases guidelines should be more widely adopted, as there already has been progress in refining these criteria.

● There are likely patients with CNS metastases on trials that have not been identified because imaging during screening typically stops at the neck. By doing more baseline screening for CNS metastases, we could collect more data.

● There is a need for both a carrot and stick approach to encourage drug development. The carrot is that drugs targeted for patients with CNS metastases would open up a whole new market. The stick would be to get the field to break bad habits, e.g. through issuing new FDA guidance on inclusion of brain metastasis patients in clinical trials.

● For trials that are including CNS metastases within the general patient population, endpoints relevant to all patients (with and without CNS metastases) should be selected.

● For trials that are CNS metastases-specific, OS can be more valuable.
  ○ In which context does ORR make the most sense?

● Single-arm studies can be appropriate if efficacy is really strong, otherwise, it’s challenging if you don’t know the effect of the drug.

● Overall, it’s the totality of the data from the trial that determines approval - thus there is a need to standardize the collection of meaningful data across trials to draw conclusions about future endpoints.
Overview of the American Brain Tumor Association Metastatic Brain Tumor Initiative:
The American Brain Tumor Association (ABTA) presented data from a survey conducted specifically for brain metastases patients and caregivers. Results from the survey found that a majority of patients diagnosed with brain metastases are given the diagnosis by the same doctor that made their primary tumor diagnosis, and confirmed that QoL and efficacy of therapy go hand-and-hand for patients when considering goals of therapy. The ABTA’s next step is to survey clinicians that treat brain metastases patients.

Summary & Next Steps:
- There is enthusiasm for including patients with CNS metastases broadly in clinical trials.
- All brain metastases patients should be able to access a clinical trial.
- Clinical trials are an important source of hope for brain metastases patients.
- The field would like to see the inclusion of these patients starting earlier in both the drug development process, and earlier in the patients’ treatment history.
- There is broad agreement that these patients can be more broadly included in trials without compromising safety or trial design.
- Simply dispelling for past assumptions and myths -- including the role of the BBB in treating CNS metastases -- should lower the barrier for enrolling more patients with brain metastases.
- However, new guidance is also needed [note: new draft guidance from the FDA (Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm633132.pdf) has already been published as of the time of this summary] to clarify recommendations for inclusion/exclusion criteria. Addition guidance from this Workshop is expected.
- Additionally, because there are differences in brain metastasis compared to the primary tumor and other (extracranial) metastasis, there is also a need to develop trials and drugs that specifically target brain metastases.
- Developing new innovative endpoints and selection of endpoints for trials involving brain metastases patients remains a major challenge, and ultimately might depend on the trial, drug, cohort of patients, and other specific facts. Appropriate endpoints may differ between early and late clinical development.
- However, there is still a need to rationally identify a small subset of things that we can measure for meaningful clinical benefit, in addition to standard tumor endpoints and survival endpoints. Moving forward, an important goal is to establish these and other surrogate endpoints that could be accepted measures for regulatory approval.
- Imaging is one area where more work needs to be done to help make radiographic endpoints more feasible in trials with brain metastases patients. This will include refinement and adoption of RANO brain metastases guidelines, as well as the development of standards for using new and advanced imaging methods.
- LMD patients comprise a subgroup of brain metastases patients that represent an even dire unmet medical need. More focus needs to be given to these patients.
- Multidisciplinary teams are needed to treat brain metastases patients. Multidisciplinary brain metastasis clinics have opened recently at both MD Anderson Cancer Center and Massachusetts General Hospital Cancer Center - representing a powerful new way to optimize care for these patients and help them get enrolled on clinical trials.
- Additionally, there is a recently opened national biomarker-driven trial in brain metastases, targeting patients by what is observed gnomically in the brain, with ORR and CNS-RR as primary endpoints assessed by RANO criteria (NCI-funded Alliance trial). This is a positive development.
- In addition to FDA guidance, sponsoring and collaborating organization will prepare a statement on inclusion criteria for patients with brain metastases in clinical trials.