



# Workshop on Product Development for Central Nervous System (CNS) Metastases

March 22, 2019, Silver Spring, MD

## MEETING SUMMARY

**Co-sponsors:** U.S. Food and Drug Administration (FDA) and National Brain Tumor Society (NBTS)

**Collaborating Organizations:** Accelerate Brain Cancer Cure, American Brain Tumor Association, Friends of Cancer Research, Kidney Cancer Research Alliance, LUNgevity Foundation, Melanoma Research Alliance, Metastatic Breast Cancer Alliance, RANO, and Society for Neuro-Oncology

### 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.

This unique workshop brought key stakeholders together to evaluate what is needed to advance development of effective products for CNS metastases and consider optimal endpoints and clinical trial designs.

### 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 optimally designing and 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
- To facilitate open discussions among major stakeholders in the field of CNS metastases

### Opening Remarks/Presenting the Challenge:

- Drug development for the treatment of 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 product development for CNS metastases.
- Context matters as there can be differences in outcomes related to the type of cancer, the trial design, the drug or drug combination, imaging techniques, and patient characteristics. All these factors should be considered when designing trials and evaluating data.
- Clarification is needed about when to include patients with brain metastases in trials, selecting endpoints, how to improve data collection, and appropriate radiographic response criteria.

**Workshop Agenda:** <https://braintumor.org/our-research/cns-mets-agenda/>

**Key Workshop Conclusions:**

- Patients with CNS metastases, including patients with leptomeningeal disease (LMD), should be included more broadly in clinical trials as early as possible in drug development. This inclusion can be accomplished without compromising safety or trial objectives.
- Participating in clinical trials offers opportunity for patients with this significant unmet need to access novel investigational agents.
- Patients with CNS metastases may be excluded from clinical trials based on assumptions, such as poor performance status or presumed inactivity of a drug due to failure to cross the blood brain barrier (BBB). These and other assumptions should be supported by data or be reconsidered.
- Participants acknowledged that exclusion of patients with CNS metastases in clinical trials is often the result of the “cut and paste” approach to writing protocols.
- Additional regulatory guidance on study design considerations for evaluating products intended to treat CNS metastases would build upon recently issued FDA draft guidance on the topic of eligibility criteria in oncology trials.<sup>1</sup>
- The biology of CNS metastases may differ from that of the primary tumor or other sites of disease. Drugs with anti-tumor activity against CNS metastases are needed.
- Selection of endpoints for trials seeking to establish efficacy for treatment of CNS metastases remains a major challenge. Defining optimal endpoints may depend on the trial, drug, patient characteristics, or other specific factors. Appropriate endpoints may vary depending on the stage of product development.
- There are multiple strategies for including patients with CNS metastases in clinical trials, including enrollment of such patients into separate cohorts or stratification of randomization by presence/absence of CNS metastases.
- Additional work is needed to make radiographic endpoints more feasible in trials evaluating CNS metastases. Participants discussed refinement and broad adoption of RANO brain metastases criteria in clinical trials. Similar to the standardized MRI acquisition protocol that is now adopted by institutions within the RTOG network for brain tumor trials, a new set of standards will need to be established for brain metastasis trials (e.g., based on T1, T1 contrast, and other sequences).
- In addition to measures of anti-tumor activity, important endpoints to demonstrate clinical benefit may include effects on neurocognitive function and relevant patient reported outcomes (PROs).
- Stakeholders across the field agreed to continue working together toward the goal of advancing endpoints suitable for regulatory use. Opportunities to pursue this objective include the Society for Neuro-Oncology (SNO) conference on Brain Metastases in August 2019.
- Opportunities to build knowledge in this field may come from ongoing trials such as the InSight biomarker-driven trial, with objective response rate (ORR) and CNS-RR as primary endpoints (assessed by RANO Brain Metastases criteria).
- Additional multidisciplinary teams are needed to optimize care for patients with brain metastases, identify appropriate clinical trials, and encourage trial enrollment.

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<sup>1</sup> *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>

## Workshop Agenda Overview:

- I. Defining the Problem of CNS Metastases
  - Clinical Management of CNS Metastases, 2019: Current Strategies, Investigations, and Key Challenges
- 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

## Session Highlights:

### Session I: Defining the Problem of CNS Metastases

- Each year 70,000–170,000 patients with cancer are diagnosed with CNS metastases.
- While the incidence of CNS metastases appears to be increasing, these patients are consistently underrepresented in clinical trials/early therapeutic development.
- Outdated assumptions may interfere with the ability to enroll patients in clinical trials. The field is learning that these assumptions may no longer be valid. For example, BBB penetration may not be as preclusive (e.g., immunotherapies may not need to cross the BBB to have effect; agents that cannot cross an intact BBB have demonstrated clinical benefit in patients with CNS metastases). The BBB can also be intentionally disrupted if needed.
- Radiation (whole brain or stereotactic) remains the primary treatment modality for brain metastases. Whole brain radiation therapy (WBRT) is still the standard approach for patients with diffuse brain metastases, despite toxicity concerns.
- It is important to understand how to best incorporate radiation (both in assessing response and managing impact on cognitive function) in terms of timing, sequence, and in combination with drugs (including traditional chemotherapy, targeted therapy, and immunotherapy).
- It is especially important to include patients with CNS metastases in a thoughtful manner as early as possible in drug development/clinical trials to evaluate efficacy against CNS metastases. In addition, more and improved preclinical models are needed to accelerate translational research and therapeutic development.
- 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 (multidisciplinary teams are needed)
- LMD is a major unmet medical need. The incidence of clinically diagnosed LMD across all solid tumors is about 5%, however it is much higher for melanoma 22%–46%, and small cell lung cancer, 10%–25%.<sup>2</sup> Median survival for LMD is 2–3 months, and there are no clear diagnostic standards.
- Many consider LMD as biologically distinct from parenchymal disease, therefore specific models and translational studies are needed to aid drug development in this setting. Patients with LMD are willing to participate in clinical trials and will travel to take part in a trial if made available. These patients could be enrolled in a separate cohort.

## 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 disease at other sites, with de novo genetic changes, divergent patterns of evolution, or changes induced by the local microenvironment of the brain. These discoveries challenge the assumption that a biopsy from a primary tissue or other metastatic sites can be used to make treatment decisions about CNS metastases or identify optimum targets.
- Different lesions within the brain seem to share driver alterations.
- Better preclinical models for CNS metastases that incorporate common mutational drivers are urgently needed to facilitate drug development. Such models will improve understanding about the role of BBB penetration and the microenvironment.
- Disease presentations for CNS metastases should be considered when designing cohorts (symptomatic/asymptomatic; active extracranial disease/stable disease).
- Building data acquisition standards for these trial-related efficacy measures (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 RANO brain metastases imaging guidelines.
  - Guidelines for assessing progression or pseudo-progression.
- Advanced imaging modalities should be explored to determine whether they could be more informative (DSC perfusion imaging; MR spectroscopy; PET imaging, including FDG-PET) in assessing treatment effects.
- For patients, trials allow access to novel experimental treatments that can offer hope.

## Session III: Clinical Benefit in Patients with Brain Metastases

### Part I:

- Demonstration of an effect on survival or how patients feel or function is required for traditional approval, whereas an effect on an endpoint, such as tumor shrinkage—that is reasonably likely to predict an improvement in survival based on the magnitude of the effect relative to available therapy—can support accelerated approval in a serious, life-threatening disease.
- It is important to consider the strength of efficacy endpoints and evaluate what is being measured, whether it is accurately measured, and the magnitude of the effect.
- Symptoms and other aspects of quality of life, particularly neurocognitive function, are often as important to patients as survival.
- Endpoints that require more subjective interpretation are at greater risk for bias. Assessing overall survival (OS) does not require subjective interpretation, whereas PROs may be influenced/biased by knowledge of the treatment or other information (tumor response status).

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<sup>2</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656567/>

Tumor shrinkage as an endpoint may provide a direct measure of a drug's effect on the disease. Location of the lesion(s) may be important to include in the assessment.

- The totality of evidence is often used to support a determination of clinical benefit. It is important to think about the intended claims prior to the trial design/initiation so all relevant data (location of tumor, depth and duration of radiographic response, delay of tumor progression, OS, physical and cognitive function, symptom information, etc.) can be collected accurately.
- When considering multiple, parallel endpoints in late stage trials, it is important to carefully develop a statistical hierarchy to address multiplicity concerns and seek to include clinically meaningful endpoints that can be measured accurately.
- Including patients with CNS metastases in early phase trials will allow for rational patient selection and secondary endpoints related to CNS disease that could be incorporated into later phase development.
- Patients with CNS metastases may be able to remain on a study, even if their CNS disease progresses, when the protocol allows the use of local therapies such as SRS for disease control.

**Part II:**

- Currently, patients with CNS metastases are under-represented in clinical trials. Historically, these patients have been excluded from trial participation completely, or enrolled in a separate cohort, especially in later-phase trials.
- Recently ASCO, Friends of Cancer Research,<sup>3</sup> and FDA have made recommendations to encourage sponsors to more regularly include patients with previously treated brain metastases or stable CNS disease. More can be done to develop strategies to include patients with previously untreated or symptomatic CNS metastases.
- Challenges of evaluating therapies for CNS metastases include definition of brain-specific efficacy endpoints and eligibility criteria; CNS imaging and response assessment criteria; study design; and sample size.
  - Efficacy endpoints require measurement of both the magnitude and durability of effects.
  - There is a need for increased baseline imaging of the CNS.
- It could be helpful to distinguish between trials specifically looking for CNS activity and those that are not, as development approaches differ depending on the scenario.
  - Studies for specific targets in CNS metastases are needed.
  - It may be beneficial to include patients with CNS metastases in early phase testing, because activity in the CNS may represent robust overall activity.
  - The relative lack of good preclinical models is a barrier to incentivizing industry to conduct trials investigating efficacy in patients with CNS metastases, because companies often use preclinical data to make decisions on the direction of future development.
- Sponsors often recycle clinical trial protocols and do not thoughtfully consider eligibility criteria, leading to exclusion of patients with CNS metastases.
- If patients are enrolled and treated earlier in the course of their disease with agents that have CNS activity, CNS metastases may be prevented.

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<sup>3</sup> <https://www.focr.org/clinical-trial-eligibility-criteria>.

#### **Session IV: Therapy Development: Challenges and Opportunities**

- The RANO brain metastases guidelines<sup>4</sup> 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.
- Drugs that penetrate the BBB and with potential efficacy for CNS metastases could potentially lead to a new market for sponsors.
- New FDA guidance encourages inclusion of brain metastasis patients in clinical trials where safe and scientifically appropriate.<sup>5</sup>
- For trials including patients with CNS metastases, endpoints relevant to all patients (with and without CNS metastases) should be selected.
- Single-arm studies may be appropriate to assess treatment effects in certain settings, such as where systemic (extra-CNS disease) is adequately controlled. However, time to event endpoints such as progression-free survival (PFS) or OS generally cannot be accurately assessed in single arm trials.
- Overall, the totality of the data from the trial will be considered in a regulatory review.
- There is a need to standardize the acquisition and 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 in patients with brain metastases and their 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. These results confirmed that quality of life and efficacy of therapy go hand-in-hand for patients when considering goals of therapy. The ABTA's next step is to survey clinicians who treat these patients.

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<sup>4</sup> [https://imaging.cancer.gov/clinical\\_trials/docs/RANO%20-%20BM%20Criteria%20-%20Lancet%202015.pdf](https://imaging.cancer.gov/clinical_trials/docs/RANO%20-%20BM%20Criteria%20-%20Lancet%202015.pdf) and <https://www.futuremedicine.com/doi/full/10.2217/cns-2018-0007>

<sup>5</sup> <https://www.fda.gov/media/121317/download>

## 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, discusses 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> **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.