#MetsCNS2019
#CNSMetsWorkshop2019

Workshop on Product Development for CNS Metastases

March 22, 2019

Welcome

David Arons, JD

Chief Executive Officer
National Brain Tumor Society

#MetsCNS2019
#CNSMetsWorkshop2019

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Welcome

Richard Pazdur, MD

Director, Oncology Center of Excellence
US Food and Drug Administration

Presenting the Challenge

Joohee Sul, MD, Workshop Co-Chair, US Food and Drug Administration

Patrick Wen, MD, Workshop Co-Chair, Dana Farber Cancer Institute

Thank You To:

- FDA
- National Brain Tumor Society
- 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
- Response Assessment in Neuro-Oncology
- Society for Neuro-Oncology
- Wendy Selig
- All the speakers, discussants and

Sponsored by Jumpstarting Brain Tumor Drug Development Coalition

National Brain Tumor Society

SNO Society for NeuroOncology

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accelerate brain cancer cure
today's hope. tomorrow's cure.

Neuro-Oncology

Neuro-Oncology 16:vii36–vii47, 2014
doi:10.1093/neuonc/nou226

Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials neuroimaging endpoint workshop (January 30, 2014, Bethesda MD)

Patrick Y. Wen, Timothy F. Cloughesy, Benjamin M. Ellingson, David A. Reardon, Howard A. Fine, Lauren Abrey, Karla Ballman, Martin Bendszuz, Jan Buckner, Susan M. Chang, M… Alma Gregory Sorensen, Martin van den Bent, and Wai-Kwan Alfr…

Neuro-Oncology

Neuro-Oncology 18:ii26–ii36, 2016
doi:10.1093/neuonc/nov270

Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials clinical outcome assessment endpoints workshop (October 15, 2014, Bethesda MD)

Jennifer L. Helfer, Patrick Y. Wen, Jaishri Blakeley, Mark R. Gilbert, and Terri S. Armstrong

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
doi:10.1093/neuonc/nov095
Advance Access date 6 August 2015

Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Benjamin M. Ellingson, Martin Bendszus, Jerrold Boxerman, Daniel Barboriak, Bradley J. Erickson, Marion Smits, Sarah J. Nelson, Elizabeth Gerstner, Brian Alexander, Gregory Goldmacher, Wolfgang Wick, Michael Vogelbaum, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Whitney B. Pope, Dewen Yang, Caroline Chung, Michael V. Knopp, Soonme Cha, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

Neuro-Oncology

Neuro-Oncology 17(9), 1179–1180, 2015
doi:10.1093/neuonc/nov158

Brain tumor clinical trials imaging: a (well-standardized) picture is worth a thousand words

Joohee Sul and Daniel M. Krainak

Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (J.S.); Division of Radiological Health, Office of In vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, Maryland (D.M.K.)

Goal

- Brain metastases is a significant and increasing cause of morbidity and mortality in cancer patients
- Need to improve development of therapies for brain metastases and provide clarity on the optimal trial designs and endpoints
  - General oncology drug development
  - Specific therapies for brain metastases
    - Systemic therapies
    - Local therapies (e.g. SRS)
- Need to focus today especially on these issues

Program

- Defining the Problem of CNS Metastases
- Key Issues for Clinical Development
  - Targets
  - Selecting drugs
  - Issues in conducting clinical trials
  - Standardizing brain metastases response assessment
- Regulatory definition of clinical benefit and regulatory challenges
- Designing Endpoints
- Rethinking Trial Designs
- Defining Strategies to Advance Product Development

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

2017

Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group

Nancy U. Lin, Tatiana Prowell, Antoinette R. Tan, Marina Kozak, Oliver Rosen, Laleh Amiri-Kordestani, Julia White, Joohee Sul, Louise Perkins, Katherine Beal, Richard Gaynor, and Edward S. Kim

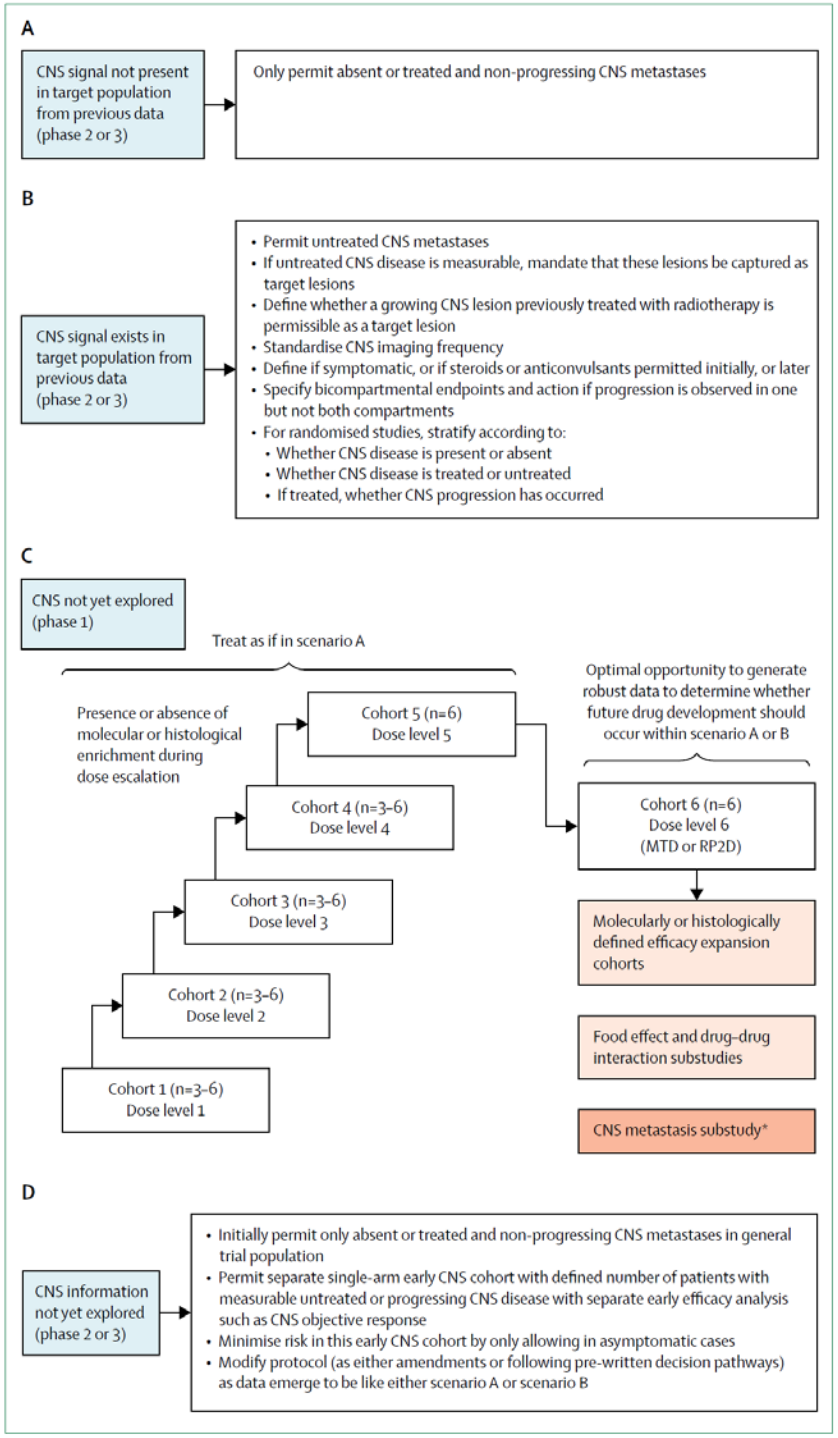
- **Pts with treated or stable brain mets**
  - Pts with treated or stable brain mets who are stable for 4 weeks are eligible for all phases of clinical trials
- **Pts with active brain mets**
  - Pts with active brain mets should be considered early in clinical development if there is a strong scientific rationale for likelihood of benefit based on molecular pathway, histology or preclinical data
  - For therapies with less robust preclinical data, inclusion of brain met pts should still be considered esp if BM common in the intended population. Consider brain met specific cohort.
- **Leptomeningeal Disease**
  - Inclusion of LMD cohort encouraged in early phase trials if CNS activity expected and when relevant in specific disease type under study
  - CSF PK measurement encouraged
  - Consider LMD cohort in later phase trials

THE LANCET Oncology

Clinical trial design for systemic agents in patients with brain metastases from solid tumours: a guideline by the Response Assessment in Neuro-Oncology Brain Metastases working group

D Ross Camidge, Eudocia Q Lee, Nancy U Lin, Kim Margolin, Manmeet S Ahluwalia, Martin Bendszus, Susan M Chang, Janet Dancey, Elisabeth G E de Vries, Gordon J Harris, F Stephen Hodi, Andrew B Lassman, David R Macdonald, David M Peereboom, David Schiff, Ricardo Soffietti, Martin J van den Bent, Jeffrey S Wefel, Patrick Y Wen

2018;19:e20



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	Definition	Advantages	Disadvantages	When this is an appropriate primary endpoint
CNS objective response	The proportion of patients with a reduction in CNS tumour size by a predefined amount using standard criteria, eg, RANO-BM	Can be assessed in single-arm studies	Requires measurable CNS disease, and clear identification and consideration of lesions with and without previous local therapy; does not evaluate duration of benefit	Might be an appropriate primary endpoint in early-phase studies
CNS disease control rate or CNS clinical benefit rate	The number of patients with stable disease (sometimes for a defined period), a partial response, or a complete response divided by the number of evaluable patients	Might be a better reflection of the population deriving true benefit, assuming stabilisation is beneficial to the patient	Inclusion of individuals with CNS disease that is not measurable or listed as non-target lesions might bias readings towards high perceived clinical benefit rate, in comparison to if only target lesions are included; does not evaluate duration of benefit unless only stable disease for more than a defined period is specified	Unlikely to ever be a primary endpoint in phase 2 or 3 trials but could be used in early-phase studies
CNS PFS or CNS TTP	CNS PFS is the time from randomisation to CNS disease progression or death (specified as either death from CNS disease or death from any cause); CNS TTP is the time from randomisation to the time of CNS disease progression (does not include death)	Addresses duration of benefit; permits bicompartmental assessment with overall or extracranial PFS or TTP readouts	Might be influenced by underlying biology or previous local therapies; death from CNS disease alone is very hard to assess; influenced by frequency of surveillance	Best addressed within randomised trials, ideally stratified by the presence or absence of CNS disease and by previous local therapy exposure; because of the impact of potential confounders, this endpoint is often required to be supported by other endpoints (eg, neurocognitive outcomes, neurological symptoms, and quality of life)
CNS duration of benefit or CNS duration of response	The time from CNS tumour response or first non-progression scan to CNS disease progression	Can be assessed in single-arm studies; adds to objective response data alone	Influenced by frequency of surveillance	Might be an appropriate primary endpoint in early-phase studies
Overall PFS or TTP	PFS is the time from randomisation to disease progression or death; TTP is the time from randomisation to the time of disease progression (does not include death)	Addresses duration of benefit; permits bicompartmental assessment with intracranial PFS or TTP readouts	Might be influenced by underlying biology; influenced by frequency of surveillance	Might be an appropriate primary endpoint in trials of drugs considered very unlikely to have CNS activity or efficacy (however, when untreated CNS disease is included in trials, a bicompartmental model for PFS or TTP should be considered); best addressed in randomised trials, ideally stratified by the presence or absence of CNS disease and by previous local therapy exposure; because of the impact of potential confounders, this endpoint is often required to be supported by other endpoints
Overall objective response	The proportion of patients with a reduction in the size of target lesions by a predefined amount using standard criteria, eg, RECIST	Can be assessed in single-arm trials	Because of the potential for both CNS under-responsive and CNS over-responsive scenarios, the overall response can be manipulated depending on whether CNS or extra-CNS lesions are chosen as the target disease	Use the bicompartmental RANO-BM approach to capture the CNS and extra-CNS overall objective response and duration of benefit separately; if the overall dataset is presented, provide information on the proportion of CNS and extra-CNS lesions within data
Overall survival	Time from randomisation until death from any cause	Gold standard for demonstration of benefit; precise; easy to measure	Requires larger sample size and longer follow-up time than other endpoints; should be evaluated in randomised trials because of the major impact of underlying biology; confounded by subsequent therapies; subject to the effects of extracranial disease	Most reliable endpoint but may be complicated by crossover in randomised trials; should be the primary endpoint in most phase 3 trials, when CNS disease is expected to portend a poor prognosis
Neurocognitive, neurological, functional, or health-related quality-of-life outcomes	Multiple	Evaluates benefits that are difficult to detect with basic neurological exams (ie, neurocognitive); evaluates benefits that might only be detected or described by the patient (ie, health-related quality of life); captures the effects of adverse events	Magnitude of benefit might be difficult to understand; optimally evaluated in randomised trials as the presence of relatively less historical control data limits their interpretability in studies without a comparison group; ideally requires pretreatment baseline assessment and longitudinal assessment	Randomised studies required for definitive trials; can be considered as a primary endpoint in single-arm phase 2 trials under specific circumstances, including to assess the feasibility and operational issues in preparation for a phase 3 trial, to refine effect size estimates to power future trials, to provide a qualitative description of the time course of recovery from treatment-related toxic effects or of symptom improvement, and to allow studies designed to explore the relation between correlative biomarkers (eg, early imaging findings or germline polymorphisms) and neurological or neurocognitive outcomes

Goal

- Need clarity by end of meeting what trials and endpoints should be performed to develop new therapies for brain metastases
- Identify issues that still need to be addressed
- Develop road map to address these issues
- Summarize the meeting in a paper

The Society for Neuro-Oncology's

Inaugural Conference on Brain Metastases

InterContinental Barclay Hotel
New York City
August 16-17, 2019

Abstract submissions due:
April 29, 2019