Session II:
Key Issues for Clinical Development for Brain Mets

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Issues in conducting clinical trials for patients with brain metastases

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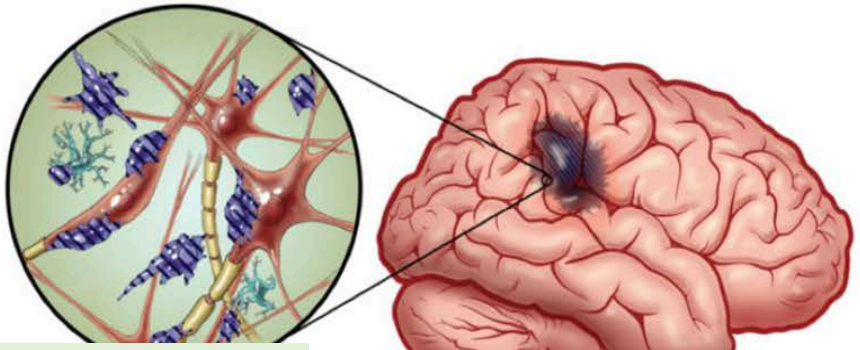
Why are we here?

- Do we need regulatory criteria/approval for agents that treat brain metastases?
  - Apparently YES—but in the context of the global cancer burden and threat
  - How do we define the needs and thus the regulatory requirements and approval strategies?
- What are the endpoints
  - Gold standard is OS
  - What are the pros and cons of other endpoints?
    - PFS—very fuzzy, least desirable
    - Intracranial ORR, PFS
    - Neurologic—quantitative plus QoL, PRO
    - Indirect criteria such as off steroids
    - How to study combinations, with risks and benefits (therapeutic index)
    - Are there meaningful surrogate endpoints? [traditionally supports accelerated approval]
- How are the endpoints measured?
  - Neurologic examinations
  - PRO
  - Use of/discontinuation of adjunctive therapies like steroids, bevacizumab
  - There are no comparators, approved Rxs as benchmarks

When and how do brain metastases occur?

- Clinical
  - First presentation of metastatic disease (~20% of pts?)
  - At time of progression on first Rx for metastatic disease [not well quantitated]
  - During response to $\geq$ first-line therapy for metastatic disease [escape metastases]
- Biological
  - Subset of original clone, thriving in CNS by natural selection after clonal evolution?
  - In response to circulation through CNS and exposure to local factors



Tumor cells that metastasized to brain have distinct molecular features

Non-CNS metastases

Non-CNS metastases

Model 4: brain mets arise from a distinct subclone of cells at an intracranial metastasis that accumulates additional molecular alterations by interaction w/ brain microenvironment

Model 1: brain mets arise from subclone of cells in 1^{o} with identical characteristics

Model 2: brain mets arise from distinct subclone of cells in 1^{o} that accumulates additional molecular alterations due to interactions with brain micro-environment

Model 3: brain mets arise from a subclone of cells in an extracranial met with identical characteristics

Chen G, Davies MA
Biochem Pharmacol 2012

Melanoma brain metastases

- Highest risk of brain metastases among solid tumors but lower prevalence
  - 10-20% at diagnosis of stage IV
  - Up to 50% over course of disease
  - Up to 70% in autopsy studies
  - Common initial site of treatment failure
  - Rare variations—immune control elsewhere?
    - Sole site of mets after primary controlled
    - Can occur very late
    - Rarely brain met(s) without known primary
- Historically median OS ~ 4 months, now longer,depending on size, #, Rx

Lung cancer brain metastases

- Highest incidence of brain metastases as incidence x frequency
  - Associations with subtypes
  - Therapy responsiveness
  - Not as common at initial dissemination as melanoma
- Historically median OS ~ 4-6 months, depends on subtype, Rx
- Concept of BBB, brain TME
  - Variably permeable in metastases, with abn vessels
  - Other factors impact therapy responsiveness
- Radiation
  - SRS
  - WBRT

Breast cancer brain metastases

- More common with longstanding metastatic disease
  - Associations with subtypes—triple-neg, Her2-positive
  - Therapy responsiveness—multifactorial
  - Historically median OS ~ 4-8 months, depends on subtype, prior Rx
- Concept of BBB, brain TME
  - Variably permeable in metastases, with abn vessels
  - Other factors impact therapy responsiveness

- For all clinical management and protocol design strategies (objectives and measurement of effect), it is critical to identify the “driver” of prognosis and indicators of clinical benefit.

Clinical trial design TODAY

- Sequencing vs simultaneous modalities—must study *prospectively*
- All of the principles of slide 1 must be considered
- Challenges in the imaging define value of endpoint assessment
  - Timing, specific types of imaging
  - Tumor size/alterations in appearance
  - Peri-tumoral edema
  - Intra-/peri-tumoral hemorrhage
  - New lesion(s)
  - CNS vs extracranial tumor
  - Radionecrosis from prior SRS

ASYMPTOMATIC AT DX OF METASTATIC DISEASE	SYMPTOMATIC, AT DX OF METASTATIC DISEASE
ASYMPTOMATIC, AT PD TO SYSTEMIC THERAPY	SYMPTOMATIC, AT PD TO SYSTEMIC THERAPY
ASYMPTOMATIC, DURING RESPONSE TO SYSTEMIC THERAPY	SYMPTOMATIC, DURING RESPONSE TO SYSTEMIC THERAPY
ASYMPTOMATIC, NO EXTRACRANIAL DISEASE	SYMPTOMATIC, NO EXTRACRANIAL DISEASE

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

Lancet Oncol 2018; 19: e20–32

Patients with active CNS disease are often excluded from clinical trials, and data regarding the CNS efficacy of