Session III:
Clinical Benefit in Patients with Brain Mets

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Regulatory Challenges With Trials Seeking CNS Efficacy Claims

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Overview of Challenges

- Efficacy Endpoints
- Eligibility Criteria
- CNS imaging
- Assessment of CNS lesions
- Criteria to assess CNS response
- Study design

Efficacy Endpoints: Challenges

- FDA approval is based on demonstration of clinical benefit (improvement in survival or how a patient feels or functions)
- Demonstration of effects on survival or quality of life require randomized trials – current trials not designed to show such effects
- Effects on tumor in one organ site (e.g., CNS-ORR or CNS-PFS) may not confer clinical benefit in a systemic disease

Eligibility Criteria: Challenges

Considering the efficacy endpoints chosen,

Should patients with CNS metastases be eligible if they

- Are asymptomatic?
- Were locally treated & are stable at study entry?
- Have no neurological dysfunction at study entry?
- Are not receiving corticosteroids at study registration?

Should patients be excluded if they have

- Untreated, symptomatic brain metastases?
- Leptomeningeal involvement?
- Have no assessment for CNS involvement at study entry?

CNS Imaging: Challenges

- Requirement for baseline CNS imaging and documented CNS disease in all patients limits eligibility
- On-treatment evaluations: CNS imaging assessments generally not scheduled at same frequency as extracranial disease assessments –leading to high censoring rates for CNS tumor endpoints.

Assessment of CNS Lesions: Challenges

- Discordance between investigator assessment and Independent Review Committee (IRC) categorizing measurable and non-measurable lesions –higher rate of discrepancy in CNS-ORR between investigator & IRC than for systemic disease.

- Lack of agreed-upon criteria for selection of CNS lesions that have been previously radiated as target lesions (e.g., time from previous irradiation to study entry) – challenges in attribution of treatment effects to study drug

Assessment of Intracranial (IC) Response - Challenges

- Lack of agreement on optimal criteria for IC response
  - RECIST v1.1 supported by RANO ± RANO LM
  - RANO ± RANO LM alone

Study Design: Challenges

- Randomized trials not stratified by
  - presence or absence of brain metastases
  - treated vs untreated brain metastases
- Lack of justification for sample size, prespecified assumptions of treatment effects, prespecified analysis plan and Type I error control.
- High rate of censoring due to systemic progression - what is the clinical benefit of IC ORR in the face of systemic progression?

Further Discussion….

Given that trials must demonstrate the clinical benefit of treatment

- What endpoint(s) would capture clinical benefit of treatment focused on involved site of a systemic disease?
- Who should be included in trials seeking claims for treatment of patients with CNS metastases ?
- Appropriate criteria (RECISTv1.1 alone vs RECIST+RANO BM/LM) to characterize clinically important reduction in intracranial metastases.
- Adequately designed trials to support claims attributable to IC ORR independent of effects on systemic disease.