Session III: Clinical Benefit in Patients with Brain Mets

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The Multiple Facets of Clinical Benefit

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Workshop on Product Development for Brain Metastases
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• I have no financial conflicts
Approval Pathways and Endpoints

• **Traditional approval**
  • Clinical Benefit Endpoints or Established Surrogate Endpoints
  • *Prolongation of life, a better life or an established surrogate*

• **Accelerated approval**
  • Endpoints other than irreversible morbidity or mortality
  • "*Surrogate endpoint “reasonably likely” to predict clinical benefit*"
  • Residual uncertainty regarding clinical benefit
  • Post-marketing trials needed to verify benefit
Strength of Efficacy Endpoint Results

• **What** is being Measured? *(Endpoint Selection)*
  • Direct Benefit (Feels/Functions/Survives) considered more meaningful

• **How** accurately is it being measured? *(Measurement Characteristics)*
  • Accuracy of the measure
  • Susceptibility to Bias
  • Accuracy of the Timing of the Event

• **How Much** effect on the endpoint is observed? *(Magnitude of Effect)*
How is the efficacy endpoint measured?

- How much interpretation / subjectivity?
  - More interpretation / subjectivity = more risk for bias / variability

- Prevent Morbid Procedure:
  - rPFS (PCWG-2): Interpret two new lesions on a bone scan
  - PFS: Interpret target lesion increases by 20%
  - Survival: No interpretation required
## No Free Lunch: Strengths and Limitations of Endpoints

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<thead>
<tr>
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<th>Clinical Outcome</th>
<th>Low Risk of Bias</th>
<th>Feasibility</th>
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<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td><img src="#" alt="Green Plus" /></td>
<td><img src="#" alt="Green Plus" /></td>
<td><img src="#" alt="Red X" /></td>
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<tr>
<td><strong>Tumor Endpoints</strong></td>
<td><img src="#" alt="Red X" /> / <img src="#" alt="Green Plus" /></td>
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<tr>
<td><strong>Clinical Outcome-PRO</strong></td>
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<td><strong>Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)</strong></td>
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Benefit is More than Efficacy

- Efficacy
- Safety
- Clinical Context
Tumor Location is Important

• Shrinkage of a likely asymptomatic pelvic lymph node may or may not predict an improvement in patient symptoms or survival…
**Where are the tumors that are responding?**

When “Response Rate” may be considered Clinical Benefit...

- Near complete responses of disfiguring or fungating skin lesions are a different context:

  *Vismodegib Response.*
  
  *Von Hoff et al., NEJM, 2009; 361: 1164-72*

  *Depsipeptide Response.*
  
  *Piekarz et al., JCO, 2009; 27: 5410-5417*
Totality of Data- Abiraterone

- COU-302 trial- co-primary PFS and OS
  - Large statistically significant PFS advantage
  - Nonsignificant trend for benefit on OS
  - Time to cytotoxic chemotherapy was delayed
  - Time to first opiate use was delayed
  - Time to PRO pain also supportive
  - Time to ECOG decline supportive
  - Favorable safety profile
  - Not an NME, survival and safety demonstrated in earlier trial

Brain Metastases and Evaluating Clinical Benefit

**Tumor Response**
- Location
- Depth of Response
- Duration of Response

**Clinical Outcomes—symptoms and function**
- Survival
- Cognitive and Physical Function
- Pain
- Ability to carry out usual activities

**Clinical Outcomes—events and need for treatment**
- Avoidance of:
  - Steroids
  - Cranial radiation
  - Opiate pain meds
  - Seizure Reduction
Message

- There is no perfect efficacy endpoint, they all balance meaningfulness with risk for bias and/or feasibility
- ALL available data are used to determine clinical benefit
- Radiographic response rate may be more meaningful in certain locations (brain, skin, joints) given higher likelihood of functional/cosmetic impacts
- Technology is facilitating better direct measurement of symptoms and function (#ePRO, #wearables, etc.)
Background Slide: Terminology

- **Surrogate Endpoint**- a substitute for a clinical outcome, intends to *predict* a clinical benefit
- **Clinical Outcome**- an outcome that describes how one “feels, functions or survives”

- **Clinical Outcome Assessment**- direct measure of how an individual feels or functions
  - Performance Outcome (PerfO) – e.g. 6 min walk
  - Patient-Reported Outcome (PRO) – e.g. pain questionnaire
  - Observer Reported Outcome (ObsRO) – e.g. parent observing vomiting episodes
  - Clinician-Reported Outcome (ClinRO) – e.g. myocardial infarction

- **Clinical Benefit is a positive meaningful effect of an intervention**
  - Clinical benefit is supported by more than one single endpoint
  - Totality of data (efficacy safety and context)