Session III:
Clinical Benefit in Patients with Brain Mets

Carey Anders, MD, Co-Chair, Duke University

Tatiana Prowell, MD, Co-Chair, US Food and Drug Administration

The Multiple Facets of Clinical Benefit

Paul G. Kluetz, M.D.
Oncology Center of Excellence

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?

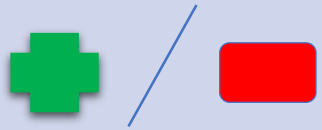
- How much interpretation / subjectivity?
  - More interpretation / subjectivity = more risk for bias / variability

High Bias Potential

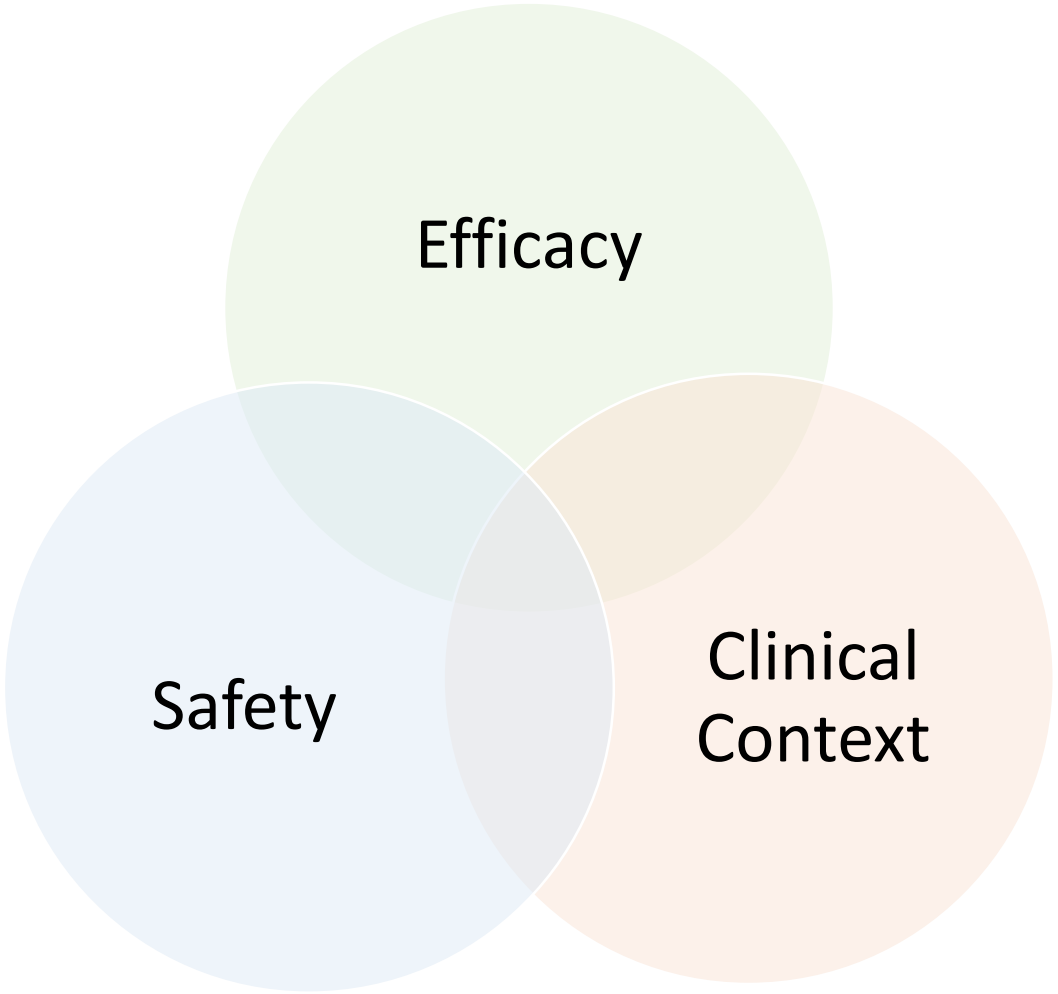
Low Bias Potential

- 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

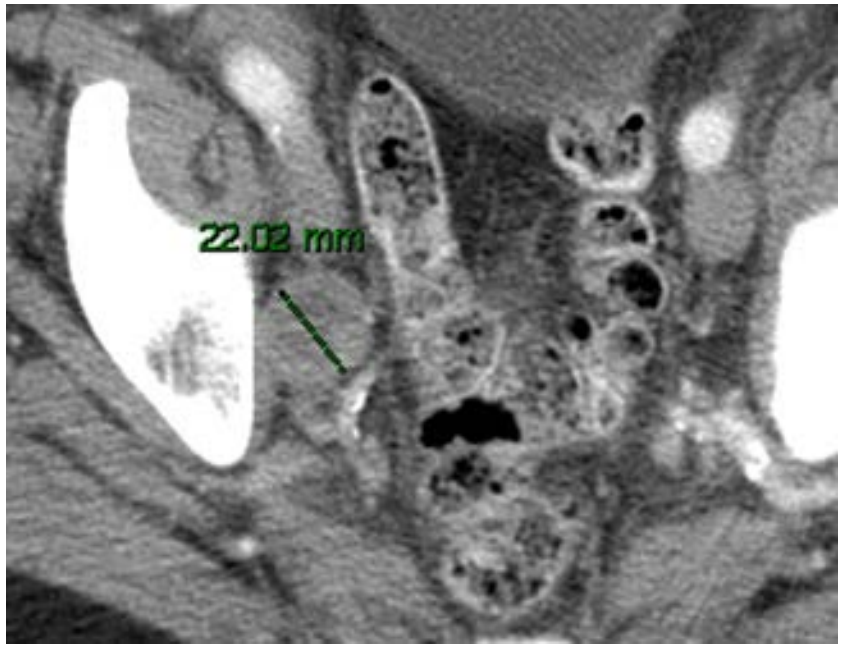
	Clinical Outcome	Low Risk of Bias	Feasibility
Overall Survival			
Tumor Endpoints			
Clinical Outcome-PRO			
Clinical Outcome-Reduction in Healthcare Utilization (e.g. Steroid Use, morbid procedure)			

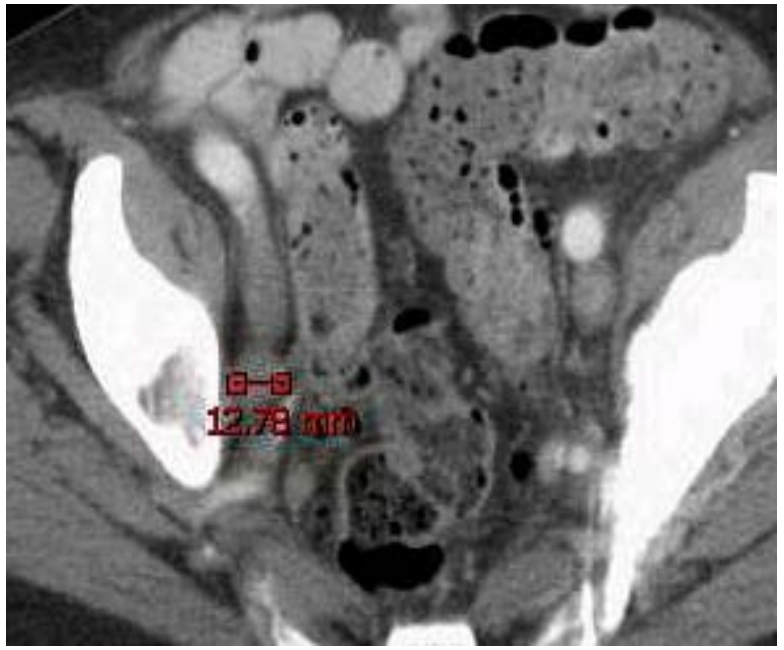
Benefit is More than Efficacy



Tumor Location is Important

•Shrinkage of a likely asymptomatic pelvic lymph node may or may not predict an improvement in patient symptoms or survival…

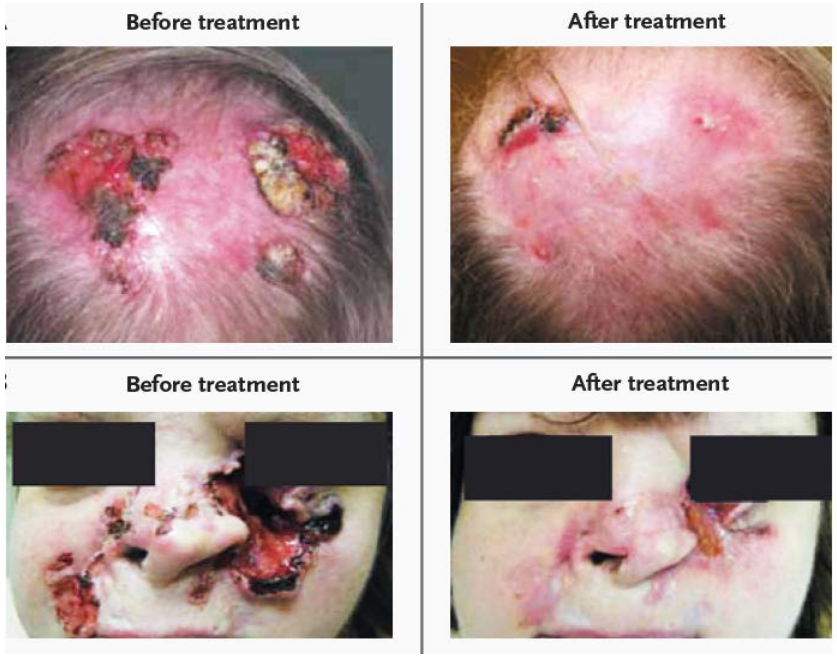




Where are the tumors that are responding?

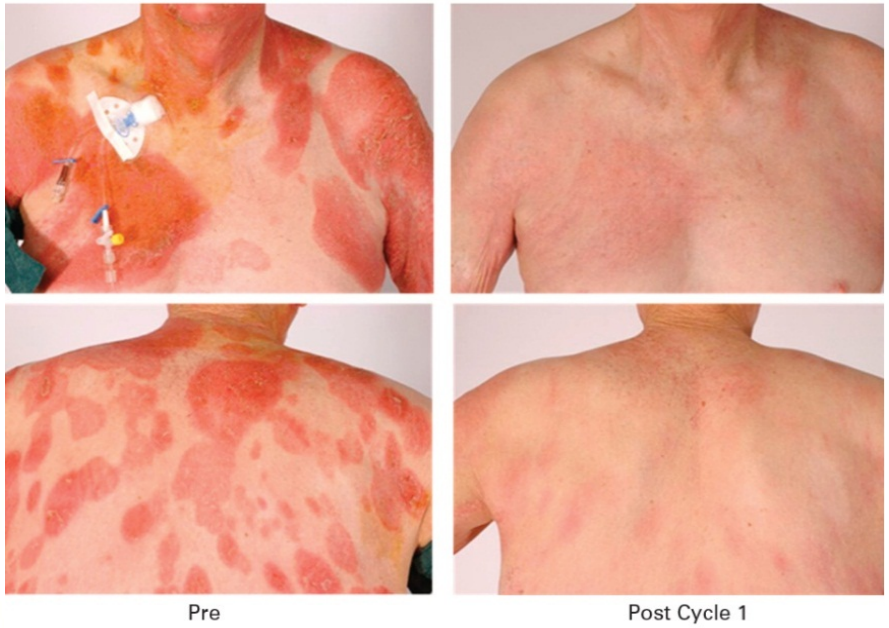
When “Response Rate” may be considered Clinical Benefit…

•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

Ryan et al. NEJM 2013 https://www.nejm.org/doi/full/10.1056/NEJMoa1209096

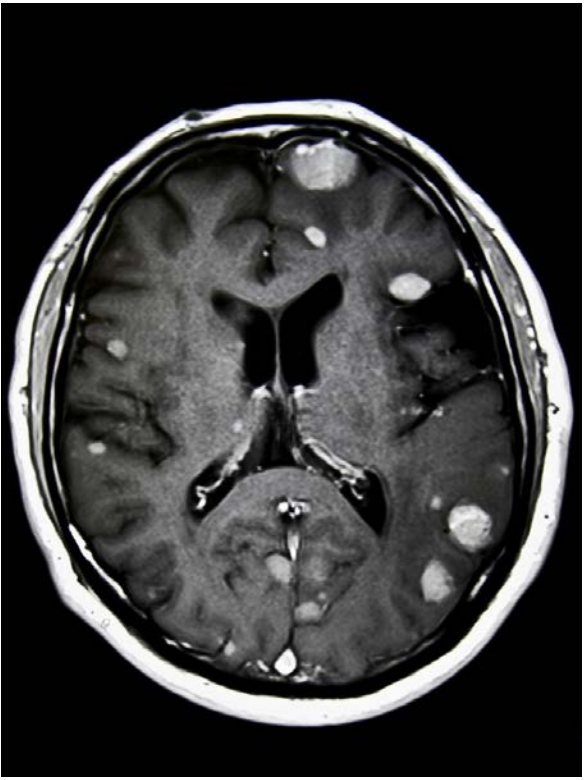
Brain Metastases and Evaluating Clinical Benefit

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)

BEST (Biomarkers, EndpointS, and other Tools) Resource- https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-P