Regulatory Background

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Outline

- Requirements for Drug Approval
- Cancer Approval Endpoints
- Primary Brain Cancer Approvals
- Questions to Panel

Requirements for Drug Approval

Labeling	1906 Pure Food & Drug Act
Safety	1938 Food, Drug, & Cosmetic Act (FDC)
Efficacy	1962 FDC Amendments

Endpoints Supporting Approval

- Regular approval ~ Clinical benefit
  - Longer life
  - Favorable effect on valid measure of how patient feels or functions
  - Favorable effect on accepted surrogate
- Accelerated approval ~ Surrogate
  - *reasonably likely* to predict clinical benefit

Accelerated Approval

- Serious or *life-threatening* disease
- *Improvement* over available therapy
- Surrogate endpoint *reasonably likely* to predict clinical benefit
- Requires *confirmation* of benefit

Oncology Surrogates

For Regular Approval	Disease
• Durable complete response	Acute leukemias
• Partial response (PR)	Advanced breast
• Disease free survival (PRS)	Adjuvant breast
For Accelerated Approval	
• Response rate with duration	Solid tumors

Survival

Time from randomization to death

- *Strengths*
  - Unambiguous, daily assessment
  - Not subject to investigator interpretation
- *Limitations*
  - Requires large sample size, long follow-up
  - Cross-over therapy may wash out effect
- *Trial design considerations*
  - Randomized trials required to show an effect
  - Likelihood and magnitude of survival benefit

Radiographic Response Rate

- *Strength*
  - Treatment “entirely” responsible for tumor reduction (contrast survival or PFS w/ natural history component)
- *Limitations*
  - Need for response duration component
  - Issues: CR’s vs. PR’s vs. SD; burden of disease
- *Trial design considerations*
  - Only endpoint reliably assessed in single arm trial
  - Prospectively identified, acceptable response criteria
  - Complemented by symptom improvement

Progression-Free Survival

Time from randomization to progressive disease or death

- *Strengths*
  - Smaller size & shorter follow-up than for survival
  - Differences not obscured by secondary therapy
  - Deaths included in events
- *Limitation*
  - Greater potential for bias than with survival endpoint
- *Trial design considerations*
  - Randomized, blinded trials required to show an effect
  - Must evaluate at baseline and regularly on follow-up: all patients with same tool / schedule / sites of disease

Symptom Palliation

- *Strength*
  - Patient's perspective
- *Weaknesses*
  - Missing data confound interpretation
  - Multiple endpoints affect statistical power and plan
  - Unblinded assessments invite observer bias
- *Trial design considerations*
  - Randomized, blinded trials required to show an effect
  - Requires hypothesis driven, valid instrument
  - Associated tumor response supportive of clinical benefit

Brain Cancer Approvals

Drug	Year	Endpoint
Nitrosoureas	1970's	Response rate
Gliadel wafer	1996	Survival
Temozolamide	1999	Durable CR
	2005	Survival

Temodar (temozolamide) Indications

- Anaplastic astrocytoma after nitrosurea & procarbazine
  - Basis of accelerated approval:
    - Single-arm trial (54 patients); 22% response rate; **5 CR's**, 7 PR's
    - Median response duration 50 weeks, **CR duration 64 weeks**

- Newly diagnosed glioblastoma multiforme
  - Basis of approval (and conversion of above accelerated approval):
    - EORTC randomized trial (573 patients)
    - Standard fractionated XRT versus XRT with daily Temodar (75 mg/m^2) during XRT followed by 6 cycles maintenance Temodar over 6 months
    - Median survival 14.6 months (T + XRT) vs. 12.1 months (XRT alone)
    - Hazard ratio 0.63 (95% CI 0.52-0.75); log-rank, P < 0.0001

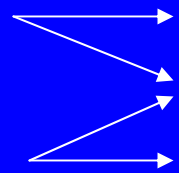
Gliadel Wafer Indications

- Recurrent glioblastoma multiforme as adjunct to surgery
  - Basis of approval:
    - Randomized, placebo-controlled trial of Gliadel vs. placebo implants in 222 glioma patients who progressed following surgery and radiation
    - Median survival 7.4 months (Gliadel) vs. 5.5 months (placebo)
    - Of 143 patients with GBM, median survival 6.4 vs. 4.6 months

- Newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation
  - Basis of approval:
    - Randomized, placebo-controlled trial in 240 patients with newly-diagnosed, high-grade glioma undergoing resection craniotomy
    - Median survival 13.9 months (Gliadel) vs. 11.6 months (placebo)
    - Hazard ratio 0.73 (95% CI 0.56-0.95); log-rank, $P < 0.05$

Workshop Agenda

- Potential Endpoints
  - Imaging Based
  - Patient Reported



Questions

Analytic Validity

Clinical Relevance

- General Discussion
  - Utility of individual endpoints?
  - Utility of composite endpoints?
  - Endpoint development?

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