What are the regulatory issues that impact endpoints for prevention trials?

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United Goal

- Development of safe and effective treatments for prevention/reduce the risk of acute graft versus host disease

Basis for NDA Approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies
- Ability to generate product labeling that
  - Defines an appropriate patient population for treatment with the drug
  - Provides adequate information to enable safe and effective use of the drug

Requirements for Drug Approval

- Safety (FDAC, 1938)
- Efficacy demonstrated in adequate and well controlled studies (1962)

NDA - Efficacy Requirement

- Regular approval
  - clinical benefit or established surrogate
- Accelerated Approval
  - uses a surrogate endpoint reasonably likely to predict clinical benefit
  - requires subsequent confirmation of benefit

Accelerated Approval Regulatory Basis

- For serious or life-threatening diseases
- Where the drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit

Accelerated Approval (continued)

- Subject to the requirement that the applicant verify and describe benefit
- Post-marketing studies would usually be underway
- The applicant shall carry out such studies with due diligence

Accelerated Approval

- Trial designs to demonstrate benefit over available therapy
  - In refractory settings: single arm trials
  - In available therapy settings: comparative trials
- Post-approval confirmation of benefit
  - related (less refractory) population
  - could use same trial/population (HIV example)

Evidence for Accelerated Approval

- Substantial evidence from well controlled clinical trials regarding a surrogate endpoint
- NOT: Borderline evidence regarding a clinical benefit endpoint

Clinical Benefit

- Improvement in quantity of life
- Improvement in quality of life

How many trials?

- Usually more than one trial is needed.

  Substantial evidence: “Adequate and well-controlled investigations”

- Sometimes a single trial may suffice.
  - FDAMA (1997) single trial plus other supportive evidence
  - 1998 FDA Effectiveness Guidance:
    - Multicenter trial
    - Statistically strong evidence
    - Important clinical benefit
    - Additional trials not ethical

Established Surrogates Supporting Regular Approval in OODP

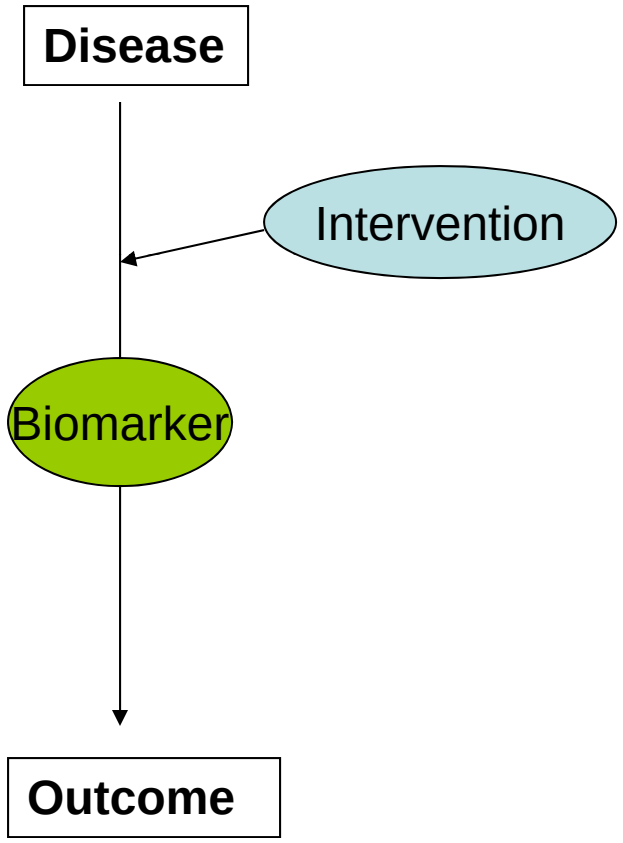
- Disease-free survival (selected settings)
- Durable complete response rates in some settings (e.g., acute leukemia)
- Partial response rates in some settings (e.g., hormonal treatment of breast cancer)

Biomarkers

- Useful for diagnosis of disease, prognosis for outcome, predictive of response, or monitoring during therapy
- Useful for measure of disease process or the drug activity on disease process

Biomarkers continued

- As a study endpoint, the effect of the drug on the clinical endpoint is reliably predicted by the effect of the drug on the surrogate biomarker (Fleming TR, 2003)



“Prevention” Trials

- Link between putative mechanism of action and disease?
- Consider what you are really able to show (what does the agent really do)
  - sufficient evidence from non-clinical or
  - early clinical testing?

“Prevention” Trials

- Randomized, double-blind if possible, comparator trials -- not single arm trials
  - Historical controls problematic
  - Need to provide patient and physician with an accurate understanding of risks and benefits

“Prevention” Trials continued

- Claim sought influences enrollment population
- Patient population
  - At risk (reasonably)
  - Well-defined
- Stratified randomization between treatment and placebo arms
- Balanced arms for known and unknown factors

“Prevention” Trials continued

- Endpoint is the prevention of the disease (not an aspect of disease)
- Endpoint chosen
  - what is known scientifically
  - study drug administration
- Absence of disease
  - Use established criteria if possible (or likely to be accepted by a majority)
  - If cannot double blind trial– consider blinded assessors

“Prevention” Trials continued

- Novel endpoints and development plans – FDA may get outside external consultants
- Statistical Analysis Plan
  - Well thought out ahead of time
  - Hierarchical testing for primary and secondary endpoints
  - Intention to Treat analysis
- One trial or more than one ? – Supportive evidence

“Prevention” Trials

- Consider the impact of protocol amendments on outcome
- Ensure enrolled subjects are not taking part in another trial
- Adhere to established guidelines for clinical research (institutional and US government)

Relevant Guidances

http://www.fda.gov/opacom/morechoices/industry/guidedc.htm

- **Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products**
- **Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics**
- **E6 Good Clinical Practice: Consolidated Guideline**
- **E8 General Considerations for Clinical Trials**
- **E9 Statistical Principles for Clinical Trials**
- **E10 Choice of Control Group and Related Issues in Clinical Trials**
- **Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Draft)**
- **Formal Meetings With Sponsors and Applicants for PDUFA Products**

Issues Regarding GVHD Prevention Trials

- What are the sources of heterogeneity in the transplant population that impact the risk of acute GVHD and how do we manage these?
- Are the diagnostic criteria for acute GVHD suitably established?
- How long should the patients be monitored for acute GVHD?
- What endpoints denote clinical benefit?
- What endpoints are reasonably likely to predict clinical benefit?
- How do we assess clinical benefit endpoints statistically in the face of competing risks?

Speakers for Morning Session

GVHD Prevention Trial Design and Endpoints

Paul Martin, MD, Fred Hutchinson Cancer Research Center, Seattle, WA

Mary Horowitz, MD, MPH, CIBMTR, Milwaukee, WI

Statistical Considerations

Eric Leifer, PhD, NHLBI, Office of Biostatical Research, Bethesda, MD

Brent Logan, PhD, CIBMTR, Milwaukee, WI

Biomarkers

John Hansen, MD, PhD, Fred Hutchinson Cancer Research Center