Trial Designs in Oncology: Regular or Adaptive?

Diane C. Young, M.D.
Vice President and Regional Head Latin America
Novartis Oncology
November 11, 2010
Traditional Oncology Drug Development

Phase I
- MTD
- Safety

Phase II
- Activity

Phase III
- Efficacy Safety
Challenges to Traditional Oncology Drug Development Model

On average, bringing a drug to market requires:
  – $800 million to $2 billion USD
  – >10 years
  – acceptance of risk: <1/10 make it to the market

Many oncology drugs in pipeline – need to be able to use resources most effectively.
Challenges to Traditional Oncology Drug Development Model

• Issues with traditional Phase III clinical trials using frequentist statistical methodology
  – Lack of data on which to make good statistical assumptions
  – Pace of new knowledge: results of trial may be outdated when results come out
  – Most trials aim to answer only one question
Definition of Adaptive Design

• “A clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial”

Types of Adaptive Designs

• Phase I: CRM (continual reassessment method)
• Multiarm multistage trials (i.e. “pick the winner”)
• Use of intermediate endpoints
• Seamless Phase II/III design
Seamless Phase II/III Designs

• Combines Phase IIb (learning phase) with Phase III (confirmatory phase)
  – Selection decision and adjustment to trial are made on the basis of the Phase IIb results
  – All data from relevant cohorts are used
• Offers advantages of time savings, use of fewer patients, availability of longer follow up (from pts in learning phase)
Statistical Issues

• Statistical methodology for adaptive design (i.e. Bayesian approaches, modelling and simulation)
• Key issue is preservation of the Type I error rate
• Scope of adaptations and decisions must be prospectively established
• Requires ability to run multiple simulations (computing power)
Logistical Issues

- More upfront work required for statistical modelling to design trial
- Rapid data collection (preferably electronic data capture)
- Flexible drug supply
- Communication plan
  - Internal personnel
  - Sites
  - Randomization center
  - Health authorities
Recommended Procedures (PhRMA Working Group)

• Data Monitoring Committee adequately “firewalled” from study personnel
  – Reporting structure to Steering Committee and Sponsor pre-defined
  – Sponsor involvement is not desirable, but if necessary, needs to be carefully defined

• Evaluate planned adaptations for potential to convey information to others

Situations Not Appropriate for Adaptive Designs

• Study endpoints or outcomes have long follow up relative to the duration of the trial
• Lack of good surrogate endpoints for learning phase
Regulatory Guidance on Adaptive Trial Designs

**EMA**

**FDA**
- FDA draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)
General comments in EMA guideline

• Quotations:
  – “[Adaptive] design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards”
  – “This is especially welcome if at the same time the basis for regulatory decision-making is improved”
  – “even with the best knowledge from a carefully planned phase II programme, there may still be uncertainty at the beginning of phase III concerning various aspects of design or analysis”

• Conflict/contradiction of learning in a confirmatory study

• Adaptive Designs in confirmatory trials require a responsible approach.

• Adaptive Designs can be appropriate in justifiable situations of “difficult experimental situations”
  – not to rescue a poorly designed study.
FDA Draft Guidance

• FDA draft Guidance for Industry:
  – Scope mainly on confirmatory trials (‘adequate & well-controlled’) but includes exploratory trials
  – Very detailed guideline (50 pages vs EMA‘s 10 pages)
  – Draft issued Feb. 25, 2010

“Compared to non-adaptive studies, adaptive design approaches may lead to a study that:
  (1) more efficiently provides the same information,
  (2) increases the likelihood of success on the study objective, or
  (3) yields improved understanding of the treatment’s effect (e.g., better estimates of the D-R relationship or subgroup effects).”
FDA Draft Guidance: Definition of Adaptive Design Study

• **IS**
  - “a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. … at prospectively planned timepoints … fully blinded manner or in an unblinded manner”

• **IS NOT:**
  - Unplanned analyses & changes to design
  - Interim changes to design due to entirely external data
“Well-understood” Adaptive Designs

• Examples of adaptations
  – Eligibility criteria, based on \textit{blinded} baseline data
  – Sample size adjustment, based on \textit{blinded} interim data
  – Adaptation unrelated to efficacy, based on \textit{unblinded} interim data
    • (e.g. dose discontinuation purely for safety)
  – Study termination for futility or demonstrated efficacy, based on \textit{unblinded} interim data
    • (?enough safety; ?enough power for subset analyses)

• Still need to avoid inflating type I error and bias
“Less well-understood” Adaptive Designs

• Based on unblinded interim analyses of treatment effect

• Examples
  1. Termination of selected dose arm(s)
  2. Randomisation to selected groups (mainly for exploratory trials)
  3. Sample size adjustment for treatment effect
  4. Population adjustment for treatment effect (balance issues)
  5.Endpoints (order of 1° & 2°, change to 1°)
  6. More-than-one design feature (creates complexity)
  7. Non-inferiority studies with 2° superiority analysis (sample size; but not non-inferiority margin)
FDA and EMA View of Adaptive Designs

- EMA and FDA guidances are very aligned
- Clear common areas for attention
  - Type I error control
  - Rigorous planning
  - Data confidentiality at interim
  - Limit number & frequency of changes
- Some adaptations well-accepted, others more risky
- Agencies invite sponsors to come for advice
When Are Adaptive Designs Being Used Currently

• Dose finding in early drug development
• Phase II exploratory studies to identify potential agents for Phase III studies
• Seamless Phase II/III designs
I-SPY-2 Trial
Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis

- Biomarkers Consortium: public-private partnership: FDA, NIH, Pharma, Academic Centers under the auspices of the NIH Biomarkers Consortium

- Objectives
  - Determine activity of novel therapies in neoadjuvant breast cancer
  - Test, validate, and qualify biomarkers
  - Adaptive trial design permits efficient learning
  - Bioinformatics and infrastructure for efficient conduct

I-SPY 2 Trial

• Phase II trial in neoadjuvant breast cancer
  – Investigators evaluate success of drug-biomarker combination (predictive Bayesian probability of success in Phase III)
    • Drop ineffective drugs
    • Drugs more effective than standard therapy go into a small Phase III focused on patients who are likely to benefit
    • New drugs can be added

I-SPY 2 Trial

Adaptive Designs: PRO

• May make clinical trials faster, cheaper, more efficient (fewer subjects)
• May increase probability of success (ensure adequate power)
• More information from the trial
• Better dose selection and toxicity characterization in Phase I
Adaptive Designs: Cons

- Regulatory precedents are limited: will they be acceptable for approval?
- Potential to introduce bias
- Seamless Phase II/III: lack of information on predictability of early endpoints, biomarkers
- More upfront work and planning: clinicians, biostatisticians, IT, drug providers, regulatory
- Complex designs may be difficult to explain to sites, regulators
Conclusion

• Adaptive trial designs are being increasingly used in oncology drug development
  – Clear advantages in earlier phases of drug development (Phase I and II)
  – Use in registration trials more challenging

• Successful implementation of adaptive trial designs requires changes to clinical trial infrastructure and processes