Accelerating Phase II-III Oncology Drug Development Through the Use of Adaptive Designs

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Outline of Presentation

- Oncology Background
- Stopping Early for Futility or for Success
- Reassessing Sample Size and/or Study Duration
- Practical & Regulatory Considerations
- Adaptive Design for Time-to-Event Data When Hazards are Non-Proportional
- Phase II/III Combination Designs Incorporating Treatment Selection & Testing
- Phase II/III Designs for both Accelerated Approval & Full Approval

Need for More Use of Adaptive Designs in Cancer Drug Development

- FDA's March 2004 "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products"
  - calls for advances in clinical trial design and analysis
- IBM's Pharma 2010: The Threshold of Innovation
  - foresees "greater use of Adaptive Trials - where information acquired during a particular trial is used to alter the course of the same trial without compromising its statistical validity"

Need for More Use of Adaptive Designs in Cancer Drug Development, cont'd

- **400+ New Molecules for Cancer** currently in clinical development [PhRMA data]
- **81 Months Average Time** from IND to NDA for Anti-Neoplastics [Tufts, based on 1996-1998]
- **Only 29% Oncology Success Rate in Phase III** (and beyond)

  [CMR data on # get to mkt/# start a pivotal study, for NMEs in 95-99]

Typical Cancer Endpoints

- Response Rate (RR) - proportion with CR or PR
  - often used for accelerated approval, sometimes for full approval
- Time to Death (TTD)
  - particularly for cytotoxics in 1st line therapy
- Time to Progression (TTP)
  - e.g., for hormonal products in breast cancer + possibly for cytostatics and for cancer vaccines
- Disease-Free Survival (DFS)
  - for certain adjuvant treatments

Hirschfeld & Pazdur (2002), Schilsky (2002), Johnson et al (2003), Simon et al (2001)

Stopping for Futility in Phase III

- Many Approaches to Futility Assessment [Dignam et al, 2001]
  - Power family boundaries, Triangular test boundaries
  - Conditional Power (CP) based methods
- Practicality of Stopping for Futility in Oncology with Time-to-Event primary endpoints
  - Most useful if able to stop trial before all patients have been enrolled
  - Not practical if all patient treatment is over before many events occur, e.g., certain adjuvant trials

Stopping Cancer Trials for Early Demonstration of Efficacy

- Some recent examples:
  - MabThera (rituximab) phase III in relapsed indolent NHL met its primary endpoints (RR and TTP) at an interim - study **stopped 2 yrs early** [Apr. 2004 press rel.]
  - Velcade (bortezomib) phase III in multiple myeloma met its primary endpoint (TTP) at interim - **stopped 1 yr early** [Dec. 2003 press rel.]
  - Irinotecan phase III in metastatic SCLC met its primary endpoint (TTD) at 2nd interim after enrolling **154/230 pts** [Noda et al, 2002]

Stopping Cancer Trials for Early Demonstration of Efficacy, cont'd

- Type 1 Error control for multiple looks
  - usually via O'Brien-Fleming boundary
  - other boundaries sometimes preferable, e.g., Wang & Tsiatis with $\Delta = 0.1$ or 0.2 can give greater chance of stopping early
- Timing of Interims
  - often includes 2 or 3 equally spaced looks
  - important to consider safety database size (for s/t and l/t data) when determining timing of 1st interim

Stopping Cancer Trials for Early Demonstration of Efficacy, cont'd

- Consider power for key secondary efficacy parameters at interims
- Ensure that design still performs well if effect size is slightly over-estimated
- Useful to incorporate covariate adjustment at each look
  - Can increase chance of stopping at earlier interim
  - Can help overcome problems due to important imbalances at early looks

Fixed Number of Events, Fixed Duration, & Alternatives

- With time-to-event primary endpoints, trials have usually been set up as either:
  - Each look at a set time - Maximum Duration Trial (MDT)
  - Each look at a set # of events - Maximum Information Trial (MIT) under logrank test
- MDT could easily be under- or over-powered and so MIT is generally preferred

Approaches to Group-Sequential Trials When the Hazards may be Non-Proportional

- MIT could lead to Early Interims having Too Few Pts with L/T Follow-up [O'Neill, 1994]
  - Particularly problematic if hazards are not proportional
- Approach that would be more robust to non-proportional hazards
  - Set up Interim #1 at later of X% of events or Y% of patients followed for 12 months
- Weighted Logrank Test may be more appropriate to reflect anticipated shape of survival curves
  - Can be used group-sequentially [Lawrence, 2002]

Approaches to Group-Sequential Trials When the Hazards may be Non-Proportional

- Alternatively, problem could be formulated in terms of:
  - Kaplan-Meier (KM) Estimate of Probability at 12m or 24m
  - (Weighted) Difference in KM Estimate over 0-24m interval
  - Difference or Ratio of the Medians
- Group-sequential testing is still possible in each case, but power comparison is needed

Sooriyarachchi & Whitehead (1998), Lin et al (1996), Simon (1994), Li (1999), Keeney & Wei (1994)

Sample Size Re-Estimation

- Blinded Sample Size Re-estimation (SSR) with time-to-event endpoints [Whitehead et al, 2001]
  - can be useful for fixed duration trials
- SSR based on Conditional Power (CP) at EOS given effect size at the interim
  - Anderson (1987), Henderson et al (1991) applied to Logrank & Gehan-Wilcoxon test
- Very many variants of SSR based on interim effect size developed over the last 10 years

Sample Size Re-Estimation, cont'd

- Type 1 Error control achieved by decreasing α or down-weighting patients after interim
  - Can save a study that may otherwise just fail to achieve statistical significance
    - Useful for this when carried out late-on
  - More efficient to use larger N at outset and build in interims [Tsiatis & Mehta, 2003]

Sample Size Re-Estimation, cont'd

- For any SSR procedure based on Interim Effect Size:

  Already Clear that:

  – Need to pre-specify fully in protocol, including method for Type 1 Error adjustment

  Less Clear under what circumstances it is fully acceptable to regulatory authorities when used to:

  – Increase only the # of patients

  – Increase the required # of events after enrollment is over

Stated Regulatory Preferences for All Types of Adaptive Design

- Show that Type 1 Error is controlled
- Fully pre-specify adaptive methods in protocol (designed flexibility)
- Have adaptation performed by an independent 3rd party
- Only unblind data that are essential for adaptation
- Ensure operational implementation avoids bias and restricts sponsor exposure to unblinded results

DSMB guidelines (2001), Hung (2003)

Phase II/III Combination Designs Incorporating Treatment Selection & Testing: Potential Role in Oncology

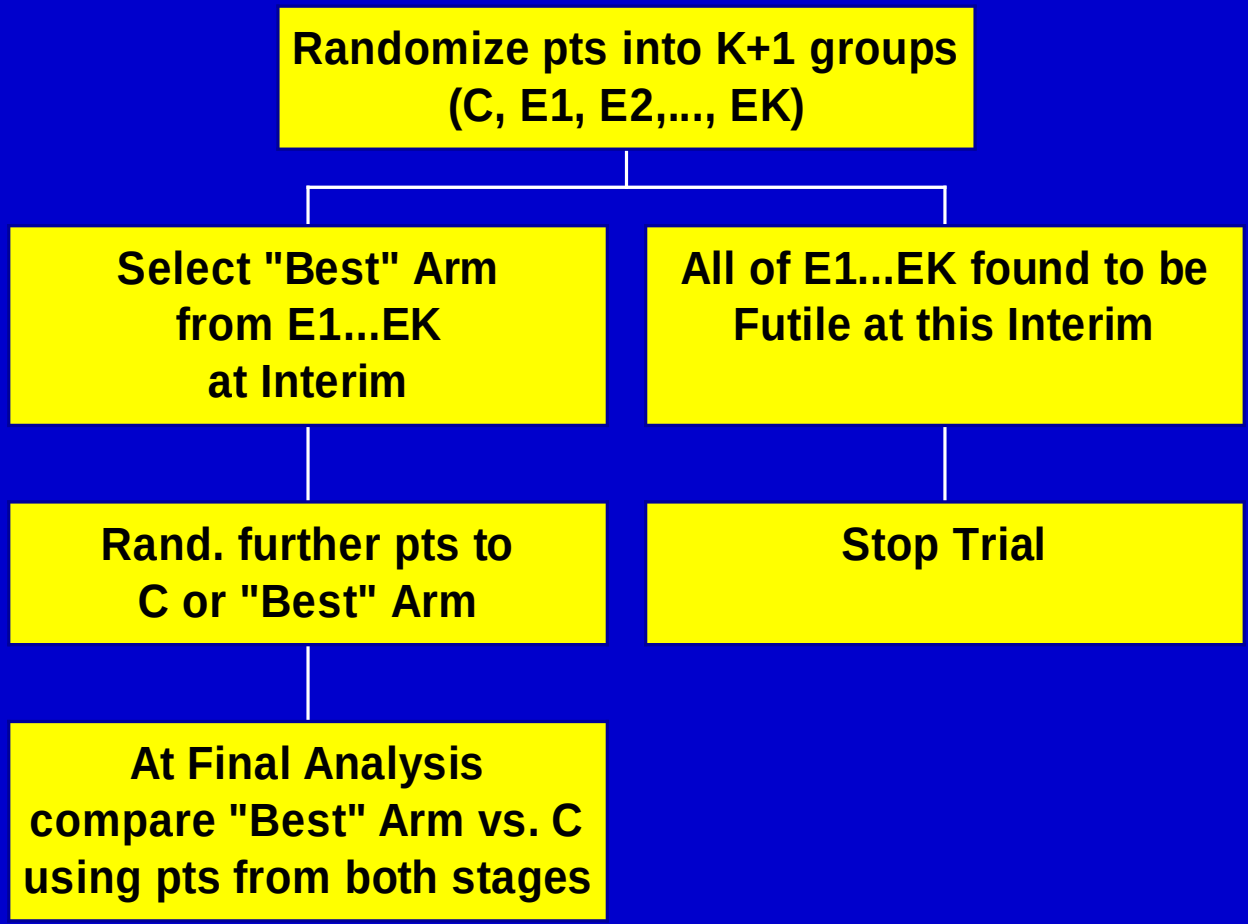
- In many cases the Experimental Arm(s) to Take Into Phase III are uncertain. We may need to decide on:
  - Different Dosing Regimens of the Same Drug
  - Different Combination Regimens
  - Different Doses of a Cytostatic
- Could carry out a Phase II randomized Selection design, but would likely cause time delays

Phase II/III Combination Designs Incorporating Treatment Selection & Testing, cont'd

- One alternative is to carry out a Phase II/III combination Design in which:
  - Selection Occurs at end of Stage 1
  - Final Testing based on Patients from Both Stages
- Niyikiza & Faries (2003), in a review of cancer trial design, state the following about such Phase II/III Designs

  "This attractive statistical methodology has not yet been fully leveraged ....in phase II/phase III cancer trial designs"

Phase II/III Combination Designs Incorporating Treatment Selection & Testing, cont'd



Thall et al (1988), Smith (2002, 2003)

Phase II/III Combination Designs Incorporating Treatment Selection & Testing, cont'd

- At end of stage 1, Experimental Arm with Highest Mean (or proportion, or hazard ratio) is Selected
- If highest mean does not exceed pre-defined cut-point, Stop for Futility
- Testing is carried out with reduced α at EOS to control Type 1 Error [α decreases with K]
- Phase II/III designs can give an Efficiency Advantage
  - Final Analysis is Based on Data From Both Stages for the 2 retained arms

Phase II/III Combination Designs Incorporating Treatment Selection & Testing, cont'd

- Variations on this theme:
  - Include/Exclude Control Group in Stage 1
  - Allow 2 (or more) Experimental Arms into Stage 2
  - Incorporate More than One Look for Efficacy Demonstration [Smith, 2002; Stallard & Todd, 2003]
  - Different Approaches to Producing "Optimal" Phase II/III
  - Possibly Incorporate Sample Size Re-Estimation

Note: Each approach has its own procedure in place to control type 1 error

Phase II/III Combination Designs Incorporating Treatment Selection & Testing By Type of Endpoint

- Binary Endpoint (e.g., RR) [Thall et al, 1988, 1989]
  - Here N for stage 1 is similar to conventional phase IIs
- Time-to-Event Endpoint based on Logrank Statistic
  [Schaid, 1990]
- Continuous Endpoint, but Fully Applicable to Binary and Time-to-Event Endpoints
  [Smith, 2002, 2003; Stallard & Todd, 2003; Soo et al, 2003; etc.]

Phase II/III Combination Designs: Practical Considerations

- Avoid using Phase II/III as an excuse for less clear objectives [Simon, 2004]
- Important to have some information prior to Phase II/III on how each arm performs in this pt population
  - Could obtain from a small pilot study
- May want to incorporate rules under which trial would stop to enable re-design of a new separate phase III

Phase II/III Combination Designs: Regulatory Considerations

- Request very early discussion with FDA if planning to use a Phase II/III combination design
  - Meeting in lieu of End of Phase II meeting?
  - Is Level of Evidence from a single Phase II/III trial (together with earlier trials in same or similar indication) sufficient?
  - Is it acceptable for trial to have a "Dose Selection Committee"? [totally separate from clinical team]
  - Other special considerations?

Phase II/III Combination Designs for Less Rapidly Progressive Cancers

- Previously discussed Phase II/III approaches work well when endpoint has relatively short median, e.g.,
  - TTD with metastatic RCC - medians 6m-8m
  - TTP for 2nd-line advanced breast cancer - medians 3m-6m
- Approaches can also work well with somewhat higher medians if accrual is relatively slow, e.g.,
  - TTD in extensive SCLC - medians 9m-13m
- Incorporation of selection component in phase II/III works less well with higher medians

Phase II/III Combination Designs for Less Rapidly Progressive Cancers, cont'd

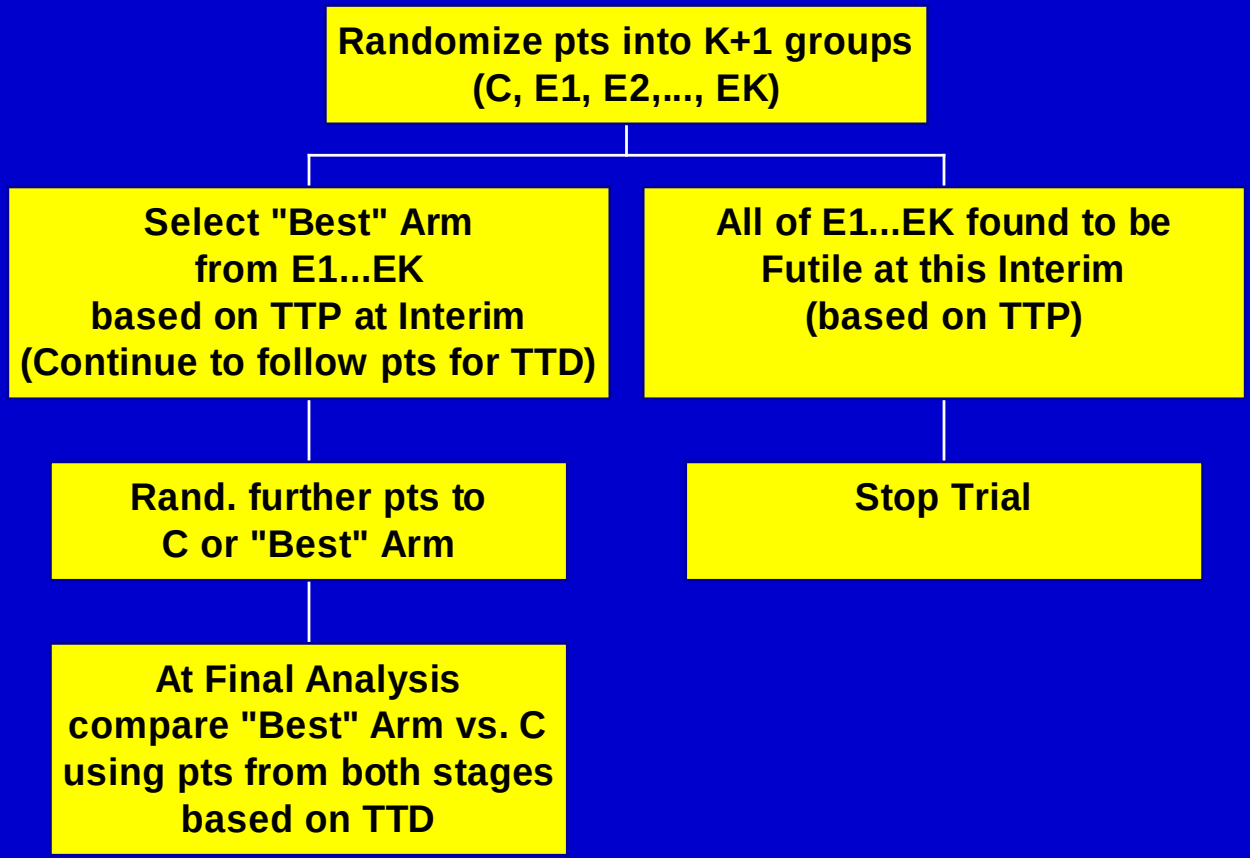
- Example - 1st line advanced ovarian cancer where full approval (for cytotoxics) will be based on TTD
  - TTD medians 24m-29m
  - TTP medians 10m-13m
- Royston et al (2003) considers the following approach to Phase II/III combination designs for this cancer:
  - Within stage 1, eliminate some arms based on TTP
  - Take "successful" arms into stage 2
  - At EOS assess based on TTD

Phase II/III Combination Designs for Less Rapidly Progressive Cancers, cont'd

- Modified version of Royston et al's approach - hybrid combining with approach of Smith (2002, 2003):
  - Incorporate full Type 1 Error control
  - Keep only 1 arm (or possibly extend to allow 2) at end of stage 1
  - Build in Futility stopping rule

Note: Inoue et al (2002) also developed a similar approach which they formulated within a Bayesian framework

Phase II/III Combination Designs Incorporating Treatment Selection & Testing, cont'd



Hybrid combining approaches of Royston et al (2003) & Smith (2002, 2003)

Phase II/III Combination Designs for Less Rapidly Progressive Cancers, cont'd

- Intermediate Endpoint (IE) could be used for Selection at end of Phase II stage when:
  - An IE exists that is highly correlated with the final Clinical Endpoint needed for full approval
  - IE occurs early enough to be practical for dose selection
- Actual choice of IE would vary by cancer type, stage, and drug class
  - TTP, RR (Proportion with CR/PR), Proportion with CR, or Proportion with PD could be considered in certain cases

Phase II/III Designs for both Accelerated Approval & Full Approval

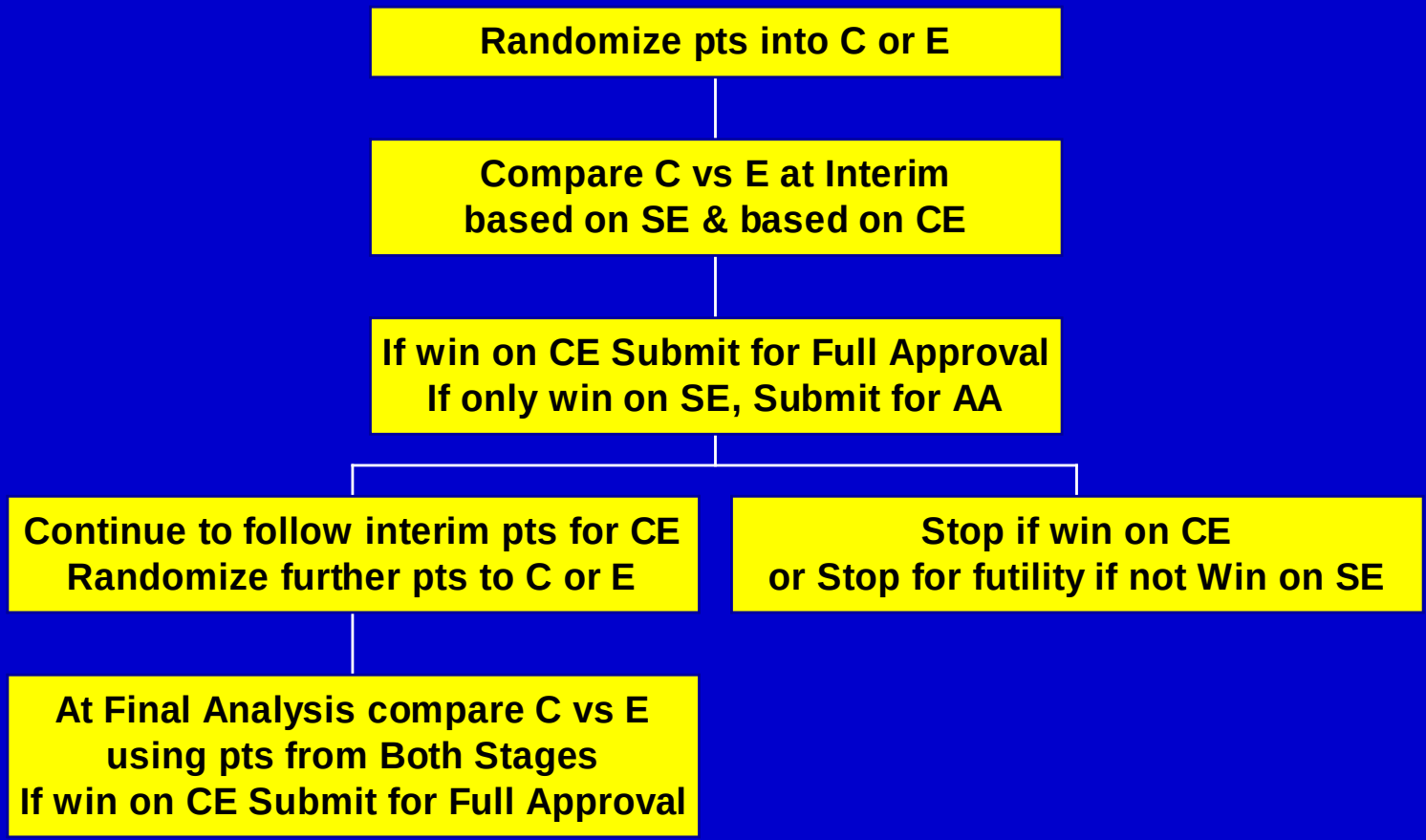
- Accelerated Approval (AA) can sometimes be granted based on a Surrogate Endpoint that is "Reasonably Likely to Predict" Clinical Benefit
- In oncology, AA based mostly on RR from 1 arm trial(s)
  - Later comparative trial required to demonstrate clinical benefit
- However, March 2003 ODAC meeting reported that only 4/19 AAs have so far met this post-approval requirement

  [Chi, 2003; Johnson et al, 2003]

Phase II/III Designs for both Accelerated Approval & Full Approval, cont'd

- Johnson et al (2003) advocates adopting paradigm used in AIDs trials
  - Use same randomized trial for AA and Full Approval
  - AA based on an Interim Analysis of the Surrogate
  - Full Approval based on Final Analysis using the Clinical Endpoint

Phase II/III Designs for both Accelerated Approval & Full Approval, cont'd



CE = Clinical Endpoint, SE = Surrogate Endpoint, AA = Accelerated Approval

Phase II/III Designs for both Accelerated Approval & Full Approval, cont'd

- Different approaches to T1E control in such trials given by Shih et al (2003) and by Chi (2003)
- This approach used for Oxaliplatin in 2nd line therapy for metastatic colorectal cancer
  - AA given based on surrogate (RR)
  - Trial continuing with aim to obtain Full Approval based on Survival

Concluding Comments on Use of Adaptive Design in Oncology

- Adaptive Design has Great Potential to Reduce Time in Oncology Drug Development
- It can, in some cases, Help Cut Attrition Rate and Cut Costs
- Some Problems that previously Limited its Use with Survival Endpoints can Now be Overcome or at least Reduced

Concluding Comments on Use of Adaptive Design in Oncology, cont'd

- Phase II/III Combination Designs that Incorporate Treatment Selection & Testing seem to hold Particular Promise
  - They can be applicable in even more cases if a Highly Correlated IE exists
- Phase II/III Designs of a different type (w/o trt selection) can be used for both AA & Full Approval instead of basing on separate trials