Practical Use of Innovative Design Approaches for Phase III Oncology Trials

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Outline of Presentation

- Introduction
- Traditional Interim Analysis for Efficacy or Futility: Time Saving through their Optimized Set Up
- Power Reassessment to provide Time Saving or Increased Chance of Success
- Regulatory Considerations for Adaptive Designs
- Phase IIB/III Combination Designs Incorporating Treatment Selection & Testing
- Phase II/III Designs for both Accelerated Approval & Full Approval

Need for Improved & Innovative Designs in Cancer Drug Development

- **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]
- **Oncology Drug's Failure Rate in Phase III is 59%**
  [Kola & Landis, 2004 based on data from 10 largest drug companies, 1991-2000]
  - CMR even quotes a **71% Oncology Failure Rate in Phase III**
    [based on # enter Ph III/# get to mkt - see Peck (2003)]

Need for Improved & Innovative Designs in Cancer Drug Development, cont'd

- 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
- FDA's March 2006 "Critical Path Opportunities List" calls for Advancing Innovative Trial Designs, incl.:
  - Greater use of (frequentist) Adaptive Trial Designs
  - More use of Bayesian methods in drug development
  - Development of New Trial Designs in Oncology

Emphasis Within this Presentation

- Focus of presentation on:
  - Design approaches to Reduce Oncology Attrition Rate (by increasing chance of meeting efficacy criteria for success)
  - Design approaches that can Cut Time (and Cut Costs)
- Late Stage Parallel Group Oncology Trials:
  - Phase III alone OR
  - Phase II/III Combined
- Primary Endpoint assumed to be Time-to-Event, e.g.,
  - Overall Survival (OS), Progression-Free Survival (PFS), or Disease-Free Survival (DFS)

Interim Analysis for Futility in Phase III

- Very important to identify early that a Ph III trial will be negative
  - Particularly important in oncology as previous trials may all have been single arm
- Practicality of Stopping for Futility in Oncology with Time-to-Event Primary Endpts
  - Most useful if able to stop trial before all patients have been enrolled
  - Cost savings can still be obtained by stopping study after enrollment has been completed
  - Could base on early endpt that is predictive of primary endpt

Interim Analysis for Futility in Phase III, cont'd

- Choice of Method for Futility Assessment is critical:
  - Needs to meet ethical needs of pts in the trial, and meet financial needs of company
  - Should have Minimal Negative Impact on Power if compound is truly efficacious
  - Traditional Conditional Power based approach at early look can be Very Misleading [see Hung(2005)]
  - Consider that a trial with "trend"(e.g., p=0.09) may be Useful Supportive Evidence
  - Consider possibility of Delayed Effect of Treatment

Interim Analysis for Early Demonstration of Efficacy

- Group-Sequential Designs (GSD) sometimes used in oncology as can Allow the Possibility of an Earlier Submission
- Changing their Set Up can often Give Large Gains
- Generally preferable to Define Interim Analyses (IAs) in Terms of Numbers of Events (NEs)
- Looks After Equal Propns of events is often Not the Best Option, e.g., having IAs at 100, 200, and final at 300 may be problematic
- No Point in having 1st IA Before reach an Adequate Safety Database Size (for both S/T and L/T)
- Best Times for Early Efficacy IAs generally not the same as Best Times for Futility IAs.

Interim Analysis for Early Demonstration of Efficacy, cont'd

- When Stopping for Success also need to ensure that:
  - Adequate Long-Term Efficacy data to Show Benefit is Not Short-Lasting
  - Statistical Significance still achieved on any Key Secondary Analyses of Primary Endpoint
    - e.g., If primary endpoint is PFS, key secondary analyses may handle differently progressions between scheduled visits
  - Results on certain Key Secondary Efficacy Parameters are considered where this could Impact Approval (or Mkt share)

Interim Analysis for Futility and for Early Demonstration of Efficacy

- Useful to incorporate Covariate Adjustment at each look
  - Will generally Increase Chance of Stopping at Earlier IA
  - Increases Overall Chance that Trial is Positive
  - Often Gives (equivalent) 10%-20% effective Increase in Total NEs
- IA Set Up (# of IAs, IA Timings, α-Spend Fn, Futility rule) should take into account earlier practical restrictions
  - Then For a Range of "Set Ups" evaluate Power, Chance of Stopping at each IA, Expected Durn. of Trial (EDT), and Max Durn. of Trial
    - Repeat for assumed Δ, and $c\Delta$ for many c values in range (-0.25,1.25)
    - Ensure desired operating characteristics are obtained

Example with Interims for Early Demonstration of Efficacy

- Primary Endpoint is Overall Survival
- Suppose we Need Only 1 Phase III Trial with $\alpha = 0.050$
- Hazard Ratio = 1.25 (60m/48m)
- Enrollment Duration = 18m
- Protocol originally had one IA (for early efficacy - w' OBF) built in at 50%, i.e., 2 looks - 50% and 100%
  - 50% IA at 24mths, Final at 42mths

Gains From Changes to Interim Analyses

- Suppose in this example, IA #1 Cannot Be Sooner Than 50% based on Safety Dbase & L/T efficacy needs
  - **3.2 Month Reduction** in Expected **Duration of Trial** (EDT) (under H_1), by having 2 IAs, at 50% & 75% (under OBF)

    [Keeping power at 90% by incr. Target # of Events]
  - Further time gains possible from changing timing of IA #1
    - If only 1 IA (under OBF), range 60%-67% gives lowest EDT (under H_1)

Gains From Changes to Interim Analyses, cont'd

- In this example we have seen:
  - Time Gains Greatest when safety dbase and l/t efficacy needs Allow 1st IA Soon After 50% (or soon after 60%)
  - Still have Large Time Gains if 1st IA cannot be until 75%
    - Provided medians are reasonably large
  - Further time gains may be possible by having 3 or more IAs, or by changing α-spending fn.
  - Gain needs to offset extra costs and complexity of having the additional IA(s)

Sample Size Re-Estimation or Power Re-Assessment

- Sample Size Re-estimation (SSR), Based on an Interim Effect Size, is advocated by many authors to "Save" a Study which may o/w Just Fail To Achieve Statistical Significance
- Very many variants of SSR but only discuss here approaches that
  - Weight all Patients Equally (and revise α to control T1E)
  - Have fully Pre-Specified Rules

Sample Size Re-Estimation or Power Re-Assessment, cont'd

- SSR itself has a problem as sponsor could back-calculate interim effect size
  - Could lead to different type of patients before/after adaptation
  - Need to show consistency of effect size before and after adaptation
  - Problem can be reduced if new sample size can only take 2 or 3 different values [Gallo et al, 2006]

Power Re-Assessment

- Power Reassessment (PR) Carried Out After End of Enrollment Avoids Problem of potential Inconsistency From Pts Before/After Adaptation
  - Most Effective if Carried Out Very Late-On during follow-up
  - Increases Target Number of Events (TNE), and Study Duration, Only if Treatment Effect at IA is "Borderline"
    - Follows a Rule Pre-Defined in Protocol
    - Carried Out by an Independent Group
  - No New Patients Enrolled, and if rule only has 2 or 3 possible values of TNE, Sponsor Learns No More Than with a GSD

Power Re-Assessment, cont'd

- Important to Compare PR Approach vs Standard GSD to Ensure that it Provides Enough Time Saving or Power Gain to offset the extra complexity
  - For a recent Ph III trial **PR Shown to Save 2 Months vs GSD**
  - See Smith (2005) for details of a similar example where PR Gives Time Saving vs. GSD
- Alternative use of Power Re-Assessment is to Increase the Power (Increase Chance of a Positive Study)

Stated Regulatory Requirements With All Types of Adaptive Design in Phase III

- Fully Pre-Specify Adaptive Methods in Protocol (Designed Flexibility)
  - Limit amount of Adaptation in any Pivotal Trial
- Show that Type 1 Error is Controlled
- Provide Bias-Adjusted Estimates and Bias-Adjusted CIs
- Have Adaptation Performed by an Independent 3rd Party

FDA's DSMB guidelines (2005), EMEA's Flexible Design guidelines (2006), Hung (2005), Gallo et al (2006) for PhRMA Working Group

Stated Regulatory Requirements With All Types of Adaptive Design in Phase III

- Ensure Implementation Avoids Operational Bias and Restricts Sponsor Exposure to Unblinded Results
- Discuss with Regulatory Authorities at an early stage if any Adaptive Design is being considered
- Useful to have FDA's Special Protocol Assessment
- Important to Get Full DSMB Buy-in

FDA's DSMB guidelines (2005), EMEA's Flexible Design guidelines (2006), Hung (2005), Gallo et al (2006) for PhRMA Working Group

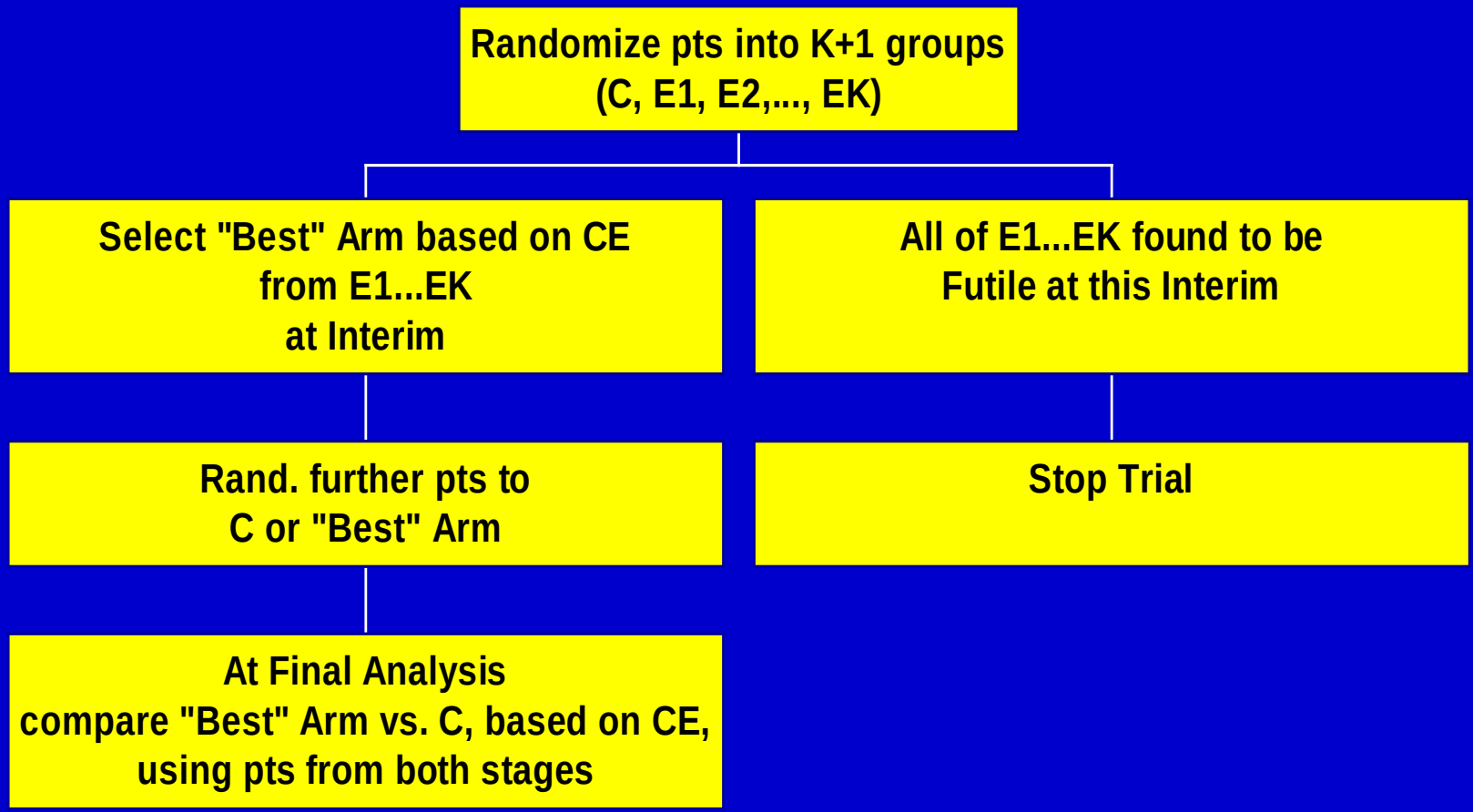
Determining the "Best" Dosage Regimen

- In many cases the Experimental Arm(s) to Take Into Phase III are Uncertain. We may need to decide on:
  - Different Doses of a Cytostatic or
    Different Doses/Schedules for a Cancer Vaccine
  - Different Dosing Regimens of a Cytotoxic
  - Different Combination Regimens
- Traditional Approaches Study Each Arm Separately in a Single Arm Trial based on Response Rate [A]

Determining the "Best" Dosage Regimen, cont'd

- Other Possible Approaches:
  - Randomized Parallel group Ph II design based on RR or Propn w' Progression by Set Time [B]
  - No Ph II & Take 2 or more Dosage Regimen into Ph III [C]
  - No Ph II, "Guess" Single Dosage Regimen, go Straight to Ph III [D]
- A, C, D Contribute to the High Oncology Attrition Rate
- B may be Preferable, but Lengthens Drug Devel. Time
- An Alternative could be a Phase IIB/III Combination Design

Phase IIB/III Combination Designs Incorporating Treatment Selection & Testing



Thall et al (1988), Schaid(1990), Smith (2002, 2003), Stallard & Todd (2003)

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

- The use of a Phase IIB/III Combination Design here is considered When Only 1 Ph III Would be Needed (maybe w' $\alpha = 0.010$)
  - If so we must have supportive evidence for submission from outside of this trial
  - Use of Phase IIB/III (& 1 Ph III) in cases where 2 Phase IIIs are needed is under development [Julious & Swank (2005)]
- I am Only Advocating Phase IIB/III Designs that:
  - provide p-values corresponding to actual pairwise comparison(s) [Some methods fail to do so!]
  - are based on "sufficient" statistics

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

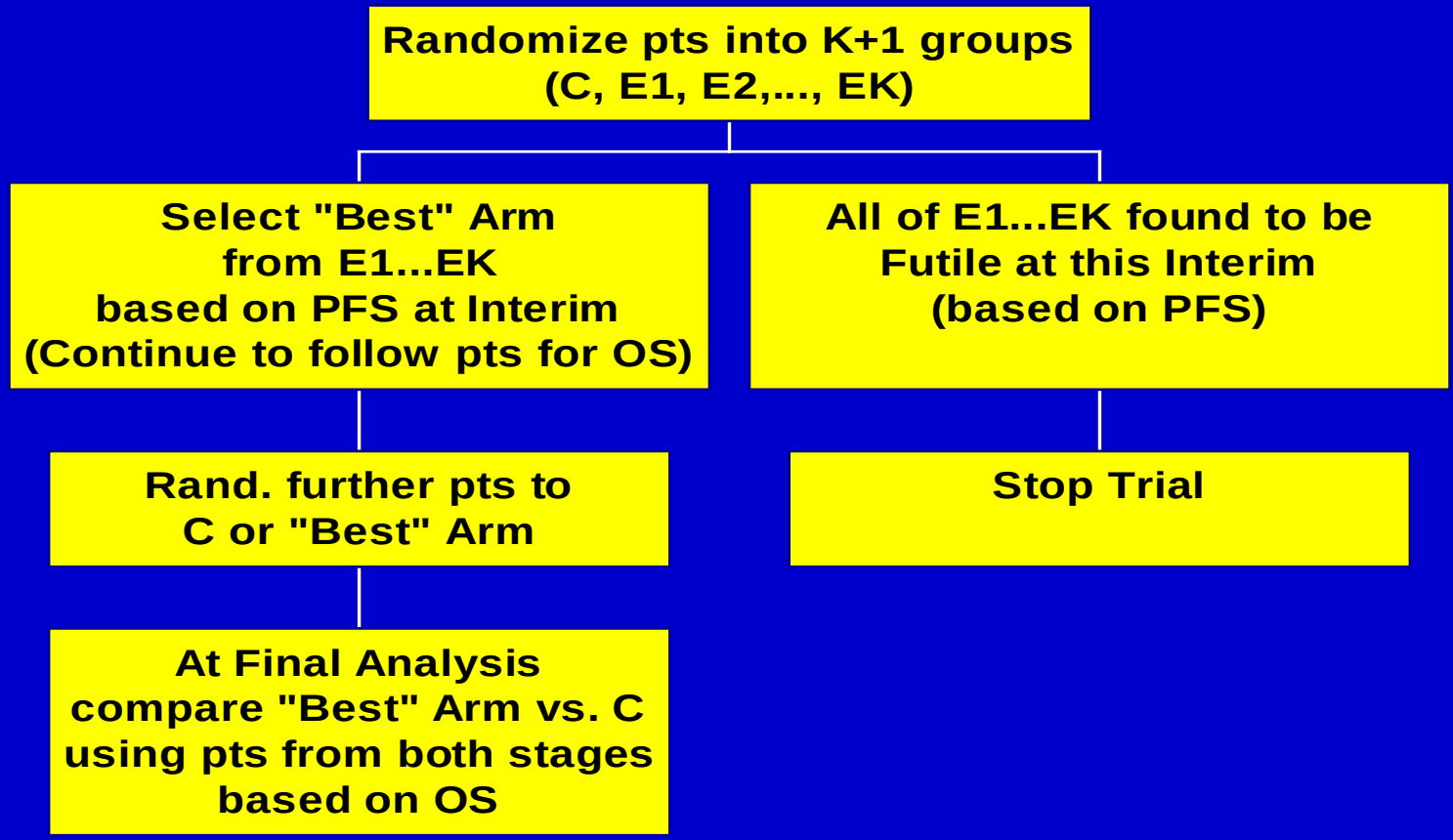
- First Approach had Selection Carried Out on CE:
  - Requires CE to have a Short Median Time (relative to duration of enrollment), e.g.,
    - OS with metastatic RCC - medians 6-8 mths
- With Less Rapidly Progressive Cancers Can Still Use Ph IIB/III Design if there is an IE that:
  - Occurs Early Enough AND is Highly Correlated with the CE

[See also Berry et al (2001), Inoue et al (2002), Berry (2006) for use of an IE in a Bayesian adaptive design setting.]

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

- Example - 1st line advanced ovarian cancer where full approval will be based on OS
  - OS medians 24m-29m
  - PFS medians 10m-13m
  - Selection of "best" arms carried out based on IE = PFS, but ultimately compare on CE = OS [Royston et al, 2003]
- For other cases (cancer types, stage, drug class) IE could be based on:
  - RR or propn. w' PD by a set time (provided it is highly correlated with CE)
  - PSA velocity (early predictor of PFS in Prostate Cancer)

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



see Royston et al (2003), Smith (2004), Todd & Stallard (2005)

Phase IIB/III Combination Designs: Practical Considerations

- Avoid Using Ph IIB/III as an Excuse For Less Clear Objectives [Simon, 2004]
- Important to Have Some Information Prior to Ph IIB/III on How Each Arm Performs in this pt population
- May want to incorporate rules under which trial would stop at end of Ph IIB, rather than continue into Ph III stage, to enable re-design of a modified Ph III

Phase IIB/III Combination Designs: Practical Considerations, cont'd

- Timing of Interim has to Consider and Balance:
  (a) High Power needed in Current Study
  (b) High Chance that "Good" Dosage Regimen is Selected
  (c) Time of IA is late enough for Sufficiently Good Dose-Response Information to be obtained (if applic.)
  (d) As Few Pts as possible Given Sub-Optimal Dosage Regimen

[See Smith (2003) for further details]

Phase IIB/III Combination Designs: Practical Considerations, cont'd

- Phase IIB/III Designs (w' K≤4) can give a Time Saving & an Efficiency Advantage [See Smith(2002, 2003), Berry (2006)]
  - Final Analysis is Based on Data From Both Stages for the 2 retained arms, w' No Gap Between Phases
  - Need to Compare Ph IIB/III vs.
    - Separate Ph II and Ph III; and
    - Ph IIB/III w' Primary Analysis based on Ph III only
- Can Extend to Account for Structure amongst E1-EK, e.g.,
  - If K=2, E1-E2 are HD and LD
  - May want to select LD unless effect size < 0.8 (or perhaps 0.9) x effect size at HD

Phase IIB/III Combination Designs: Regulatory Considerations

- Request very Early Discussion with FDA/EMEA if Planning to use a Ph IIB/III Combination Design
  - Discuss at End of Ph IIA Meeting w' FDA
  - Determine if supportive information is sufficient?
  - Agree on required overall α level in Ph IIB/III
  - Determine if acceptable for trial to have a "Dose Selection Committee"? [totally separate from clinical team]

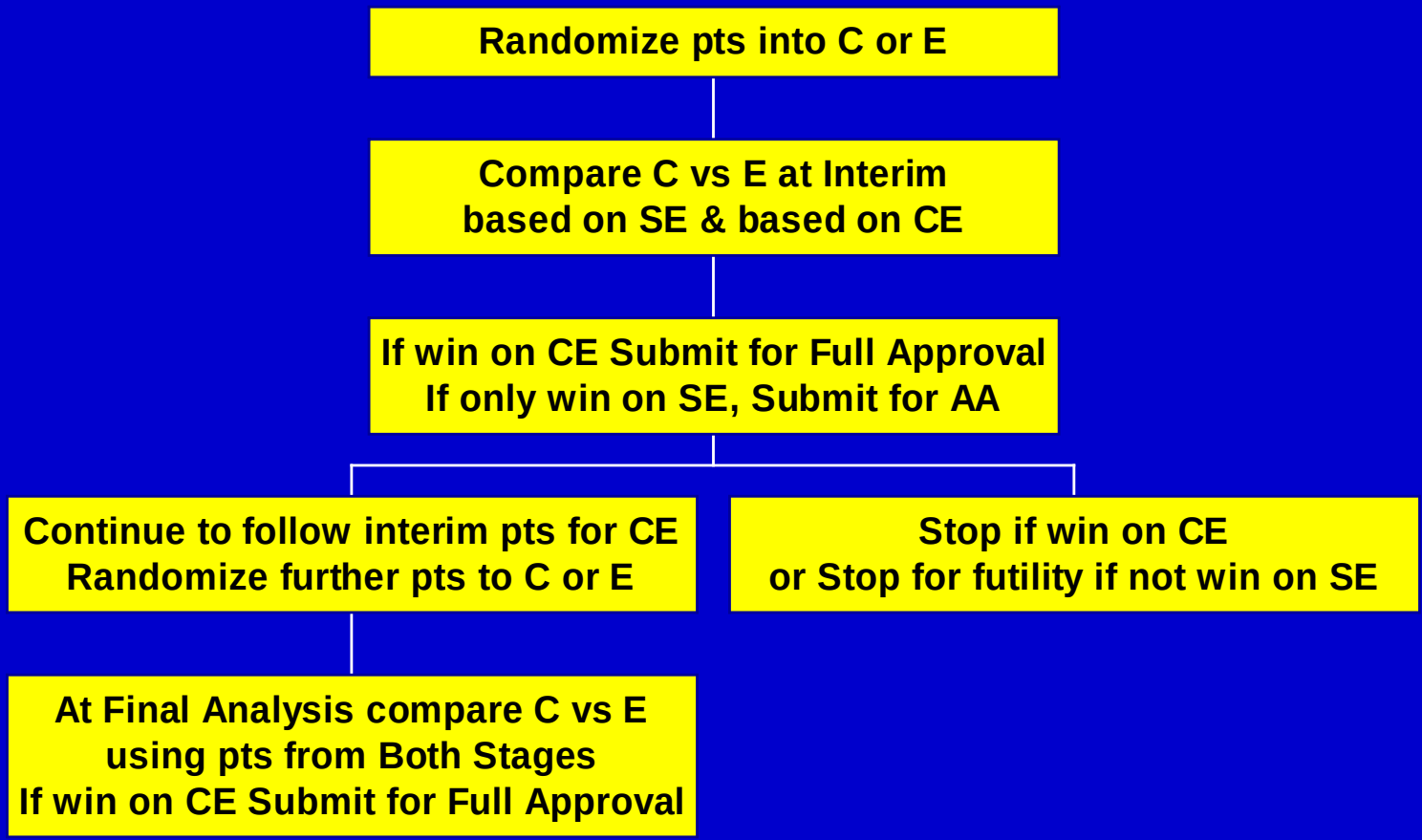
Phase II/III Designs for Both Accelerated Approval & Full Approval

- Accelerated Approval (AA) can sometimes be granted by the FDA 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
  - Only 4/19 AAs had met this Post-Approval Requirement (by Mar 03) [Chi, 2003; Johnson et al, 2003]

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

- Johnson et al (2003) advocated Adopting Paradigm Used in AIDs Trials
  - Use Same Randomized Trial for AA and Full Approval
  - AA based on IA of Surrogate Endpoint (SE)
  - Full Approval based on Final Analysis using CE
- This Design Approach used for Oxaliplatin in 2nd line therapy for metastatic colorectal cancer
- Also being used or considered in many other cases

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

- Method for T1E control in such trials needs to be specified and agreed w' FDA [see Shih et al (2003), Chi (2003)]
- Many variations on this theme including:
  - Whether or not assess CE itself at IA (may not have a big enough safety database for full approval at this time)
  - If CE is assessed at IA, approach to "spending" α
  - "Best" time for IA
  - Whether or not to randomize further patients after IA

Concluding Comments on Use of Innovative Design in Oncology

- By Optimized Set Up of Interims in a GSD it is possible to Meet Needs of Submission and obtain worthwhile **Time Savings**
- Power Re-Assessment offers the potential to provide **Time Savings** or **Increase Chance of Positive Trial**
- Bayesian Adaptive Designs (see Berry, 2006) also can offer time savings

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

- Phase IIB/III Combination Designs, Incorporating Treatment Selection & Testing (w' or w/o an IE) in some cases can provide a **Large Time Saving** and provide **Efficiency Gains**

- Phase II/III Designs, of a different type, are starting to be used for Both AA & Full Approval instead of basing on separate trials

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

- Innovative Design Approaches are Already Being Used to **Reduce Time** in Oncology Drug Development
- Innovative Design Approaches can, in many cases, help **Cut Attrition Rate** and **Cut Costs** of Phase III Oncology Trials