Testing Monotherapy and Combination Therapy in One Trial with Biomarker Consideration

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

Linda Sun, S. Peter Kang, Cong Chen

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Outline

- Motivation
- Proposed Design
  - Analysis method
  - Multiplicity consideration
- Power and sample size
- Discussion

Motivation

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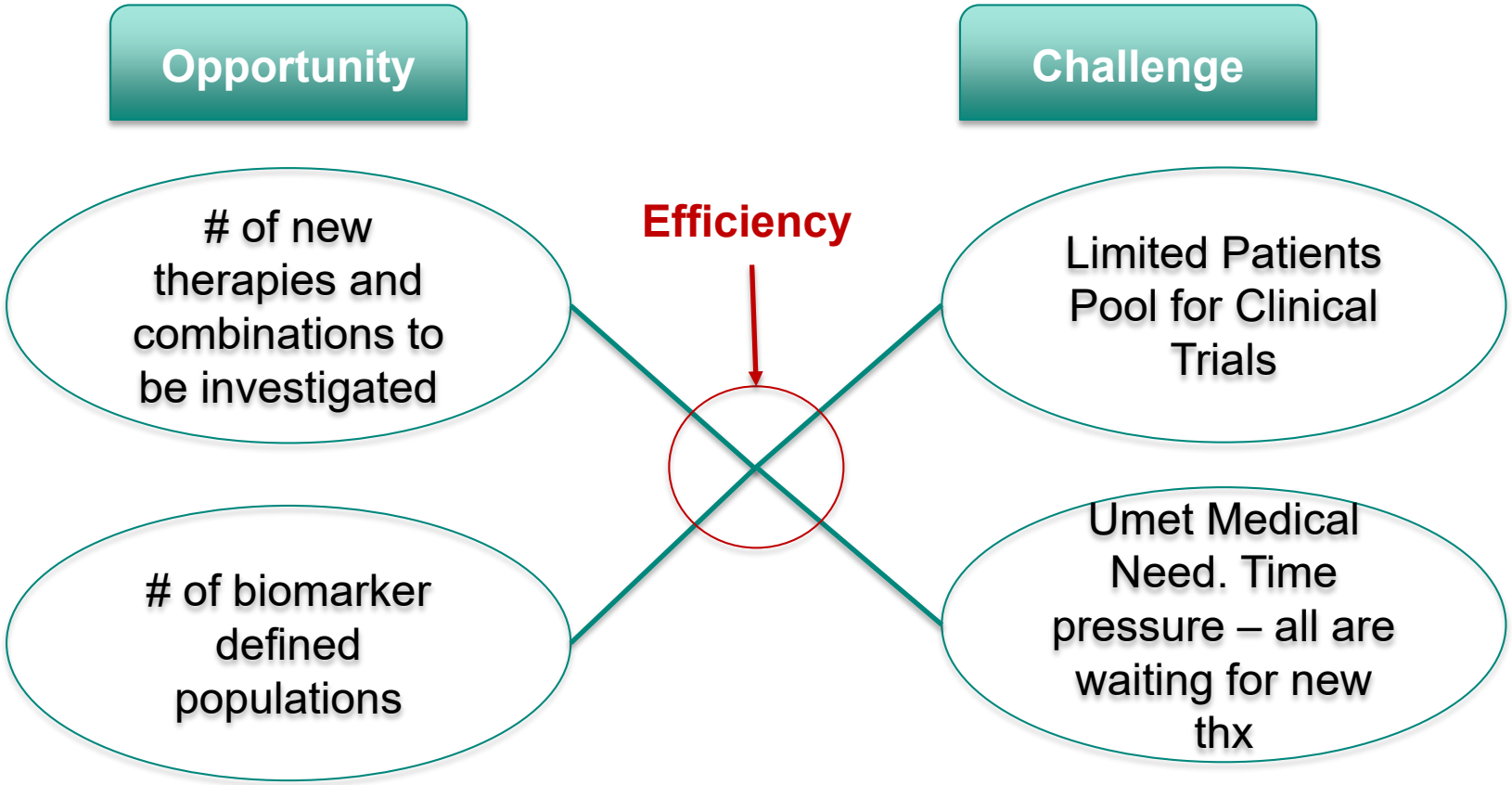
Called to be efficient

- Trial Design in Oncology Drug Development



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A common scenario in oncology drug development

- Monotherapy of experimental drug (E)
  - Treatment effect is bigger in BMX enriched population
  - Maybe superior to SOC in BMX+ population
  - Maybe comparable or even inferior to SOC in BMX- population
- Combination of E + SOC
  - Maybe superior to SOC in both BMX+ and BMX-, i.e. all-comer population

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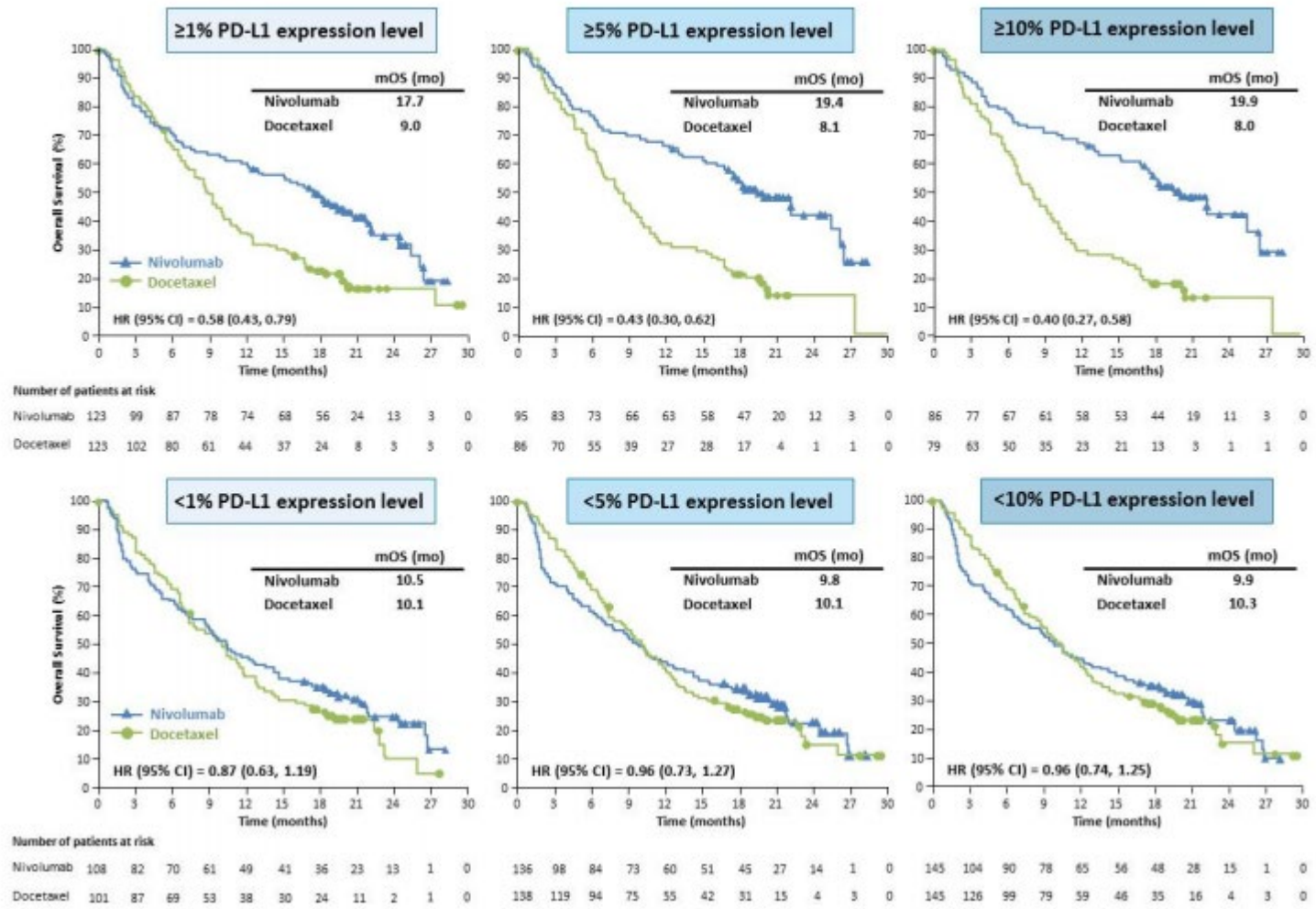
Example – PD1 check point inhibitor in NSCLC

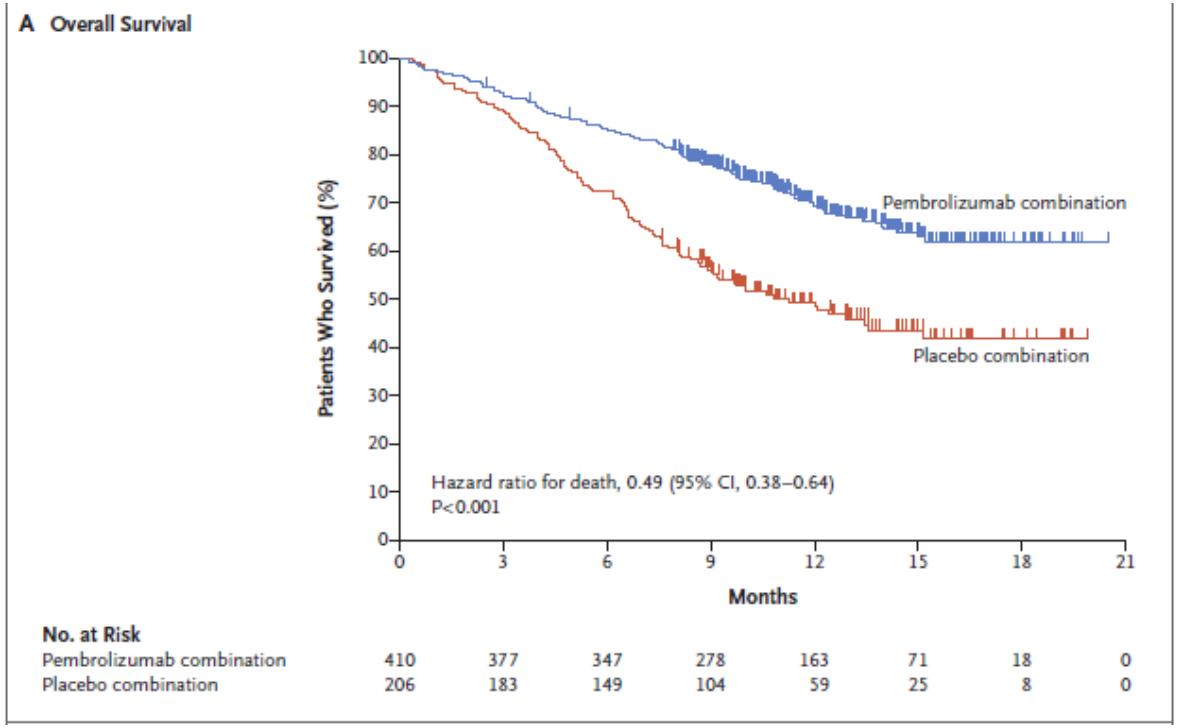
Figure S8B. Kaplan-Meier Plots of Overall Survival With Extended Follow up at the 1%, 5% and 10% PD-L1 Expression Levels.



Monotherapy treatment effect by PD-L1 level in 2L NSCLC

- Nivolumab, Checkmate 057, NEJM 2015

Example – PD1 check point inhibitor in NSCLC



Combination therapy is superior to SOC in all- comers and all PD-L1 subgroups

- Pembrolizumab, Keynote-189, NEJM 2018

Example – PD1 check point inhibitor in NSCLC

- For monotherapy
  - Even though it's comparable to 2L chemo in in PD-L1 - patients, there was concern that it may not be able to measure up to 1L chemo
  - Therefore, testing monotherapy in 1L PD-L1- patients may expose patients to potentially inferior treatment
  - Monotherapy PD1 is to be tested in BMX+ enriched 1L NSCLC
- For combination
  - Since the experimental treatment is add-on, there is no concern to test the combination thx in all-comer population

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Motivation

- Notice: the same SOC on the control arm for mono and combo trials, why not share control in one trial?
- Possible reasons for the two-trial strategy
  - The dose for combination therapy is determined later than the monotherapy dose
  - The populations are different

Proposed design provides an solution

No longer an issue for follow on tumor types

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Proposed Design

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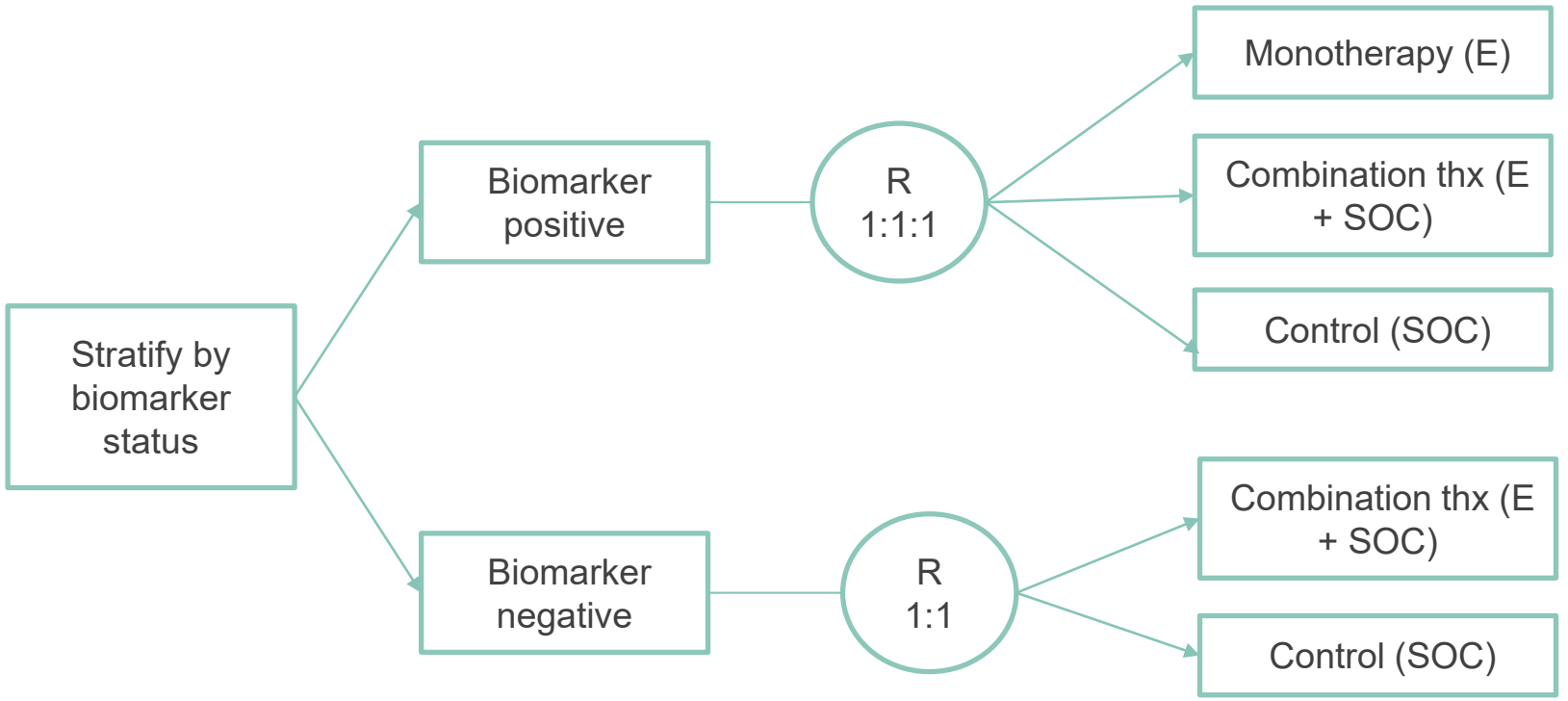
Study Design



Hypotheses (Primary endpoint: OS)

H1: Monotherapy vs. SOC in BMX+ population

H2: Combination thx vs. SOC in all-comer population

Analysis Method

- For H1 (monotherapy)
  - Regular log-rank test and Cox-regression method
- For H2 (combination therapy)
  - Population is skewed – BMX+ prevalence is lower than the prevalence in true all-comer
  - Two-step log-rank test and Cox-regression method
    - Step 1: analyze BMX+ and BMX- separately
    - Step 2: weighed sum to combine.
  - Weight of BMX+ patients vs BMX- patients = 3:2, pre-determined by randomization ratio and no estimation
  - Minor loss of efficiency with two-step log-rank test

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Multiplicity Consideration

- The proposed design is a multi-arm design with shared control group.
- Is it necessary to adjust for multiple comparison (experimental arms vs. control) in the multi-arm single trial when no such adjustment would be required had these comparisons been made in separate two-arm trials?
- Key question: Were the experimental arms put together in a single trial because the corresponding research questions are related, or primarily, because of efficiency and logistical reasons?
- No multiplicity adjustment is needed in multi-arm trials that are designed for logistical efficiency. (Freidlin 2008, Howard 2018)
- (Same thinking for multiplicity consideration in Umbrella/Platform studies)

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A distinction

- Distinction between factorial design and the proposed design
  - Factorial design
    - A+B, A, B, vs. SOC
    - Arm A and B are in the trial for component contribution
  - The proposed design
    - **H1**: E vs. SOC in BMX+ population
    - **H2**: E+SOC vs. SOC in all-comer population
    - The monotherapy arm (E) in the proposed design doesn't serve as component contribution
    - Arm E and E+SOC in one trial are purely for logistical efficiency
- No multiplicity adjustment
  - If H1 and H2 are tested in two separate trials, each with alpha = 0.025 (one-sided), then in the proposed design, H1 and H2 will also each be tested at 0.025 (one-sided) in the proposed design
  - The sharing of a common control actually reduces the FWER as compared to separate trials

Power and Sample Size

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Sample Size Comparison - The Hypothetical Example

	One-trial Design (Proposed Design)	Two-trial Design
Sample size for H1	326	326
Sample size for H2	489	472
Sample size saved due to shared control for H1/H2	(-) 61	0
Total sample size	754	798
# of screened patients who cannot be enrolled solely due to being BMX-	408	652

Biomarker prevalence = 1/3, HR (OS) mono vs SOC = 0.65, HR (OS) combo vs SOC = 0.70, one-sided alpha = 0.025, power = 90%, 70% randomized patients have events by the time of final analysis.

Trial cost per patient > $100K

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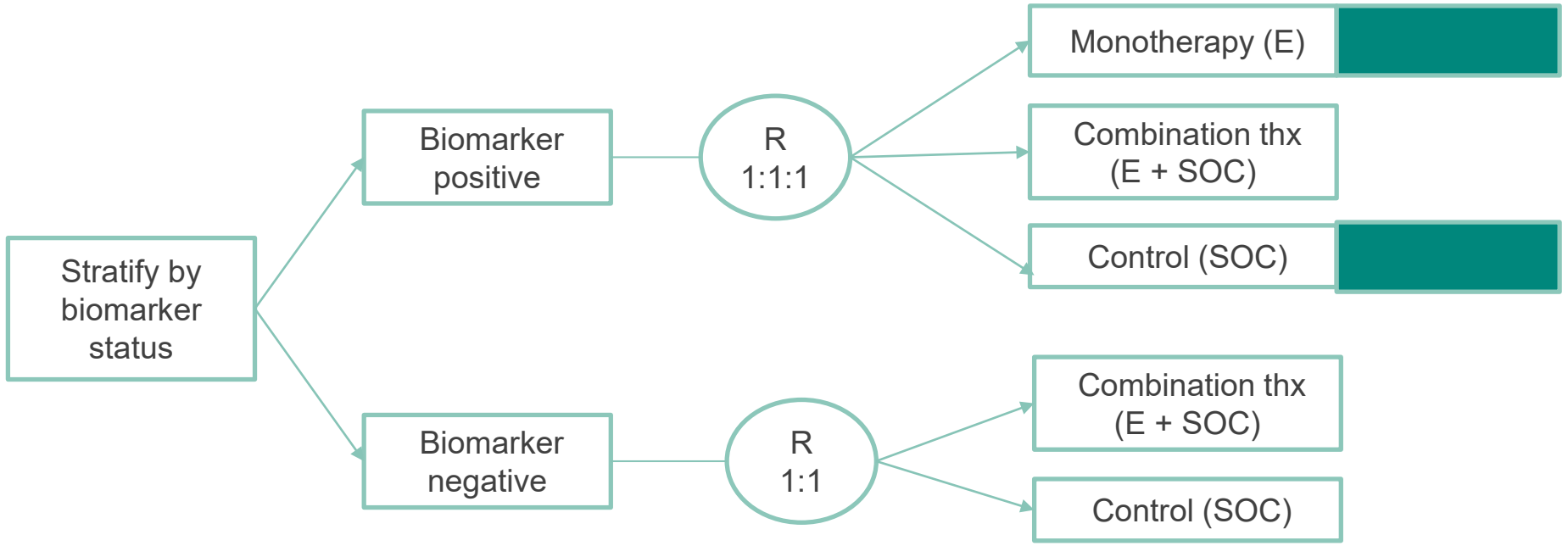
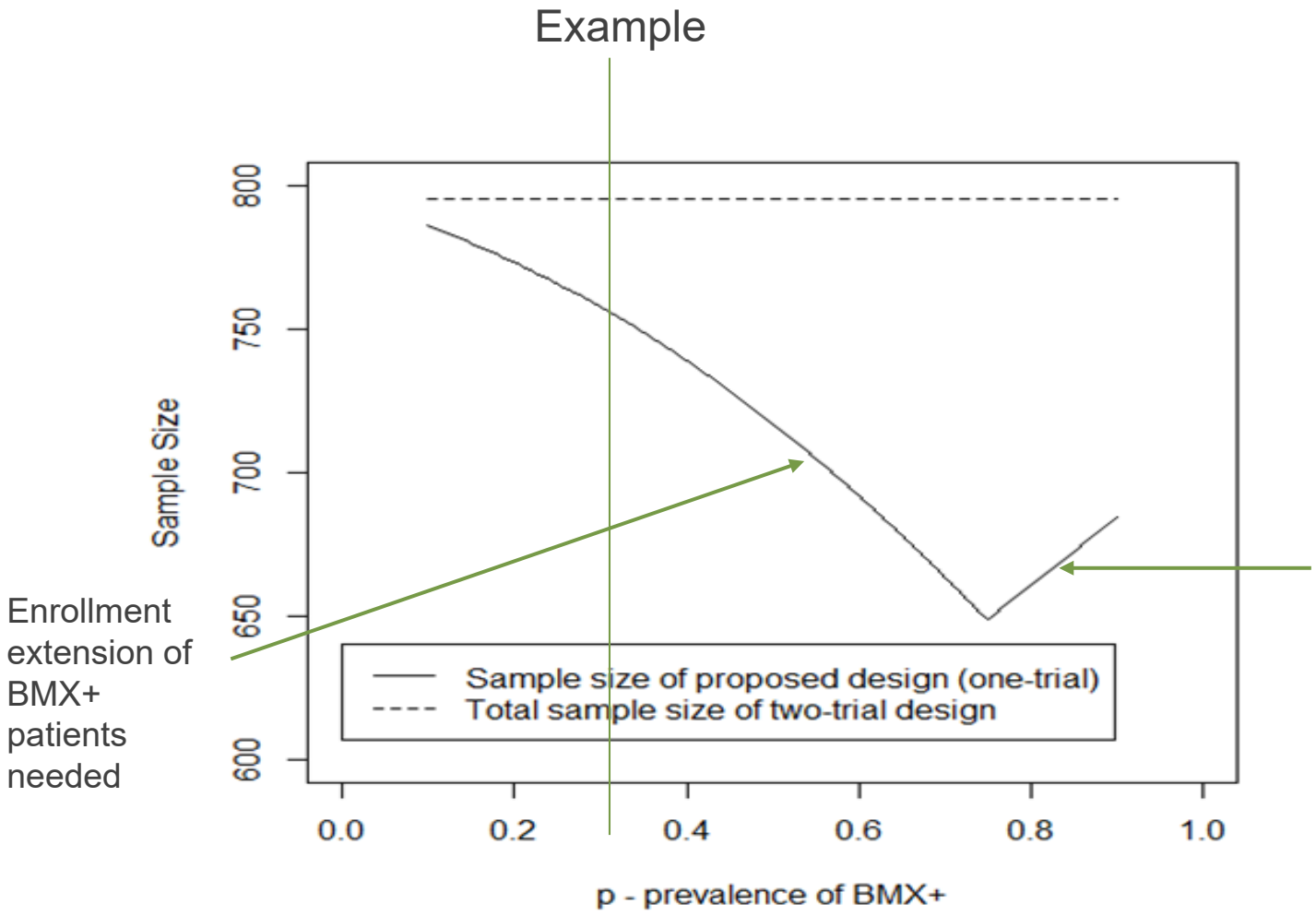
How much sample size the proposed design can save?

- Depends on sample size for H1 relative to H2
  - Biomarker prevalence *p*
  - Target HR for H1 and H2
  - May need enrollment extension for H1



Impact of BMX+ Prevalence on Sample Size



- The BMX+ patients randomized to the control arm contributes to test both H1 and H2
- **In general, the higher the BMX+ prevalence, the more efficient the proposed design**
- However, when BMX+ prevalence is higher than a certain point, the sample size of the proposed design is driven by H2 only. For ease of operation, we don't cap the enrollment of BMX+. Thus the design loses some efficiency.

Discussion

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Logistical Advantages of the Proposed Design

- If the two-trial design are conducted sequentially, the proposed design can save time
- If the two-trial design enroll at the same time,
  - For BMX- patients, screen failure from Trial 1 cannot be automatically considered for Trial 2
  - For BMX+ patients, which trial to enroll? Trial 1 or Trial 2?
    - Due to toxicity consideration, investigators may enroll poor prognostic BMX+ patients to Trial 1

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Extensions of Design and Methodology

- Design extension
  - Add group sequential feature
  - Population adaptation:
    - Start with three-arm all-comer trial
    - Futility of BMX- patients for either monothx or combination, or both
- Two-step method
  - Umbrella platform, evaluating treatments targeting different biomarkers
  - How to assign patients with multiple biomarkers of interest
  - Population adjustment to recover true all-comer

Further Multiplicity Consideration

- If multiplicity adjustment is required for H1 and H2 in one-trial design (due to philosophical consideration), but not in two-trial design
  - The one-trial design requires more sample size when BMX+ prevalence is low (e.g. 33%)
  - The one-trial design may require the same sample size as the two-trial design when BMX+ prevalence is higher (e.g. 67%)

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Summary

- Cancer drug development
  - Fast-growing
  - Complex
- Proposed design is efficient
  - Sample size
  - # of patients screened
  - Time
- The use of the two-step approach can be extended to other areas

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References

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Back Up

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Multiplicity

- Distinction between research questions and test statistics
  - If H1 and H2 are considered as separate research questions when tested in two trials, then the same when tested in one trial.
  - The test statistics are related due to shared control in the one-trial design. This correlated reduces FWER compared to two-trials design

$$FWER = \Pr(X_1 > Z_\alpha \text{ or } X_2 > Z_\alpha) = 2\alpha - \Pr(X_1 > Z_\alpha, X_2 > Z_\alpha) \leq 2\alpha - \alpha^2$$

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Impact of BMX+ Prevalence on Sample Size

- Total sample size
- When enrollment extension of BMX+ is needed

$$T = (1 - \frac{2}{3}p)(1 + \frac{1}{2}p)\frac{(Z_{1-\alpha}+Z_{1-\beta})^2}{\log(HR_2)^2} \cdot 4 + \frac{(Z_{1-\alpha}+Z_{1-\beta})^2}{\log(HR_1)^2} \cdot 4$$

- When enrollment extension is not needed

$$T = \left(1 + \frac{1}{2}p\right)\frac{(Z_{1-\alpha}+Z_{1-\beta})^2}{\log(HR_2)^2} \cdot 4$$

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