INVENTING FOR LIFE

Contribution of Components in Different Perspectives: From Individual Investigational Drugs and From Different Treatment Periods

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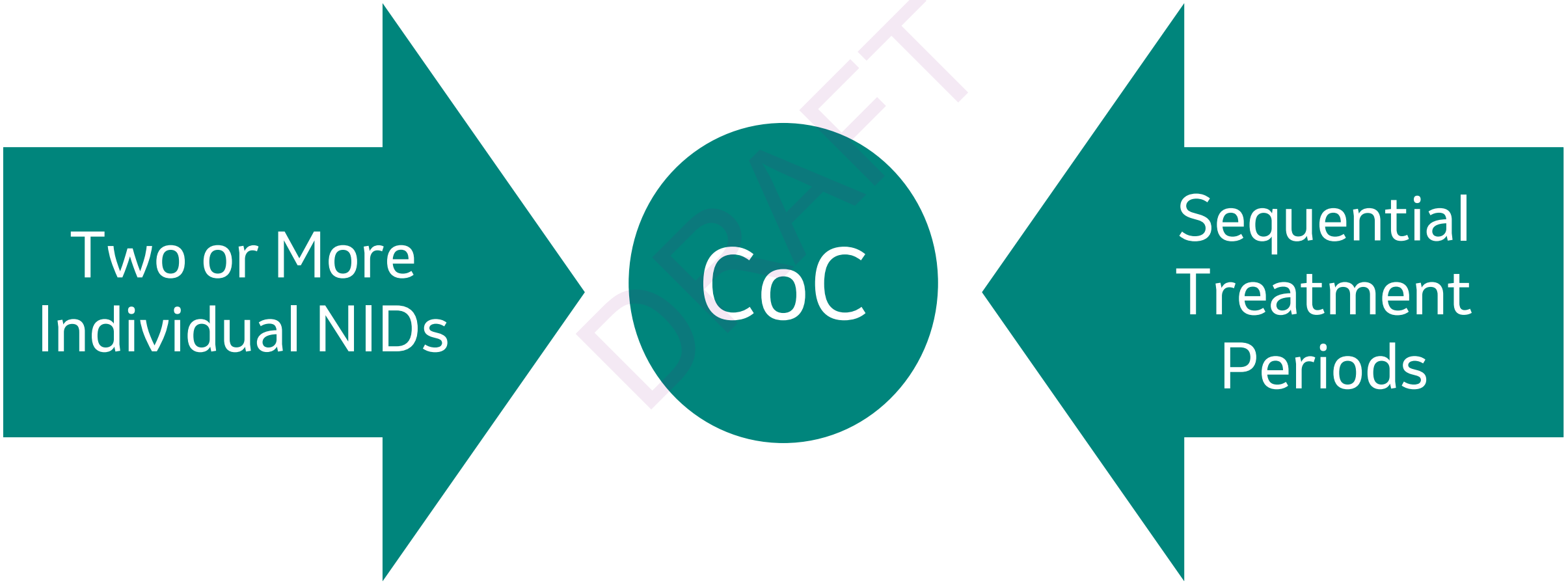
BASS XXIX 29TH ANNUAL BIOPHARMACEUTICAL APPLIED STATISTICS SYMPOSIUM

*Presenter

Outline

- Contribution of Components (CoC) from Two Perspectives
- CoC of Two and More New Investigational Drugs in Combination
- Coc of Sequential New Treatments Focusing in Oncology
- Motivated Example of 2-arm Trial of Neoadjuvant/Adjuvant Trial
- Research Question to Establish CoC
- Propensity Score Method
- Summary

Contribution of Components (CoC)



NID: New Investigational Drugs

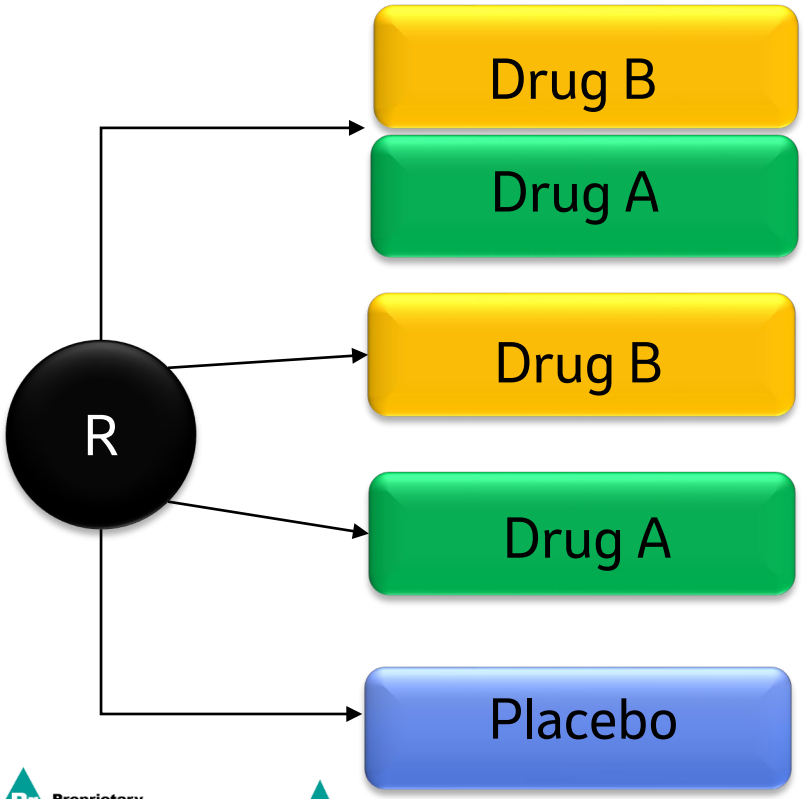
CoC for Development of New Drug Combination

- Co-development of Two or More New Investigational Drugs for Use in Combination[1]
  - The combination for serious disease or condition
  - Strong biological rationale for combination
  - Compelling reason NID can't be developed independently (e.g. limited activity in monotherapy)
  - Nonclinical model of the combination well established
- NonClinical and Clinical Co-development

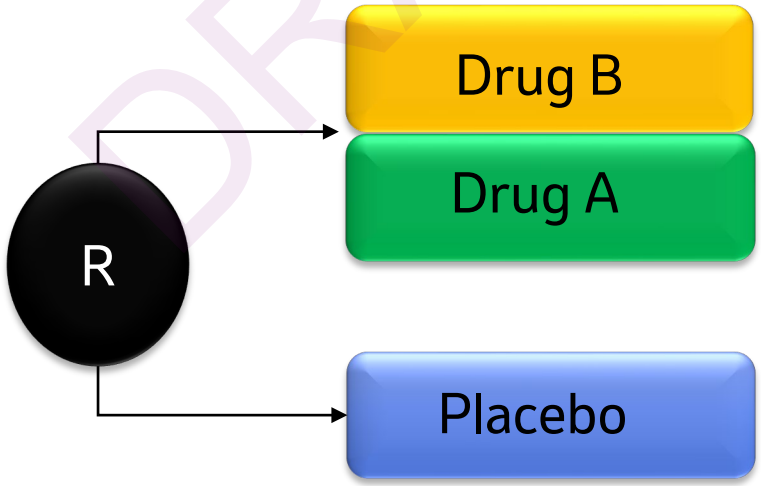
1. FDA Guidance for Industry: https://www.fda.gov/media/80100/download

CoC (NID) Clinical Study Design --- Phase 2 (PoC)

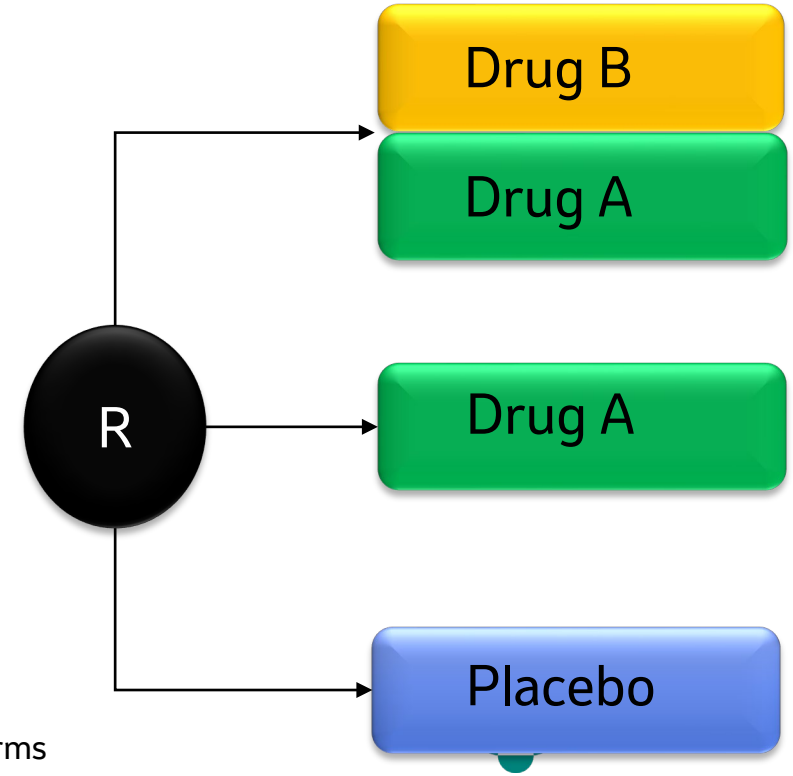
Scenario 1
Active Individuals



Scenario 2
Only Eff. In Combo



Scenario 3
One More Active



Note: SOC be the possible background therapy to all arms

CoC (NID) Clinical Study Design --- Phase 3

Confirmatory Phase 3 Design: A Case-by-Case Decision

1. If CoC adequately demonstrated in early studies (in vivo, in vitro and/or phase 2), a two-arm study of Combination vs. Control (AB vs. C) is sufficient;
2. If CoC is not clear and it's feasible to use one or more individual drug as monotherapy, a factorial design (AB vs. A vs. B) is suggested but may not be always chosen;
3. If phase 2 data not sufficient for each contribution but strongly shows combination is superior to monotherapy, a 2-arm design (AB vs. A) is possible to show B's activity while A may study more than 1 dose
4. Per FDA, if SOC is well-established and known to be small, control arm in 2&3 is not required (given PoC is established in Phase 2)

Sequential Treatments in Oncology

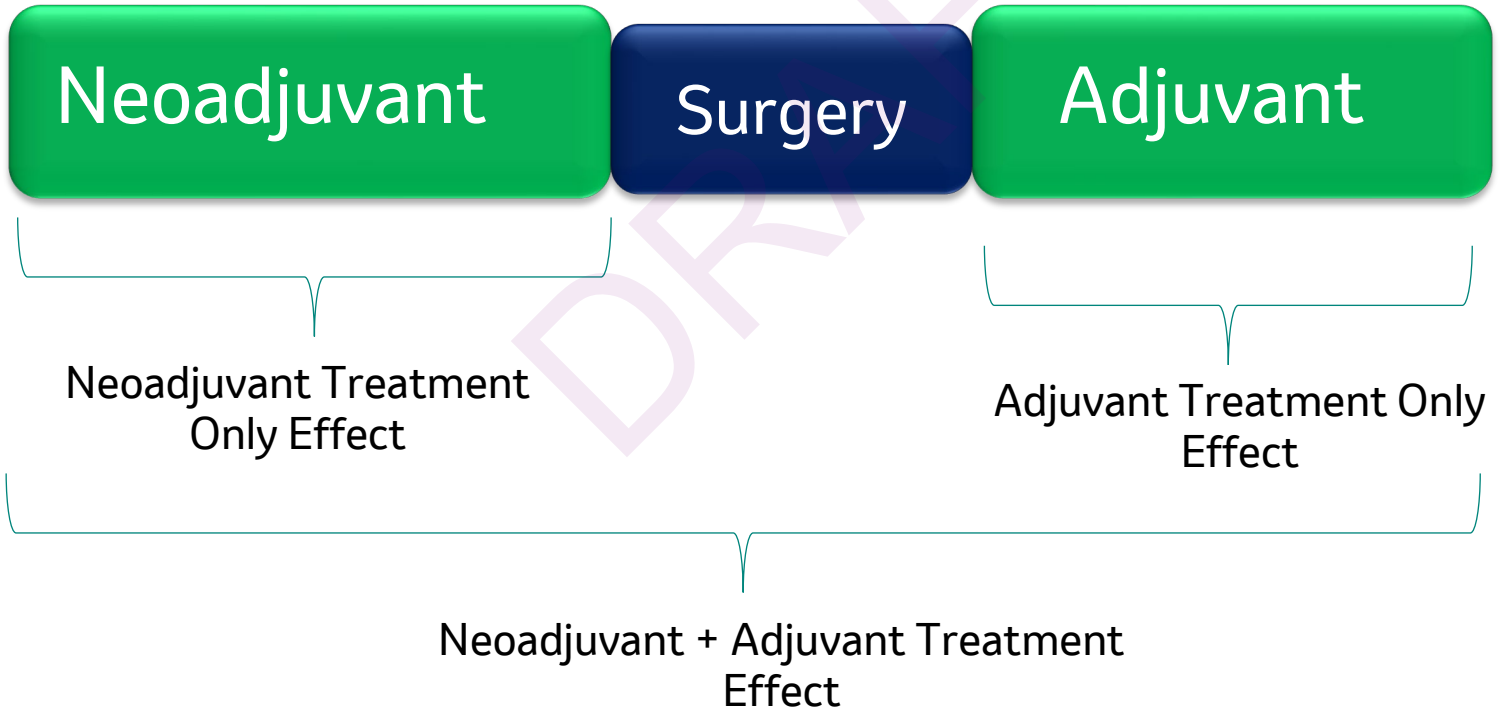
In Oncology, special cancer treatments provided to patients sequentially

- Neoadjuvant treatment: prior to surgery, uses as an initial step to shrink or even eliminate locally advanced tumors for better surgery outcome
- Adjuvant treatment: after surgery to reduce the risk of recurrence
- Neoadjuvant+Adjuvant fixed length of treatment: e.g. 1 year

- A need to develop an entire treatment including a full course of neoadjuvant, surgery and adjuvant.

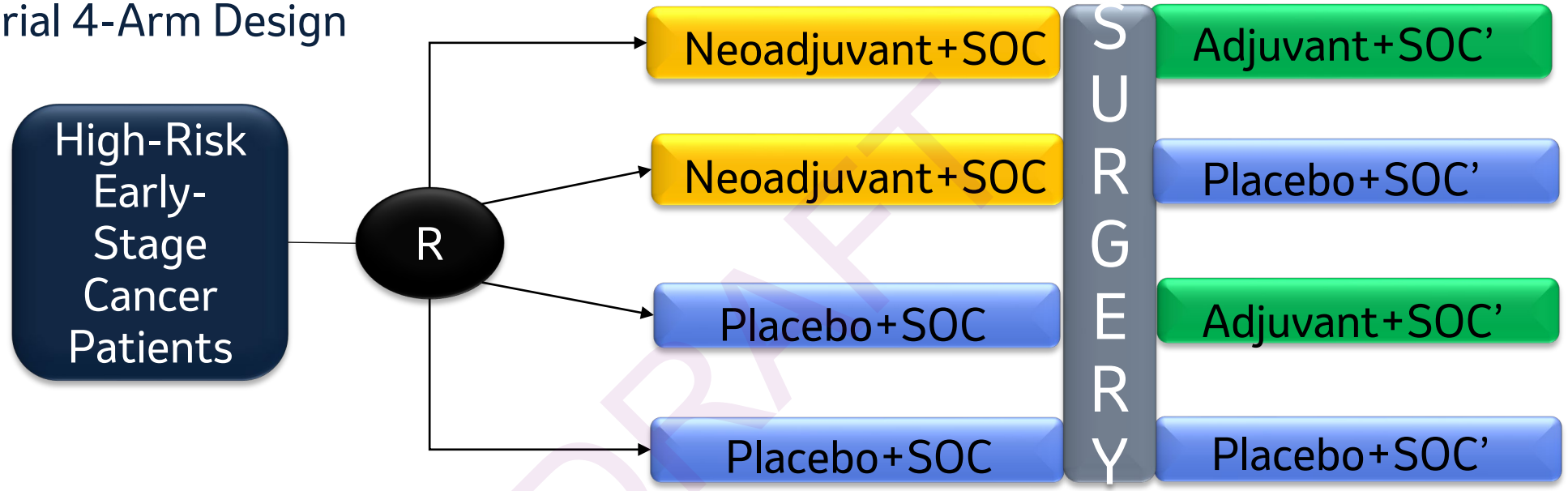
CoC from Neoadjuvant and Adjuvant Treatments

CoC: The treatment effect from either neoadjuvant or adjuvant or both?



Design to Evaluate Sequential Treatments (1)

A Factorial 4-Arm Design

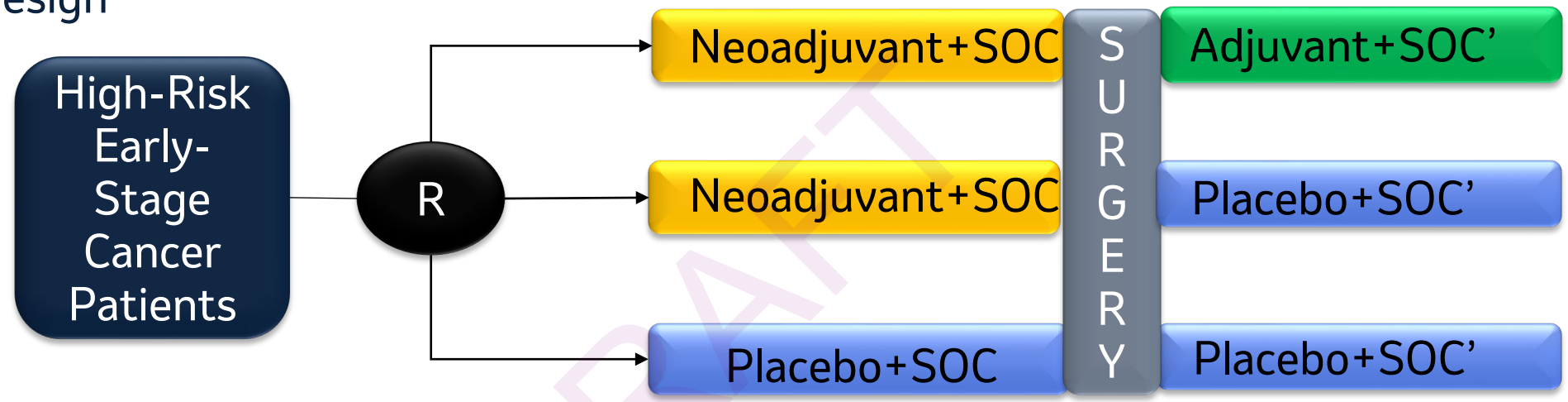


PROs:
- CoC is clear in the design on paper

CONSIDERATIONS:
- Complex design with multiple phases of treatments
- Multiplicity adjustment (type 1 error control) w/ biggest N
- Operational difficulty of multiple arms w/ diff. SOCs
- Least feasible due to different patient populations before surgery vs. after surgery
- Critical surgery timing, delay may not be ethical

Design to Evaluate Sequential Treatments (2)

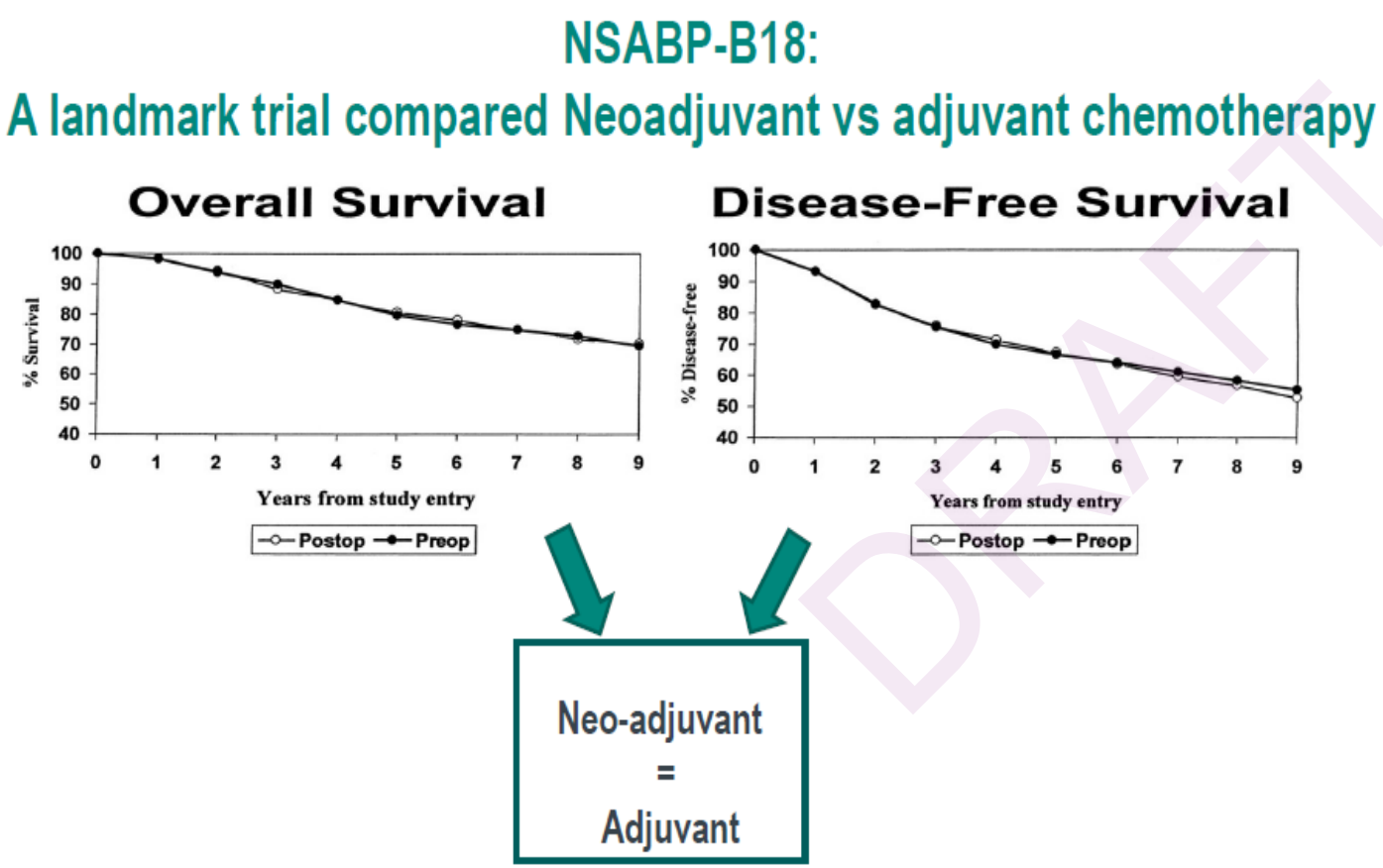
A 3-Arm Design



PROs:
- Simplified from (1)
- Adjuvant effect from Arm 1 vs. Arm 2
- Neoadjuvant effect from Arm 2 vs. Arm 3
- Neoadjuvant+adjuvant effect from Arm 1 vs. Arm 3

CONSIDERATIONs:
- Large sample size w/ multiplicity adjustment
- Neoadjuvant only arm may not be adequately treated

Clinical Perspectives of the Treatment Duration



- From Clinical perspective, 4-cycles neoadjuvant chemo provides similar efficacy as 4-cycles adjuvant chemo.
- The critical part is NOT whether before or after surgery, it is the treatment duration
- Shorter period of neoadjuvant (Design 1 or 2) may contain insufficient treatment thus may not be feasible in conduction

Fisher B, Brown A, Mamounas E, et al. 1997. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J. Clin. Oncol.* 15(7):2483–93

Fisher B, Bryant J, Wolmark N, et al. 1998. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J. Clin. Oncol.* 16(8):2672–85

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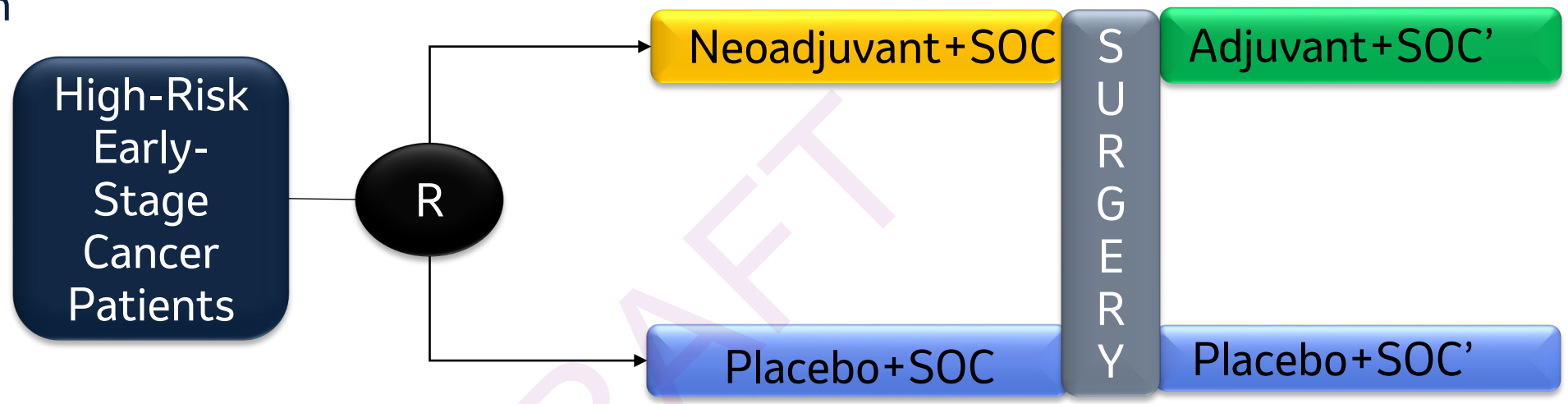
Design to Evaluate Sequential Treatments (3)

A 2-Arm Design

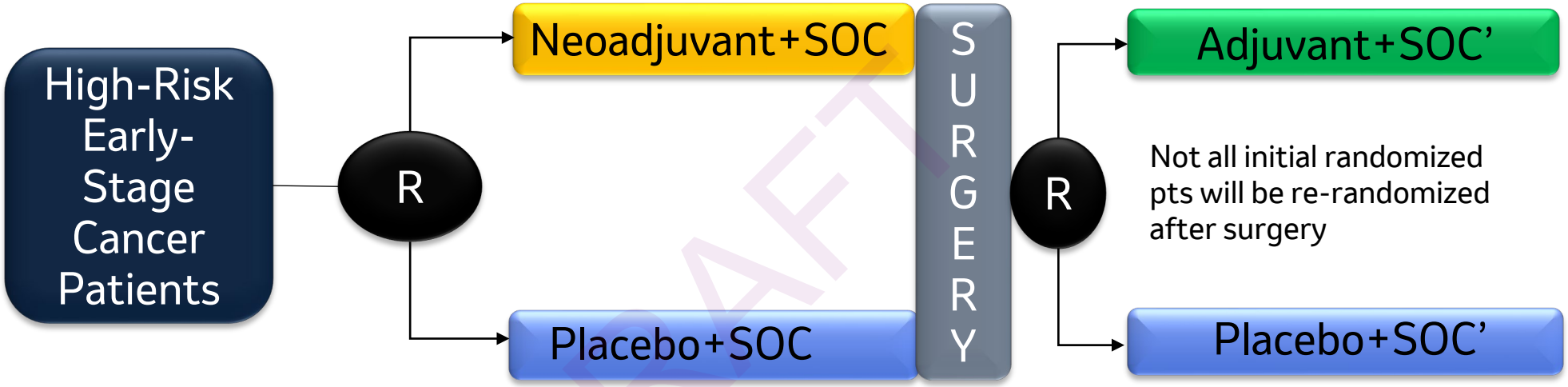


PROs:
- Straightforward design
- Detect add-on effect
- Neoadjuvant/adjuvant as an entire regimen
- Reasonable sample size
- For IO, 1 year treatment duration is considered adequate

CONSIDERATIONSs:
- CoC of neoadjuvant and adjuvant unclear

Design to Evaluate Sequential Treatments (4)

A 2-Arm Design w/ Re-Randomization after Surgery



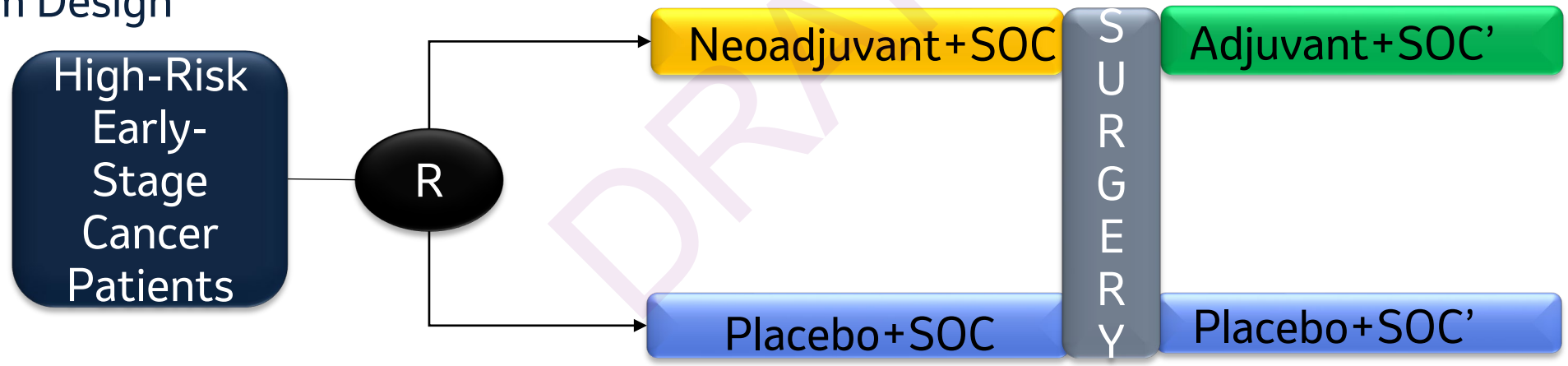
PROs:
- Randomized comparison in each phase of treatment
- CoC of each phase is clear

CONSIDERATIONs:
- Significantly bigger sample size to power adjuvant period
- Multiplicity adjustment
- No randomized comparison of the entire regimen (neoadjuvant+adjuvant) effect

IO Neoadjuvant/Adjuvant Development – 2-Arm

- A viable design to develop IO neoadjuvant/adjuvant treatment of early-stage cancer in breast, lung, gastric, H&N and bladder, etc.
- I/Os: pembrolizumab, nivolumab and atezolizumab etc..

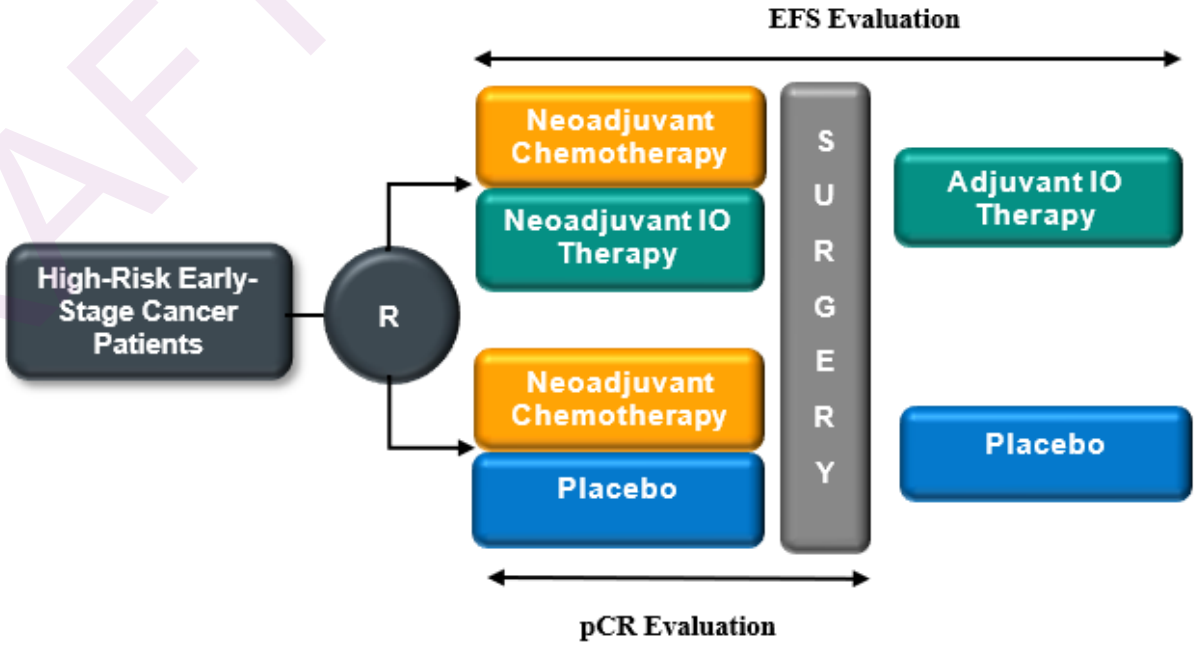
A 2-Arm Design



Can we establish CoC based on a 2-arm Design by borrowing the available external data?

Motivated Example of One Year of IO Therapy Add-on to Standard of Care Treatment Before and After Surgery

- Dual Primary Endpoints
  - Pathological Complete Response (pCR) (ypT0/Tis ypN0)
    - Evaluate neoadjuvant treatment effect at the time of surgery
  - Event-Free Survival (EFS)
    - Evaluate entire treatment regimen effect (neoadjuvant + adjuvant)



Research Question

Research Question:

- How much of the EFS benefit seen in the trial can be attributed to neoadjuvant only IO therapy and continued adjuvant IO therapy, respectively?

Post Hoc Exploratory Solution:

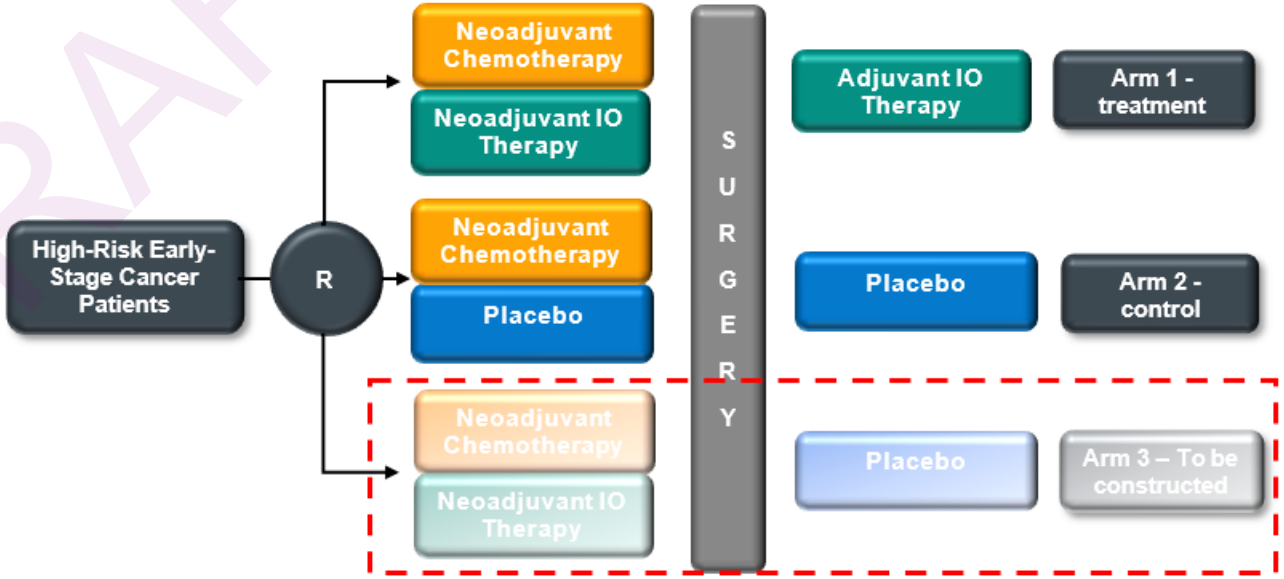
- To construct Arm 3 using certain observed neoadjuvant clinical trial data
- To calculate marginal survival curve and marginal hazard ratio for
  - Neoadjuvant IO therapy only effect (Arm 3 vs. Arm 2)
  - Continued adjuvant IO therapy effect (Arm 1 vs. Arm 3)

Challenge:

- Cross-trial comparison may introduce bias

Statistical Method

- Propensity score is used to reduce bias by balancing baseline characteristics



Propensity Score: Reduce Bias by Balancing Baseline Covariates

- The conditional probability of assignment to treatment given baseline covariates
- **Formula**: $e = P(Z = 1|X)$
  - e: propensity score; Z: treatment received ($Z = 1$ treatment group, $Z = 0$ control group); X: baseline covariates
- **Property**: conditional on the propensity score, the distribution of baseline covariates is the same for the treatment group and control group

$$X \perp Z \mid e$$

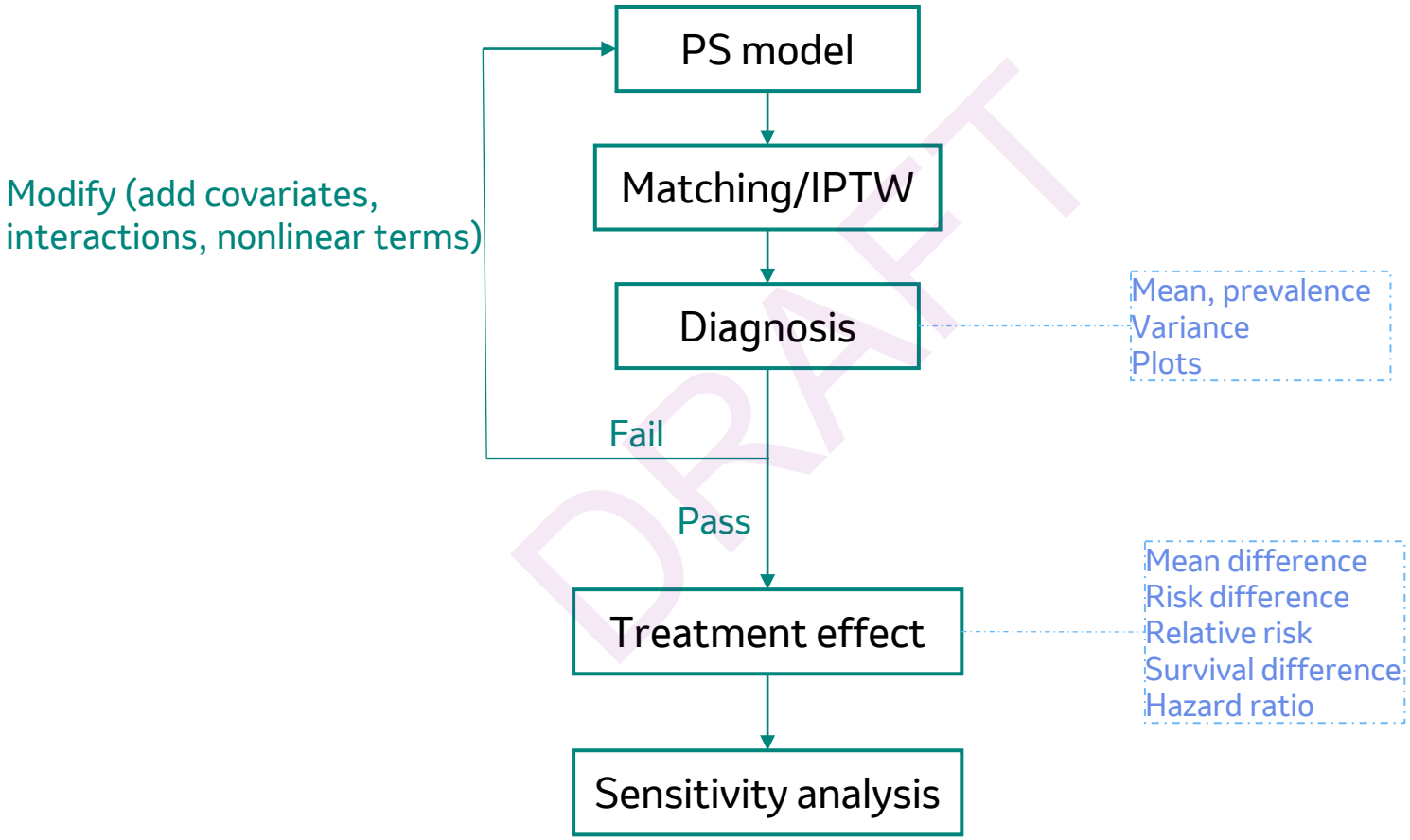
- **Estimation of Propensity Score**
  - Commonly used model: Logistic model

$$\log\left[\frac{P(Z=1)}{1-P(Z=1)}\right] = \beta^T f(X)$$

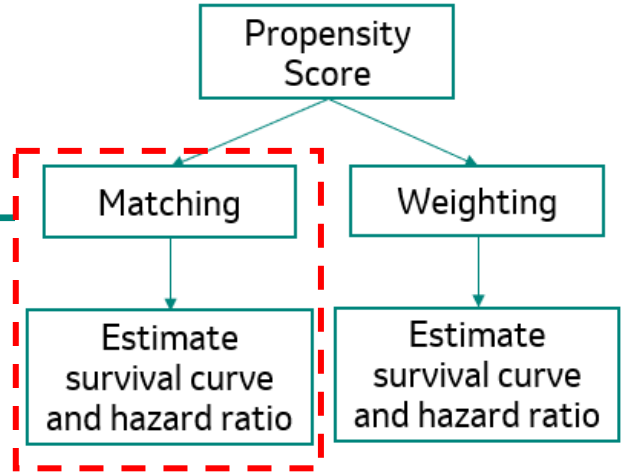
$$\hat{e} = \hat{P}(Z = 1|X) = \frac{\exp(\hat{\beta}^T f(X))}{1 + \exp(\hat{\beta}^T f(X))}$$

    - β: regression coefficients
    - $f(X)$: a function of X; linear terms, higher-order terms and interaction can be included

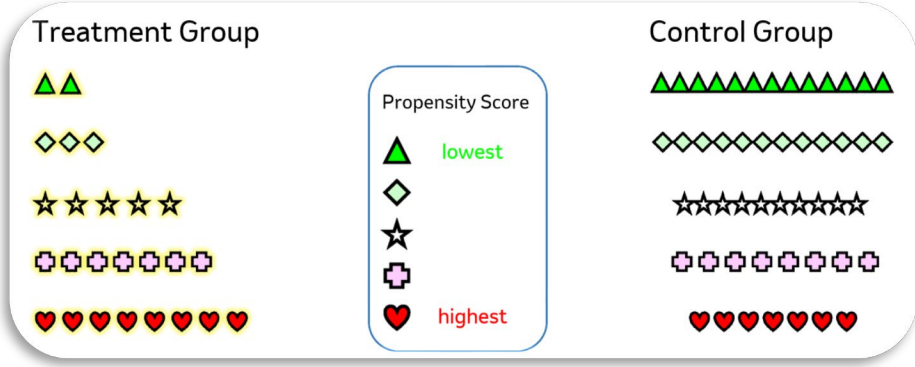
Flowchart

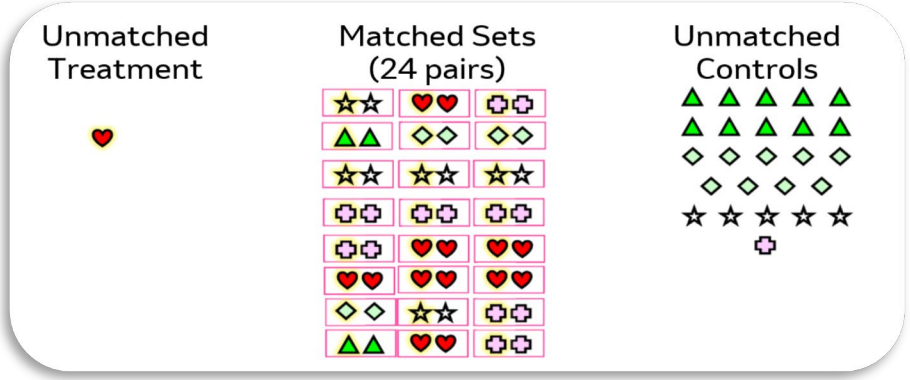


Method 1. Propensity Score Matching (Matching)

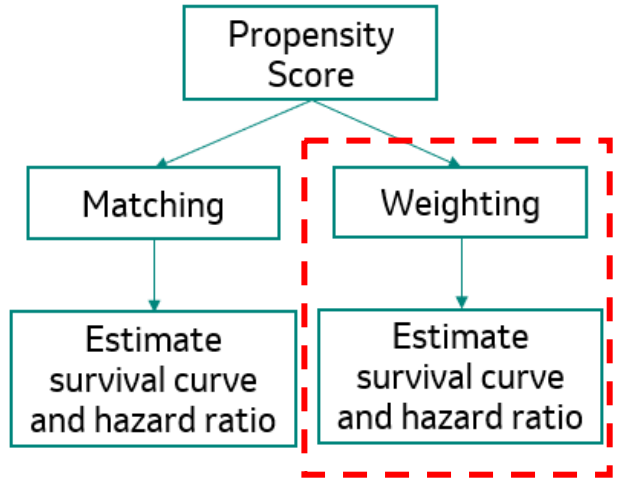


- Form a matched dataset of treatment and control subjects who share similar values of the propensity scores
  - Step 1. Randomly select a subject from treatment group
  - Step 2. Find a subject from control group who has similar propensity score. They form a matched pair
  - Step 3. Repeat this process until no one left in treatment group or no match exists.
- Time to event analysis using the matched dataset
  - Estimate Kaplan Meier curve by treatment and control group
  - Fit Cox model with treatment group as covariate to estimate HR

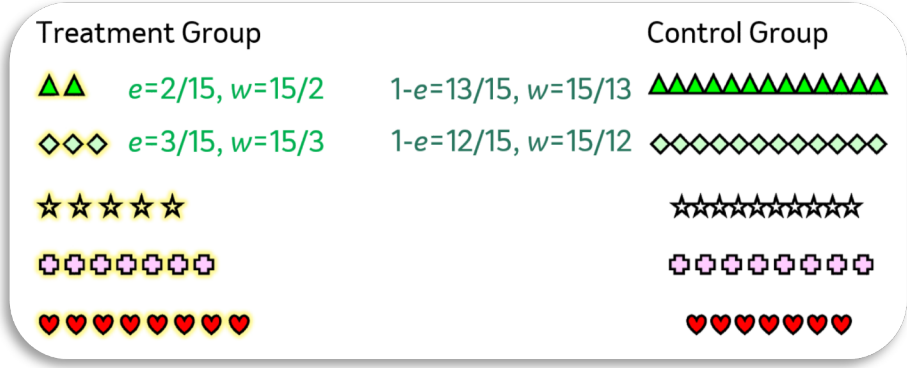


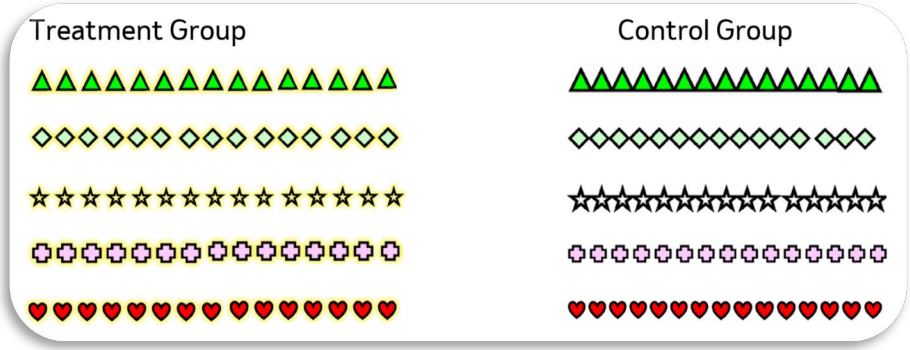


Method 2. Inverse Probability of Treatment Weighting (**Weighting**)



- Form a weighted dataset of treatment and control subjects with weights (w) based on the propensity score
  - For treatment group $Z = 1$, $w = \frac{1}{e}$; for control group $Z = 0$, $w = \frac{1}{1-e}$
  - Stabilized weight (w_s) : Use the marginal probability of treatment instead of 1 in the weight numerator
    - For treatment group $Z = 1$,$w_s = \frac{P(Z=1)}{e}$; for control group $Z = 0$,$w_s = \frac{P(Z=0)}{1-e}$
- Time to event analysis using the weighted dataset
  - Estimate Kaplan Meier curve considering weights
  - Fit weighted Cox model with treatment group as covariate to estimate HR

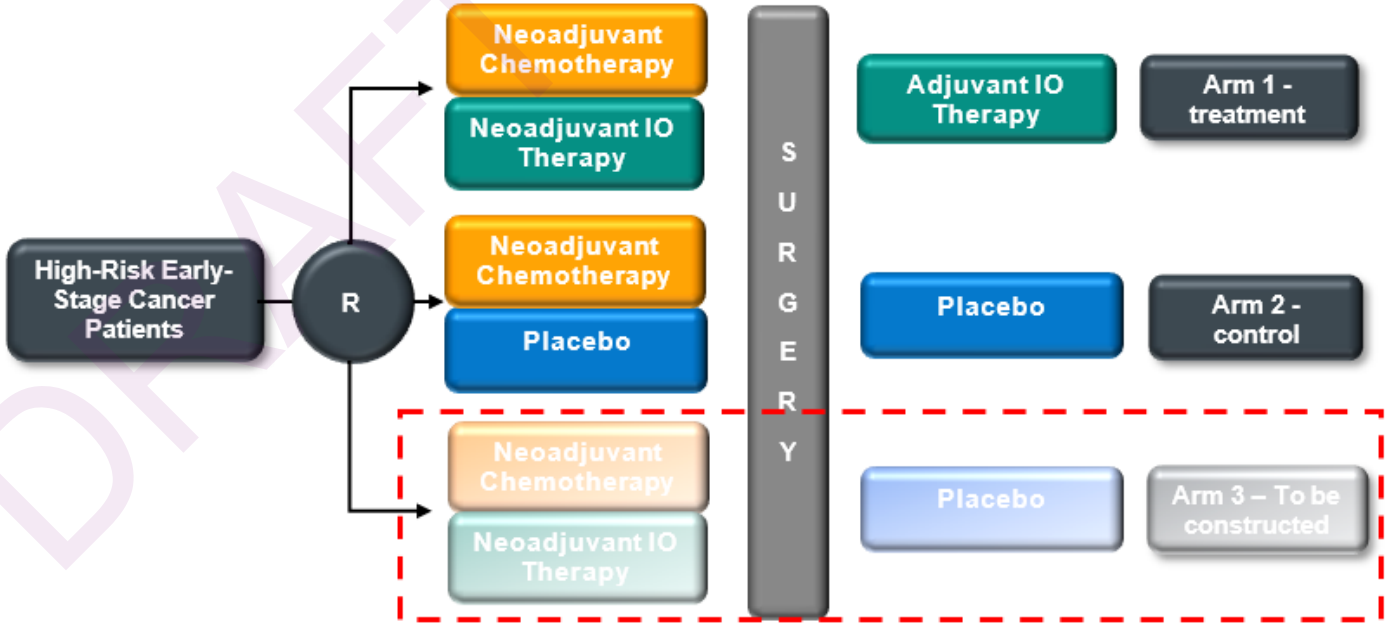




Constructing Arm 3 Using Phase 2 Clinical Trial Data

Option 1. Using phase 2 clinical trial data

- Step 1. Select an appropriate phase 2 clinical trial which treated patients with neoadjuvant chemotherapy plus IO therapy.
- Step 2. Identify baseline covariates in both phase 3 trial and phase 2 trial. Estimate propensity score based on the logistic model with covariates



Potential Bias due to Cross-trial Comparison from Trial Factors May Not Be Full Addressed by Propensity Score Method

Limitation of cross-trial comparison:

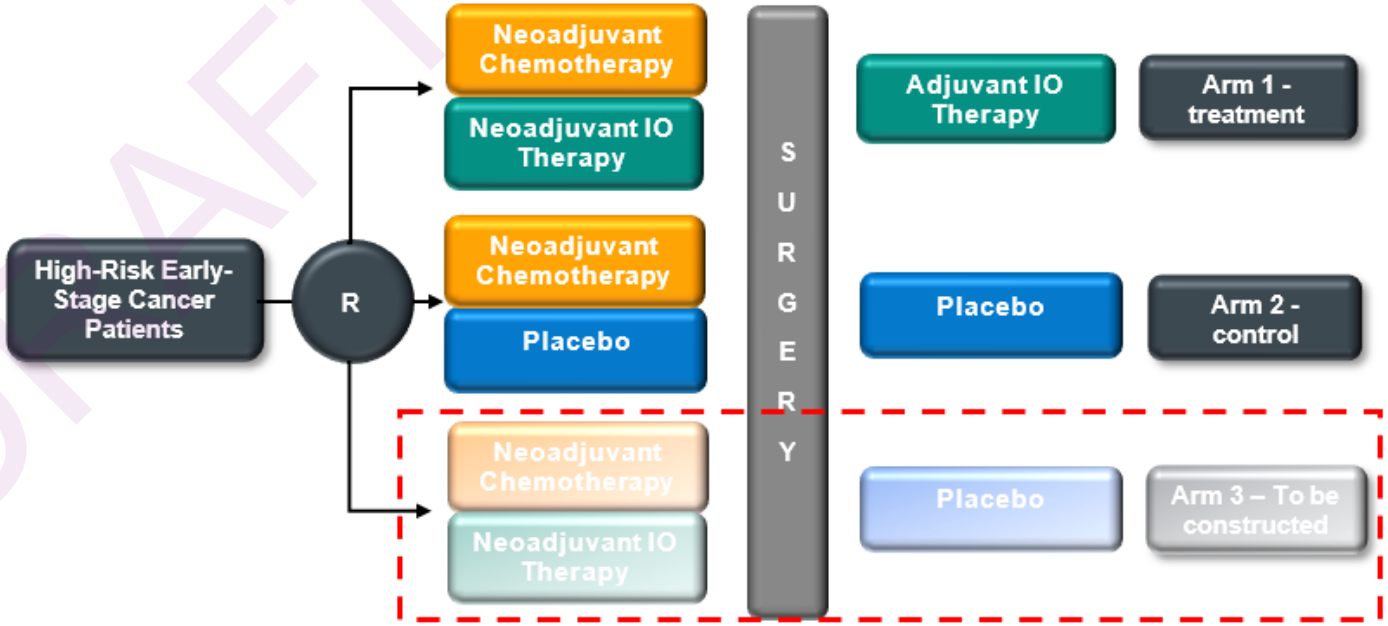
- Patients enrolled from limited sites in the phase 2 trial may not reflect same patient population in the global phase 3 trial
- Efficacy data collected in a short follow up duration in the phase 2 trial may not reflect true patient population EFS rate.
- Due to the nature of phase 2 trial (safety is the primary endpoint), efficacy data collection may not be the priority

Results using phase 2 clinical trial data to construct the 3rd arm may not be interpretable. Because the bias from the difference of trial population, design, and goal, may not be fully addressed by propensity score method.

Constructing Arm 3 Using The Same Phase 3 Trial Data

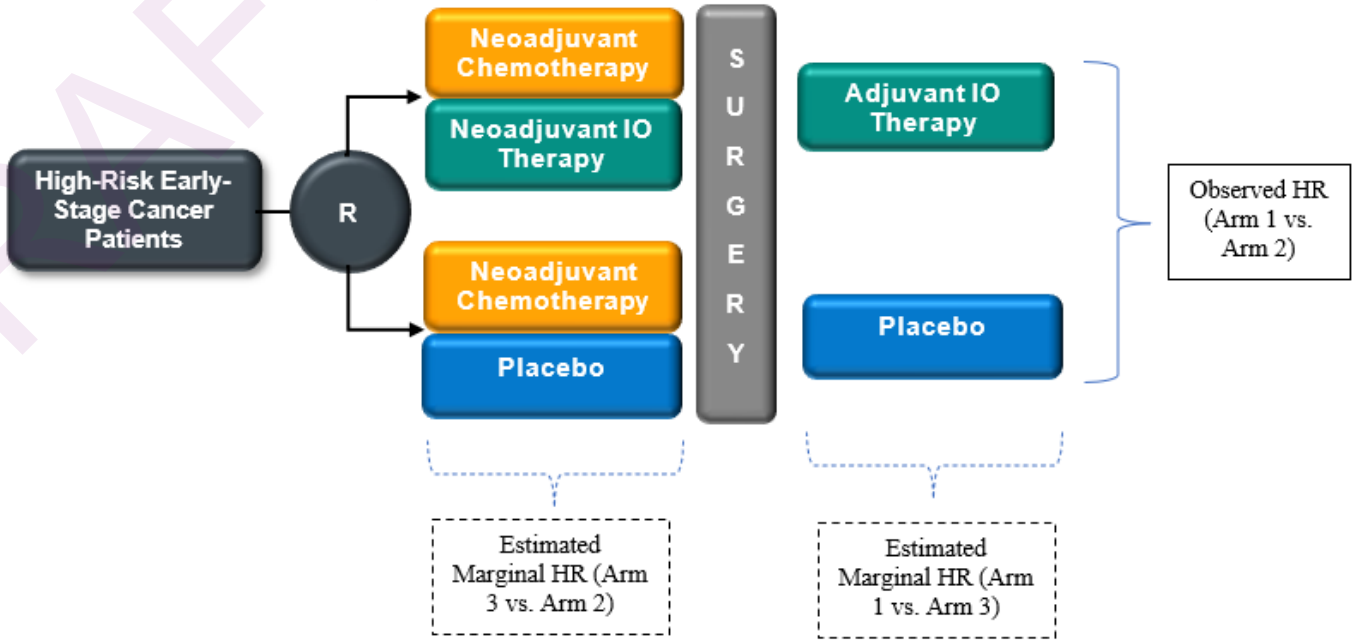
Option 2. From the same phase 3 trial data

- Step 1. From Arm 1, select **patients who did not receive adjuvant IO therapy**
- Step 2. Balance the rate of surgery by selecting patients who underwent surgery
- Step 3. Balance the rate of pCR by **resampling** the selected patients to achieve same pCR rate as in treatment arm
- Step 4. Estimate propensity score based on the logistic model with covariates



Results Interpretation: Continued Adjuvant IO Therapy May Reduce Additional Risk of EFS Events

- Results using clinical trial data to construct the 3rd arm shows
  - Median estimated neoadjuvant IO therapy only effect is **Estimated Marginal HR (Arm 3 vs. Arm 2)**
  - Median estimated continued adjuvant IO therapy effect is **Estimated Marginal HR (Arm 1 vs. Arm 3)**
  - Neoadjuvant IO therapy with chemo may **reduce risk** of EFS events compared with chemo alone.
  - Continued adjuvant IO therapy may **reduce additional risk** of EFS events.
- Results from post hoc exploratory analyses should be interpreted with caution. Cross-trial comparison bias could be introduced by factors other than baseline characteristics.



Discussion

Pros and Cons for Matching and Weighting

Method	Matching	Weighting
Pros	• Straightforward idea, easy to understand	• Use all observations, more efficient, higher power • Extension to longitudinal setting: use Marginal Structural Model to control for time-varying confounding

Cons	• Discard observations without good match
	  • Distort the target population: Matched sample might not be representative of the target population anymore
	  • Less efficient, lost in power
	• Usually require treatment sample size larger than control
	• Making many choices (matching ratio, replacement, matching criteria)
	• For matching with replacement, some subjects could be used many times, leading to high variance
		• Using all observations is not always a good thing
		• Large weight can be problematic: distort your target population

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Thanks to Jing Zhang, our summer intern from Case Western Reserve University

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Q and A