SESSION 2B: THE FUTURE OF REGISTRATIONAL TRIALS WITH MULTIPLE ARMS

FDA U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research®

FDA-AACR Workshop on

HOW MUCH IS ENOUGH? TRIAL DESIGNS FOR TREATMENT REGIMENS WITH MULTIPLE PHASES

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Industry Perspective on Future Perioperative Trials: Efficacious vs Optimal Treatment Regimens

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Disclosure Information

Minghua Shan

I have the following relevant financial relationships to disclose:

Employee of: Bayer

Consultant for: N/A

Speaker's Bureau for: N/A

Grant/Research support from: N/A

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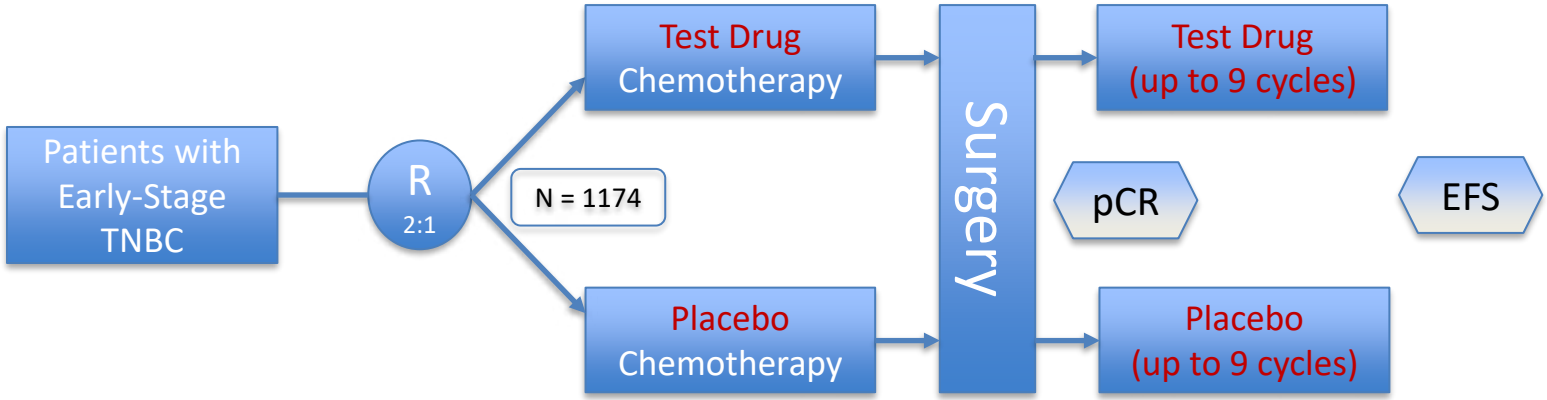
Honoraria from: N/A

- and -

My additional financial relationship disclosures are: None

Case Study: Keynote-522

Pembrolizumab for Early Triple-Negative Breast Cancer

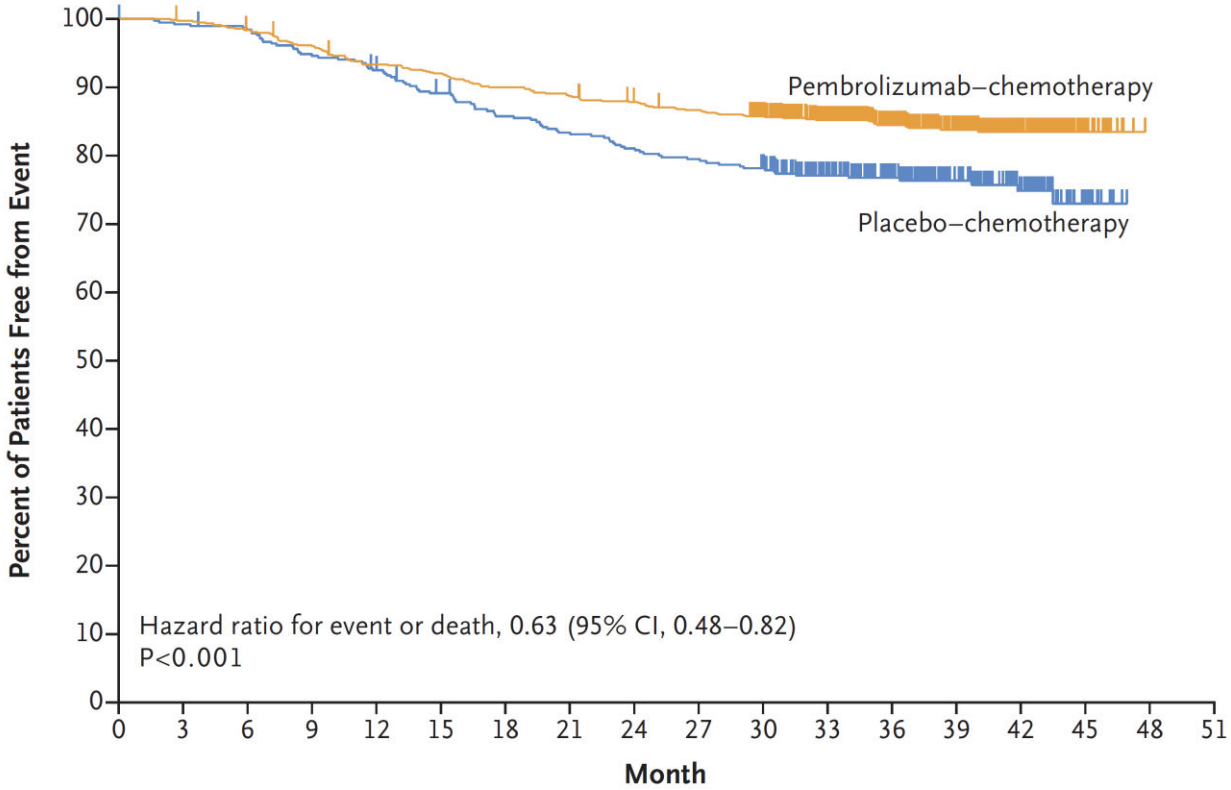


Sample size for EFS:

- 332 events
- 80% power targeting HR of 0.71
- alpha = 0.02 (1-sided)

Test Drug: Pembrolizumab
pCR: pathologic complete response
EFS: event-free survival

Keynote-522 EFS Results



Source: N Engl J Med 2022;386:556-567 VOL. 386 NO. 6 (DOI:10.1056/NEJMoa2112651)

Questions Answered and Remaining

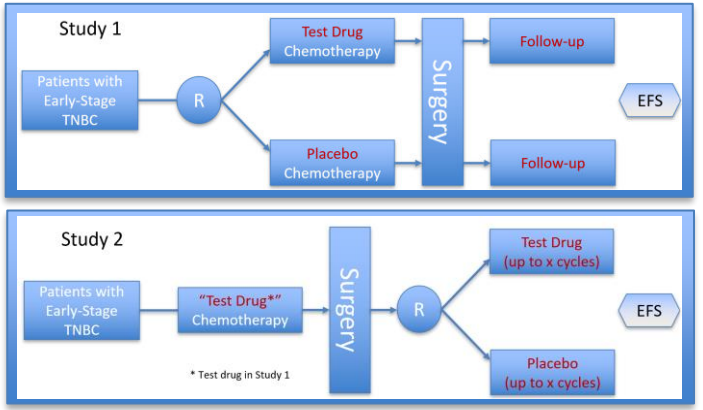
- **Question Answered**: Pembrolizumab regimen (including neo-adjuvant and adjuvant phases) is efficacious (and safe)
- **Questions Remaining**:
  - Contribution of each phase (neo-adjuvant and adjuvant)
  - Do pCR patients need adjuvant treatment?
- **In other words**: The regimen is overall beneficial, but we don't know whether it can be improved (by eliminating potentially unnecessary treatment phase for some or all patients).

Efficacious versus “optimal” treatment

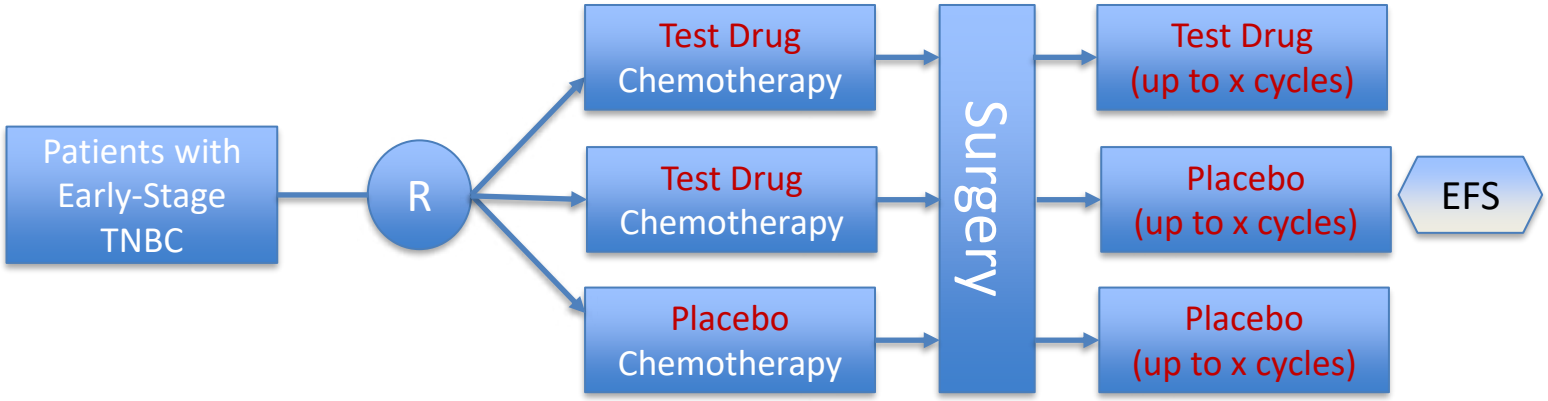
- Ideally, we would like to provide “optimal” treatment
  - Neo-adjuvant and/or adjuvant treatment only for those patients who benefit from them
- Minimum requirement for a treatment regimen to be useful: it is efficacious (and safe)
- Establishing “optimal” treatment may require substantially more time and resources

Option 1: Two studies sequentially

- Study 1: neo-adjuvant vs no neo-adjuvant only
- If study 1 is positive, follow up with study 2
  - Adjuvant vs no adjuvant use only (either for all patients after the tested neo-adjuvant treatment in study 1 or just for non pCRs)
- Additional resources requirement:
  - Two studies and larger sample size overall
  - If both neo-adjuvant and adjuvant phases add to overall efficacy, each study itself will need to be larger (than the “2-arm regimen” approach)
    - If each phase contributes equally, HR for each could be sqrt(0.71) = 0.84.
    - Targeting HR 0.84 would require sample size about 4 times as large (overall sample size ~8 times that of “2-arm regimen” design).
    - Power would only be ~27% for HR 0.84 if sample size is not increased.

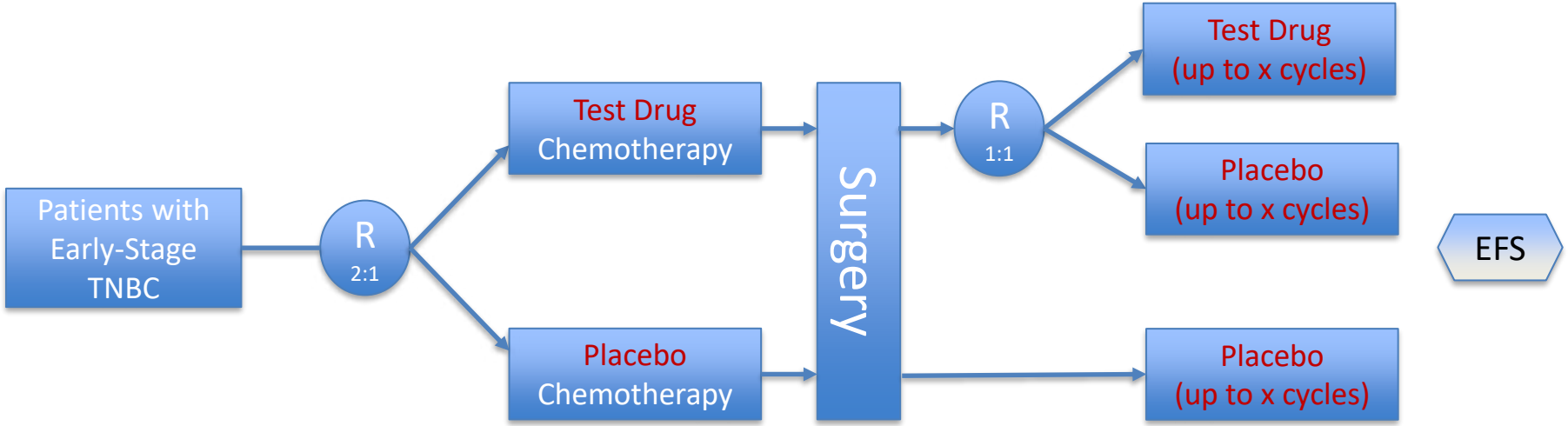


Option 2: 3-arm study



- Similar challenges regarding larger sample size as for option 1
  - Somewhat more efficient than Option 1
  - Up to 6 times the sample size of “2-arm regimen” approach (even without alpha splitting)

Option 3: Rerandomization



- Similar challenges regarding sample size as for options 1 and 2
- Even though may be somewhat more efficient
- But rerandomization may compromise data for the neo-adjuvant question

All these options …

- Could potentially inform on improved benefit/risk over the current neo-adjuvant plus adjuvant treatment regimen approach
- But would require substantially more time and resources
  - Delayed access for patients
- However, they still don't give us the "optimal" treatment
  - Do all patients benefit from adjuvant treatment or only non pCRs?
  - What about duration of adjuvant treatment (e.g., why 9 cycles)?
  - etc.

Realistic future trial designs?

- To obtain some supportive data on phase contributions based on
  - Surrogate endpoint (e.g., pCR in KEYNOTE-522 for neo-adjuvant use) or biomarkers, rather than clinical endpoints such as EFS
  - Less stringent alpha requirement regarding phase contributions (i.e., data suggestive of phase contributions rather than definitive proof)
- Overall study is designed to show efficacy (and safety) of perioperative regimen:
  - 2-arm regimen design (plus supportive data on phase contributions), or
  - 3-arm (or re-randomization) design with much smaller third arm (as it would be needed only for supportive and not definitive data)

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Regulatory Considerations for the Design of Perioperative Trials in Early-Stage Solid Tumors

FDA/AACR Workshop
May 9, 2024

Chi (Chuck) Song, PhD
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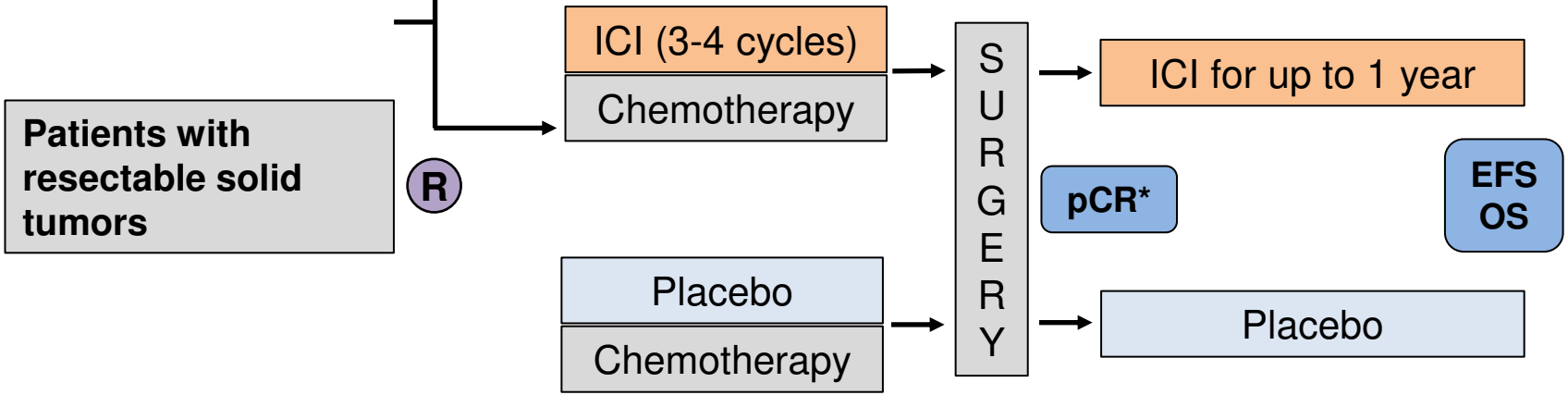
Concerns for Contribution of Phase

- The relative contribution of neoadjuvant and adjuvant treatment on the EFS and OS endpoints is unclear in 2-arm trial designs.



- Patients with early-stage cancers are potentially overtreated and may experience avoidable toxicity and burden

*pCR: pathologic complete response

Can we just use external data from other adjuvant/neoadjuvant trials?

- In general, cross-trial comparisons to establish contribution of component or phase of therapy to the overall treatment effect are not preferred

- In some cases where patient-level data are available, comparisons to external data (using appropriate statistical methods) may be considered as supportive evidence

- However, when considering peri-operative treatment regimens, there are many issues with this approach:
  - Definitions of endpoints may be different for single phase treatment studies
  - Unclear index date for endpoints (and likely immortal time bias)
  - In peri-operative trials, up to 40% of patients may not get adjuvant treatment
  - Patient selection for treatment is related to surgery:
    - In neo-adjuvant trials, not all patients get surgery (no adjuvant treatment)
    - In adjuvant setting, only those patients with resected tumors are eligible

Moving Forward with Better Designs

- In the perioperative setting, it is critical that study design provide evidence of contribution of each phase of therapy
- This is particularly true as additional drugs are being added to both phases of immune checkpoint inhibitor perioperative regimens, in which the contribution of phase was not established
- The best way to accomplish this is with additional trial arms that explore neoadjuvant or adjuvant treatment only

Some Trial Design Options

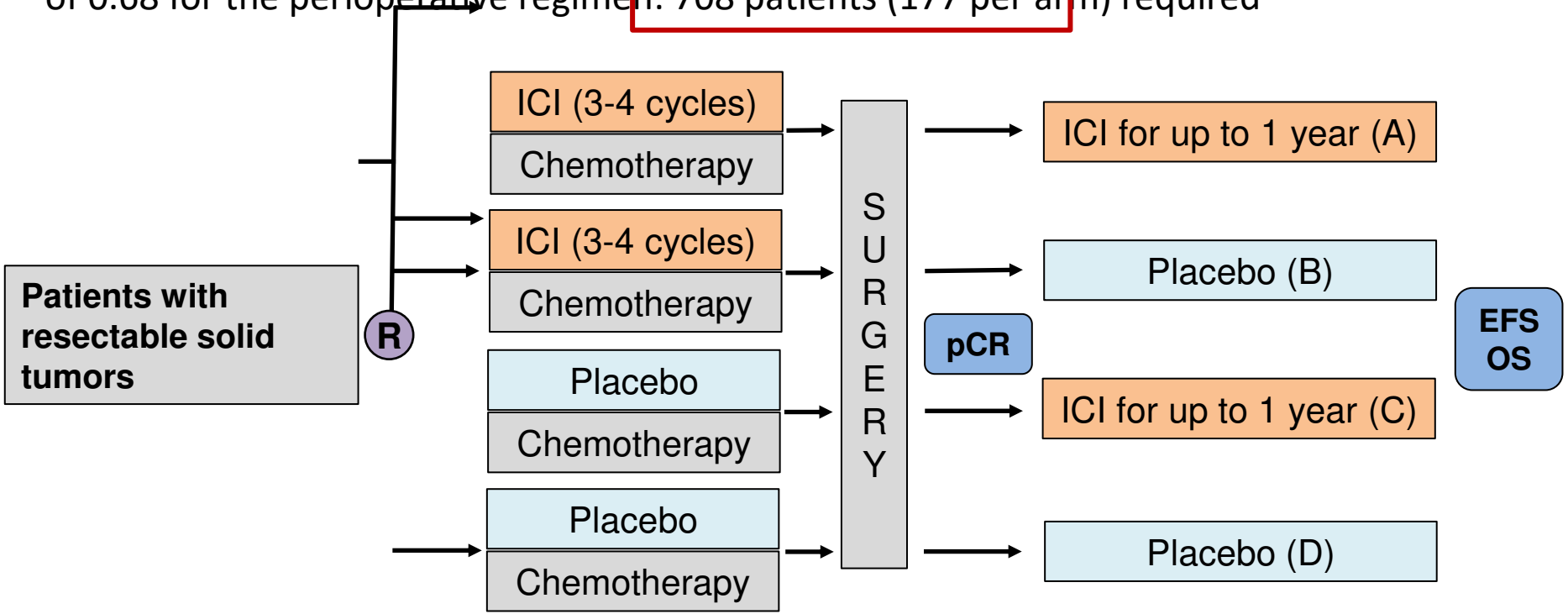
These designs should be considered for both the immune checkpoint inhibitor perioperative regimens, as well as studies with add-on drugs to these regimens

- **4 arm designs:** Ideally, a factorial design is preferred in establishing contribution of components or phase to a combination therapy regimen
- **3 arm designs:** In many cases, only one of the component arms is needed due to prior knowledge of the established SOC and/or disease characteristics
- **SMART designs:** Sequential multiple assignment randomized trials (SMART), e.g. ones with dynamic treatment regimens determined by sequential randomization in each phase of treatment, can explore treatment benefit in multiple phases

The trial designs on the following slides are powered for the primary comparison only, with comparisons of additional arms of the study considered secondary objectives (may not be formally tested)

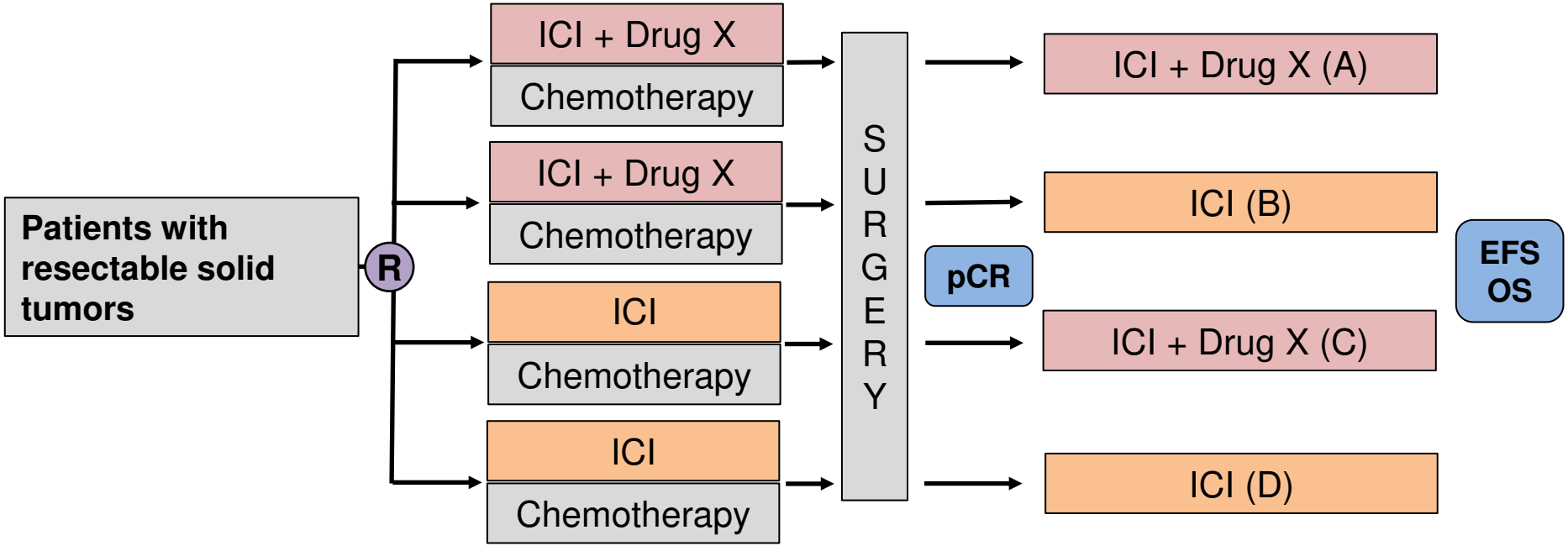
4 Arm Trial Design (Factorial)

Assuming 85% power, type I error (TIE) rate of 0.05 (2-sided), and an EFS hazard ratio (HR) of 0.68 for the perioperative regimen: 708 patients (177 per arm) required



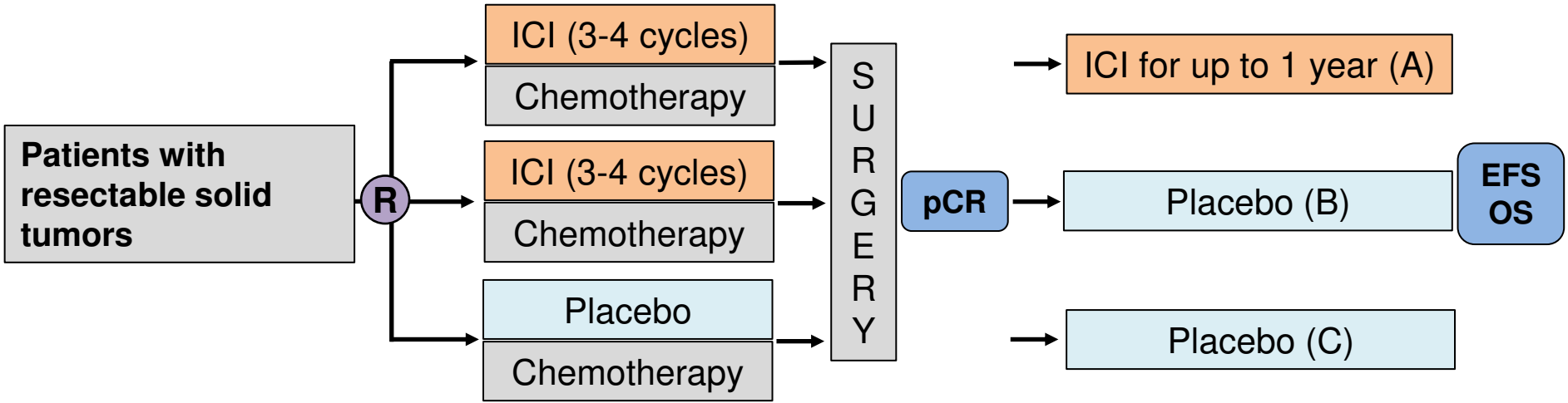
4 Arm Trial Design for Add-on

When adding another drug to the ICI perioperative regimen, the sample size would depend on the expected additional benefit of Drug X to the ICI regimen



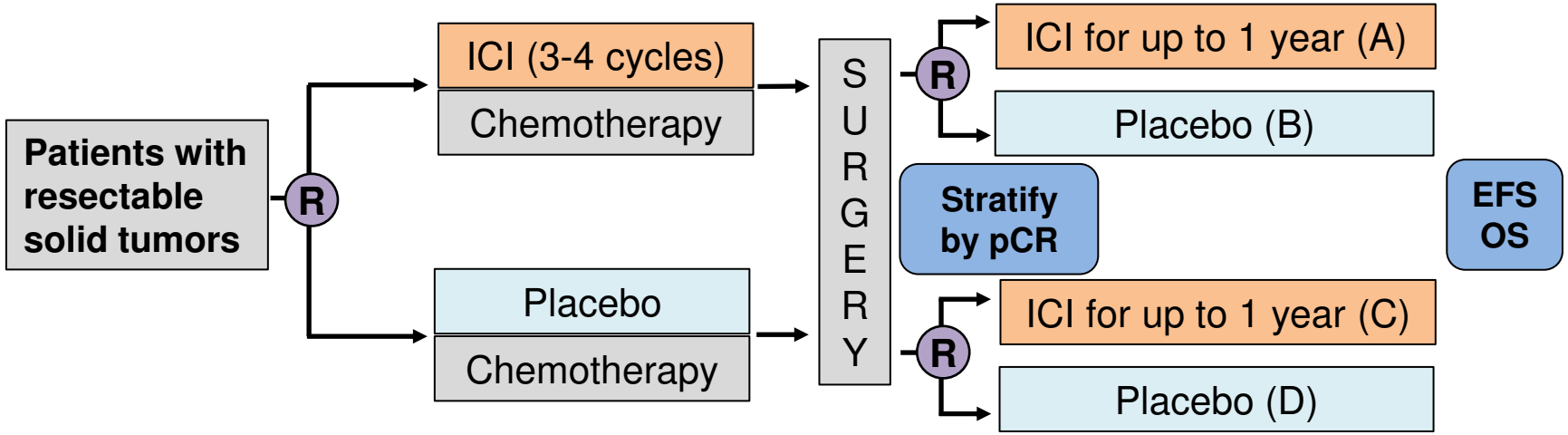
3 Arm Trial Design

Assuming 80% power, TIE rate of 0.05 (2-sided), and an EFS HR of 0.65 for the perioperative regimen: 531 patients (177 per arm) required



SMART Design

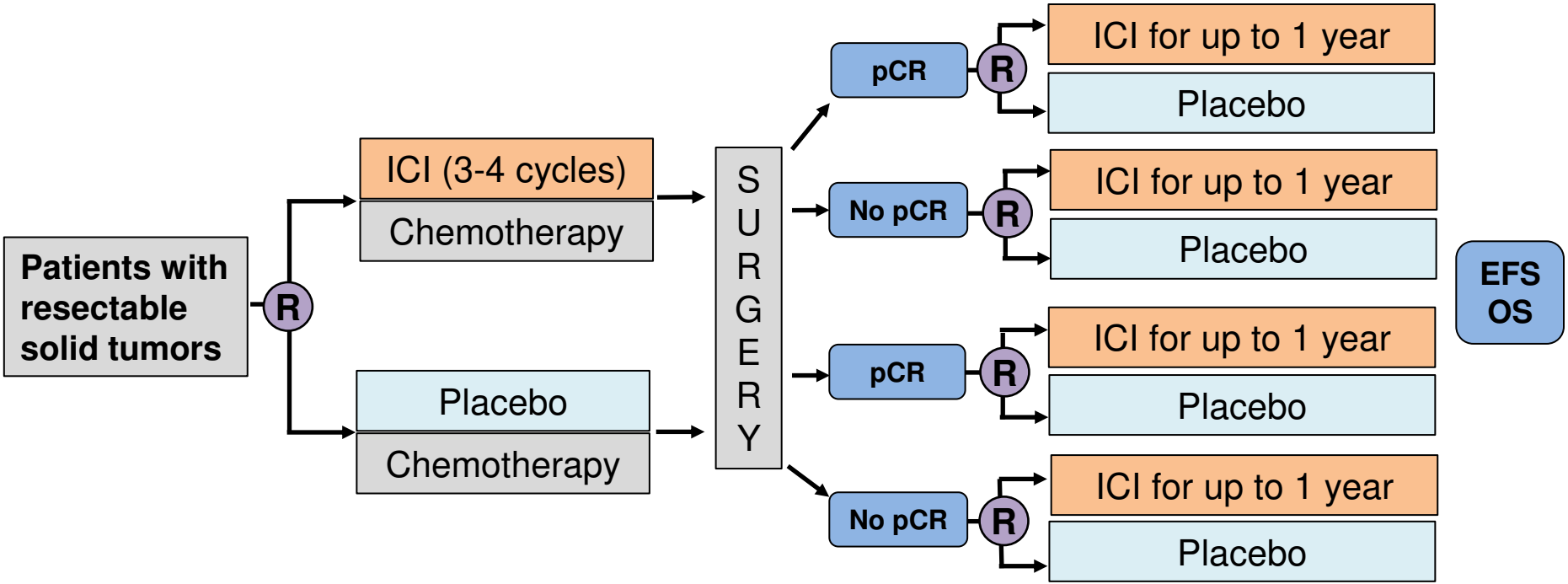
Assuming 85% power, TIE rate of 0.05 (2-sided), and an EFS HR of 0.68 for the perioperative regimen: 708 patients required



Primary comparison: A vs D, which is the same as our 2-arm trials
Secondary comparisons: A vs B and A vs C, which allows for evidence for contribution of phase (also can consider pCR subgroup analyses)

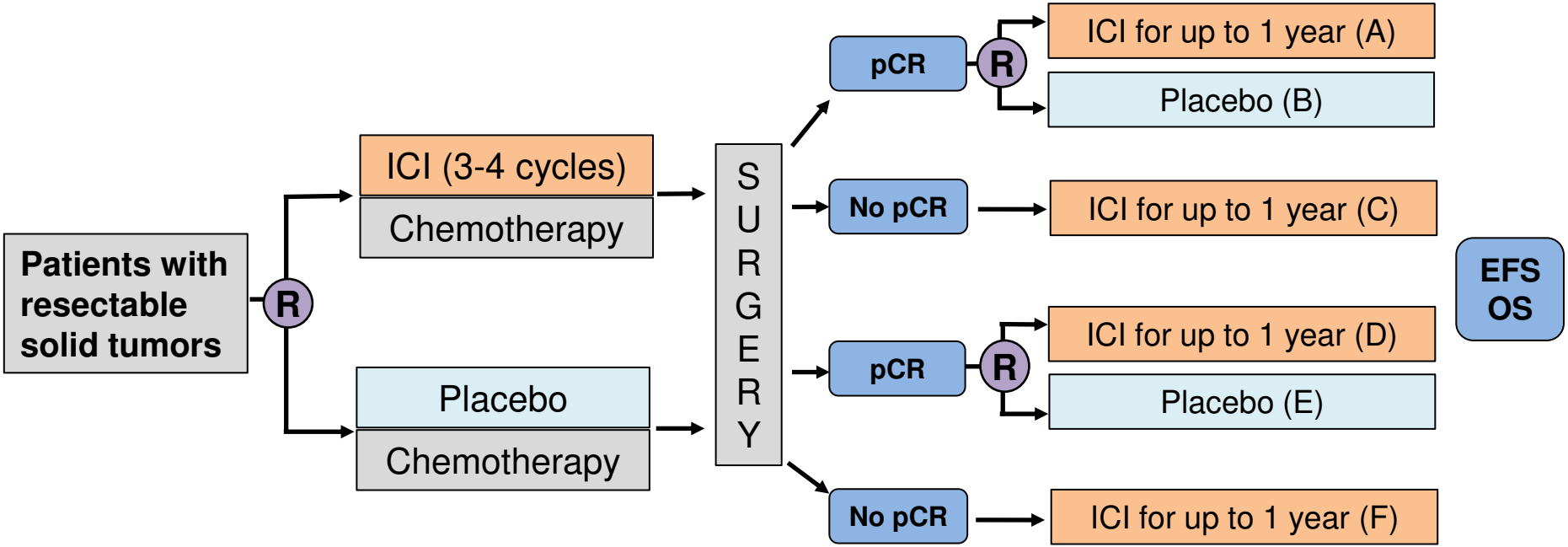
SMART Design, Response Adaptive Randomization

Using SMART designs, randomization within subgroups (e.g. pCR) may be utilized to gain further clinical insight, but may be challenging for subgroups with low prevalence



SMART Design, Response Adaptive Randomization

Hypothesis testing may be altered to reflect real-world questions and usage of phase of therapy according to observed patient biomarkers



Comparisons of Trial Designs

Trial Design	Pros	Cons	Notes
4-arm trial	Answers the COP question; analytically straightforward	Requires larger sample size	Arms for adj/neo-adj contribution could be smaller than perioperative arm (e.g., N:N:1:1)
3-arm trial	Reduced sample size from 4-arm design	Will not formally establish contribution of both phases	Need to have strong rationale for not including a factorial arm
SMART	Can answer more clinical questions than a 4-arm trial; Gives patients greater chance at some therapy than 2-arm design; Potential for biomarker/response based randomization	May be operationally challenging; analytical plans must account for complex design	Unlikely to reduce sample size; Offers comparison of embedded dynamic treatment regimens

Summary and Discussion

- Recent and ongoing perioperative trials indicate benefit to patients who have early-stage solid tumors, but contribution of each phase of treatment is unclear
- Future trials must adequately characterize the contribution of phase to the regimen
- Formal comparison between experimental arms may or may not be required
- Future trials that aim to isolate contribution of phase of treatment may also provide evidence that can support the development of endpoints and/or important biomarkers (e.g. pCR, ctDNA)

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Session 2B Panel Discussion

- Statistical considerations and feasibility of multiple arm studies
- Regulatory considerations for multiple arm studies
- Landscape of perioperative regimens in hematology
- Advantages and disadvantages of trials with rerandomization or multiple arms