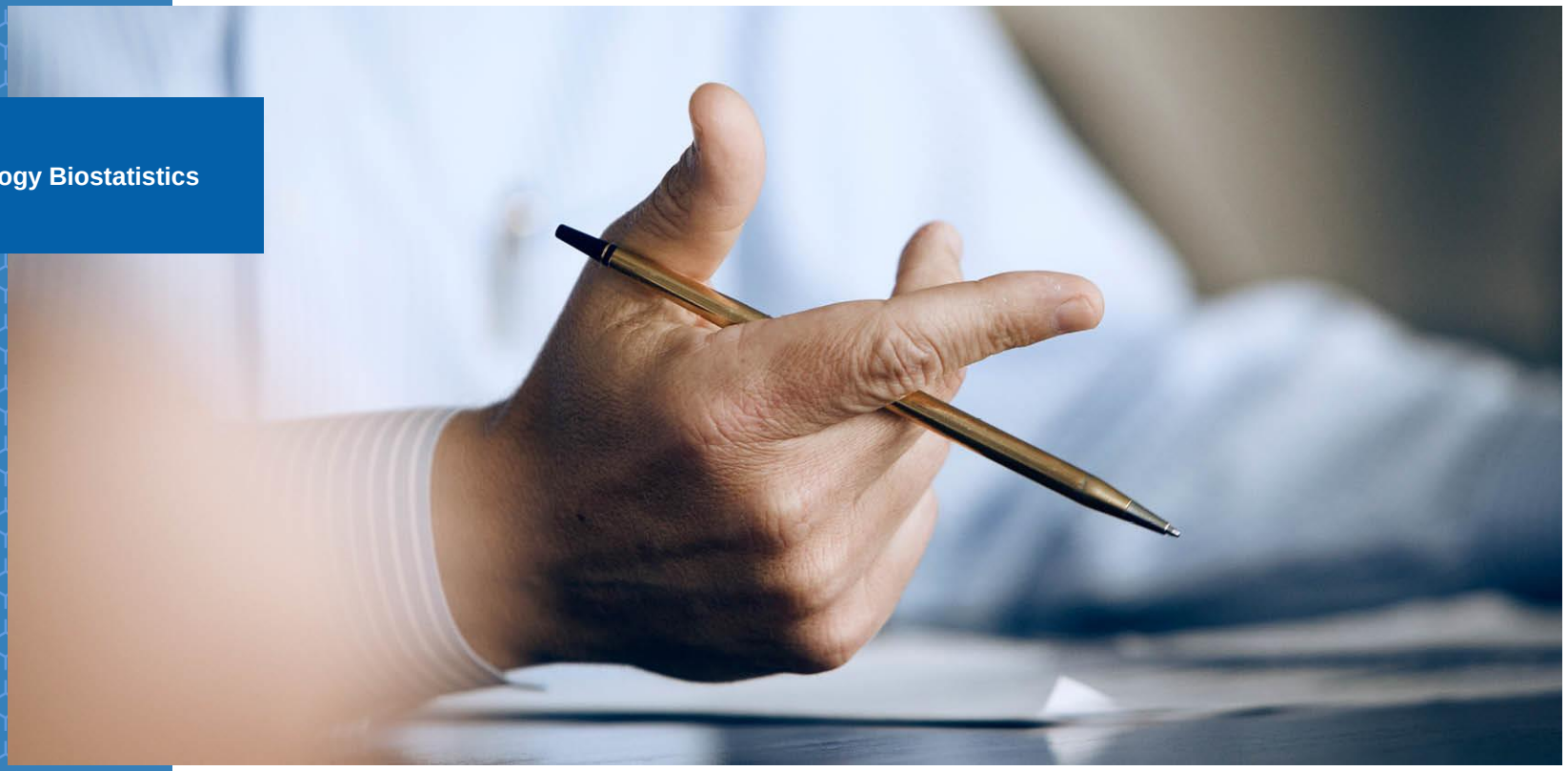
Oncology Biostatistics



Estimand and analysis considerations of clinical trials involving CAR-T – A case study in lymphoma

Evgeny Degtyarev
on behalf of Novartis Team

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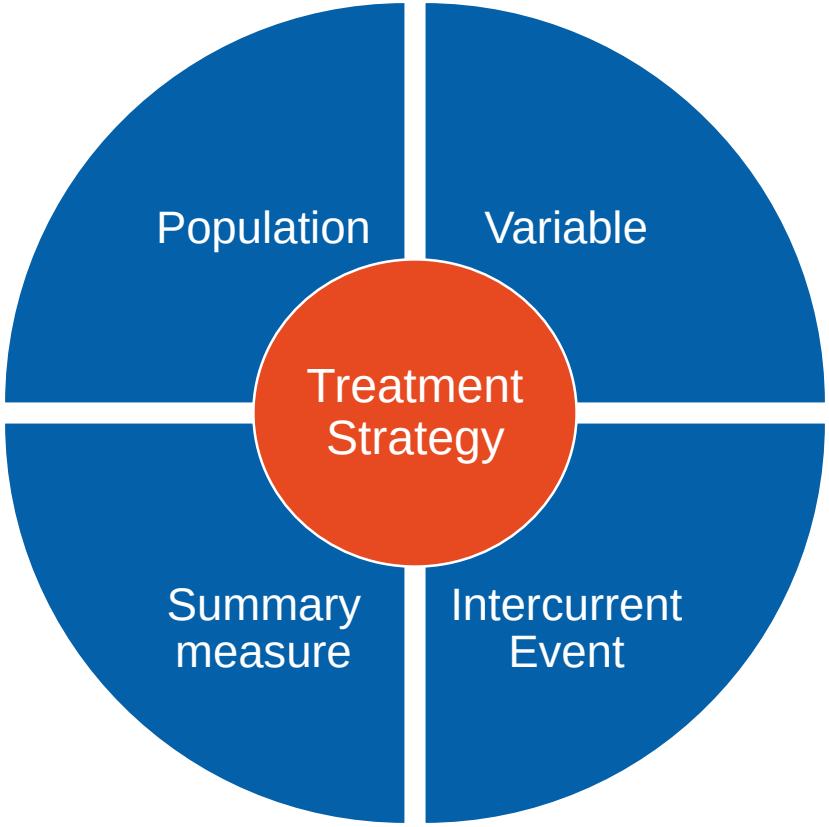
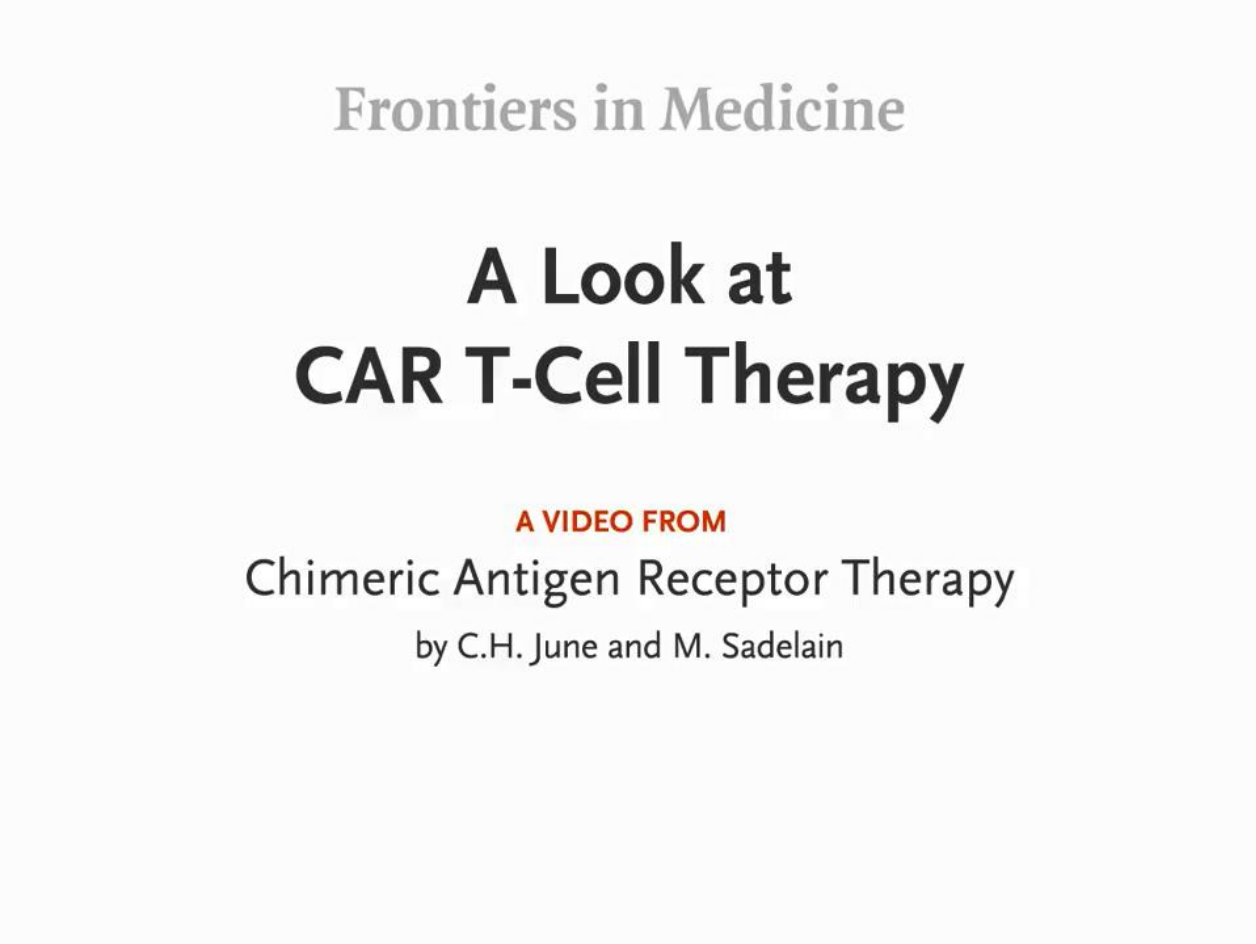
Estimand framework

Need for treatment strategy as an estimand attribute?!

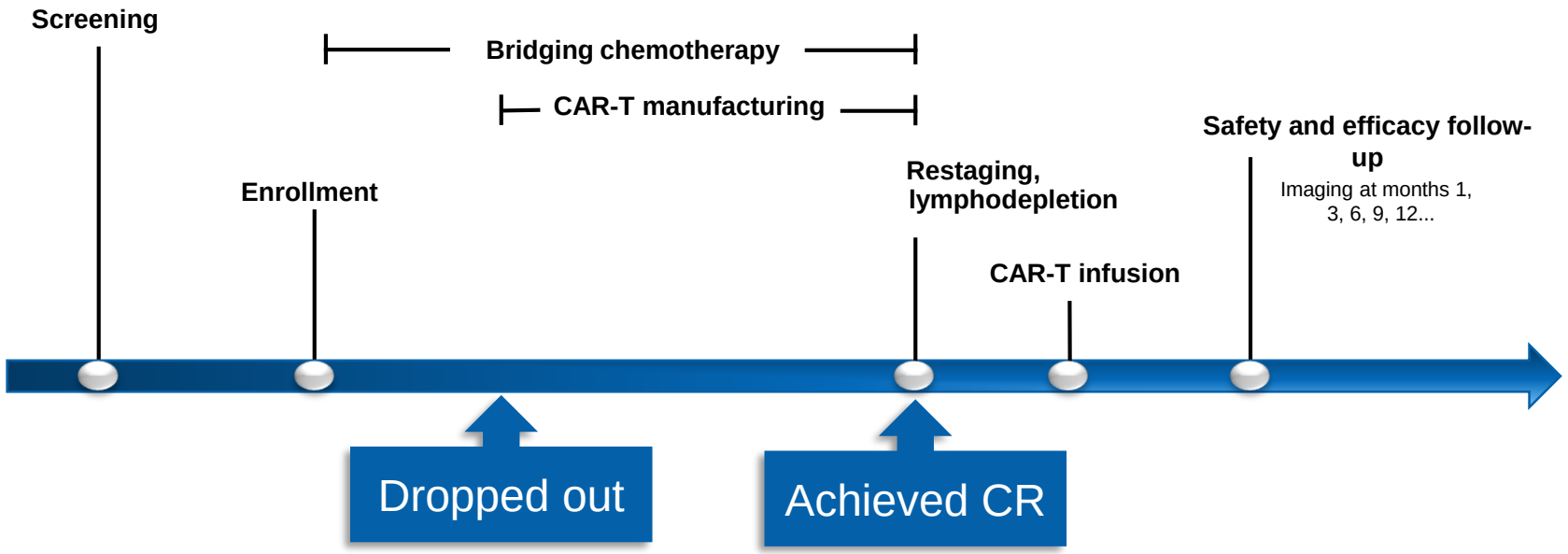


Chimeric antigen receptor T cell (CAR-T) therapy



NEJMvideo Frontiers in Medicine: A look at CAR T-Cell Therapy, a video from the article «Chimeric Antigen Receptor Therapy» by C.H.June and M.Sadelain

Key challenge in designing CAR-T trial



- CAR-T treatment not readily available at study start:
  - Patients in CAR-T arm need to wait, and may take bridging therapy to control the disease
  - Tumor may progress or respond to bridging therapy, before receiving CAR-T
  - Manufacturing process may fail and patients may not receive CAR-T

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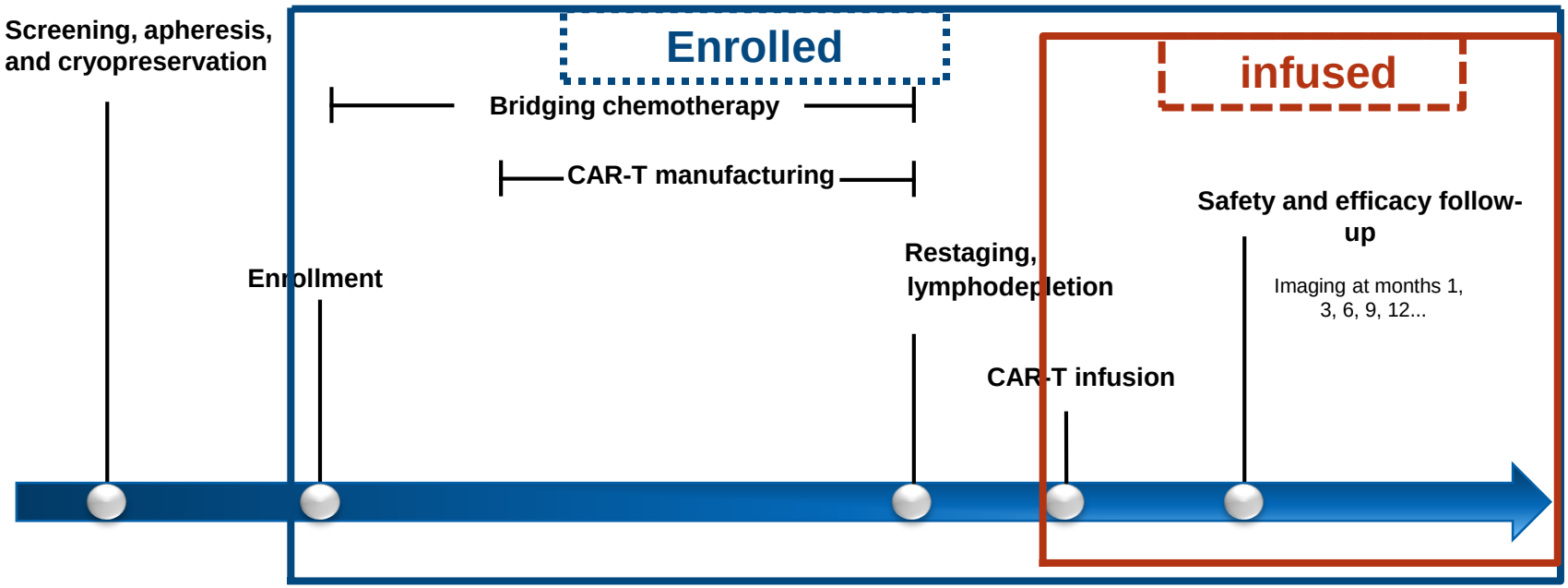
What is the treatment effect of interest?



- CAR-T infusion? (Infused set)
- Bridging chemo followed by CAR-T infusion? (Enrolled set)

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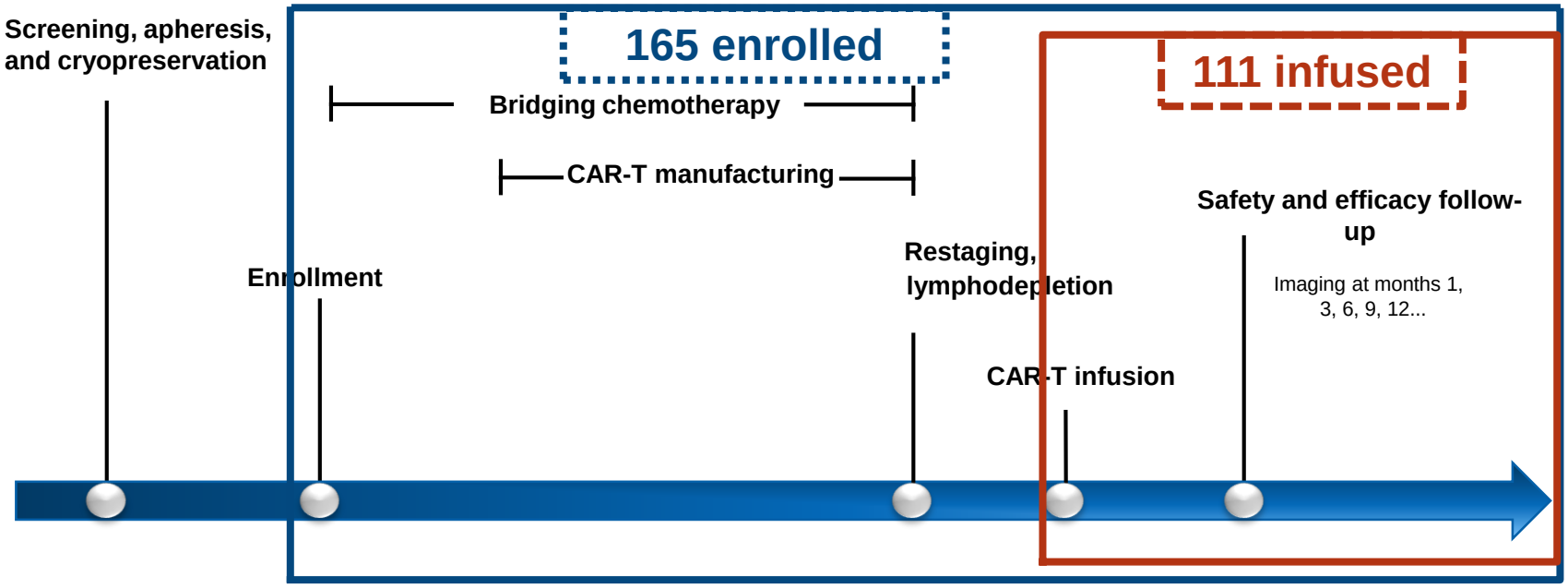
Phase II Single Arm Study in DLBCL

- Adult relapse or refractory diffuse large B cell lymphoma (DLBCL) patients after 2 systematic therapies
- **Primary endpoint: Overall Response Rate (ORR) in Infused set**



JULIET trial, Schuster et al. (2018)

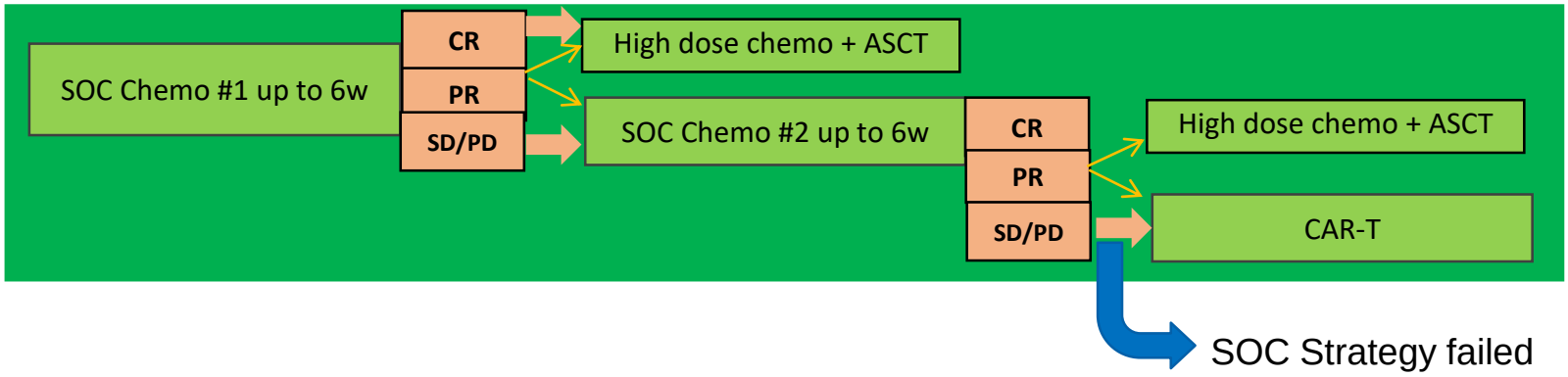
Regulatory feedback during Kymriah approval process

- EMA: Focused on enrolled patients with evidence of disease at enrollment
  - Analyses performed using **all enrolled patients regardless of disease status prior to CAR-T infusion** for all relevant endpoints

- FDA: Focused on infused patients with evidence of disease prior to infusion
  - Retrospectively identified **sub-group among infused patients**
    - Excluded patients without documented disease after bridging therapy

DLBCL treatment landscape after CAR-T approval

- CAR-T approved in US & EU in patients after 2 or more lines of treatment and represents the main option for this population
- Of interest to assess in a randomized trial whether CAR-T therapy is more efficacious than current SOC in earlier line
- For patients eligible for allogeneic stem cell transplant (ASCT) Standard of Care (SOC) represents a complex treatment algorithm:



Study objective in DLBCL

- Comparison of CAR-T vs ASCT?

  → requires randomization of patients for whom manufacturing of CAR-T is completed and remission for ASCT is achieved in run-in

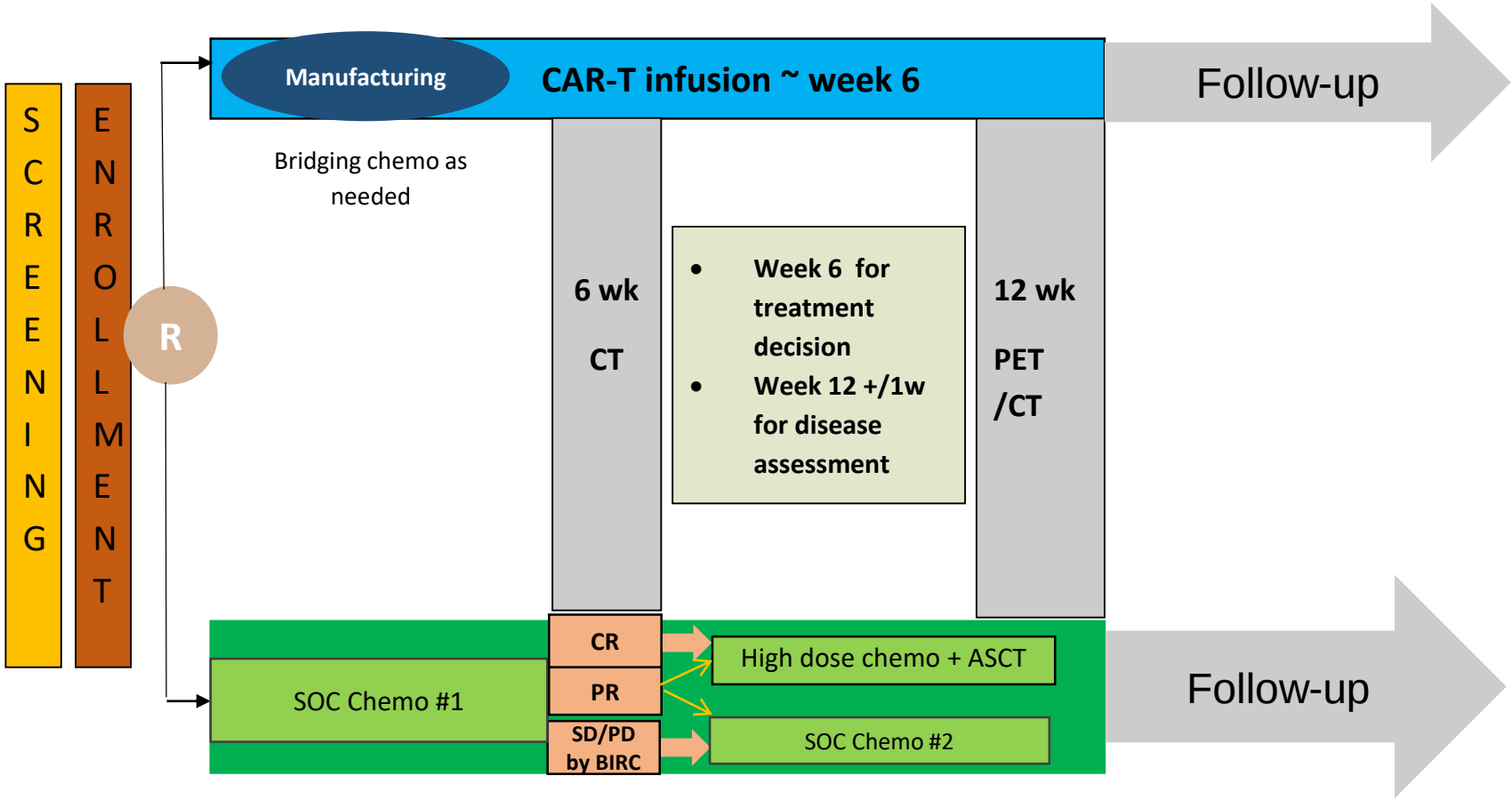
  → is comparison in such population (CAR-T manufacturing completed and CR with chemo achieved) relevant for physicians?

- **Comparison of treatment strategies?**
  - **CAR-T strategy: Bridging chemo followed by CAR-T infusion**
  - **SOC strategy: Chemos followed by transplant**
  - Patients may not receive all components of each strategy!

  → requires randomization prior to the first step of the strategy

  → addressing the question “What is the relative clinical benefit once a CAR-T or SOC treatment strategy is prescribed?”

Phase 3 Study in DLBCL comparing treatment strategies



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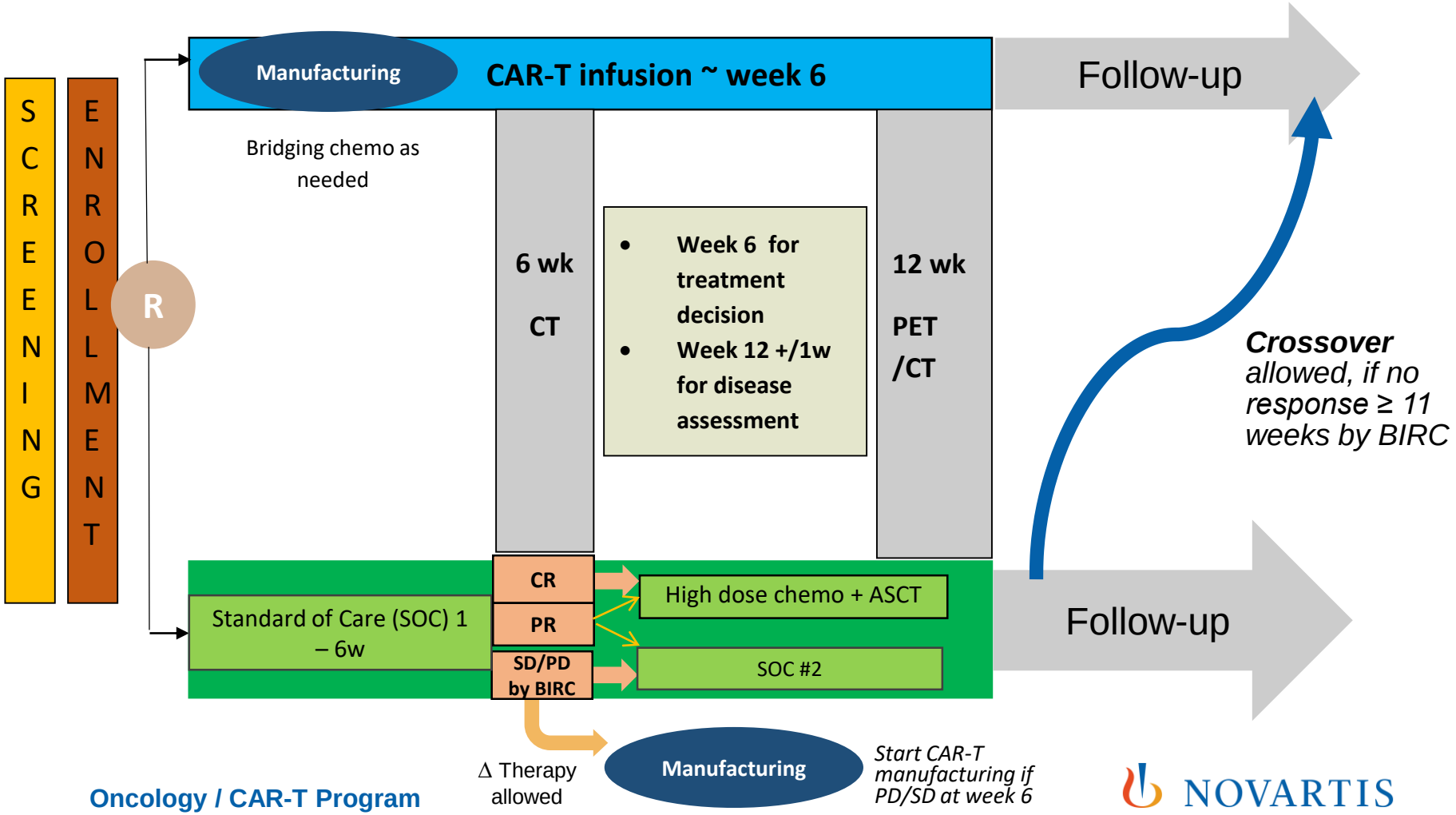
Phase 3 Study in DLBCL comparing treatment strategies

Cross-over allowed as CAR-T the main option after SOC failure



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Primary endpoint

- should represent the time until the treatment strategy is not expected to provide benefit anymore

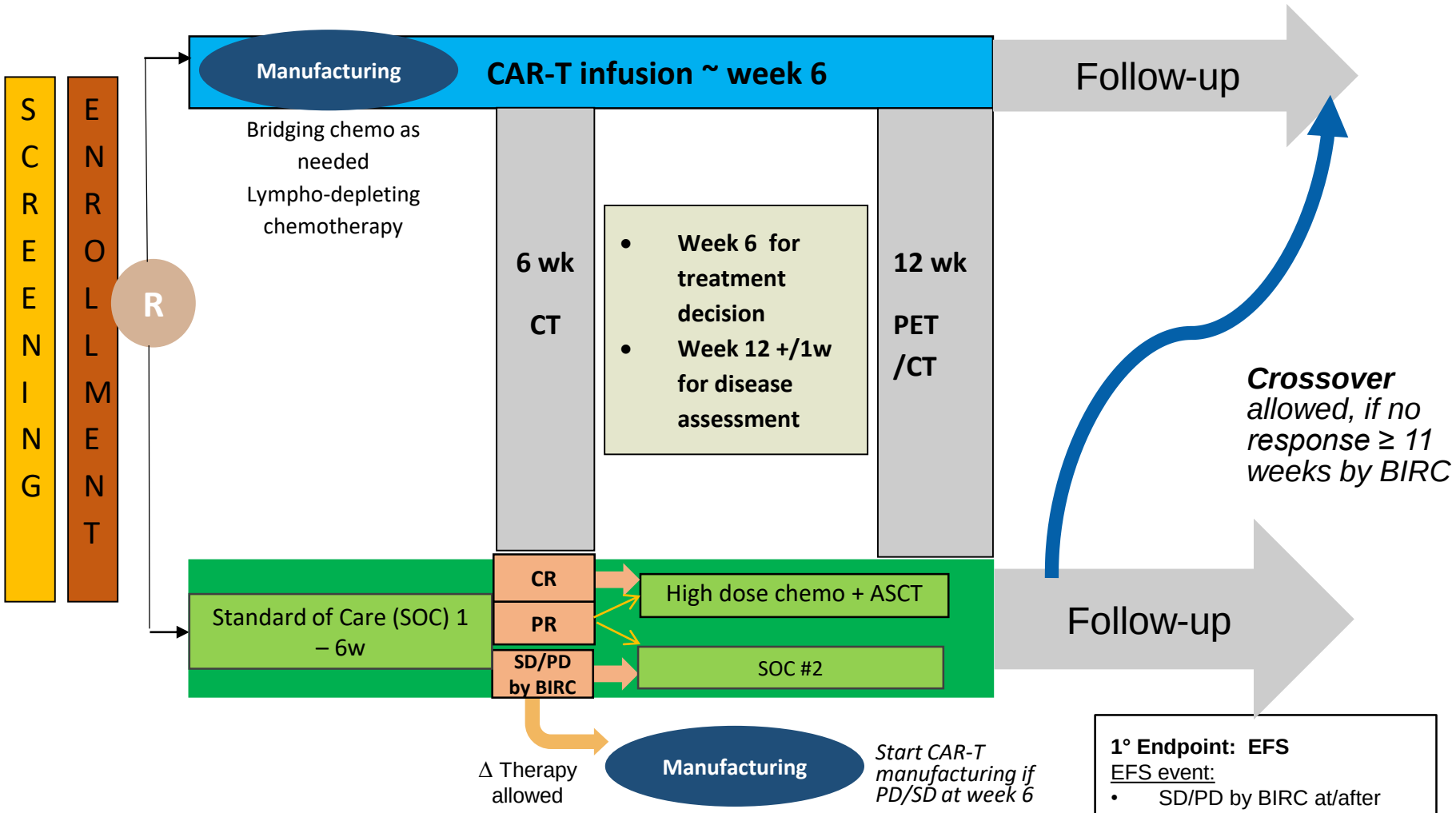
Event-free survival (EFS):

- Composite event of disease progression / stable disease at or after 11 weeks; or death at any time

Intercurrent event	Handling strategy	Justification
PD/SD at week 6 assessment	**Treatment policy**	does not constitute the failure of SOC treatment strategy
Manufacturing failure in CAR-T arm, or failing to receive ASCT in SOC arm	**Treatment policy**	Intrinsic to treatment strategy: those events reflect the clinical reality of the treatment strategy

- **Choice of treatment strategy implies handling of intercurrent events!**

Phase 3 Study in DLBCL comparing treatment strategies



1° Endpoint: EFS

EFS event:

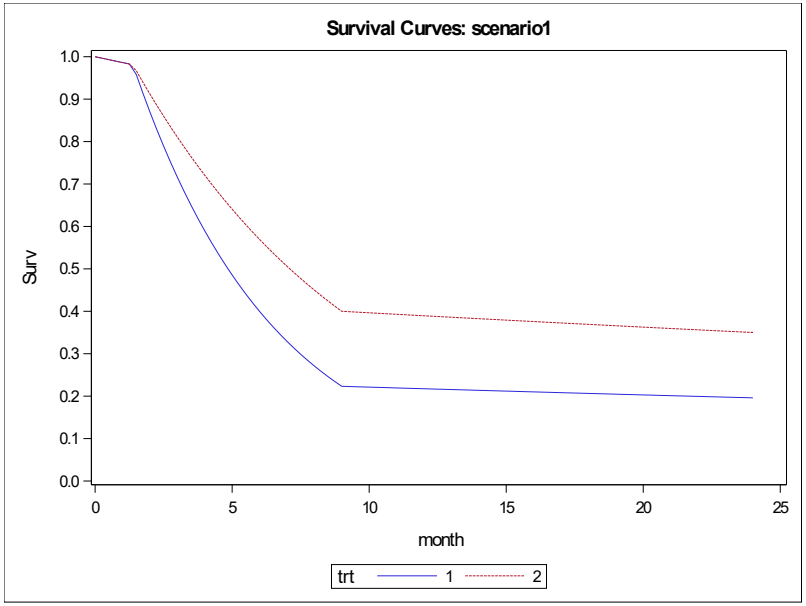
- SD/PD by BIRC at/after week 11
- Death at any time

Summary measures

Challenge:

Non-proportional hazards

- Both arms are on a very similar treatment before CAR-T is available (in case of bridging therapy).
- Curative effect (Plateauing after ~9 month)



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Estimation of treatment effect

Which one (or which ones) should be of interest?

- Cox HR
- Weighted HR
- Piecewise HR
- Difference in restricted mean survival time
- Difference in milestone survival
- Difference in median survival
- Other?

Hypothesis testing

What is the primary focus?

Focus on the comparison during all periods after randomization

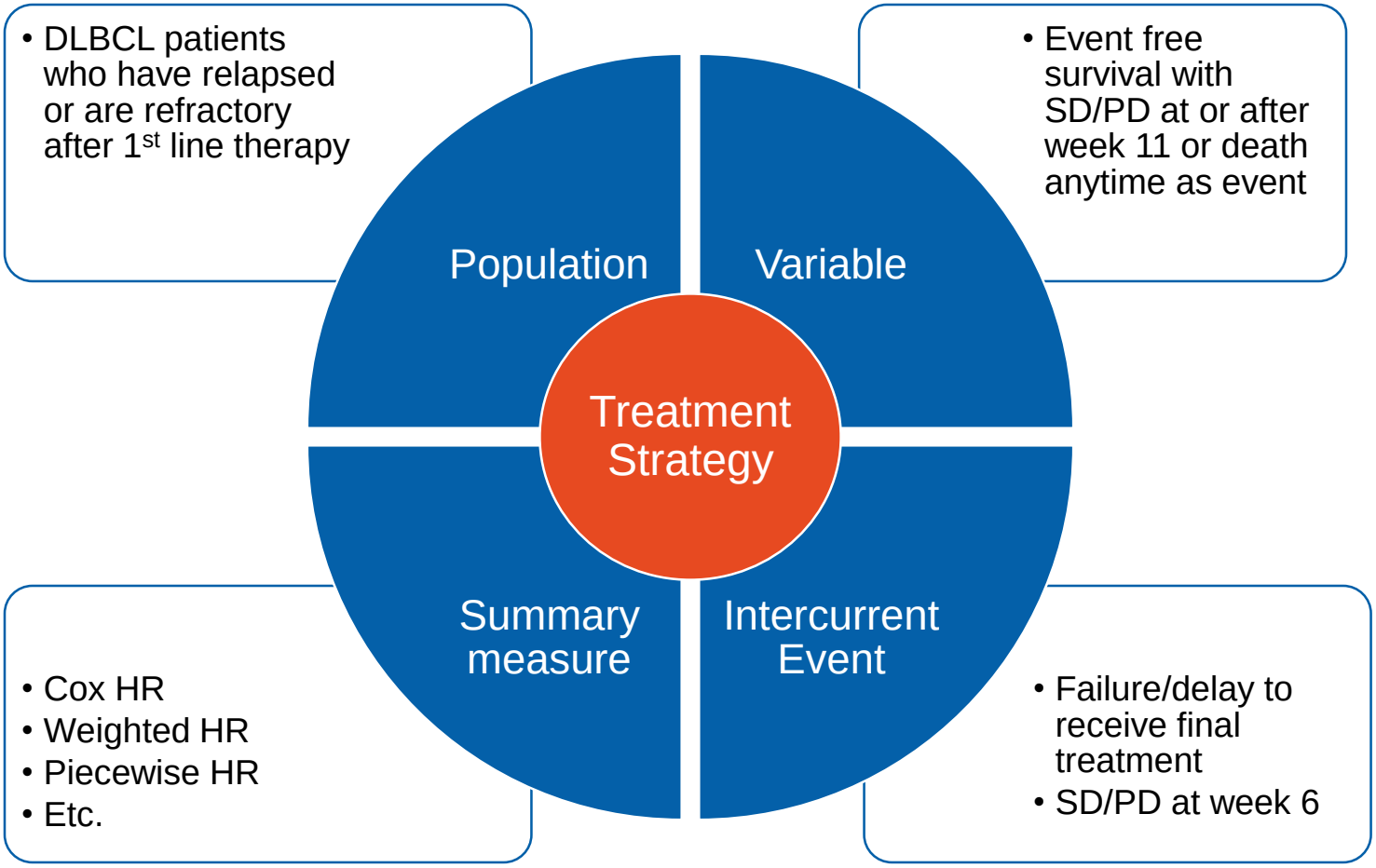
- Regular log-rank test
- Weighted log-rank tests (e.g. Fleming-Harrington)
- Max combo tests

More focus on comparison during periods where differences are expected

- Piecewise weighted log-rank test (e.g. assigning 0 weight during period there is no difference expected)

Both can be of interest!!

Estimand



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Treatment strategy discussions not unique to CAR-T trials

Other Oncology examples:

- Studies with Induction-Consolidation-Maintenance phases
- Studies with neoadjuvant treatment followed by surgery followed by adjuvant treatment

Acknowledgement

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Thank you

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