

CAR T-Cell Therapy Case Study (Principal Stratification)

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Abstract

This case study explores the application of principal stratification in CAR T-cell based therapies for treating blood cancers. By focusing on a specific patient subpopulation based on their potential response to bridging therapy, we aim to address key scientific questions related to treatment effects that go beyond traditional intent-to-treat and as-treated with the investigational compound.

You will gain insights into the diverse perspectives of various stakeholders, including patients, sponsors (i.e. pharmaceutical companies), and regulators, while understanding the relevance of these scientific questions across different clinical study phases. Additionally, you will learn the importance of defining the causal effect(s) – i.e. estimand(s) – of interest and the utility of causal diagrams to communicate these clinical questions effectively to non-statistical collaborators.

This case study will help you understand some challenges in designing early development studies, proposing analytical methods, and interpreting results, all while exploring the nuances of principal stratification and its role in drug development.

CAR T-Cell Therapy Case Study (Principal Stratification)

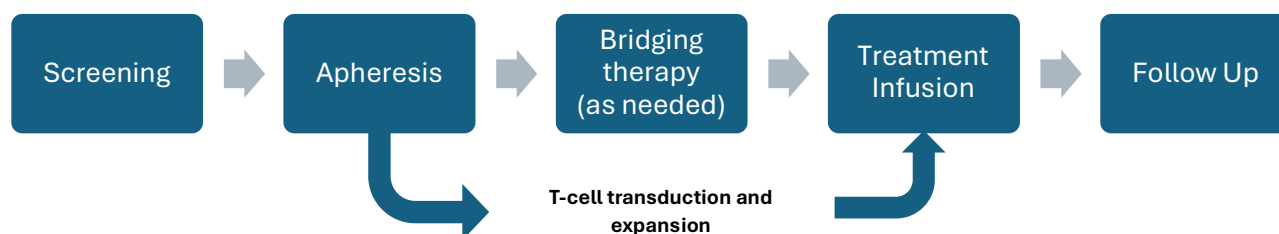
Background

CAR T-cell therapy is an innovative cancer treatment that utilizes genetically modified T-cells from a patient's own immune system. It begins with collecting the patient's T-cells through apheresis, which are then engineered to express chimeric antigen receptors (CARs) that specifically target cancer cells. After expanding these CAR T-cells to millions, they are infused back into the patient, where they can recognize and attack cancer cells.

Typical CAR T-cell therapy study flow

1. **Screening:** During the screening phase, eligible patients are identified based on disease and study specific inclusion and exclusion criteria.
2. **Apheresis:** Apheresis is the process of collecting T-cells from the patient's blood.
3. **Bridging Therapy (as needed):** Prior to the administration of CART therapy, some patients may require bridging therapy such as additional radiation therapy, chemotherapy or targeted therapy. This step is intended to manage the disease while waiting for the CART treatment manufacturing.
4. **Study Intervention Administration:** The re-introduction of genetically modified T-cells into the patient.
5. **Follow Up:** Following the intervention, regular follow-up visits are conducted to monitor response and assess safety.

Figure 1: Study Flow Chart



Role of Bridging Therapy

Bridging therapy serves as an interim treatment for patients awaiting the production and availability of their CAR-T cells. During the initial phases of clinical drug development for new CAR-T therapies, the manufacturing time can be significantly prolonged, often lasting several months. As development transitions to later phases and enters production use, the manufacturing timeline is generally shortened to just a couple of weeks. This improvement comes from refined procedures and the increased expertise gained during earlier phases, leading to more streamlined production.

Consequently, response to bridging therapy is a critical intercurrent event that can have an effect on outcomes when evaluating CAR-T cell therapies. Understanding the influence of the use of bridging therapy is crucial for drug developers involved in CAR-T therapy. Notably, the impact of bridging therapy can vary considerably between earlier and later phase studies, highlighting the need for careful consideration in each stage of development.

Principal Stratum Strategy

Defines a subpopulation of interest according to the potential occurrence of an intercurrent event on one or all treatments.

Scientific Questions of Interests

1. **On Treatment Estimand:** For patients with a specified blood cancer, what is the probability of achieving a response following treatment infusion but prior to potential subsequent anti-cancer therapy?
2. **ITT Estimand:** For patients with a specified blood cancer, what is the probability of achieving a response following apheresis but prior to potential subsequent anti-cancer therapy?
3. **Principal Statum Estimand:** For patients with a specified blood cancer that would not respond to bridging therapy, what is the probability of achieving a response following apheresis but prior to potential subsequent anti-cancer therapy?

CAR T-Cell Therapy Case Study Prompts

- Brainstorm in the team which scientific question may be most relevant to which stakeholder of drug development
 - Patients
 - Sponsors (i.e. pharmaceutical companies)
 - Regulatory bodies (e.g., FDA and EMA)
 - Health technology assessors (HTAs) that evaluate the clinical, economic, and social impacts of health technologies to inform healthcare decision-making
 - Phase of Clinical Development (early/late).
- How would you formally define these estimands?
- How would you communicate these clinical questions to a non-statistical collaborator? Draw a causal diagram to communicate your problem with your collaborators.
- Create a flow diagram for an early development study (Phase 2a/b) addressing these scientific questions of interest.
- What analysis method or model would you propose? Discuss how principal stratification is different from subgroup analysis.

When you're done, please email a picture of your results to iscb.causal.symposium@gmail.com and feel free to cc your team members to share the work.

CAR T-Cell Therapy Case Study – On Treatment Estimand

Clinical question of interest

For patients with a specified blood cancer, what is the probability of achieving a response following treatment infusion but prior to potential subsequent anti-cancer therapy?

Estimand Definition

Treatment:

-
-

Population:

Endpoint (variable):

Population-level summary:

Intercurrent events (ICEs) and corresponding strategies:

Intercurrent Event	Strategy	Description/Notes

Key Implementation Elements

CAR T-Cell Therapy Case Study – ITT Estimand

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