Challenges and Lessons Learned in Autologous CAR T-Cell Development from a Statistical Perspective

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Outline

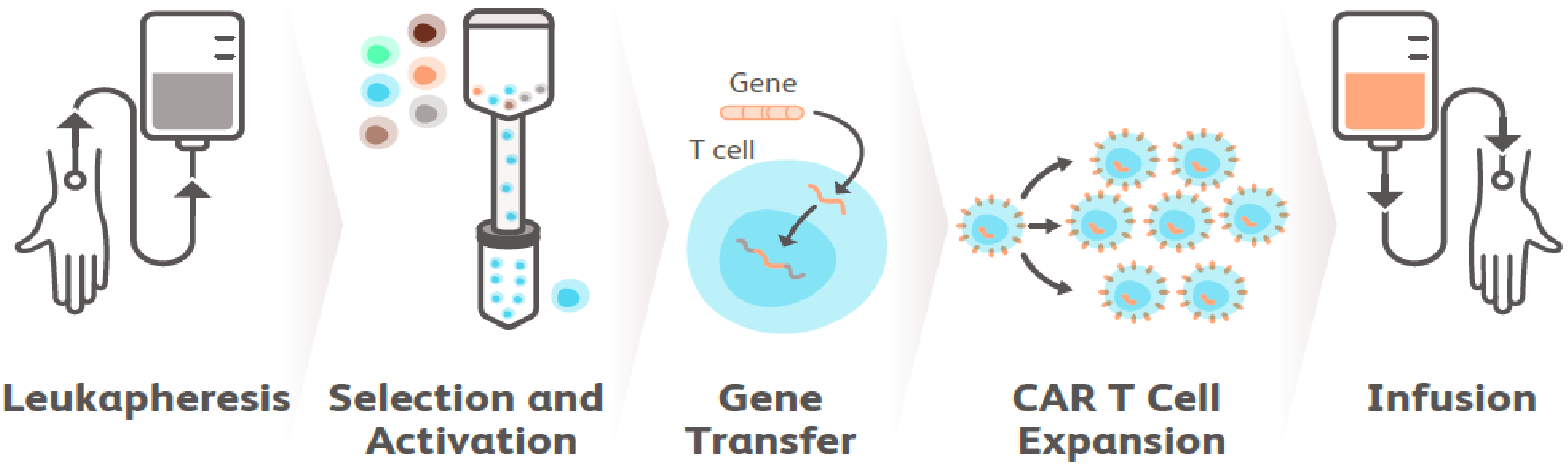
- What's CAR T-cell therapy?
- ASA CGT Scientific Working Group
- Challenges and Lessons Learned
  - Dose-finding
  - Estimand framework
  - Other Key lessons

Chemotherapy versus Immunotherapy

- Chemotherapy is a treatment with drugs that kill cancer cells directly
- Chemotherapy drugs do not differentiate between cancer cells and healthy cells
- Immunotherapy is a treatment that enhances a patient's own immune system to fight cancer
- Types of immunotherapy
  - ❑ Immune checkpoint inhibitor
  - ❑ Monoclonal antibody
  - ❑ Drug-conjugated monoclonal antibody
  - ❑ Bispecific monoclonal antibody
  - ❑ Cell therapy, in particular **CAR (Chimeric antigen receptor) T-cell therapy**

CAR T-Cell Therapy

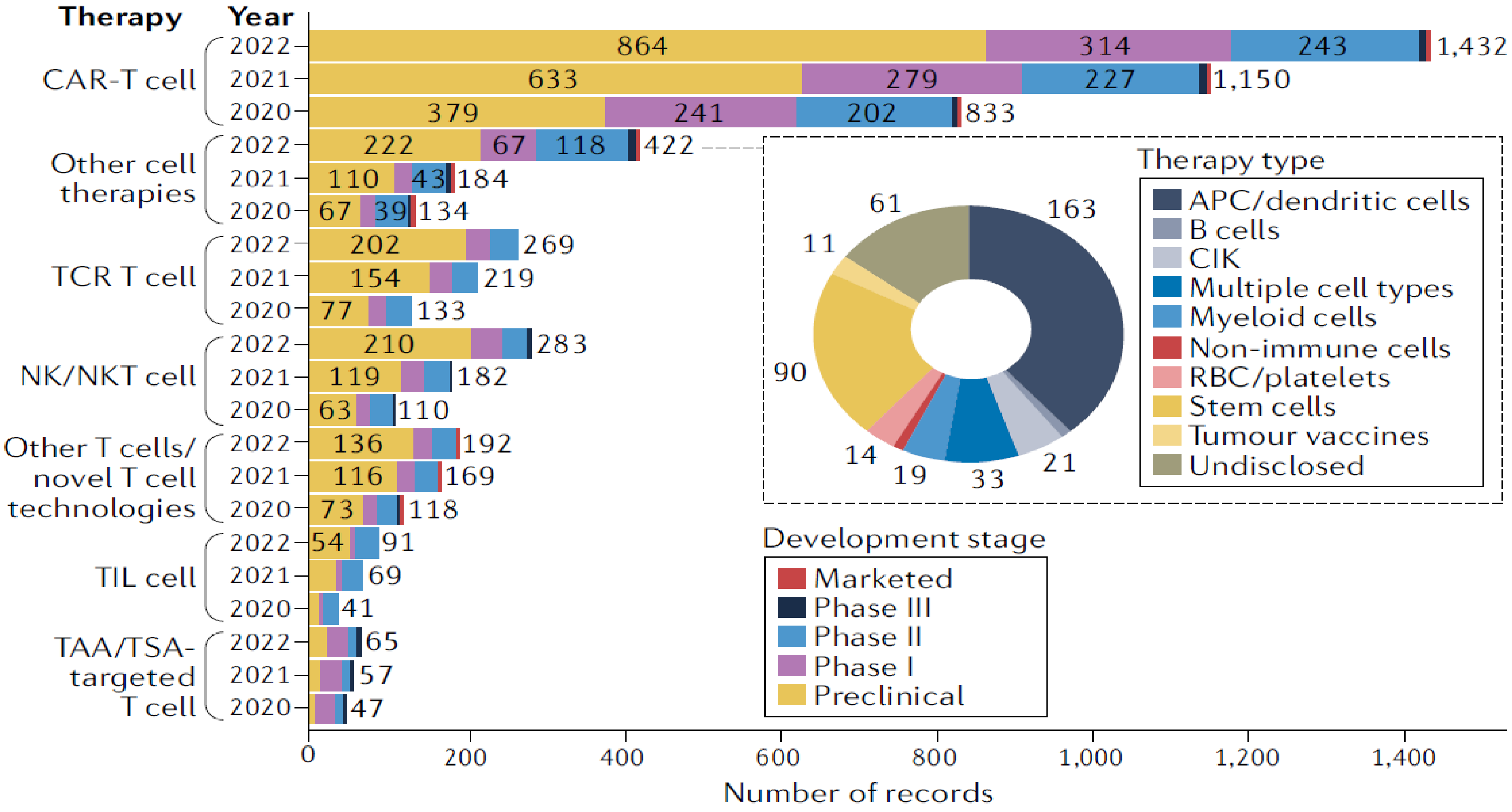
- Different from small molecule or biologic treatments intended to treat a broad range of patients, CAR T-cell therapy is highly personalized and uses a patient's own reprogrammed T cells to attack cancer cells
- Overview of autologous CAR T-cell product manufacturing process



Six autologous CAR T-cell products approved by the US Food and Drug

- **2010**: 1ST patient treated with CD-19 CAR T cells
- **2017**: Kymriah® (r/r ALL); Yescarta® (r/r LBCL)
- **2018**: Kymriah® (r/r LBCL)
- **2020**: Tecartus® (r/r MCL)
- **2021**: Breyanzi® (r/r LBCL); Abecma® (r/r MM); Tecartus® (r/r ALL); Yescarta® (r/r FL)
- **2022**: Carvykti® (r/r MM); Kymriah® (r/r FL)
- **2024**: Breyanzi® (r/CLL); Breyanzi® (r/MCL); Breyanzi® (r/FL); Abecma® (r/r MM); Carvykti® (r/r MM)

Rapid Growing Cell Gene Therapy Pipeline



Saez-Ibañez AR, Upadhaya S, Partridge T, Shah M, Correa D, Campbell J. Landscape of cancer cell therapies: trends and real-world data. Nat Rev Drug Discov. 2022 Sep;21(9):631-632. doi: 10.1038/d41573-022-00095-1. PMID: 35650421.

Key Features of CAR T-cell Therapy

- One-time Treatment
  - How to properly set up the dose?
  - How to quantify this benefit in comparison to alternative therapies (daily, cycles, etc.)?
- Unique safety profiles (e.g., CRS, ICANS for CAR-T cell therapies)
- 15-year long-term follow-up for safety
- Autologous cell therapy manufacturing (each patient is a lot, variability in vein-to-vein time, potential failure, bridging therapy considerations)
- Large amount of data collected per patients (including manufacturing data)

ASA Biopharmaceutical Cell and Gene Therapy Scientific Working Group (CGT SWG)

Purpose: Bring together a collective group of statistical experts to collaborate on sharing experiences and developing strategic solutions to improve patient outcomes and advance the development of cell and gene therapy.

CORE MEMBERS:

- ALAN CHIANG, LYELL (CO-CHAIR)
- ALLY HE, CRISPER THERAPEUTICS
- DANIEL LI, BMS (CO-CHAIR)
- EVGENY DEGTYAREV, NOVARTIS
- JAMES WHITMORE, GILEAD
- JOSHUA CHEN, VERTEX
- KHADIJA RERHOU RANTELL, MHRA
- PATRICIA ANDERSON, ICON PLC.
- REVATHI ANANTHAKRISHNAN, BMS
- RONG LIU, REGENERON
- SHIHUA WEN, NOVARTIS
- YEONHEE KIM, LYELL
- ZHENZHEN XU, FDA (CO-CHAIR)

https://community.amstat.org/biop/workinggroups/cellandgenetherapy

CGT SWG Sub-teams

Sub-team	Lead (Affiliation)	Objectives
Chemistry, Manufacturing and Control (CMC)	Sangwook Choi (BMS)	Identify/address key CMC challenges and serve as key opinion leaders in CGT CMC within biopharmaceutical communities.
Continuing Education and Outreach	Patricia Anderson (ICON plc)	Promote best practices in the design and analysis of CGT trials through knowledge sharing of current global development, short courses and outreach.
Data Science and AI	Qinghua Song (Kite), Shams MD (BMS)	Understand the opportunities and challenges associated Data Science and application of AI and Data Science in CGT
Dose-Finding	Revathi Ananthakrishnan (BMS), Rong Liu (Regeneron)	Increase the awareness of the dose finding methods and designs that CGT development can already adopt and identify improvements in these methods for the future as well as key challenges.
Real-world Evidence	Khadija Rantell (MHRA), Shihua Wen (Novartis)	Develop recommendations for generating robust RWE/RWD to support regulatory approval for CGT products. Specifically, review methods for direct and indirect comparisons using RWD and reflects on the opportunities and challenges of these approaches in the setting of CGT drug development using case studies as examples.
Pivotal and New Product Trial Design	Weidong Zhang (Sana)	Understand how to design next generation cell and gene therapy trials along with the associated challenges, and how the value of these new therapies versus that of the traditional therapies or the approved cell and gene therapies can be demonstrated.
Long-Term Follow Up (LTFU)	Shihua Wen (Novartis)	Advance statistical thinking and best practices in the design and conduct of LTFU studies for cell and gene therapy products through sound statistical methodology and innovative technology.

Mian Publication from CGT SWG

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-024-00652-3

DIA

ORIGINAL RESEARCH

Check for updates

Challenges and Lessons Learned in Autologous Chimeric Antigen Receptor T-Cell Therapy Development from a Statistical Perspective

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Abstract

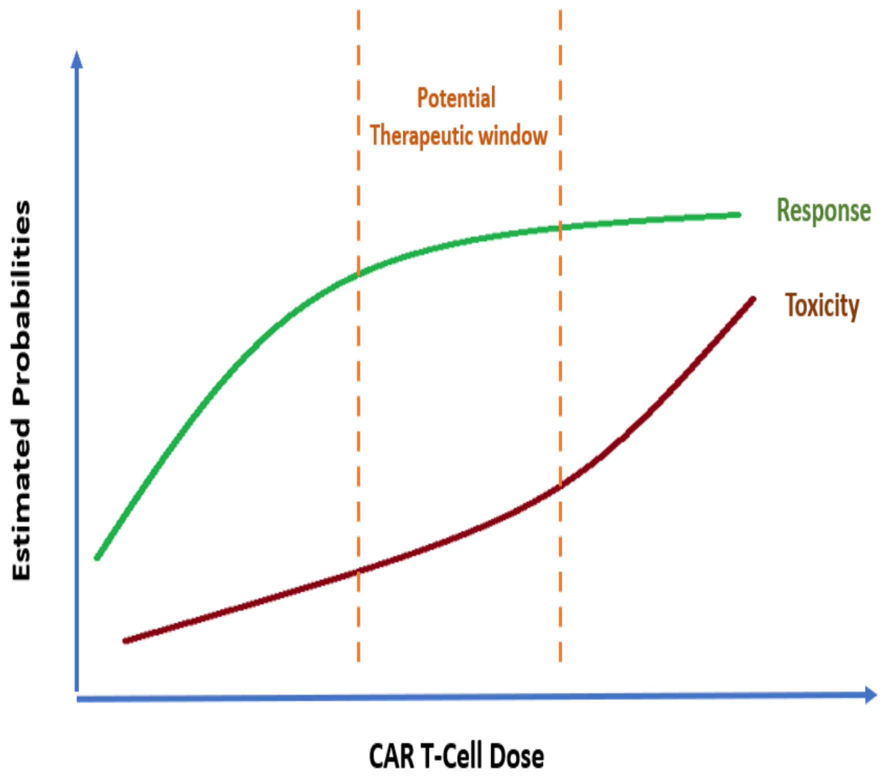
Chimeric antigen receptor (CAR) T-cell therapy is a human gene therapy product where T cells from a patient are genetically modified to enable them to recognize desired target antigen(s) more effectively. In recent years, promising antitumor activity has been seen with autologous CAR T cells. Since 2017, six CAR T-cell therapies for the treatment of hematological malignancies have been approved by the Food and Drug Administration (FDA). Despite the rapid progress of CAR T-cell therapies, considerable statistical challenges still exist for this category of products across all phases of clinical development that need to be addressed. These include (but not limited to) dose finding strategy, implementation of the estimand framework, use of real-world data in contextualizing single-arm CAR T trials, analysis of safety data and long-term follow-up studies. This paper is the first step in summarizing and addressing these statistical hurdles based on the development of the six approved CAR T-cell products.

Distinct Characteristics of CAR T-cell Dose Finding Studies

- Maximum Tolerated Dose (MTD) may not be attainable
- Increasing doses beyond a certain level may not enhance antitumor activity
- Dose-finding often limited and only small number of dose levels studied, i.e <=4
- Response to therapy or a biomarker for response can be observed quickly
- Median time to response = ~1 month
- Certain subgroups (e.g., high tumor burden) more prone to toxicity
- Dosing regimen can be flat or weight based

Consideration in Dose-finding CAR T-cell Trials

A Simulated Model Demonstrating a Potential CAR T-Cell Dose Relationship With Toxicity And Efficacy Outcomes

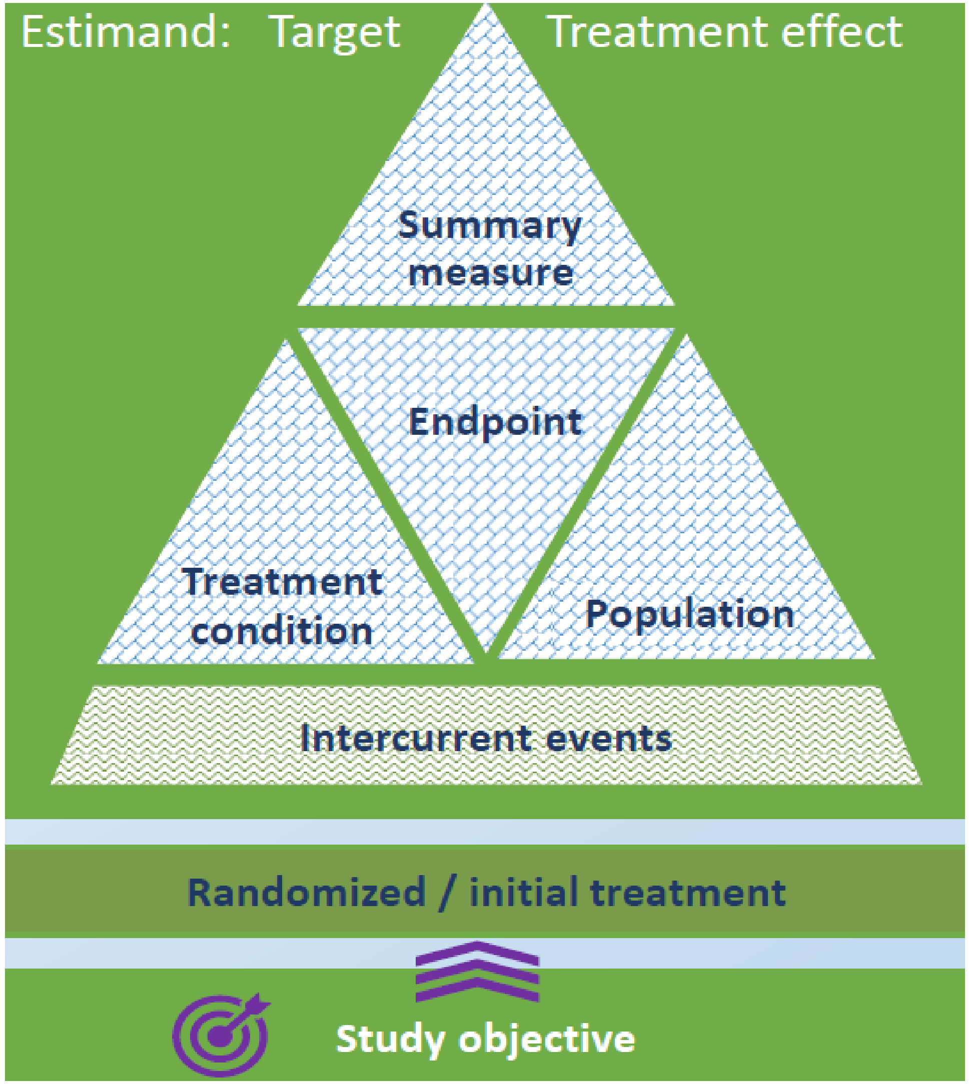


- Given the distinct feature of CAR T cells, **optimal biological dose (OBD)** based on the benefit-risk tradeoff, rather than only toxicity, may be more appropriate
- Use of Efficacy-integrated dose-finding strategy, e.g., BOIN12 and TEPI
- Early efficacy exploration is crucial to avoid unnecessary dose escalation
- Group averaged Bayesian Optimal Interval (BOIN) to account for subgroups

Top Questions to ask when design a cell therapy dose finding study

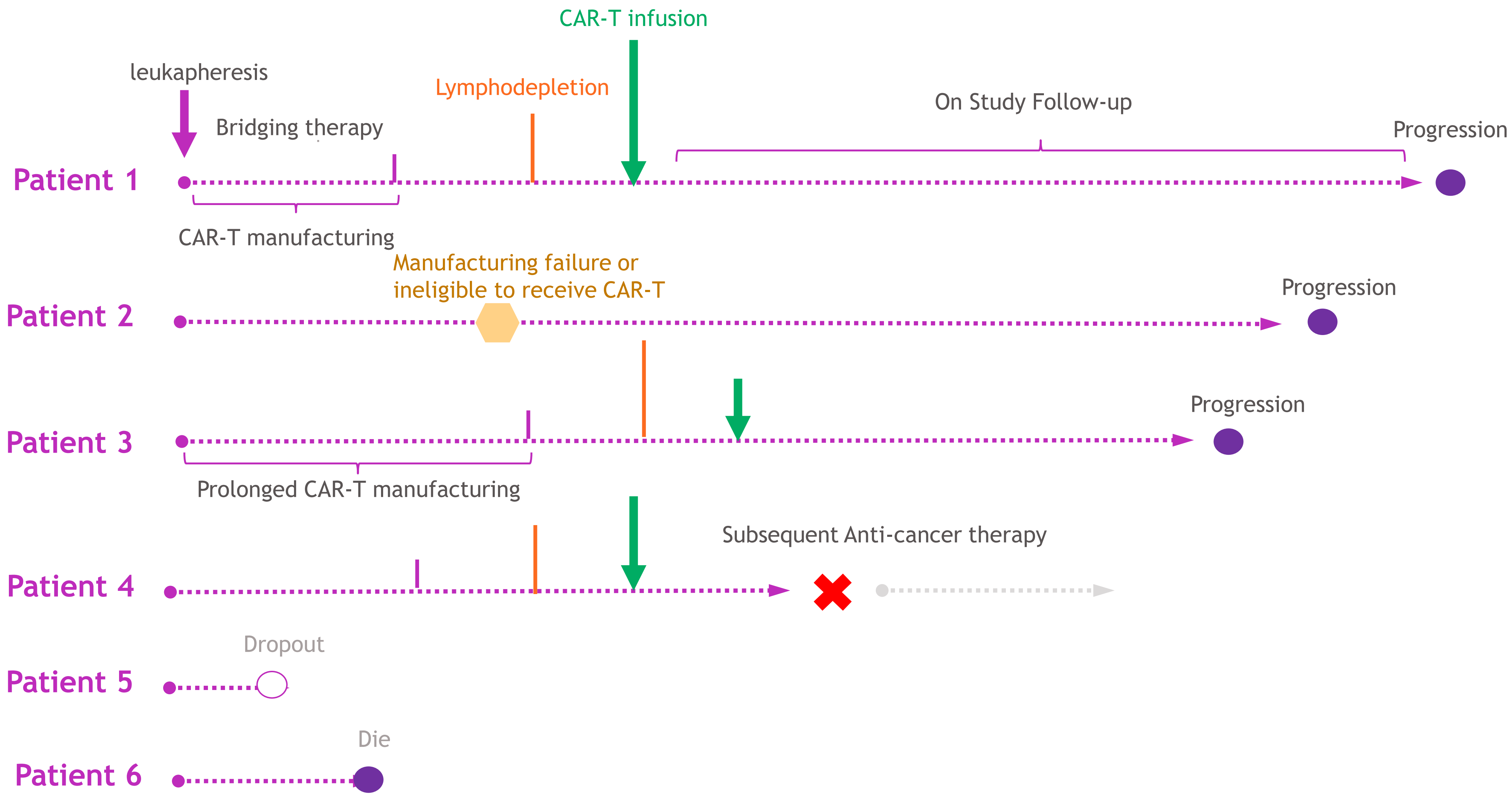
1. What is the objective of the design i.e. MTD vs OBD?
2. If OBD, what is the expected time to response?
3. What is the starting dose?
3. How many dose levels should be studies?
4. Is weight based versus flat dosing more appropriate?
5. What should be the target rate of DLT?
6. What is the DLT population?
7. Is there any subgroup of interest?
8. Can PK/PD be incorporated in dose finding decisions?

Estimand: Focus on the Right Research Questions

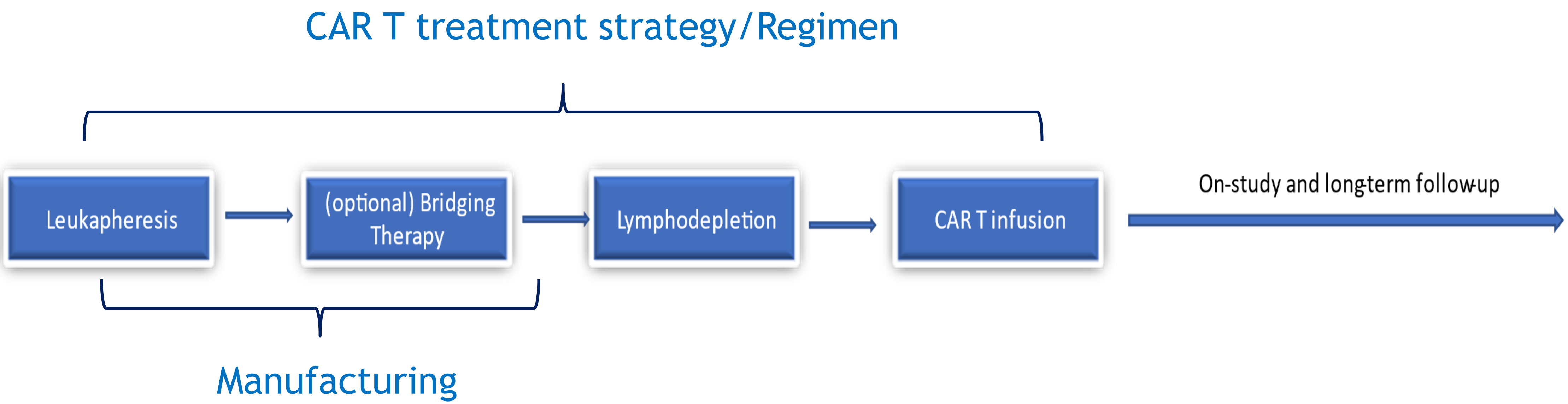


- ICH E9 (R1) provides a framework for **translation** of the trial objective into a **precise** definition of the treatment effect to be estimated using five attributes
- **Foundation for Study Design**, estimators (primary & sensitivity), and hypothesis testing

Example of CAR T Patient Journeys

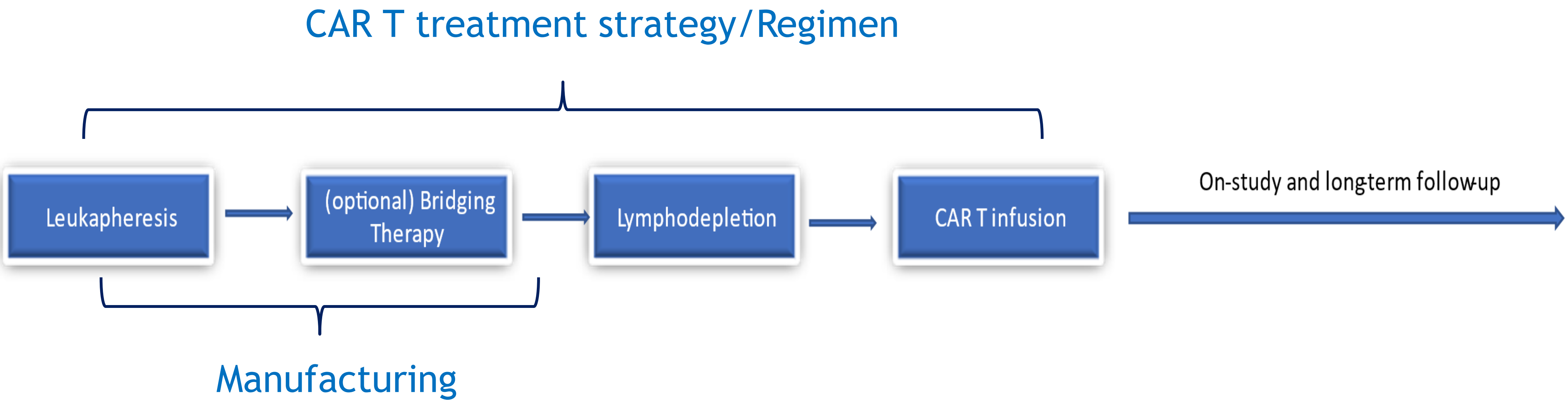


Single-Arm Trials for a CAR T-cell Product



- Endpoints:
  - Tumor response rate (ORR, CRR), duration of responses
  - Safety, time-to-event endpoint (e.g., PFS, OS)

Single-Arm Trials for a CAR T-cell Product



- Main research questions:
  - What is the **effect of CAR T-cell therapy** (i.e. CAR T infusion along)?
  - What is the **effect of the CAR T treatment strategy** (i.e. leukapheresis + bridging + lymphodepletion + CAR T-cell infusion)?

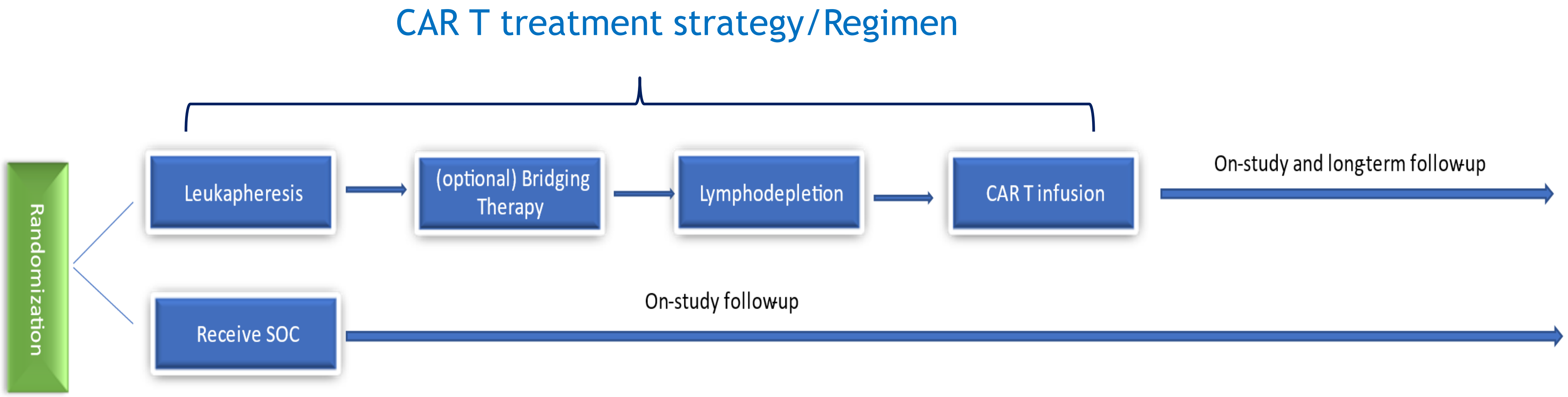
Analysis Sets in Single-Arm Trials

- Efficacy-evaluable analysis set, excluding
  - failing to receive a CAR T-cell product infusion
  - absence of measurable disease prior to CAR T-cell infusion
  - infusion of a product outside of the intended dose range, or
  - infusion of a product that did not meet the product specification

- Leukapheresis (i.e. enrolled or ITT) analysis set
  - Manufacturing failures and drop-outs are considered as non-responders in the ORR calculation

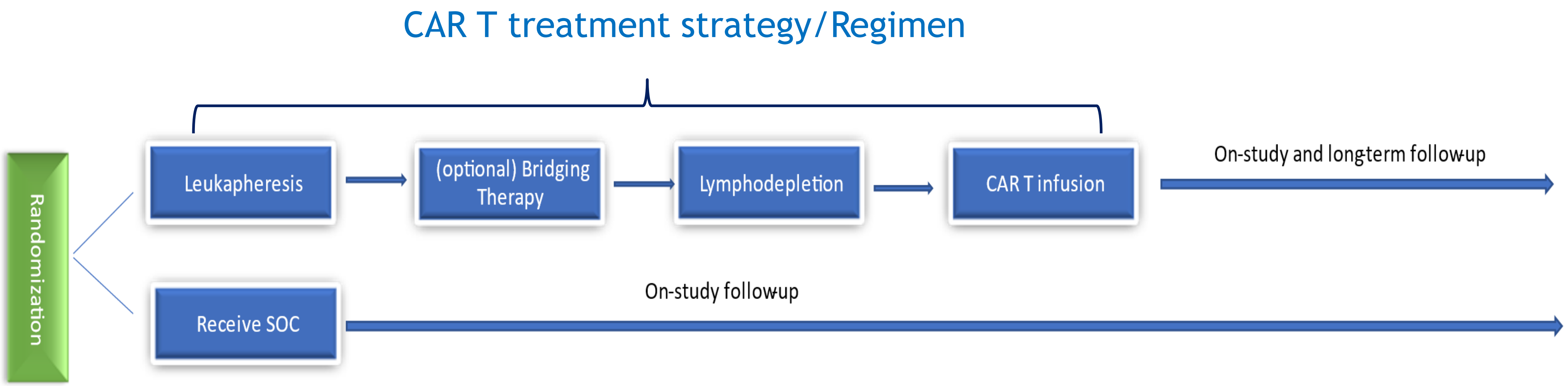
Randomized Controlled Trials for a CAR T-cell Product

- Study design schema for a Randomized Controlled Trial (RCT)



- Primary Efficacy Endpoint
  - Time-to-event variable, e.g., EFS or PFS

Randomized Controlled Trials for a CAR T-cell Product



- Main research questions:
  - What is the effect of the **CAR T treatment strategy** versus standard of care (SOC) based on all randomized subjects?

Addressing ICEs

Intercurrent Events	Analysis Strategy #1	Analysis Strategy #2
Manufacturing issue (e.g., manufacturing failure, delays)	Treatment policy	Hypothetical?
Subsequent anti-cancer therapy	Hypothetical strategy, e.g., PFS in ZUMA-7 and TRANSFORM	Treatment policy

The selection of a suitable strategy hinges on the unique characteristics of each clinical study and should be made on a case-by-case basis

AI/ML to expedite Cell Therapy Development

- Generative AI
- Large Language Models
- Computer vision
- Digital health

- Wearable technology
- Multi-modal analysis
- Causal modeling

- Predictive modeling
- Time-series Analysis

Start

Go to Proof of Concept

- Develop data driven insights to support registrational development
- Develop exploratory endpoints to predict efficacy benefits
- Develop patient profile insights to minimize safety risk

Go to registrational study

- Comparative evidence driven development decision
- Development of I/E criteria
- Data driven insights on patient selection and enrollment
- Multi-variate analysis identifying patients who are likely to have both good efficacy, safety and manufacturing outcome
- Algorithms to project long term overall survival to demonstrate comparative benefits

Go to File

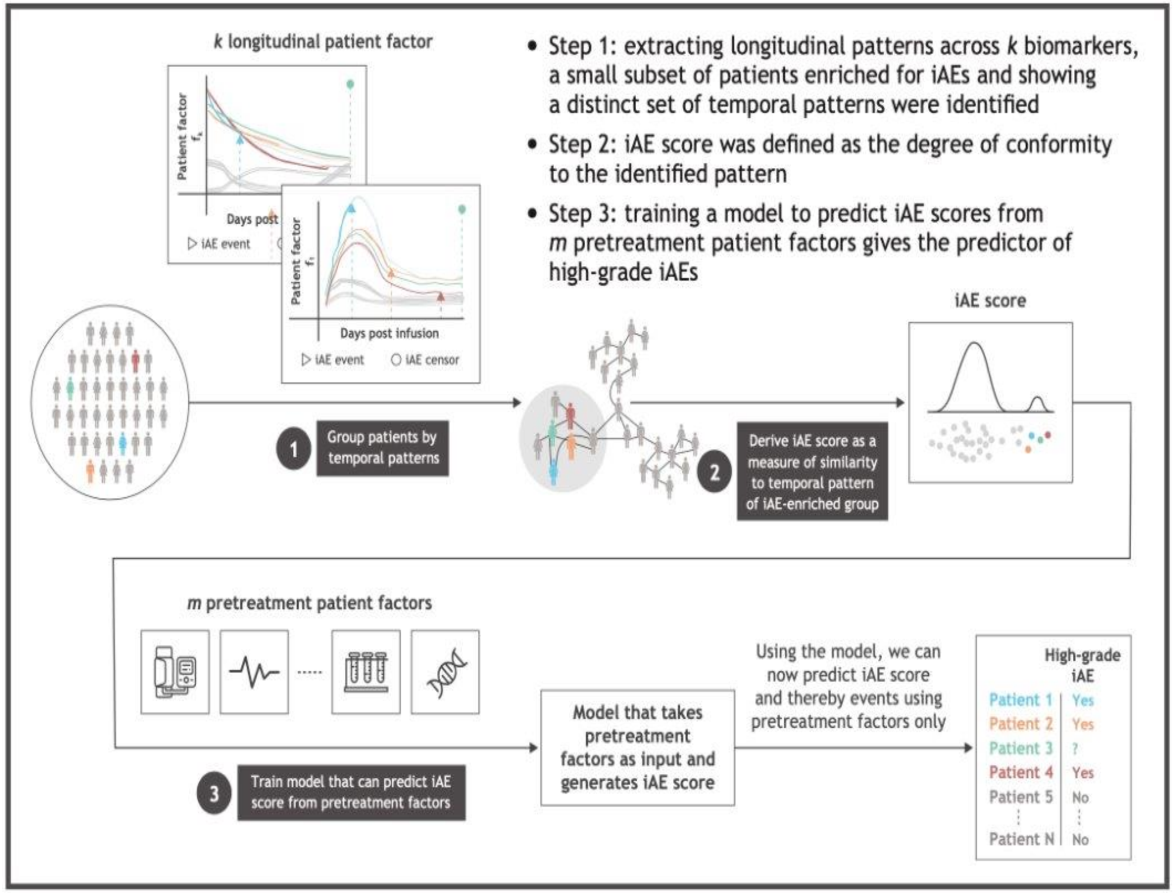
- Multivariate multimodal analysis demonstrating efficacy and safety benefits supporting submissions

Approval

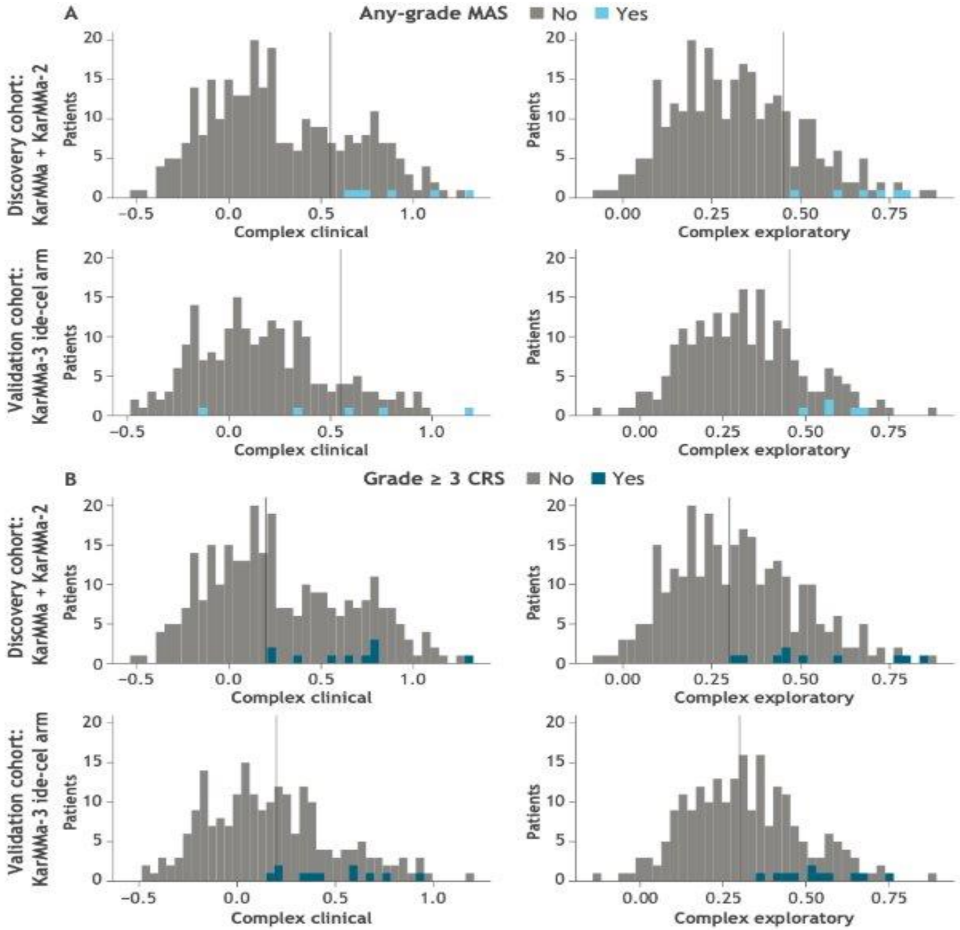
- Multivariate multimodal analysis demonstrating efficacy and safety benefits supporting medical communication
- Develop, communicate and deploy AE prediction / early detection algorithm
- Develop algorithms to project long term overall survival to demonstrate comparative benefits

Scott et al. Artificial Intelligence Applied to clinical trials: opportunities and challenges. Health Technol (Berl). 2023;13(2):203-213

Application of AI/ML to Detect CRS



Process for identifying pretreatment predictors of iAE subsets



iAE composite biomarkers predicted grade ≥ 3 CRS in the KarMMa-3 ide-cel arm

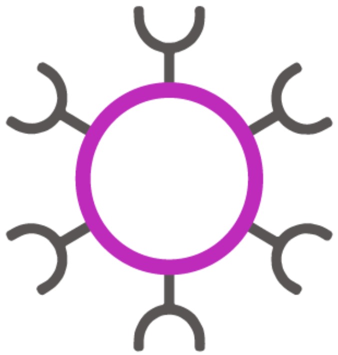
Martin et al. EHA 2023
Martin et al. ASCO 2024

Other Key Lessons for Future CAR T-cell Study Design

- Choice of study design (SAT, RCT with SOC, Head-to-Head CAR T RCT), must be informed by:
  - the disease setting,
  - existing therapies,
  - manufacturing supply of the control arm CAR T-cell product

- Analysis considerations:
  - Non-PH including crossing KM curves
  - Cross-over from SOC to CAR T-cell therapy after progression
  - Heterogeneous population

- Role of RWD/RWE, digital technologies, AL/ML



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