CAR T-cell Therapies: Challenges, Lessons Learned, and Implications for Future Studies

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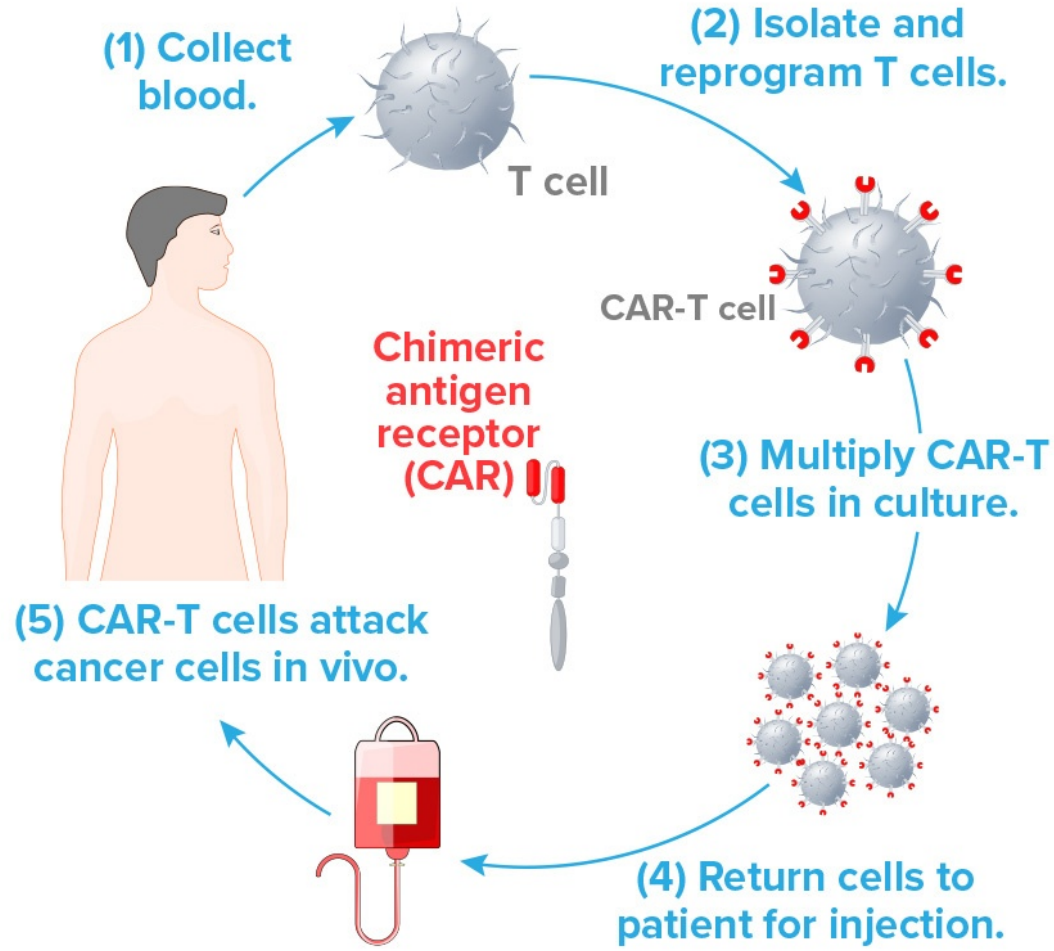
On behalf of the Cell and Gene Therapy ASA Scientific Working Group
https://community.amstat.org/biop/workinggroups/cellandgenetherapy

Bristol Myers Squibb™

CAR (Chimeric Antigen Receptor) T-Cell Therapy

- CAR T-cell therapy is an immunotherapy that uses altered T cells, immune cells, to fight cancer.
- T cells collected from a patient via a blood sample are modified to produce chimeric antigen receptors (CARs) on their surface.
- When the CAR T cells are reinfused into the patient (say 90-110 million T cells), the CAR receptors enable them to attach to a specific antigen on the patient's tumor cells and kill them.



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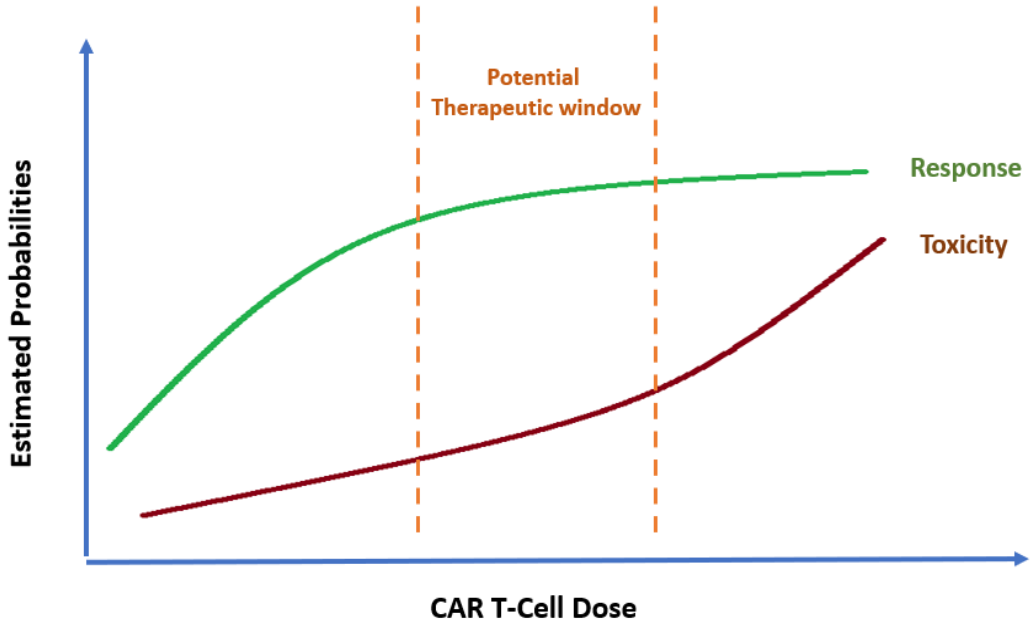
Increasing Dose (Number of T-cells infused) May Not Increase Anti-tumor Activity in CAR T-cell therapies

- Increasing dose (=number of T-cells infused) may not increase anti-tumor activity.



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

- In the approved CAR T-cell therapies with a dose finding study, a maximum tolerated dose (MTD) was not reached - the data suggested that the efficacy plateaus with dose.

Dose Finding in Immunotherapies

- Starting dose should be safe but also not sub-therapeutic.

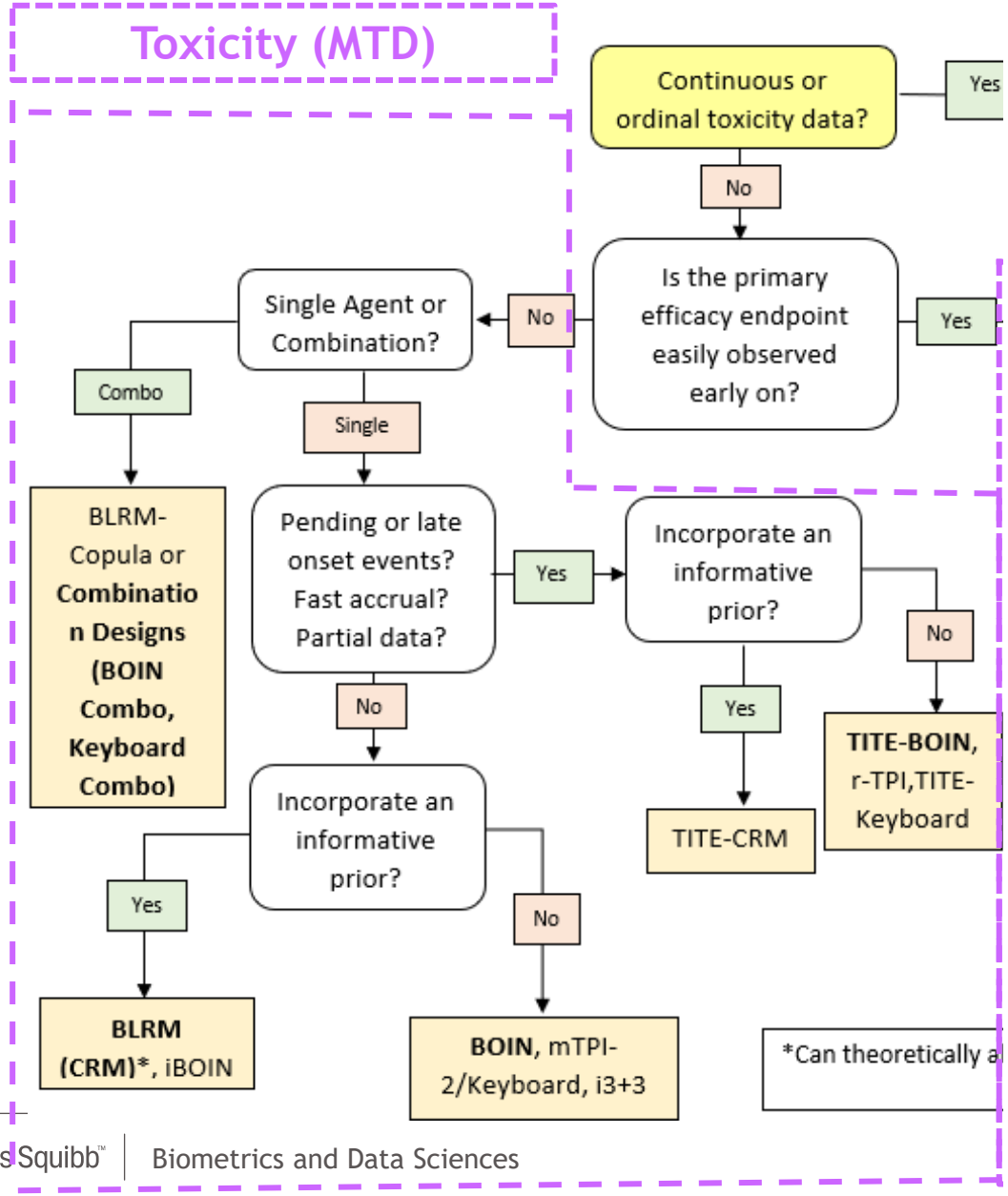
- The starting dose can be determined by leveraging the use of previous clinical experience from a different version of the CAR T-cell therapy or a different indication.

- Designs that incorporate toxicity and efficacy to determine the optimal dose/optimal biological dose e.g. BOIN12*, TITE-BOIN12*, Eff-Tox and bCRM* are preferred for CAR T-cell therapies.
  - DLTs* may not be observed at clinically active doses; no MTD was identified for the approved CAR T-cell therapies.
  - Responses are typically observed quickly – say within a month.
  - Practical limits on the dose of the product that can be produced or delivered and limited number of dose levels studied, i.e <=4.

* BOIN12 – Bayesian Optimal Design 12; TITE-BOIN12 – Time-to-Event BOIN12; bCRM – Bayesian Continual Reassessment Method; DLT – Dose Limiting Toxicity

FDA Guidance for Industry. (2023). Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products.

Oncology dose escalation design selection considerations



Initiative for Dose Optimization

- **Project Optimus: FDA's Oncology Center of Excellence***

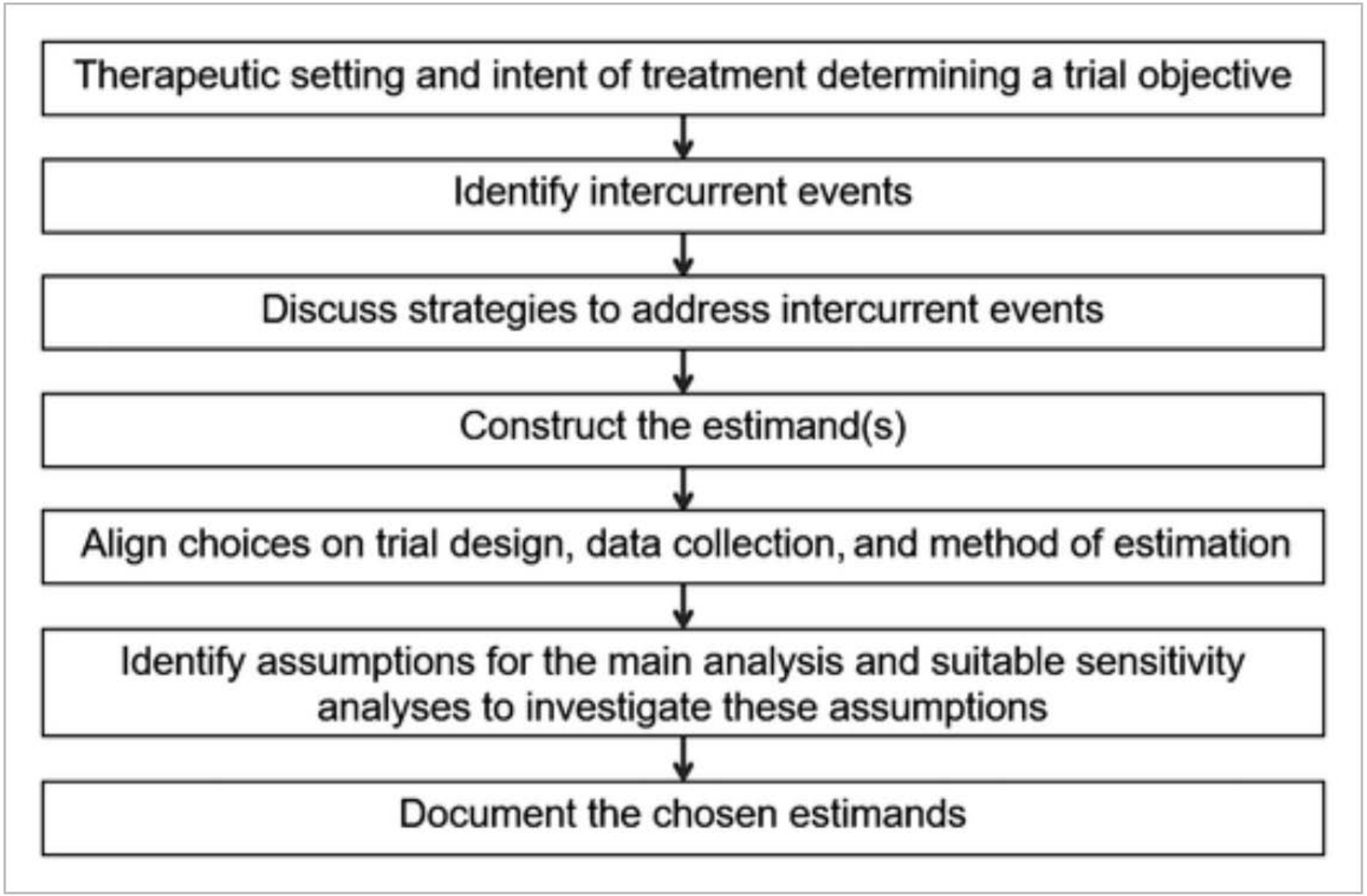
"The goal of Project Optimus is to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well."

Two recent designs in response to Project Optimus:

Multiple-dosE RandomIzed Trial (MERIT) design

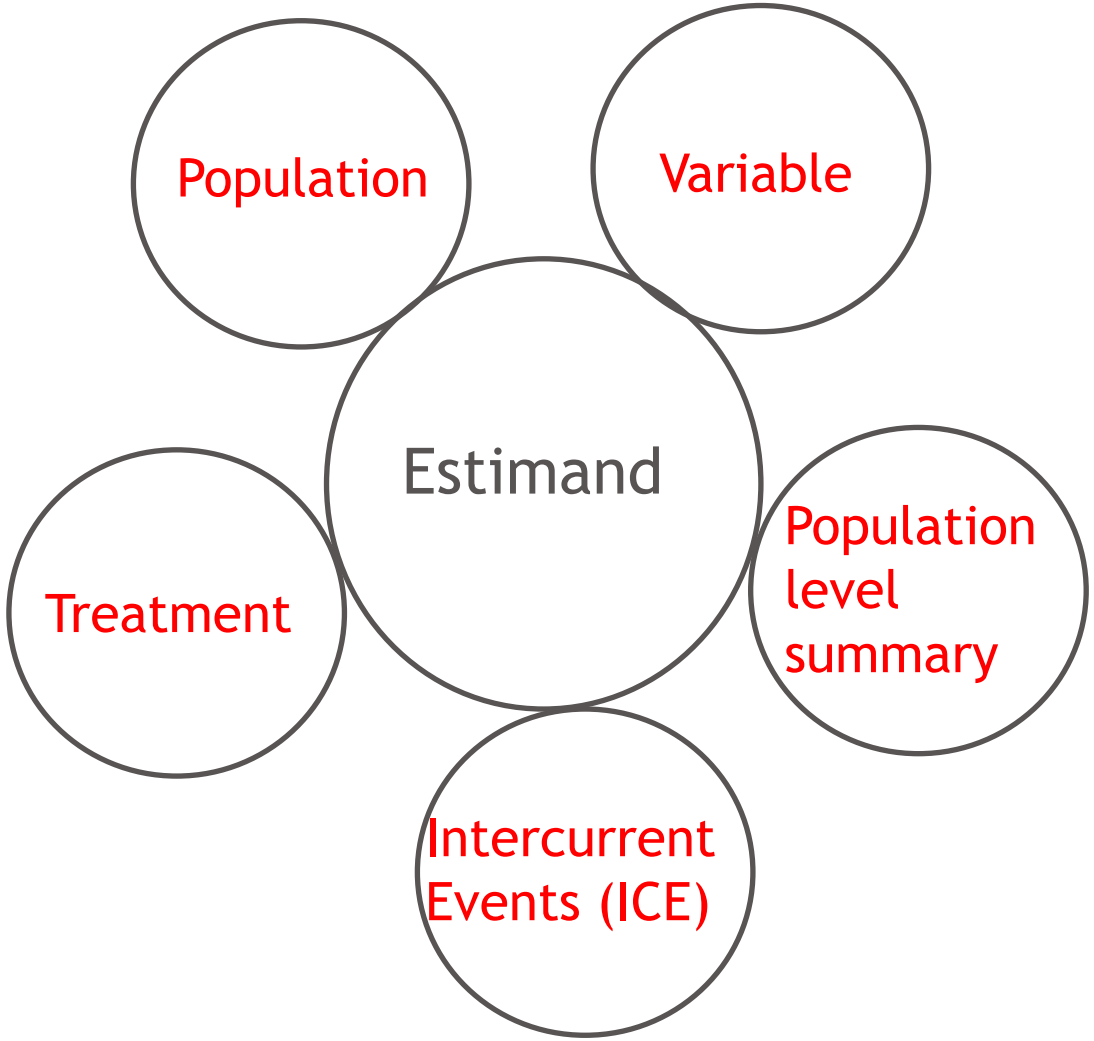
Dose-ranging approach to optimizing dose in oncology drug development (DROID) design

* Project Optimus guidance does not explicitly cover Cell Therapy but may likely cover it in the future.

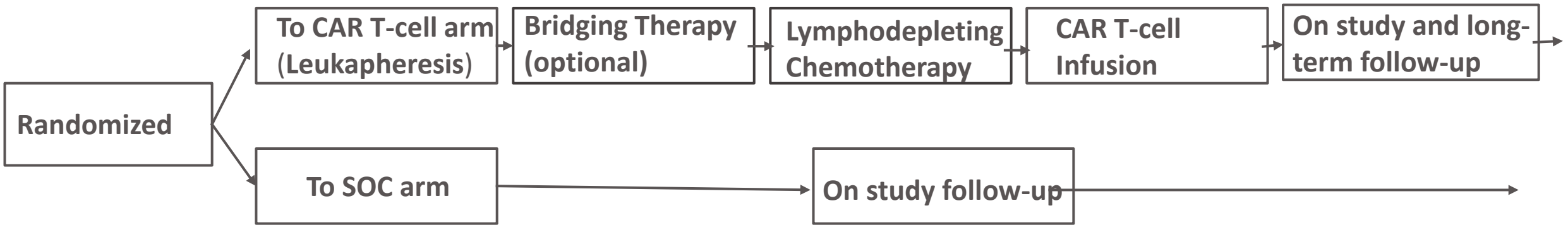


https://ascpt.onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.2575

Establishing Efficacy: Estimand framework



Setting Trial Objectives – Randomized Controlled Trial (RCT)



- For a randomized trial, the question of interest is to compare the treatment effect of CAR T-cell therapy treatment strategy versus standard of care (SOC) based on all randomized subjects.

Analysis Population, ICEs, Measures of Treatment Effect – RCT

- Population, Treatment will differ from trial to trial.
- Typical variables of interest or endpoints are 1) Progression-free survival (PFS), defined as time from randomization to earliest of progression or death, or 2) Overall Survival (OS), defined as time from randomization to death.
- Manufacturing failure of the CAR T- cell product is an ICE (treatment policy strategy).
- For PFS for e.g., start of new anti-cancer therapy is an ICE, and patients who start a new anti-cancer therapy without PD may be censored at the last disease assessment before starting the new therapy (hypothetical strategy). This ICE may also be ignored (treatment policy strategy).
- Typical measures of treatment effect are hazard ratio (HR) for PFS or OS.
- The primary analysis is conducted on the ITT set, which is all randomized subjects.

Treatment Policy Strategy: The occurrence of the intercurrent event is considered irrelevant.
Hypothetical Strategy: A scenario is envisaged in which the intercurrent event would not occur.
Composite Strategy: Intercurrent event is informative of the outcome and is incorporated into the definition of the variable.
While on Treatment Strategy: Measurements up until the time of the event are considered.

Setting Trial Objectives – Single Arm Trial (SAT)

- For a single arm trial, two questions can be answered:
  - What is the effect of the CAR T-cell treatment regimen (CAR-T cell therapy infusion)?
  - What is the effect of the CAR T-cell treatment strategy (Leukapheresis + Bridging therapy (optional) + LD Chemo + CAR-T cell therapy infusion)?

Analysis Populations, ICEs, Measures of Treatment Effect – SAT

- **For SATs for the effect of the CAR T-cell treatment regimen:**
- Typical variables of interest or endpoints are CR (complete response) or OR (overall response), defined as a complete (or partial response for OR), that occurs after infusion of the CAR T-cell therapy until progression, subsequent anti-cancer therapy or end of study (earliest of events).
- The ICEs include receiving prohibited concomitant medications (treatment policy strategy), loss of follow-up (while on treatment strategy), new anti-cancer therapy (while on treatment strategy) and death (while on treatment strategy).
- Typical measures of treatment effect: ORR (overall response rate), CRR (complete response rate)
- Analyses are done on CAR-T infused set or efficacy evaluable set.

- **For SATs for the effect of the CAR T-cell treatment strategy:**
- The additional ICEs could include manufacturing failures and drop-outs prior to CAR T infusion. These patients will be considered non-responders.
- Typical measures of treatment effect are ORR or CRR.
- Analyses are done on leukapheresed set.

Real World Evidence (RWE) in CAR T-cell Therapy Trials

- RWD (real world data) were used to support approval of many CAR T-cell therapies.
- In most cases for the single arm studies, propensity score matching was used to match patients in the trial with real world patients who met the trial inclusion/exclusion criteria.
  - —By constructing such a cohort, the real world cohort and the CAR T-cell therapy trial cohort can be compared for efficacy outcomes such as ORR, CRR, PFS and OS.
- Analysis of RWD must be prospectively planned. Ideally the protocol should be published.

Fda guidance for RWE: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.fda.gov/media/171667/download

FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

Recommendations for Future CAR T-cell Study Design

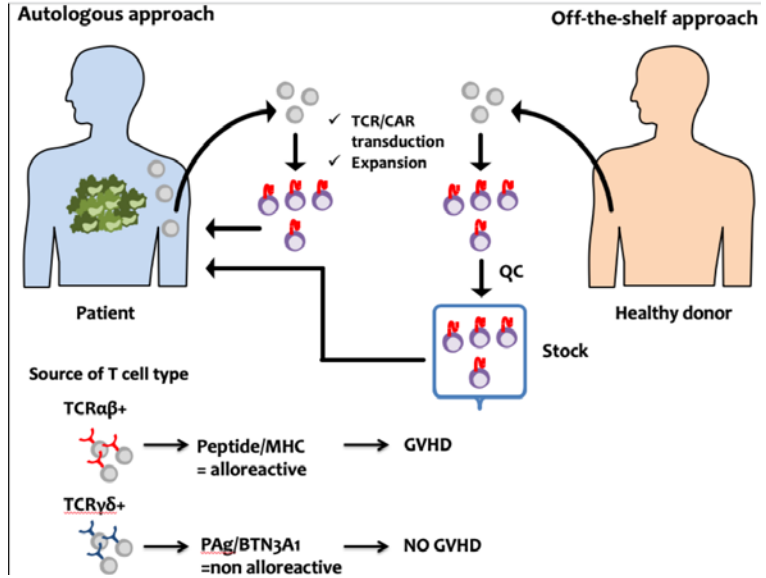
- Choice of study design (SAT?, RCT with another cell therapy as control, RCT with SOC) must be informed by:
  - the disease setting,
  - existing therapies,
  - manufacturing supply of the approved product.

- Analysis methods must account for non-proportional hazards (NPH) which can arise due to:
  - Delayed treatment effect
  - Cross-over from SOC to CAR T-cell therapy after progression
  - Heterogeneous population

Future of CAR T-cell Therapies

Autologous CAR T-cell therapies:

- CAR T-cell therapies in solid tumors
- Reduction in manufacturing time
- Dual targets



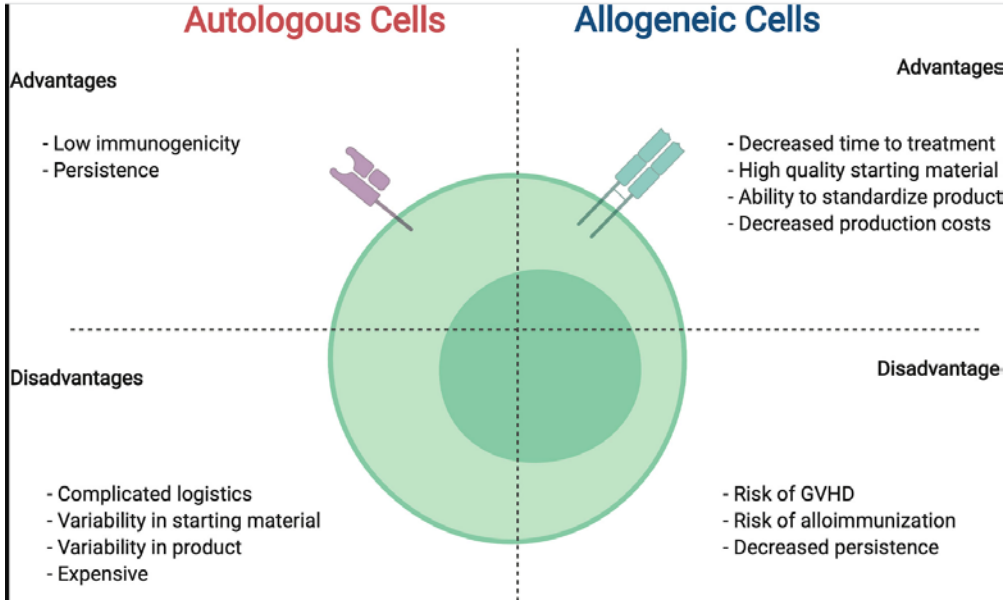
https://www.shikuken.jp/en/basic-rserach/04-2/

Off the Shelf CAR T-cell therapies:

- Healthy Donor Derived
- Induced Pluripotent Stem Cell (IPSC) Derived

No leukapheresis, no wait time, no bridging therapy
Reduced manufacturing costs
High engineering flexibility for IPSCs

Proof of biology is still being worked on.



https://www.frontiersin.org/articles/10.3389/fimmu.2020.618427/full

Summary

- 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.
- Implementation of the estimand framework will provide a clear and transparent description of treatment effect and therefore it should be implemented in future trials.
- RCTs remain the gold standard for assessing the effect of a therapy and the preferred study design for generating evidence for regulatory approval.
- Future CAR T-cell therapy trials may need to consider NPH in design and analyses.
- When planning a study using RWD it is important to demonstrate that the data source is of sufficient quality for the intended use for e.g. contextualizing the results of single arm trials.
- Future development of CAR T-cell therapies lies in solid tumors and off-the-shelf therapies, and in the area of CMC process improvement.

Key References

- Lin R, Zhou Y, Yan F, Li D, Yuan Y. BOIN12: Bayesian Optimal Interval Phase I/II Trial Design for Utility-Based Dose Finding in Immunotherapy and Targeted Therapies. JCO Precis Oncol. 2020 Nov 16;4:PO.20.00257. doi: 10.1200/PO.20.00257. PMID: 33283133; PMCID: PMC7713525
- Zhou Y, Lin R, Lee JJ, Li D, Wang L, Li R, Yuan Y. TITE-BOIN12: A Bayesian phase I/II trial design to find the optimal biological dose with late-onset toxicity and efficacy. Stat Med. 2022 May 20;41(11):1918-1931. doi: 10.1002/sim.9337. Epub 2022 Jan 31. PMID: 35098585; PMCID: PMC9199061
- Yang, P., Li, D., Lin, R., Huang, B., Yuan, Y. (2023). Design and Sample Size Determination for Multiple- dose Randomized Phase II Trials for Dose Optimization, https://doi.org/10.48550/arXiv.2302.09612
- FDA Guidance for Industry (2015): Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products. https://www.fda.gov/media/106369/download
- Pohl M, Baumann L, Behnisch R, Kirchner M, Krisam J, Sander A. Estimands-A Basic Element for Clinical Trials. Dtsch Arztebl Int. 2021 Dec 27;118(51-52):883-888.
- Bachy, E., Le Gouill, S., Di Blasi, R. *et al.* A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med* **28**, 2145–2154 (2022).
- Ananthakrishnan R, Green S, Previtali A, Liu R, Li D, LaValley M. Critical review of oncology clinical trial design under non-proportional hazards. Crit Rev Oncol Hematol. 2021 Jun;162:103350.

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