Statistical Challenges Arising in the Design and Analysis of Trials of CAR T Cell Therapies, Including Strategies for Accounting for the Delayed Treatment Effect of the CAR T Cell Treatment Strategy

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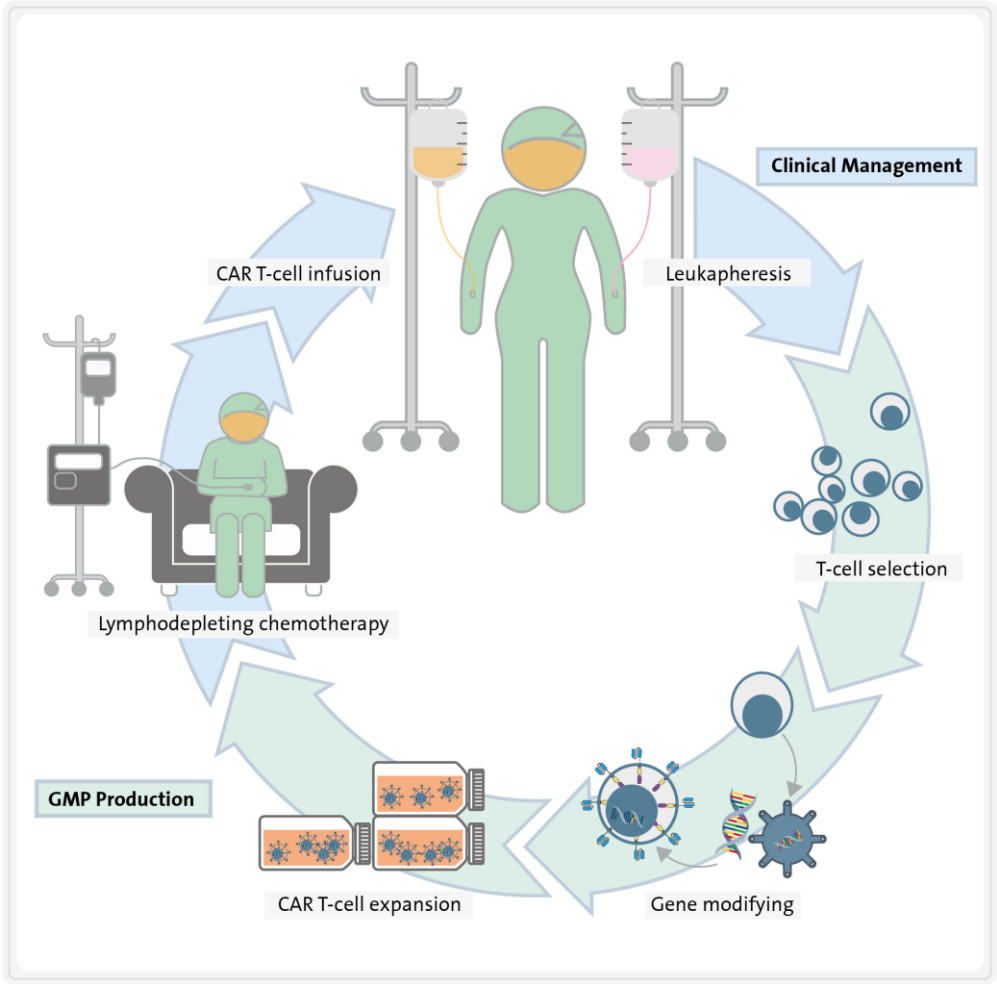
Overview of Delayed Treatment Effect and Statistical Techniques

- Delayed treatment effect, as seen with CAR T cell therapies, occurs due to the time required for T-cell preparation before treatment takes effect.
- This delay creates challenges in survival analysis, as traditional statistical models may not capture non-proportional hazards.
- The presentation will cover techniques such as weighted models, piecewise approaches, and multistate models to address this.
- A practical example will demonstrate how we handle the delay to ensure accurate analysis and interpretation of clinical trial data.

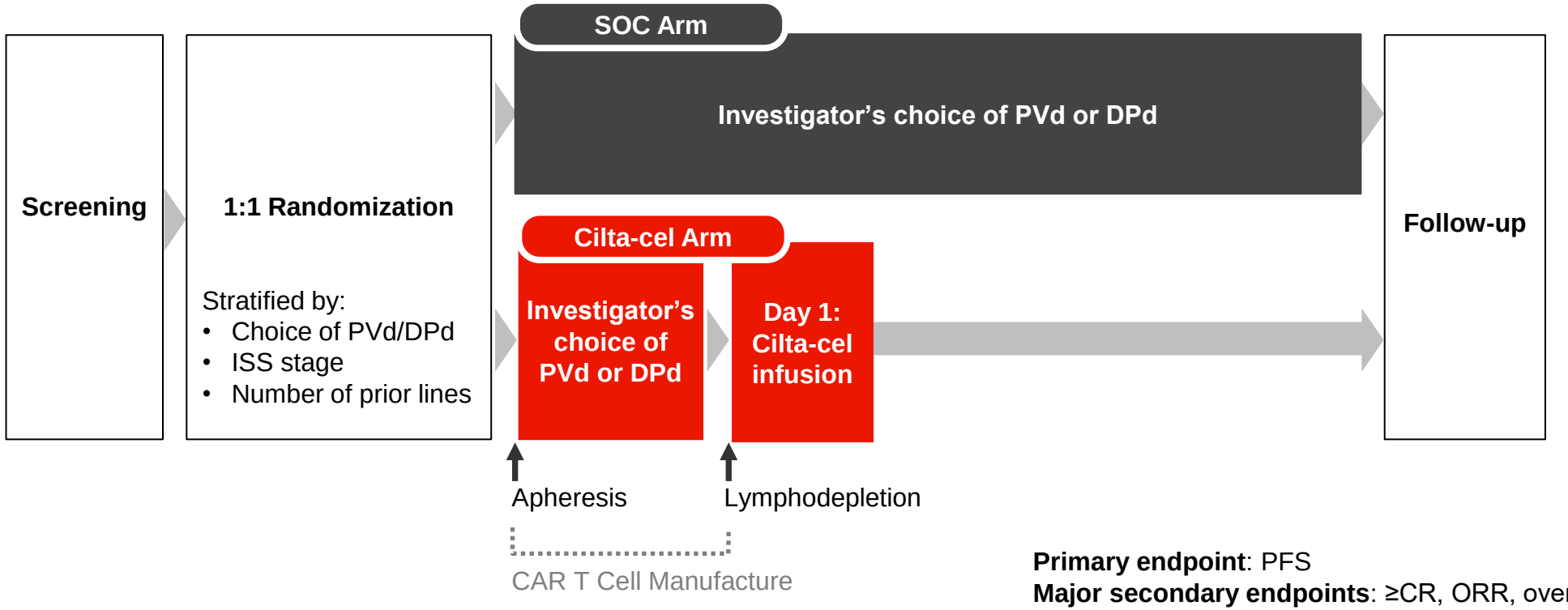
Typical Patient Journey/Vein-to-Vien for CAR T Cell Therapy



Source: Pérez-Amill L, Bataller À, Delgado J, Esteve J, Juan M, Klein-González N. Advancing CART therapy for acute myeloid leukemia: recent breakthroughs and strategies for future development. Front Immunol. 2023;14:1260470.

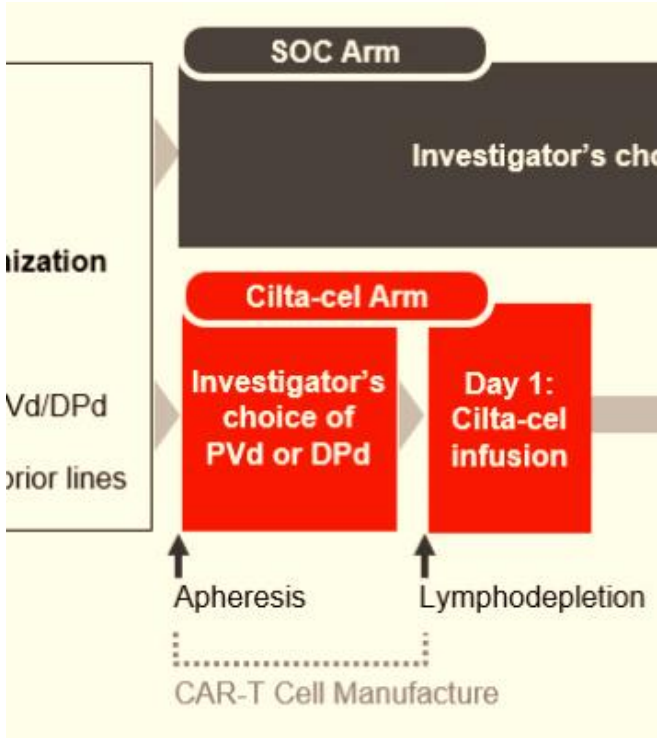
A Case Study: CARTITUDE-4 Study Design

- The first Phase 3 trial under the Cilta-cel (CARVYKTI) clinical development program
- CARTITUDE-4 is a trial that evaluates Cilta-cel versus standard of care (SOC) in patients with lenalidomide-refractory multiple myeloma and 1-3 prior lines of therapy



Primary endpoint: PFS
Major secondary endpoints: ≥CR, ORR, overall MRD negative, OS

Anticipated Delayed Treatment Effect in CARTITUDE-4



Delayed Treatment Effect

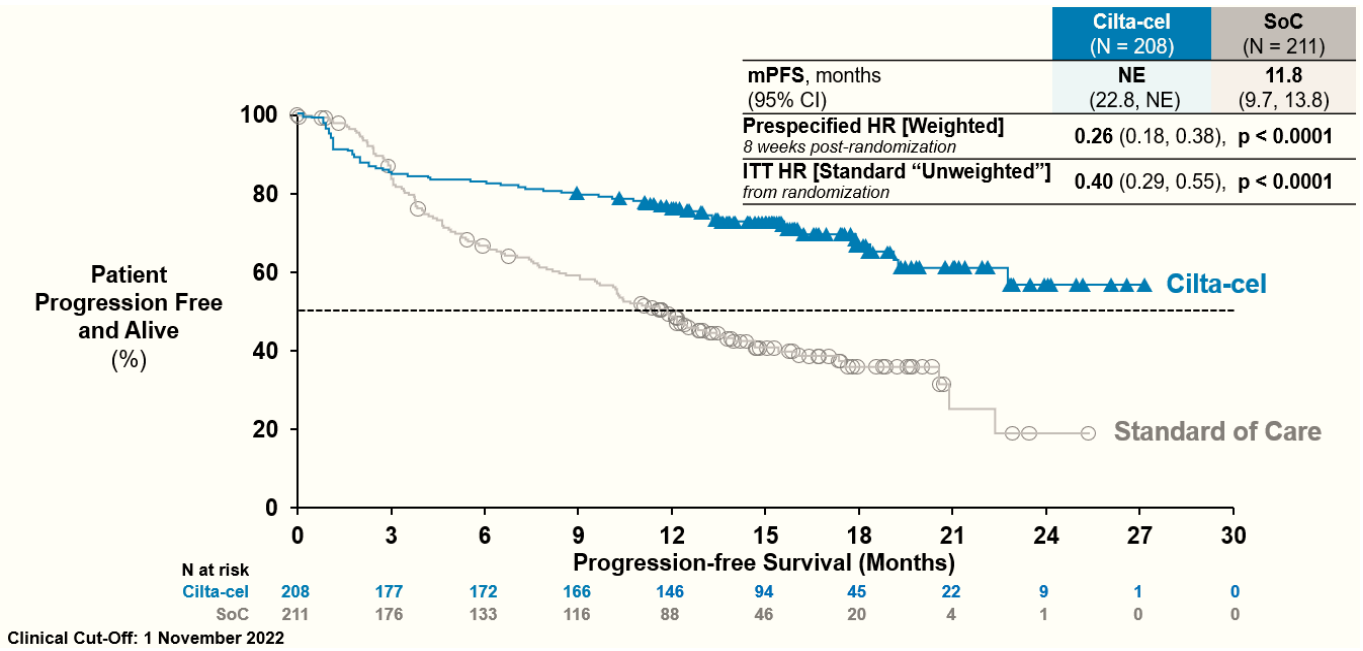
- The delayed treatment effect occurs when there is a gap between the initiation of treatment and the onset of its therapeutic impact as seen in therapies like CARVYKTI, where T-cells need to be engineered before the cancer-fighting effects begin.
- This delay can lead to the non-proportional hazards (NPH) over time, impacting survival analysis, which requires specialized modeling techniques to accurately capture the eventual treatment benefit.

Tools for Delayed Treatment Effects/NPH

1	Weighted Models	Apply weights to different time periods to adjust for varying treatment efficacy
2	Piecewise Analysis	Divide survival time into segments with different hazard rates
3	Smoothed Hazard Function	An alternative to characterize time varying HR, offering additional info that may not be very apparent from KM curves
4	Flexible Parametric Model	Offers alternative measures of treatment effect which do not rely on a time-independent HR
5	Multistate Models	Represent different patient health states to model transitions, offering a detailed approach to characterize clinical efficacy profile

These tools are essential for providing more accurate survival estimates under complex treatment effect scenarios

Weighted vs. Unweighted Analysis on PFS in CARTITUDE-4



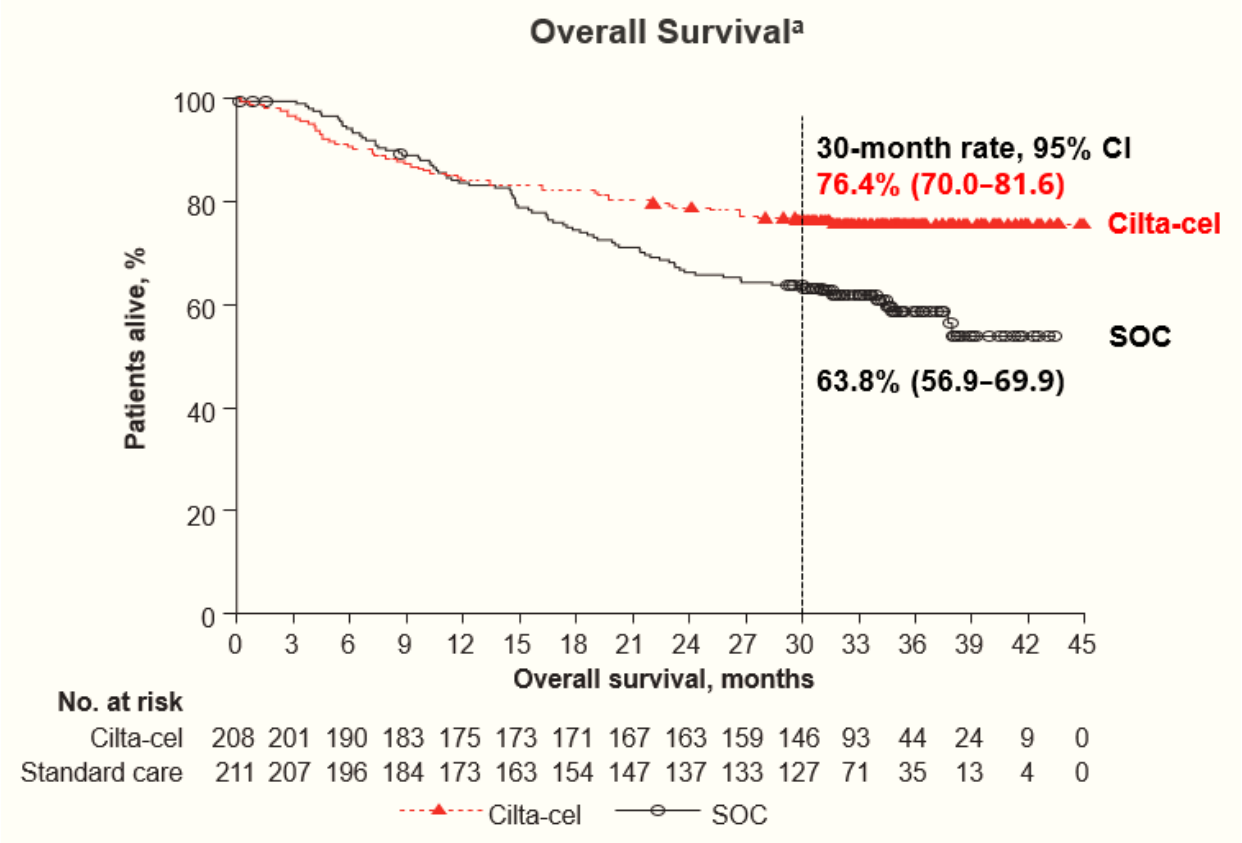
Source: March 15, 2024 Meeting of the Oncologic Drugs Advisory Committee- Janssen Presentations (CARVYKTI)

- Unweighted Analysis: Provides an estimate by calculating a hazard rate that is an average over the follow-up time
  - FDA adopted unweighted analysis to minimize overestimation of treatment efficacy and maintain a cautious approach.
- Weighted Analysis: A commonly used approach because it effectively captures the delayed treatment effect of Clita-cel, resulting in hazard ratios that focus on a period that is more relevant
- Key Difference: Weighted analysis accounts for varying hazard rates over time, leading to potentially more accurate results in treatments with delayed efficacy.

Overall Survival Curves in CARTITUDE-4

The NPH pattern of the curves raises additional questions, such as

- When does hazard ratio drop below 1?
- How to best quantify treatment effect?
- Do hazards cross when we look within subgroups?



Source: Mateos M, San-Miguel J, Dhakal B, et al. Overall Survival With Ciltacabtagene Autoleucel Versus Standard of Care in Lenalidomide-Refractory Multiple Myeloma: Phase 3 CARTITUDE-4 Study Update. International Myeloma Society 2024 Annual Meeting. September 2024

When Does Hazard Ratio for OS Drop Below One? Piecewise Analysis

- It's difficult to analyze hazards, i.e., instantaneous risks of suffering clinical outcome
  - They are very noisy when there are few events
- Simple methods, as used by FDA, involve **binning** of data
  - Results highly sensitive to how data is binned
- From FDA briefing document for the advisory committee meeting:

  This increased rate of early deaths is reflected in the Kapan-Meier curves as a crossing hazards pattern favoring the standard therapy arm up to approximately 11 months

Table 18: Piecewise Hazard Ratio Assessment, ITT Population

Time Interval	Piecewise HR	95% CI
Time interval of 3 months		
0-≤3	6.24	(0.75, 51.85)
3-≤6	1.07	(0.46, 2.47)
6-≤9	0.65	(0.25, 1.68)
9-≤12	0.72	(0.29, 1.78)
Time interval of 5 months		
0-≤5	2.40	(0.99, 5.85)
5-≤10	0.69	(0.33, 1.42)
10-≤15	0.35	(0.14, 0.90)
Time interval of 11 months		
0-≤11	1.04	(0.62, 1.73)

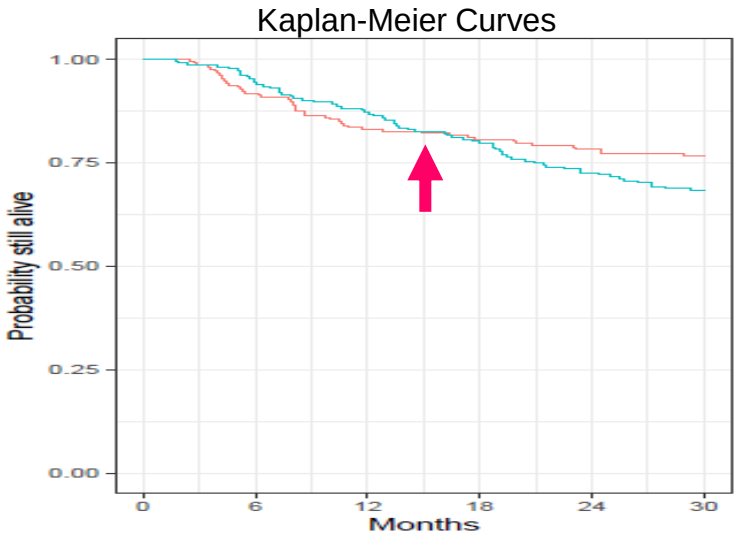
Source: FDA analysis
*> 15 months not reported due to heavy censoring
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat

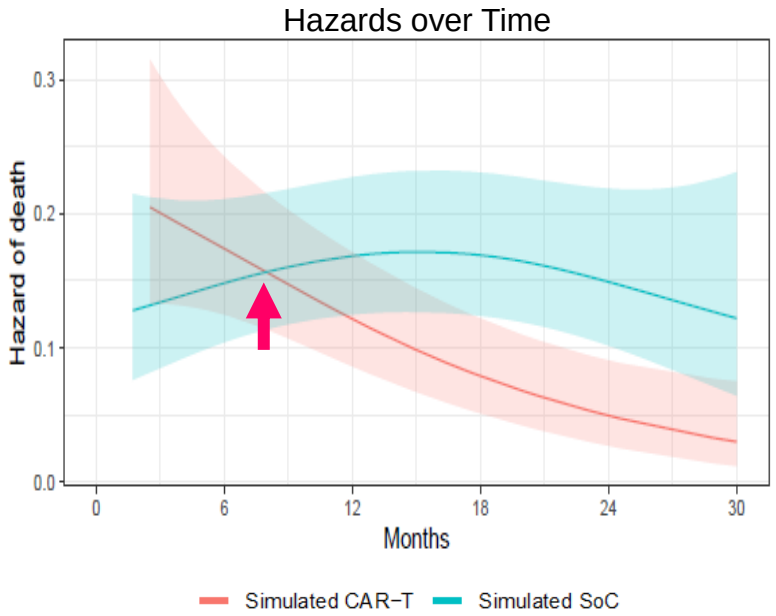
Source: March 15, 2024 Meeting of the Oncologic Drugs Advisory Committee- FDA Briefing Document (CARVYKTI)

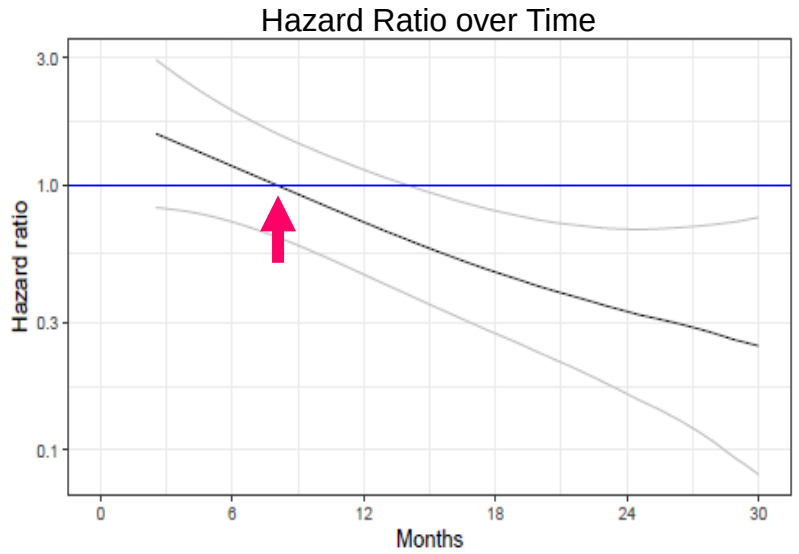
An Alternative to Binning: Nonparametric Estimation of Changing Hazards/HR (Simulated Data)

In general, it's not ideal to bin continuous data

- Method of Rebora et al. does not require binning, and gives comprehensive picture of changing hazards and hazard ratios over time
- Allows for robust data-driven smoothing
- Implemented in `bshazard` package, result shows that hazards (risks) of death cross months earlier than KM curves cross



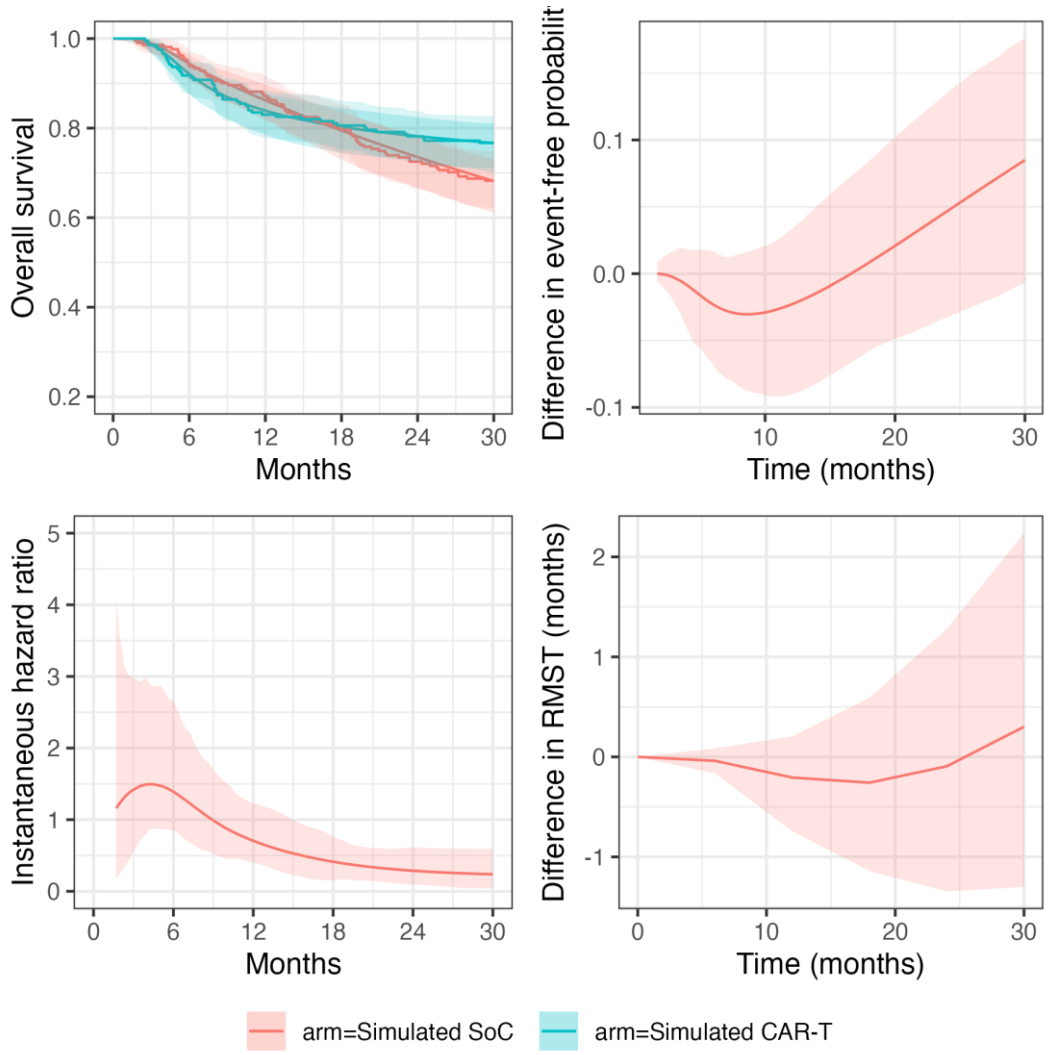




Rebora P, Salim A, Reilly M (2014) bshazard: A Flexible Tool for Nonparametric Smoothing of the Hazard Function. The R Journal Vol. 6/2:114-122.

Flexible Parametric Model of Hazard Functions (Simulated Data)

- Approach of Royston and Parmar (Stat Med 2002)
- Implemented in `flexsurv` package, the model makes it easy to characterize instantaneous hazard ratio, and differences in survival probabilities and Restricted Mean Survival Time (RMST)
- Useful in assessing if hazards cross across subgroups, assuming HR can change over time in a different way in different subgroups



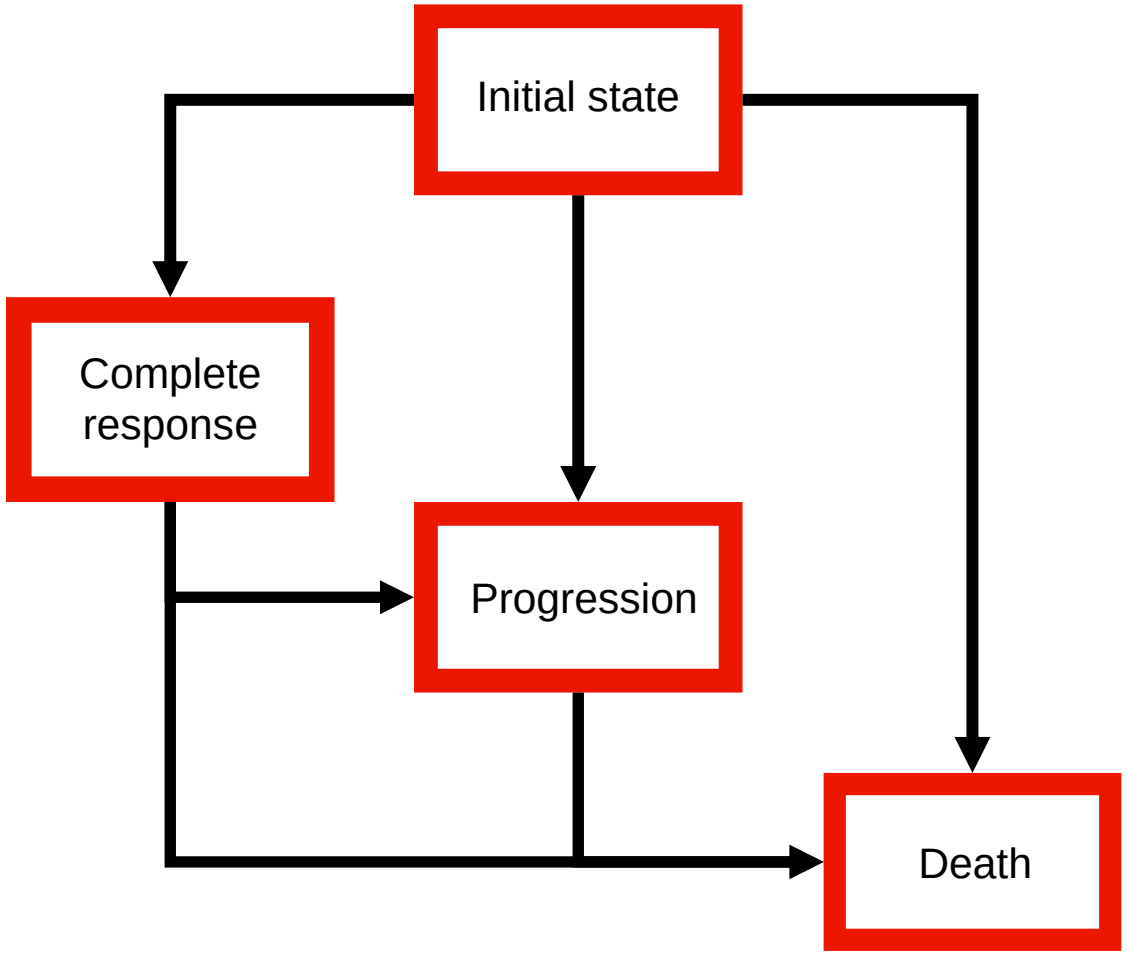
Royston, P., Parmar, M.K. An approach to trial design and analysis in the era of non-proportional hazards of the treatment effect. Trials 15, 314 (2014).

Multistate Analysis

A comprehensive way to characterize treatment effect

- To understand relationship between different clinical endpoints, we can model patient journeys through the course of the trial as their disease state changes

- Patients can transition from:
  - Initial state (when follow-up starts, no complete response/progression/death observed yet) to any other state
  - Complete response to progression or death
  - Progression to death



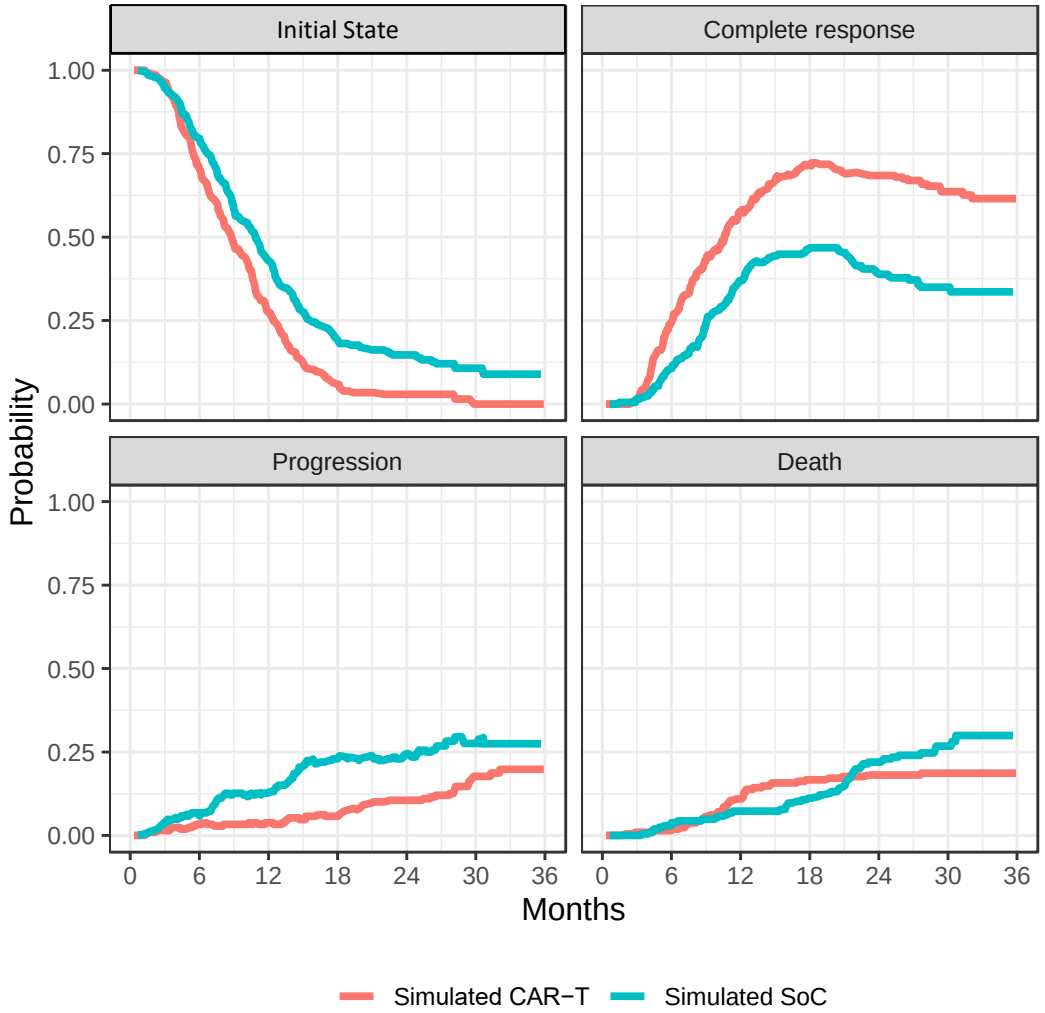
Therneau T, Crowson C, Atkinson E. Multi-state models and competing risks. https://cran.r-project.org/web/packages/survival/vignettes/compete.pdf

Multistate Analysis (Simulated Data)

Allows to comprehensively characterize clinical efficacy profile of the treatment regimen

- We interpret the curves as the probability of a patient from a given arm being in a particular state at a given time

- Simulated exercise shows:
  - Simulated CAR-T offers substantial advantages in complete response
  - Complete response is durable
  - Proportion of patients progressing or dying substantially lower in Simulated CAR-T



Therneau T, Crowson C, Atkinson E. Multi-state models and competing risks. https://cran.r-project.org/web/packages/survival/vignettes/compete.pdf

Treatment-Free Survival

Being treatment-free is one of the key patient experiences in CAR T cell therapies

- Based on the outcome measure proposed by Regan (2019), we define treatment-free survival as the average amount of time in the first 2.5 years (30 months) after randomization in which a subject has ended study treatment and has not yet started subsequent therapy

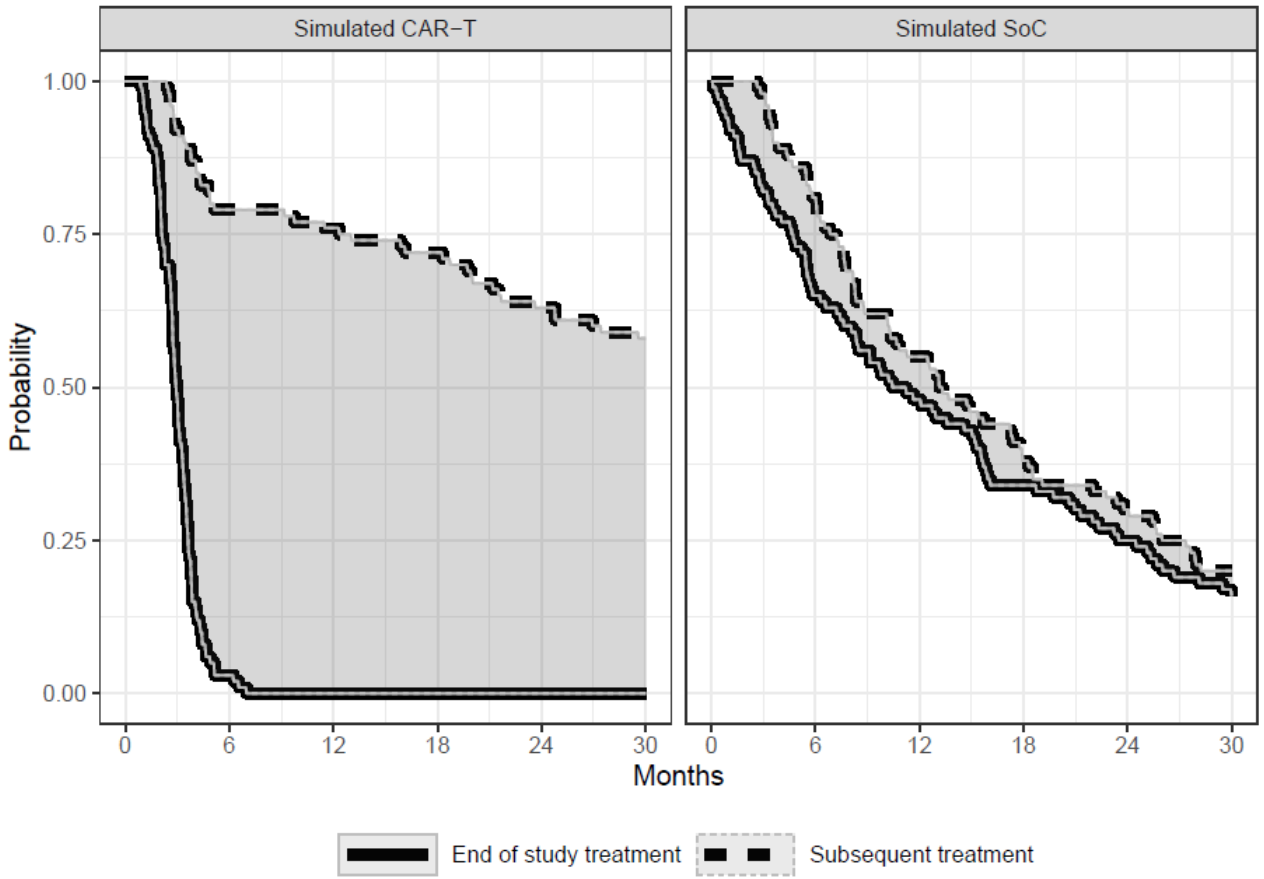
- This is estimated as the difference between:
  - RMST for time from randomization to subsequent therapy (censored at last time known alive)
  - RMST for time from randomization to end of treatment (censored at last time known alive if subject still receiving treatment at end of follow-up)
    - Confidence intervals around treatment-free survival (and difference in treatment-free survival between arms) are calculated using bootstrap

Regan MM, Werner L, Rao S, et al. Treatment-Free Survival: A Novel Outcome Measure of the Effects of Immune Checkpoint Inhibition-A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol. 2019;37(35):3350-3358.

Treatment-Free Survival Result (Simulated Data)

Of the 30-month period after randomization, the mean treatment-free survival is:

- CAR-T: 20.0 months (95% CI: 17.9, 22.1)
- SoC: 2.0 months (95% CI: 1.8, 2.2)
- Delta (CAR-T minus SoC): 18.0 months (95% CI: 15.9, 20.0)



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Conclusion and Summary

Delayed Treatment Effect: CAR T cell therapies involve a delay before treatment, which poses challenges for traditional survival analysis.

- Analytical Techniques: Weighted models, piecewise approaches, modeling estimation of hazard functions and multistate states analysis provide more accurate representations of delayed treatment effect and comprehensive characterizations of complex treatment effect pattern compared to unweighted methods.
- Regulatory Perspective: The FDA adopted conservative unweighted analyses, however is open to discussing other approaches.
- Key Takeaway: Using the appropriate statistical techniques ensures robust and accurate interpretation of clinical trial results, crucial for therapies with delayed effects like CAR T cell therapy.

Acknowledgments

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Thank you