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803.EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

Comparative Analysis of Methods for Analyzing Clinical Results of Immuno-Oncology Therapy with Delayed Treatment Effects

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Introduction: CAR-T therapy is a groundbreaking therapy that involves modifying patient's T cells to recognize and combat cancer cells. This therapy requires a period of CAR-T manufacture following apheresis, delaying the actual receipt of the CAR-T. During this period the patient may receive bridging therapy. CAR-T therapies are increasingly being studied in randomized controlled clinical trials and delays potentially affect the proportional hazards assumption, reduce log-rank test statistical power, and complicate reporting and interpretation. To address this, we assessed available statistical methods for analyzing immune-oncology outcomes, specifically CAR-T therapy's delayed treatment effects, with a focus on current and emerging tools to improve analysis and reporting.

Methods: We systematically reviewed and compared existing and emerging tools to evaluate survival analysis methods suitable for assessing outcomes in CAR-T studies. These methods included standard, stratified, and weighted log-rank tests, cox proportional hazards (time dependent), parametric survival (weibull, etc.), time-dependent covariates, landmark analysis, joint modeling and restricted mean survival time (RMST). We simulated trial results, highlighted features, underlying assumptions, and interpretability.

Results: Results were based on a simulated dataset (N=240) and revealed distinct characteristics and implications of each method used to analyze data (Table). Standard log-rank tests, which give equal weight to all time points and assumes proportional hazards, resulted in less discerning outcome measurements compared to weighted techniques such as censored weighted estimation/constant piecewise weighted (CWE/CPW) and Fleming-Harrington which do not assume proportional hazards and can be weighted towards early or late events. RMST summarized average time until progression, which may be a more intuitive measure for clinicians and patients and was presented along with other analytical techniques. Cox proportional hazards modeling provided ratios to quantify and compare efficacy across different time points. Parametric survival models captured survival dynamics and offered precise estimation of survival probabilities at specific intervals. Time-dependent covariates accounted for time-varying factors influencing treatment response, while landmark analysis evaluated treatment efficacy beyond a specific duration and was used in combination with other analytical techniques. Joint modeling simultaneously assessed treatment effects on both longitudinal and survival outcomes, accounting for their interdependencies. Stratification identified patient subgroups with differential treatment responses and outcomes, enabling precise reporting of categorical CAR-T treatment approaches.

Conclusions: Our comparative analysis of analytical techniques underscores the critical role of selecting an appropriate approach in the context of CAR-T therapies. Conventional methods such cox regression and the standard log-rank test, while useful in most contexts, may underestimate key outcomes associated with CAR-T therapy due to violations of proportional hazard assumption. Weighted techniques, which can be weighted towards early or late events, may provide a more nuanced picture, and better accommodate CAR-T therapies. Similarly, the RMST offers an intuitive average time to progression, offering complementary insights to other methods. These findings highlight the importance of careful method selection in survival analysis for CAR-T therapy studies. Rigorous, tailored analytical approaches will be crucial in accurately determining the efficacy of these promising therapies and informing future clinical study designs. By considering these methods, researchers can gain deeper insights regarding CAR-T therapy and improve the design and analysis of clinical trials, ultimately advancing the understanding and application of this transformative therapy.

Disclosures Amato: *Legend Biotech:* Consultancy, Current Employment, Current equity holder in publicly-traded company. **Koneru:** *Legend Biotech:* Current Employment. **Antoine:** *Legend Biotech:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company. **Liang:** *Legend Biotech:* Current Employment, Current equity holder in publicly-traded company. **Yeh:** *Janssen R&D:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Xu:** *Johnson & Johnson:* Current Employment. **Roccia:** *Janssen:* Current Employment, Current equity holder in private company. **Lendvai:** *Janssen R&D:* Current Employment, Current holder of *stock options* in a privately-held company.

Table. Methods for Analyzing Clinical Results of Immuno-Oncology Therapy with Delayed Treatment Effects

Test/Method	Methods	Sensitivity to Timing of Events	Assumptions	Implications for Immuno-Oncology
Standard Log-Rank	Compares survival distributions between two or more groups	Equal weight to all time points (most sensitive to differences when the hazard ratios are constant)	Non-informative censoring, Proportional hazards	Useful for comparing overall survival between CAR-T and control group
Stratified Log-Rank	Compares survival distributions between groups, while controlling for one or more other factors	Similar to standard log-rank, but allows for strata (groups) that may have different baseline hazard functions	Non-informative censoring, Proportional hazards within each stratum	Useful for controlling confounding factors in CAR-T trials
CWE/CPW Analysis	Assigns weights to events based on observed event times and censoring distribution	Can handle different types of censored data and involves assigning weights based on a weight function	Non-informative censoring	Can handle a variety of censored data situations common in CAR-T trials
Piecewise Log-Rank	Breaks down follow-up time into intervals and applies log-rank test within each interval	Sensitive to differences in hazard within specified time intervals	Non-informative censoring, Assumes proportional hazards within each time interval	Useful when there are time-dependent changes in hazard due to CAR-T therapy
Cox Proportional Hazards	Regression model for survival data that includes time-dependent covariates	Can handle time-dependent covariates, making it sensitive to changes over time	Non-informative censoring, Proportional hazards for time-independent covariates	Useful for modeling survival time with covariates that change over time, such as disease severity
Restricted Mean Survival Time (RMST)	Compares the area under the survival curves up to a specified time point	Compares the area under the survival curves up to a specified time point	Non-informative censoring, Does not assume proportional hazards	Useful when proportional hazards assumption does not hold, such as when late side effects influence survival

Figure 1

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