Introduction to Special Issue on ‘Statistical Methods for Cancer Immunotherapy’

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With decades of progress in medical research and advance in understanding the biology of cancer microenvironment, clinical development of novel cancer drugs including immunotherapies and targeted therapies is booming in recent years. In 2018 alone, the FDA approved 19 new cancer drugs and biologics. In 2013, Science names cancer immunotherapy as the scientific breakthrough of the year. Common immunotherapy approaches include cancer vaccine, effector cell therapy and T-cell stimulating antibody. Checkpoint inhibitors such as CTLA-4 and PD-1/PD-L1 antagonists, and CART-T therapies have shown exciting results in multiple indications in solid tumors and hematology. However, the mechanisms of action of these novel drugs pose unique statistical challenges in the accurate evaluation of clinical safety and efficacy, such as late-onset toxicity, dose optimization, evaluation of combination agents in dose-finding studies and master protocols, non-proportional hazards and delayed treatment effect [1, 2]. Traditional statistical methods may not be the most accurate or efficient. In this special issue of Statistics in Biosciences, 10 innovative and thought-provoking articles by forward-thinking statisticians cover a wide spectrum of relevant topics in the clinical development of cancer immunotherapies to address these mechanisms and challenges.

Buyse et al. [3] wrote a review article on assessing treatment benefit in Immunology, with an overview of the conventional and novel statistical methods for assessing treatment benefit in IO clinical trials. Their focus is on advanced disease, the setting in which most of the current evidence on immunotherapies has been generated. The authors begin by considering the direct effect of immunotherapies on tumors, discuss the translation of these effects into patient benefit, and end by exploring measures of treatment effect that may capture such benefit.

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Wages and Slingu [4] propose a Phase I–II design for partially ordered regimens with application to therapeutic cancer vaccines that violate the common assumption that the dose–toxicity curve is monotonically increasing, and that the dose–efficacy curve either plateaus or decreases beyond an intermediate dose. A Bayesian model-based design is described in determining the optimal biologic regimen, based on bivariate binary measures of toxicity and biologic activity.

Zhou et al. [5] propose a novel phase I design, the probability-of-decision toxicity probability interval (PoD-TPI) design, to accelerate phase I trials. PoD-TPI enables dose assignment in real time in the presence of pending toxicity outcomes. A new and useful feature of PoD-TPI is that it allows investigators and regulators to balance the trade-off between enrollment speed and making risky decisions by tuning a pair of intuitive design parameters.

Fan et al. [6] introduce a curve-free, Bayesian decision-theoretic two-stage design to select biological efficacious doses for phase Ia/Ib trials in which both toxicity and efficacy signals are observed. No parametric models are assumed to govern the dose–toxicity, dose–efficacy, and toxicity–efficacy relationships. They assume that the dose–toxicity curve is monotonic non-decreasing and the dose–efficacy curve is unimodal. In the phase Ia stage, a Bayesian model on the toxicity rates is used to locate the maximum tolerated dose. In the phase Ib stage, the authors model the dose–efficacy curve using a step function while continuing to monitor the toxicity rates.

Jin et al. [7] present a novel approach for the PoC detection in early phase basket trials under a Bayesian framework. The authors classify cancer types into either a “sensitive group” that responds positively to the treatment or an “insensitive group” that does not respond to the treatment. They then assess PoC using the posterior probability that at least one cancer type is sensitive.

In recent years, the marker strategy design (MSGD) has been proposed to assess and validate predictive markers for targeted therapies and immunotherapies. Under this design, patients are randomized into two strategies: the marker-based strategy, which treats patients based on their marker status, and the non-marker-based strategy, which randomizes patients into treatments independent of their marker status in the same way as in a standard randomized clinical trial. The strategy effect is then tested by comparing the response rate between the two strategies. Han et al. [8] show that this commonly used between-strategy test is flawed, which may cause investigators to miss the opportunity to discover important predictive markers or falsely claim an irrelevant marker as predictive. Then they propose new procedures to improve the power of the MSGD to detect the predictive marker effect. One is based on a binary response endpoint; the second is based on survival endpoints.

With the rapidly evolving landscape of cancer immunotherapy, new strategies have been developed over the last several years to help expedite the drug development process. One of these strategies, umbrella design, tests the effect of multiple investigational treatments in patients with same type of cancer. In their article, Liu et al. [9] evaluated the impact of clinical center variation on the efficiency of an umbrella trial where clinical centers are shared among all investigational treatments, compared to that of the traditional approach where each experimental drug is evaluated in a separate trial using different clinical centers. They demonstrate

mathematically that the umbrella trial setting is more efficient than the traditional trials in terms of identifying more efficacious drugs, as sharing clinical centers among investigational treatments can reduce the impact of clinical center variation.

In late phase randomized clinical trials, weighted log-rank statistics and recently weighted win loss statistics are often used to test the null hypothesis that the treatment group and the control group have no difference. However, they usually do not provide meaningful treatment effect estimates. Luo and Quan [10] investigate a few weighted log-rank statistics and weighted win loss statistics that will provide meaningful treatment effect estimates.

Leon et al. [11] expand on the ideas of combining various weighted log-rank tests allows for tests that are capable of detecting treatment effects across a broad range of non-proportional hazards scenarios. They propose a framework based on a flexible resampling approach which allows for the combination of various testing procedures in addition to weighted log-rank tests. In particular, the authors describe how tests based on restricted mean survival time comparisons can be included within combinations of weighted log-rank tests as well as other test statistics such as Tarone-Ware and Renyi-type supremum families. For estimation, they propose companion weighted Cox model which utilize the weighting form that is “selected” through the combination test and provide simultaneous confidence intervals.

Last but not least, Zhang et al. [12] consider estimation of Mann–Whitney-type effect measures in randomized clinical trials where the outcome variable is a survival time subject to independent censoring. In this setting, a plug-in estimator based on Kaplan–Meier estimates of survival functions is readily available, and can be used to generate a class of augmented estimators that incorporate baseline covariate information. The optimal augmentation, which leads to the most efficient non-parametric estimator, can be estimated by minimizing an empirical version of the asymptotic variance of an augmented estimator using machine learning methods. Implementing this approach requires estimating the influence function of the initial plug-in estimator, for which the authors propose to use the empirical influence function available in the jackknife method.

References

Other References

1. Huang B (2018) Some statistical considerations in the clinical development of cancer immunotherapies. *Pharm Stat* 17(1):49–60
2. Chen TT (2013) Statistical issues and challenges in immuno-oncology. *J Immunother Cancer* 1(1):18

References to Articles in This Special Issue

3. Buyse M, Saad ED, Burzykowski T, Péron J (2020) Assessing treatment benefit in immuno-oncology. *Stat Biosci.* <https://doi.org/10.1007/s12561-020-09268-1>
4. Wages NA, Slingluff CL (2020) Flexible phase I-II design for partially ordered regimens with application to therapeutic cancer vaccines. *Stat Biosci.* <https://doi.org/10.1007/s12561-019-09245-3>
5. Zhou T, Guo W, Ji Y (2020) PoD-TPI: probability-of-decision toxicity probability interval design to accelerate phase I trials. *Stat Biosci.* <https://doi.org/10.1007/s12561-019-09264-0>
6. Fan S, Lee BL, Lu Y (2020) A curve-free Bayesian decision-theoretic design for phase Ia/Ib trials considering both safety and efficacy outcomes. *Stat Biosci.* <https://doi.org/10.1007/s12561-020-09272-5>
7. Jin J, Liu Q, Zheng W, Shun Z, Lin TT, Gao L, Dong Y (2020) A Bayesian method for the detection of proof of concept in early phase oncology studies with a basket design. *Stat Biosci.* <https://doi.org/10.1007/s12561-020-09267-2>
8. Han Y, Yuan Y, Cao S, Li M, Zang Y (2019) On the use of marker strategy design to detect predictive marker effect in cancer immunotherapy and targeted therapy. *Stat Biosci.* <https://doi.org/10.1007/s12561-019-09255-1>
9. Liu F, Li N, Li W, Chen C (2019) Impact of clinical center variation on efficiency of exploratory umbrella design. *Stat Biosci.* <https://doi.org/10.1007/s12561-019-09263-1>
10. Luo X, Quan H (2020) Some meaningful weighted log-rank and weighted win loss statistics. *Stat Biosci.* <https://doi.org/10.1007/s12561-020-09273-4>
11. León LF, Lin R, Anderson KM (2020) On weighted log-rank combination tests and companion cox model estimators. *Stat Biosci.* <https://doi.org/10.1007/s12561-020-09276-1>
12. Zhang Z, Li W, Zhang H (2019) Efficient estimation of Mann–Whitney-type effect measures for right-censored survival outcomes in randomized clinical trials. *Stat Biosci.* <https://doi.org/10.1007/s12561-019-09246-2>