Clinical Trial Designs for Testing Biomarker-Based Personalized Therapies

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Advances in molecular therapeutics in the past decade have opened up new possibilities for treating cancer patients with personalized therapies, using biomarkers to determine which treatments are most likely to benefit them, but there are difficulties and unresolved issues in the development and validation of biomarker-based personalized therapies. We use generalized likelihood ratio tests of the intersection null and enriched strategy null hypotheses to derive a novel clinical trial design for the problem of advancing promising biomarker-guided strategies toward eventual validation. We also investigate the usefulness of adaptive randomization and futility stopping proposed in the recent literature. Simulation studies demonstrate the advantages of testing both the narrowly focused enriched strategy null hypothesis related to validating a proposed strategy and the intersection null hypothesis that can accommodate to a potentially successful strategy. Adaptive randomization and early termination of ineffective treatments offer increased probability of receiving the preferred treatment and better response rates for patients in the trial, at the expense of more complicated inference under small-to-moderate total sample sizes and some reduction in power. The paper shows the advantages of using likelihood inference and interim analysis to meet the challenges in the sample size needed and in the constantly evolving biomarker landscape and genomic and proteomic technologies.

Key Words: Adaptive randomization, biomarkers, generalized likelihood ratio statistics, personalized therapies.