Two-stage Randomization Designs in Drug Development

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One challenge in oncology drug development is to determine whether a new agent to the care of patients should be added concurrently as a new component to standard of care (SOC) induction treatment, be used sequentially as an extended maintenance treatment after SOC induction for patients responding to induction therapy, or be used in both the induction and the maintenance setting. A two-stage randomization design (TSRD) addresses these questions simultaneously. In such trials patients are initially randomized to two induction therapies followed by another randomization to maintenance therapy contingent upon disease remission under induction therapy. We survey recently proposed methods for analyzing time-to-events in TSRDs and discuss several issues related to the use of TSRDs including sample size calculation and multiplicity. An alternative drug development strategy is to perform several single randomization designs (SRDs) comparing induction or maintenance regimens, respectively. We present a simulation study which compares TSRDs to several strategies based on SRDs in terms of total sample size and time to reach clinical decisions.