Recent developments in the implementation of novel designs for early-phase combination studies

Recently, Riviere et al. [1] conducted a literature review of designs for drug-combination phase I trials in oncology. We commend the authors for undertaking such a review, as well as for their advocacy for use of more innovative approaches in designing these contemporary trials. We agree that combination dose-finding studies would benefit from more frequent application of efficient designs. This letter reports our experience in using novel approaches for several ongoing early-phase combination trials.

Riviere et al. [1] provide a discussion of the complexity inherent in designing drug-combination trials, namely the partial order associated with the dose-limiting toxicity probabilities. The authors point out that, despite this complexity, modified forms of the traditional 3 + 3 method continue to receive the most frequent use in clinical trials involving partial orders. They cite the recent development of several novel approaches, yet acknowledge their lack of use in practice. One method omitted from this discussion is the continual reassessment method for partial ordering (POCRM) [2]. Here, we expand on the work of Riviere et al. [1] by highlighting the implementation of POCR for several ongoing drug-combination trials designed at the University of Virginia (UVA) Cancer Center.

After the introduction of POCR in 2011 [2], Wages and Conaway [3] published a follow-up paper addressing practical considerations and design specifications for its implementation. These guidelines were initially developed through the process of designing a combination trial at UVA that completed accrual and is currently in follow-up (NCT01585350). A particular area in which Riviere et al. [1] stressed the need for improved design is in early-phase cancer vaccine trials. The POCR was implemented as part of a multi-site, phase I/II trial of combination immunotherapies that is currently open to enrollment at UVA and M.D. Anderson Cancer Center (NCT02126579) [4]. The estimation procedure employed by POCR is used to adaptively monitor safety and to identify an acceptable set of regimens in high-risk melanoma patients. After each patient inclusion, POCR updates the acceptable set of safe regimens, and the next patient is allocated to the acceptable regimen exhibiting the highest immunogenicity. Most recently, a bivariate extension [5] of POCR was implemented in a phase I/II design for a trial combining two small molecule inhibitors in relapsed/refractory mantle cell lymphoma. This pharmaceutical industry-sponsored trial has FDA approval, and is slated to open within the next 2 months. In each of these studies, the practical challenges described at the end of the ‘Introduction’ section of Riviere et al. [1] were given thorough consideration to aid in approval of scientific review committees, IRBs and the FDA. The two trials NCT01585350 and NCT02126579 have been approved by local IRBs and the FDA, highlighting the acceptability and feasibility of these designs in practice. We hope that inclusion of these ongoing studies into the conversation initiated by Riviere et al. [1] will aid in promoting more frequent implementation of efficient approaches in combination studies.

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disclosure

CLS is an inventor on patents of peptides for use in clinical trials of cancer vaccines; these patents are held by the University of Virginia Licensing and Ventures Group. He also is on and the University receives funding for his roles as external advisory board member for Immatics, Inc., and as PI for a clinical trial of a cell-based vaccine sponsored by Polynoma. He also receives support for investigator-sponsored cancer immunotherapy clinical trials from GlaxoSmithKline and Merck. All remaining authors have declared no conflicts of interest.

references


doi: 10.1093/annonc/mdv075
Published online 19 February 2015