Challenges, opportunities, and innovative statistical designs for precision oncology trials

Jun Yin[1#], Shihao Shen[2#], Qian Shi[1]

[1]Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA; [2]Dermbiont, Inc., Boston, MA, USA

Contributions: (I) Conception and design: J Yin, Q Shi; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jun Yin, PhD. Mayo Clinic, 200 1st ST SW, Rochester, MN 55905, USA. Email: Vivien.jyin@gmail.com.

Abstract: In the era of precision oncology, improved understanding of tumor heterogeneity, particularly at the molecular level, has caused a shift from traditionally histology based cancer drug development to molecularly targeted drug development. The shift to the molecular view of cancer leads to increasingly small cancer populations for clinical trials which may be underpowered using traditional statistical designs. This paradigm shift lead to the recent developments of innovative clinical trial designs to address the challenges from precision oncology clinical trials. Hence, this paper reviewed and described innovative trial designs for precision oncology. Different strategies were discussed to account patient and treatment effect heterogeneity, including precision dose-finding designs that tailor the optimal dose to different patients at different time points, master protocol designs that match patients' molecular alterations with specific targeted agents, and adaptive enrichment designs that dynamically modify eligibility criteria and enroll patients that are most likely to benefit from the novel agents. Despite their superior performance, better understanding of practical barriers is needed to widen their implementation for precision oncology trials. Therefore, this paper also reviewed the practical challenges regarding the implementation of precision oncology clinical trials, along with the strength and weakness of various approaches of precision oncology clinical trial designs.

Keywords: Clinical trial design; platform trial; basket trial; umbrella trial; adaptive design

Submitted Jan 09, 2022. Accepted for publication Aug 27, 2022.

doi: 10.21037/atm-22-356

View this article at: https://dx.doi.org/10.21037/atm-22-356

Introduction

Conventionally, oncology clinical development has been conducted separately for distinct histologies and tumor locations. With the pursuit of precision medicine, there has been a surge in scientific discovery of tumor heterogeneity, the development of novel targeted therapies, and the use of next-generation sequencing in guiding treatments for patients. As a result, the conventional histology-focus clinical development has been supplemented by focus on genomic aberrations. For example, more recently oncology drugs approved by FDA are for a genomic marker restricted population: midostaurin for FLT-3 mutated adult acute myeloid leukemia (1), larotrectinib for TRK fusion-positive tumors across multiple histologies for adults and children (2). These marker specific trials match investigational agents with patients' targetable mutations, and have shown great potentials to deliver effective treatments to the patients based on their molecular biomarkers. However, the increased complexity of these marker specific trials and their often narrower inclusion criteria can lead to smaller patient population relative to "all comers" designs. Therefore, more effective methods are needed to detect and quantify biomarker-driven treatment effects in precision oncology trials.

Novel clinical trial designs have been developed to

identify and incorporate patient heterogeneity in clinical decision making, to make precision oncology trials more efficient in trial performance characteristics, reducing resource use and shortening trial duration and while still maintaining high statistical rigor. In this article, we aim to summarize recent development of novel trial designs that utilize the rich information in the precision oncology settings to improve trial performance, and how the novel designs could tackle the challenges facing precision oncology trials. The statistical designs covered in this article include both frequentist and Bayesian frameworks.

The remainder of the paper is organized as follows. Section "Precision dose-finding designs" describes innovative precise dose-finding designs, including both individualized dose-finding across treatment cycles and subgroup-specific dose-finding designs. Section "Master protocol designs" describes innovative master protocol designs that evaluate multiple drugs and/or disease populations simultaneously, including basket, umbrella, and platform designs. Section "Adaptive enrichment designs" describes adaptive enrichment designs that select patients based on biomarkers and interim responses. We conclude with a brief discussion in the last section.

Precision dose-finding designs

Phase I oncology trials are designed to identify a safe dose with an acceptable toxicity profile [i.e., the maximum tolerated dose (MTD)] for subsequent testing. The traditional 3+3 design was developed for cytotoxic chemotherapy, and has been shown to lack the efficiency and accuracy for molecularly targeted agents in precision oncology trials (3-5). Recent dose-finding designs have been developed to incorporate rich data from precision oncology trials, to account for heterogeneity within the same patient across multiple treatment cycles (i.e., individualized dosing), or heterogeneity across patient sub-populations (i.e., subgroup-specific dosing).

Individualized dosing across treatment cycles

In traditional phase I dose-finding designs, the MTD is typically determined based on the probability of severe toxicity observed during the first treatment cycle. For precision oncology trials, targeted therapy often induces manageable toxicity profiles allowing patients to undergo prolonged treatment cycles (6). Additionally, although dose modifications (dose escalation and reductions) are routinely conducted over the treatment cycles in modern clinical trials, toxicity beyond the first cycle is rarely taken into consideration in the study designs. Intra-patient dose escalation can occur when there is mild or no toxicities or when patients have built up tolerance and therefore higher dose level can be deemed safe for patients' subsequent treatment cycles. Another scenario is to reduce the dose level in the later treatment cycles due to toxicities or quality-of-life concerns. The latter scenario is more common as targeted agents are more likely to induce late on-set or chronic toxicities which, if not adequately assessed, could result in a high proportion of dose modification, dose interruptions, and discontinuation of the drug in later phase trials. Therefore, there is a need to develop novel designs that can incorporate comprehensive, longitudinal toxicity profile.

A few dose-finding designs have been proposed to optimize patient doses over multiple cycles (7-10), assuming some parametric models for the dose-toxicity relationship (i.e., model-based designs). In the Lee's design (8), a latent-state space model was used to draw inference on the change of toxicity states over treatment cycles. Yin *et al.* (9,11,12) and Doussau *et al.* (13) used mixed effect models based on repeated measures of graded toxicities to generate per-cycle toxicity estimates Du *et al.* (14) with a compound symmetric covariance structure to model the within-patient correlation. However, because of the complex nature of these model-based designs, e.g., latent-state space and mixed effect models, they are often viewed as "black-box" to clinicians, which is the main stumbling block to implement them in clinical practice. To overcome this challenge, Lyu *et al.* (10) proposed and implemented a simple Bayesian adaptive dose-cycle finding (BaSyc) design which could tabulate decision rules at the trial outset, allowing clinicians to visualize the dose decision rules at the trial design stage. Because its simplicity in application and transparency, BaSyc design has been implemented in an acute lympholytic leukemia trial to identify the MTD sequence of ruxolitinib (NCT03571321).

Another concern for conventional phase I dose-finding designs is that they assume efficacy increases with increasing dose. Although a valid assumption for cytotoxic agents, ample evidence has shown that targeted agents have different dose-response relationships than cytotoxic chemotherapies (15) (i.e., patients on lower dose do not fare worse). Recent development of dose-finding designs has relaxed the assumption that efficacy monotonically increase with dose, and utilized both toxicity and efficacy

information to choose the optimal dose. Du and Yin *et al.* has extended their repeated measures design to incorporate biomarker data as early efficacy signals, in order to identify the optimal dose that maximize the efficacy with acceptable toxicity profile across multiple treatment cycles (14).

Subgroup-specific dose-finding

Conventional dose-finding designs assume that the trial participants are homogeneous, such that the optimal dose is the same for all participants in a phase I trial. However, precision oncology has shifted the paradigm from the "one-size-fit-all" rationale. More recently, targeted agents have given rise to the need for subgroup-specific dosing, as the dose-toxicity curves may differ between biomarker subgroups. However, due to the small sample size for phase I trials, conducting separate trials for different molecular subgroups may render the trials infeasible for genomic mutations with low prevalence. Therefore, novel statistical methods are needed to account for the possible heterogeneity in a single trial, where efficacy and toxicity are dependent on subgroups with various status of biomarkers, patient characteristics or pharmacokinetic profiles.

Several methods exist that address the problem of patient heterogeneity in phase I trials.

O'Quigley *et al.* proposed a two-sample continual reassessment method (CRM) to find the optimal dose for each of two possibly ordered subpopulations of patients (16,17). Ivanova and Wang proposed a non-parametric design with bivariate isotonic regression to address the same problem (18). Yuan and Chappell extended the up-and-down design, the CRM, and the isotonic design, to deal with multiple risk subgroups with two-way isotonic regression (19). The dose-limiting toxicity (DLT) definitions were also extended in some approaches. Yuan proposed the Quasi-CRM to incorporate equivalent toxicity scores (20). A generalized Bayesian optimal interval (generalized BOIN) design was proposed for dose-finding accounting for efficacy and toxicity grades (21). Toxicity tumor burden design was proposed by Bekele and Thall to account for toxicity grades (22). All of these approaches assume that the subgroups can be ordered according to their probability of toxicity. Morita *et al.* addressed this by generalizing the CRM method based on a hierarchical Bayesian dose-toxicity model (23) that borrows strength between subgroups; however, their methods assumed exchangeability between subgroups. Chapple and Thall (24) extended Salter's methods (25,26) based on the TITE-CRM to handle more than two subgroups, and relaxed two assumptions in their design: it doesn't require a priori ordering of subgroups by toxicity rates or the assumption of exchangeability as in a hierarchical model. Specifically, they utilized an adaptive Bayesian clustering approach based on spike-and-slab prior. A spike and slab prior is a generative model, in which the random variable either attains some fixed value, called the spike, or is drawn some other prior slab. In this method, subgroups are collapsed and separated from one MCMC iteration to the next, allowing borrowing when appropriate but accommodating heterogeneous scenarios by not forcing borrowing. Also, their method allows for clinician-specified priors for each subgroup, unlike hierarchical models which can only use a single dose-toxicity prior determining the prior probability of experiencing DLT for all subgroups.

Master protocol designs

Different from the traditional "one indication at a time" approach in clinical testing that only tests one drug, or one histology in a clinical trial, master protocols evaluate multiple drugs, multiple histologies, and/or multiple molecular subtypes in parallel under a single clinical trial infrastructure, aiming for enhanced efficiency in small patient subpopulations for precision oncology trials (27). Such trials allow logistic efficiency (centralized screening, biomarker profiling, collection of tissue or blood, and etc.) and potentially accelerated clinical development than separate studies. There are three types of master protocol trials: basket trials, umbrella trials, and platform trials (28).

Innovative basket trial designs

A basket trial is designed to test one investigational drug or drug combination in multiple cancers or cancer subtypes with a common biomarker linked to the therapeutic target of the drug (29). The underlying hypothesis is that response to the targeted therapy is determined by the biomarker and independent of tumor histology [e.g., larotrectinib was approved for TRK fusion-positive cancers in adults and children (30)]. They are usually exploratory in nature, using single-arm designs with overall response rate as the primary endpoint for each sub-study ("the basket"). Benefits of basket trials are that they are accessible for patients with rare tumors with the respective molecular signature where individual tumor types cannot be adequately powered. Challenges are that molecular variant(s) may not be the only

driver of tumor response and unpredicted heterogenous treatment effect may exist across tumor types [e.g., vemurafenib works in BRAF mutated melanoma but not in BRAF mutated colorectal cancer (31,32)].

Conventional basket trial designs use either pooled analysis across tumor types or independent tests for each tumor types. The former approach (pooled analysis) ignores potential treatment effect heterogeneity; and one negative indication can lead to a failed study for all indications in a basket trial. The latter approach (independent analysis) ignores potential correlated responses to the same agent that targets the same mutation; and for rare tumors, it could be infeasible to enroll patients to each of the sub-studies. Several innovative basket designs have emerged to tackle these challenges. Simon et al proposed a Bayesian basket design which considered two possible scenarios: sub-studies are either all independent from each other or they are homogeneous in terms of the treatment effects (33). Cunanan et al developed an adaptive basket trial design in which the interim analysis would assess the heterogeneity and determine whether the subsequent analysis should be conducted separate for each tumor type or pooled across all tumor types (34). Chu and Yuan (35) proposed Bayesian latent subgroup design to control for potential treatment effect heterogeneity, which used a latent grouping indicator to indicate whether each sub-study belongs to the treatment sensitive or insensitive subgroup. Psioda *et al.* proposed an adaptive basket design using model averaging (36).

Bayesian hierarchical models were also proposed in a basket trial setting to allow information borrowing across tumor types to increase power. Berry (37) & Krajewska (38) proposed hierarchical models to cluster patient population in the basket trials. However, these models have been showed to yield inflated type I error in case of heterogeneous treatment effect (39,40). If the hierarchical model assumes homogeneous treatment effects across the treatment arms, it's important to check whether the observed treatment effect is consistent with the homogeneous assumptions. Otherwise, models accounting for heterogeneous treatment effects across groups should be used. To better control the type 1 error in Bayesian hierarchical models for heterogeneous effects, Liu *et al.* (41) proposed Bayesian mixture clustering models where sub-studies with similar response to treatment were clustered and hierarchical modeling was used to allow information sharing only within the clusters. Chu and Yuan (42) proposed a calibrated Bayesian hierarchical model for basket trials in which the shrinkage parameter is defined as a function of a treatment effect similarity measure. Neuenschwander *et al.* (43) proposed a robust approach for Bayesian hierarchical models in which the exchangeability assumption does not need to hold for every subpopulation, thus allowing some subpopulations to have similar treatment effects and some to have unique treatment effects. Hobbs and Landin (44) also propose a Bayesian hierarchical model basket trial design that evaluates pair-wise exchangeability among the sub-studies (i.e., multi-source exchangeability models).

Innovative umbrella and platform trial designs

An umbrella trial is designed to test multiple investigational drugs or drug combinations in a single disease (single tumor type or histology) with different molecular subtypes (sub-studies) (29). A platform trial also tests multiple investigational drugs in a single disease, but with the flexibility of adding or dropping arms (29). Each sub-trial is either single-arm or randomized. Randomization to a common control can make more sense in the context of an umbrella or platform trial because it studies a single disease population. Strength of umbrella trials is that they can make more meaningful statements specific to a given single disease population, which could result in support of a therapeutic confirmatory result (28). In addition, if randomization to treatment arms within a subgroup takes place, predictive and prognostic biomarkers can be distinguished (28). The major difficulty of an umbrella trial is that it may have difficult enrolling patients for rare molecular subtypes in a single tumor, as it decreases the sample size by stratifying on molecular targets. In practice, a very specific molecular target requirement can often lead to slow patient enrollment. Therefore, existing statistical methods focus on information borrowing across sub-studies or from historical studies to increase trial efficiency while controlling for multiplicity.

Bayesian hierarchical models were proposed in umbrella and platform trial settings as well for information borrowing across sub-studies. Kaizer *et al.* proposed a platform design with adaptive randomization and information borrowing through Bayesian hierarchical modeling with a multi-source exchangeability method, and illustrated their design using the PREVAIL II Ebola trial (45). Normington *et al.* proposed a Bayesian adaptive-randomization platform trial design with time-to-event endpoints and a common control arm, with control information borrowing through

a commensurate prior method (46). Jiao *et al.* evaluated various strategies of sharing control arms and information from historical data, and proposed a procedure for shared controls in a platform trial setting (47). Li *et al.* (48) developed a phase I/II platform trial design of targeted cancer therapies which combined the CRM methods for estimating the MTD and the Bayesian hierarchical modeling for estimating efficacy. Kang *et al.* (49) developed the Hierarchical Bayesian Clustering Design of Multiple Biomarker Subgroups (HCOMBS) design for multi-arm genetic screening trials, which is a 2-stage umbrella phase II design with effect size clustering and information borrowing across arms with similar response to treatment.

Another advantage of umbrella trials for screening is that it is possible to cycle quickly through ineffective treatments. And strategies such as response adaptive randomization in the Bayesian setting have been used to ethically enroll more patients into more promising treatments (50). For example, the BATTLE (Biomarker-integrated Approaches to Targeted Therapy for Lung Cancer Elimination) study (an umbrella trial with five sub-studies of lung cancer) utilized the Bayesian hierarchical model with response-adaptive randomization (51). The GBM AGILE (Glioblastoma adaptive, global, innovative learning environment) trial (NCT03970447) implements a seamless phase II/III response-adaptive platform design (52). In this trial, treatment arms that show success in the first part of the trial can graduate to the next stage for confirmation through the interim analysis. Additionally, the adaptive adjustment of randomization probabilities at the interims allows the trial resource to be focused on the sub-studies with more promising results, thus accelerates the testing of new precision oncology treatments. Gajewski *et al.* further investigated Bayesian response-adaptive designs in the context of multi-arm trials and found that they perform favorably compared with other Bayesian adaptive and fixed randomization designs (53).

Additional statistical methods aim to increase flexibility in a platform trial with mid-trial adaptations, such as seamlessly adding new treatments as they emerge and dropping poorly performing treatments with frequent interim looks, while maintaining strong type I error control. For example, Hobbs *et al.* developed a Bayesian platform trial design that accepts new arms throughout the trial, facilitates a shared control arm, and allows for frequent interim looks for futility based on Bayesian predictive probabilities (54). RAMPART (55) is a multi-arm multi-stage adaptive platform trial that investigates the addition of checkpoint inhibitors in renal cell carcinoma. In addition to the three arms originally started in the trial, it allows the adaptive decision to open a new experimental arm during the course of the trial based on interim results. Another adaptive feature of RAMPART is that the control arm can be altered if new standard of care emerges.

Adaptive enrichment designs

Adaptive enrichment designs allow the eligibility criteria of a trial to be adaptively updated during the trial. The identification and confirmation of subgroups of patients where a treatment is (most) effective is one of the most important consideration in designing a clinical trial. The specification of the optimal target population is usually first evaluated in a phase II trial, before being employed in a confirmatory phase III trial through the inclusion and exclusion criteria. For precision oncology trials, there is a higher uncertainty regarding the optimal target population, because of the complex nature of treatment and biomarker interactions [e.g., uncertainties, with regards to the PD-L1 protein expression level as a predictive biomarker for immune checkpoint inhibitors (56)]. The fast pace at which precision oncology drugs are being developed and approved leads to more challenges in determining the optimal target population. Therefore, there is a need for adaptive enrichment designs for precision oncology trials, which can select potential patient subgroups based on accumulated data at the interim, and confirm the efficacy in selected subgroups at the end of the trial.

FDA has published guidance on "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products", which stresses the importance of prospective planning and control of type I error rate. To ensure strong type I error control for regulatory approval, several existing designs have used a p-value combination method to synthesize pre- and post-adaptation information, for normally distributed endpoints (57) and time-to-event clinical endpoints (58,59). Rosenblum and Van der Laan (60) and Rosenblum *et al.* (61) considered adaptive enrichment designs in the case of a single binary biomarker; while Magnusson and Turnbull (62) have considered a small number of pre-specified subsets. Simon and Simon (63) developed a block adaptive enrichment design which includes single and multiple biomarkers of any type; they based their design on Bayesian methods to estimate effect size, optimize the enrichment decisions during the trial, and characterize the target population at the

end of the trial. They further extended their methods to use a joint frequentist and Bayesian design in their later work (64). Notably, these designs explicitly factor in the possibility that the new drug might differentially benefit distinct biomarker subgroups, and allow data-dependent mid-course enrichment with preservation of type I error. In terms of application, both Rosenblum and Hanley (65) and Lai *et al.* (66) have applied their adaptive enrichment designs to the setting of stroke trials. This does not restrict its relevance of this to deal with trial designs for precision oncology.

Discussion

Cancer is becoming largely a collection of diseases defined by molecular subtype with low prevalence, even within major tumor types. Enrolling enough subjects for trials in these indications in a timely fashion is challenging. In this review article, we conducted a comprehensive literature review on innovative clinical trial designs due to the shift to molecular view of cancer and the need to characterize treatment effect heterogeneity in precision oncology trials. These novel designs are motivated by the widespread use of cancer biomarkers as surrogate endpoints, patient selection, and treatment stratification criteria. Precise dose finding designs use the combined profile of toxicities and surrogate efficacy biomarkers to search for the better solution of the recommended phase 2 dose. Some designs also allow for the intra-patient dose modification of patients to allow for a more precise dosing delivery over the treatment course. Master protocols allow the use of a single infrastructure to test the multiple treatment strategies in the precision oncology setting, and innovative master protocol designs have allowed information borrowing to further expedite the drug development of precision oncology. Adaptive enrichment designs use accumulated information during an ongoing trial to enrich patients to allow for decreased variability in estimates and increased likelihood of responding to the treatment if truly effective.

The increased flexibility of precision oncology trials come with increased complexity which naturally implies some limitations. Complicated designs can be vulnerable to concerns about reproducibility of reported findings, control of type I error rate if the results are intended to support regulatory approval, as well as interpretability. Detailed documentation of parameter specification, operating characteristics, and statistical analysis plan, and dissemination of user-friendly software are the keys to make these complex designs more trustworthy. And most importantly, complex designs involve enormous logistic hurdles during the trial design and conduct stage. The number of real-life trials using the innovative designs is still limited. A better understanding of further challenges from investigators, sponsor, and regulatory views are needed. Despite these limitations, innovative clinical trials continue to hold great promise to revolutionize clinical drug development for precision oncology.

A variety of the statistical packages have been developed in R for innovative clinical trials. CRAN (The Comprehensive R Archive Network) maintains a list of these R packages at https://github.com/cran-task-views/ClinicalTrials/.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine* for the series "Challenges in Clinical Trials". The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-356/coif). The series "Challenges in Clinical Trials" was commissioned by the editorial office without any funding or sponsorship. Jun Yin and Qian Shi served as the unpaid Guest Editors of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med 2017;377:454-64.
2. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-9.
3. Ivy SP, Siu LL, Garrett-Mayer E, et al. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clin Cancer Res 2010;16:1726-36.
4. Kurzrock R, Lin CC, Wu TC, et al. Moving Beyond 3+3: The Future of Clinical Trial Design. Am Soc Clin Oncol Educ Book 2021;41:e133-44.
5. Postel-Vinay S, Collette L, Paoletti X, et al. Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents--dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies, an European Organisation for Research and Treatment of Cancer-led study. Eur J Cancer 2014;50:2040-9.
6. Postel-Vinay S, Gomez-Roca C, Molife LR, et al. Phase I trials of molecularly targeted agents: should we pay more attention to late toxicities? J Clin Oncol 2011;29:1728-35.
7. Lee J, Thall PF, Ji Y, et al. A decision-theoretic phase I-II design for ordinal outcomes in two cycles. Biostatistics 2016;17:304-19.
8. Lee J, Thall PF, Ji Y, et al. Bayesian Dose-Finding in Two Treatment Cycles Based on the Joint Utility of Efficacy and Toxicity. J Am Stat Assoc 2015;110:711-22.
9. Yin J, Qin R, Ezzalfani M, et al. A Bayesian dose-finding design incorporating toxicity data from multiple treatment cycles. Stat Med 2017;36:67-80.
10. Lyu J, Curran E, Ji Y. Bayesian Adaptive Design for Finding the Maximum Tolerated Sequence of Doses in Multicycle Dose-Finding Clinical Trials. JCO Precis Oncol 2018;2:1-19.
11. Yin J, Paoletti X, Sargent DJ, et al. Repeated measures dose-finding design with time-trend detection in the presence of correlated toxicity data. Clin Trials 2017;14:611-20.
12. Yin J, Du Y, Qin R, et al. phase1RMD: An R package for repeated measures dose-finding designs with novel toxicity and efficacy endpoints. PLoS One 2021;16:e0256391.
13. Doussau A, Thiébaut R, Paoletti X. Dose-finding design using mixed-effect proportional odds model for longitudinal graded toxicity data in phase I oncology clinical trials. Stat Med 2013;32:5430-47.
14. Du Y, Yin J, Sargent DJ, et al. An adaptive multi-stage phase I dose-finding design incorporating continuous efficacy and toxicity data from multiple treatment cycles. J Biopharm Stat 2019;29:271-86.
15. Jain RK, Lee JJ, Hong D, et al. Phase I oncology studies: evidence that in the era of targeted therapies patients on lower doses do not fare worse. Clin Cancer Res 2010;16:1289-97.
16. O'Quigley J, Shen LZ, Gamst A. Two-sample continual reassessment method. J Biopharm Stat 1999;9:17-44.
17. O'Quigley J, Paoletti X. Continual reassessment method for ordered groups. Biometrics 2003;59:430-40.
18. Ivanova A, Wang K. Bivariate isotonic design for dose-finding with ordered groups. Stat Med 2006;25:2018-26.
19. Yuan Z, Chappell R. Isotonic designs for phase I cancer clinical trials with multiple risk groups. Clin Trials 2004;1:499-508.
20. Yuan Z, Chappell R, Bailey H. The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach. Biometrics 2007;63:173-9.
21. Takeda K, Morita S, Taguri M. gBOIN-ET: The generalized Bayesian optimal interval design for optimal dose-finding accounting for ordinal graded efficacy and toxicity in early clinical trials. Biom J 2022. [Epub ahead of print]. doi: 10.1002/bimj.202100263.
22. Bekele BN, Thall PF. Dose-finding based on multiple toxicities in a soft tissue sarcoma trial. J Am Stat Assoc 2004;99:26-35.
23. Morita S, Thall PF, Takeda K. A simulation study of methods for selecting subgroup-specific doses in phase 1 trials. Pharm Stat 2017;16:143-56.
24. Chapple AG, Thall PF. Subgroup-specific dose finding in phase I clinical trials based on time to toxicity allowing adaptive subgroup combination. Pharm Stat 2018;17:734-49.
25. Salter A, O'Quigley J, Cutter GR, et al. Two-group time-to-event continual reassessment method using likelihood estimation. Contemp Clin Trials 2015;45:340-5.
26. Salter A, Morgan C, Aban IB. Implementation of a two-group likelihood time-to-event continual reassessment method using SAS. Comput Methods Programs Biomed 2015;121:189-96.

27. Meyer EL, Mesenbrink P, Dunger-Baldauf C, et al. The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review. Clin Ther 2020;42:1330-60.
28. Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann Oncol 2017;28:34-43.
29. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017;377:62-70.
30. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-40.
31. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-14.
32. Kopetz S, Desai J, Chan E, et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol 2015;33:4032-8.
33. Simon R, Geyer S, Subramanian J, et al. The Bayesian basket design for genomic variant-driven phase II trials. Semin Oncol 2016;43:13-8.
34. Cunanan KM, Iasonos A, Shen R, et al. An efficient basket trial design. Stat Med 2017;36:1568-79.
35. Chu Y, Yuan Y. BLAST: Bayesian latent subgroup design for basket trials accounting for patient heterogeneity. J R Stat Soc Ser C Appl Stat 2018;67:723-40.
36. Psioda MA, Xu J, Jiang Q, et al. Bayesian adaptive basket trial design using model averaging. Biostatistics 2021;22:19-34.
37. Berry SM, Broglio KR, Groshen S, et al. Bayesian hierarchical modeling of patient subpopulations: efficient designs of Phase II oncology clinical trials. Clin Trials 2013;10:720-34.
38. Krajewska M, Rauch G. A new basket trial design based on clustering of homogeneous subpopulations. J Biopharm Stat 2021;31:425-47.
39. Kopp-Schneider A, Calderazzo S, Wiesenfarth M. Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control. Biom J 2020;62:361-74.
40. Cunanan KM, Iasonos A, Shen R, et al. Specifying the True- and False-Positive Rates in Basket Trials. JCO Precis Oncol 2017;1:ePO.
41. Liu R, Liu Z, Ghadessi M, et al. Increasing the efficiency of oncology basket trials using a Bayesian approach. Contemp Clin Trials 2017;63:67-72.
42. Chu Y, Yuan Y. A Bayesian basket trial design using a calibrated Bayesian hierarchical model. Clin Trials 2018;15:149-58.
43. Neuenschwander B, Wandel S, Roychoudhury S, et al. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharm Stat 2016;15:123-34.
44. Hobbs BP, Landin R. Bayesian basket trial design with exchangeability monitoring. Stat Med 2018;37:3557-72.
45. Kaizer AM, Hobbs BP, Koopmeiners JS. A multi-source adaptive platform design for testing sequential combinatorial therapeutic strategies. Biometrics 2018;74:1082-94.
46. Normington J, Zhu J, Mattiello F, et al. An efficient Bayesian platform trial design for borrowing adaptively from historical control data in lymphoma. Contemp Clin Trials 2020;89:105890.
47. Jiao F, Tu W, Jimenez S, et al. Utilizing shared internal control arms and historical information in small-sized platform clinical trials. J Biopharm Stat 2019;29:845-59.
48. Li Y, Wang M, Cheung YK. Treatment and dose prioritization in early phase platform trials of targeted cancer therapies. J R Stat Soc Ser C Appl Stat 2019;68:475-91.
49. Kang D, S Coffey C, J Smith B, et al. Hierarchical Bayesian clustering design of multiple biomarker subgroups (HCOMBS). Stat Med 2021;40:2893-921.
50. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clin Trials 2016;13:358-66.
51. Zhou X, Liu S, Kim ES, et al. Bayesian adaptive design for targeted therapy development in lung cancer--a step toward personalized medicine. Clin Trials 2008;5:181-93.
52. Alexander BM, Ba S, Berger MS, et al. Adaptive Global Innovative Learning Environment for Glioblastoma: GBM AGILE. Clin Cancer Res 2018;24:737-43.
53. Gajewski BJ, Statland J, Barohn R. Using Adaptive Designs to Avoid Selecting the Wrong Arms in Multiarm Comparative Effectiveness Trials. Stat Biopharm Res 2019;11:375-86.
54. Hobbs BP, Chen N, Lee JJ. Controlled multi-arm platform design using predictive probability. Stat Methods Med Res 2018;27:65-78.
55. Meade A, Oza B, Frangou E, et al. RAMPART: A model for a regulatory-ready academic-led phase III trial in the adjuvant renal cell carcinoma setting. Contemp Clin Trials 2021;108:106481.
56. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer 2019;7:278.

57. Wang SJ, Hung HM, O'Neill RT. Adaptive patient enrichment designs in therapeutic trials. Biom J 2009;51:358-74.
58. Brannath W, Zuber E, Branson M, et al. Confirmatory adaptive designs with Bayesian decision tools for a targeted therapy in oncology. Stat Med 2009;28:1445-63.
59. Jenkins M, Stone A, Jennison C. An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints. Pharm Stat 2011;10:347-56.
60. Rosenblum M, Van der Laan MJ. Optimizing randomized trial designs to distinguish which subpopulations benefit from treatment. Biometrika 2011;98:845-60.
61. Rosenblum M, Liu H, Yen EH. Optimal Tests of Treatment Effects for the Overall Population and Two Subpopulations in Randomized Trials, using Sparse Linear Programming. J Am Stat Assoc 2014;109:1216-28.
62. Magnusson BP, Turnbull BW. Group sequential enrichment design incorporating subgroup selection. Stat Med 2013;32:2695-714.
63. Simon N, Simon R. Adaptive enrichment designs for clinical trials. Biostatistics 2013;14:613-25.
64. Simon N, Simon R. Using Bayesian modeling in frequentist adaptive enrichment designs. Biostatistics 2018;19:27-41.
65. Rosenblum M, Hanley DF. Adaptive Enrichment Designs for Stroke Clinical Trials. Stroke 2017;48:2021-5.
66. Lai TL, Lavori PW, Tsang KW. Adaptive enrichment designs for confirmatory trials. Stat Med 2019;38:613-24.

Cite this article as: Yin J, Shen S, Shi Q. Challenges, opportunities, and innovative statistical designs for precision oncology trials. Ann Transl Med 2022;10(18):1038. doi: 10.21037/atm-22-356

