Biomarker-Driven Oncology Clinical Trials: Novel Designs in the Era of Precision Medicine

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Abstract

Oncology drug development historically has followed a path of sequential phase I, II, and III clinical trials using traditional trial designs, with the goal of achieving regulatory approval. These studies are often conducted with inclusion criteria that limit enrollment to a single tumor type or tumor site of origin, excluding other patients who might also respond. Increased use of precision medicine targeting biomarkers or specific oncogenic mutations has led to novel clinical trial designs that can evaluate these therapies in a less limited fashion. Master protocols such as basket trials, umbrella trials, and platform trials can, for example, evaluate histology-specific therapies targeting a common oncogenic mutation across multiple tumor types or screen for the presence of multiple different biomarkers rather than a single one. In other cases, they can lead to more rapid evaluation of a drug and evaluate targeted therapies in tumor types for which they are not yet currently indicated. As the use of complex biomarker-based master protocols increases, advanced practitioners must understand these novel trial designs, their advantages and disadvantages, and how their use may advance drug development and maximize the clinical benefits of molecular precision therapy.

In recent years, there have been substantial and significant advancements in the development of targeted anticancer therapies to better leverage and personalize cancer treatment. While traditionally patients with cancer have been treated based on tumor site of origin and histology, advancements in molecular technology, next-generation sequencing, and the development of drugs targeting tumor-specific biomarkers have ushered in a new era of precision and personalized cancer therapeutics.

Oncology drug development has historically followed the drug approval process through the traditional clinical trial designs and the approval pathway of sequential phase I, II, and III clinical trials (Fountzilas et al., 2022). Phase I clinical trials

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have often been dose-escalation or dose-finding studies, such as those with a 3+3 design, to assess for dose-limiting toxicities, maximum tolerated dose, and the recommended phase II dose. Phase II studies have typically been nonrandomized, single-arm trials to evaluate drug efficacy and safety. Phase III randomized, controlled trials that evaluate the efficacy and safety outcomes of a drug in development compared with a standard-of-care treatment have traditionally been the means for leading to regulatory approval of new cancer drugs. These trials are often conducted with inclusion criteria that focus on one cancer type based on the tumor site of origin.

With advancements in the drug development of cancer therapies targeting specific mutations or biomarkers, there has been a need to further advance how clinical trials are designed and conducted in the context of precision medicine. This has given rise to the concept of master protocols, consisting of several types of precision medicine clinical trials based on the presence of biomarkers, including basket trials, umbrella trials, and platform trials (Park et al., 2020). The number of master protocols has rapidly increased in recent years and is expected to continue to grow (Park et al., 2019). With the increasing prevalence of novel precision medicine clinical trials, it is imperative that hematology/oncology advanced practitioners be aware of how these trials are designed and conducted. This will help them better understand, evaluate, and appraise the data derived from these studies as more personalized cancer therapeutics are used in direct patient care. Herein, we will review the implications of master protocols for the hematology/oncology advanced practitioner, including their unique designs, key examples in the literature, and the pros and cons of each type of master protocol.

BASKET TRIALS

Basket trials are prospective, agnostic, and separate from the individual types of cancer (Park et al., 2020). The commonality between trial subjects is generally a predictive factor based on the intervention's pharmacology and mechanism of action. The common eligibility criterion for inclusion in a basket trial may be a specific biomarker that can be present across multiple different cancer histologies, with the trial assessing an intervention targeting that specific biomarker (Figure 1). Essentially, basket trials hypothesize and test the notion that the presence of a specific biomarker or molecular target may predict response and drug efficacy to a matched targeted therapeutic agent, irrespective of the cancer type (Li & Bergan, 2020).

An example of a basket trial is the VE-BASKET study, which was a histology-nonspecific phase II trial conducted to investigate the efficacy and safety of vemurafenib in *BRAF* V600-positive nonmelanoma cancers (Hyman et al., 2015). This trial enrolled 122 subjects across multiple different prespecified cohorts based on disease states, which included non–small cell lung cancer (NSCLC), cholangiocarcinoma, Erdheim-Chester Disease/Langerhans cell histiocytosis (ECD/LCH), anaplastic thyroid cancer, breast cancer, ovarian cancer, multiple myeloma, colorectal cancer, and an "all-others" category that included many other types of malignancies. Patients received vemurafenib (Zelboraf) 960 mg orally twice daily on a continuous basis. The primary endpoint was overall response rate; secondary endpoints included progression-free survival (PFS) and overall survival (OS). This study was notable as it was the first basket trial to lead to an approval by the US Food and Drug Administration (FDA). In this trial, patients with ECD had an overall response rate of 54.5% (Diamond et al., 2018). The 2-year PFS and OS rates were 83% and 95%, respectively, in the ECD cohort. These results led to the approval of vemurafenib for the treatment of ECD with a *BRAF* V600 mutation in November 2017 (FDA, 2017). While the vemurafenib basket trial led to approval of this agent for a single disease state, other similar trials have led to broader approvals, such as dabrafenib (Tafinlar) approved for treatment of unresectable or metastatic solid tumors with a *BRAF* V600E mutation following progression on prior therapy.

UMBRELLA TRIALS

Umbrella trials are another example of a biomarker-driven, precision medicine clinical trial design being used in cancer drug development. Umbrella trials differ from basket trials as they include a single cancer type or histology but screen and assess for multiple different biomarkers (Park et al., 2020). These trials often assess the efficacy of multiple different drugs and interventions, and patients

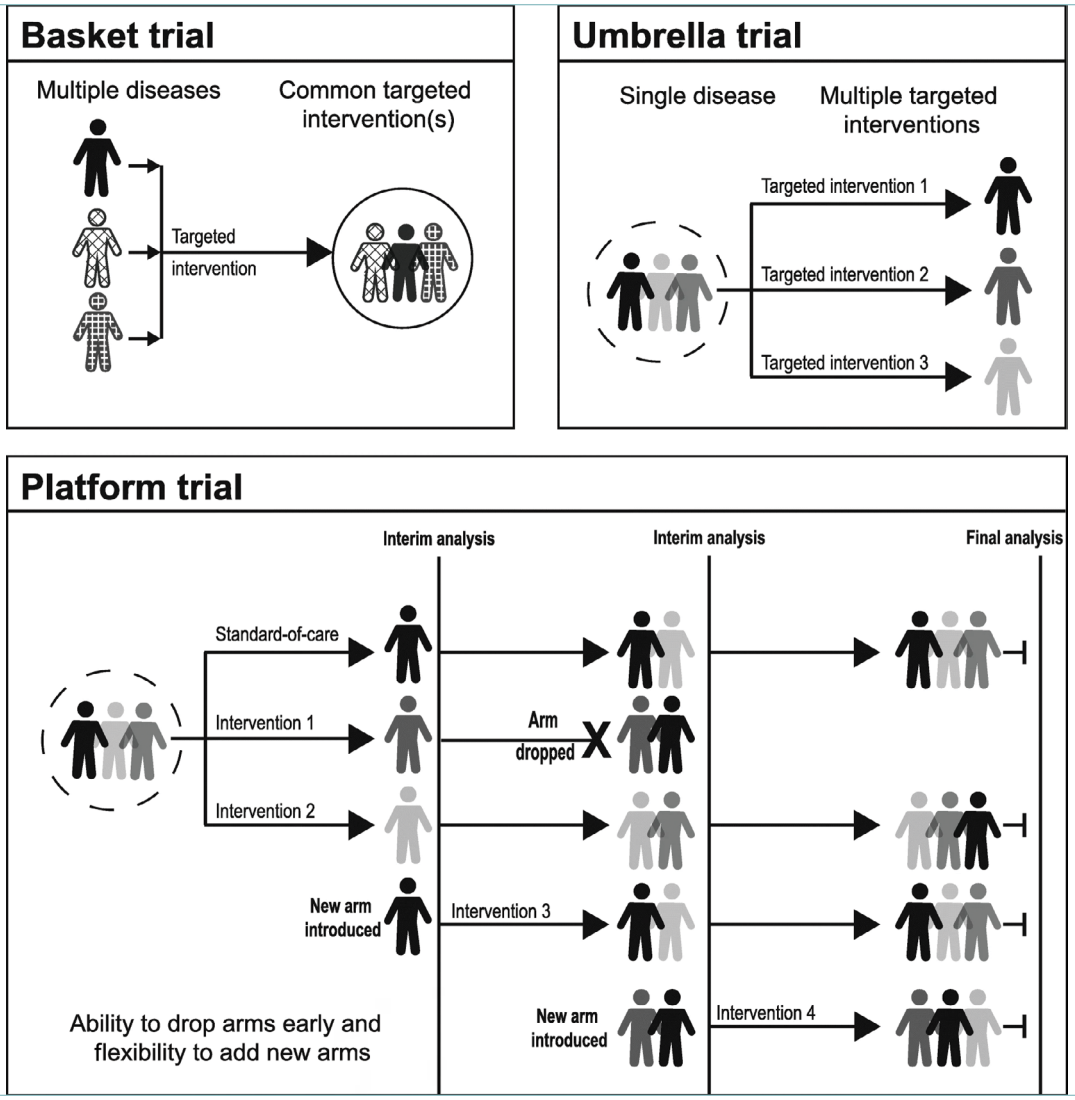

Figure 1. Master protocols depicting novel biomarker-based clinical trial designs. Reproduced from Park et al. (2019).

will typically receive a drug that targets the specific biomarker identified (Figure 1). Umbrella trials are uniquely suited for those disease states in which multiple different targetable biomarkers may be present, such as NSCLC and breast cancer.

An example of an umbrella trial is the plasmaMATCH study, which evaluated five different therapies for advanced or metastatic breast cancer (Turner et al., 2020). This open-label, multicohort, phase II umbrella trial used circulating tumor DNA (i.e., liquid biopsy) to assess the genomic profiles of patients with advanced breast cancer. Patients were stratified into one of five different cohorts and assigned to various treatments based on the presence (cohorts A, B, C, and D) or absence (cohort E) of specific biomarkers. Cohort A included patients with an estrogen receptor gene 1 mutation (*ESR1*), and these patients received fulvestrant (Faslodex). Cohort B included patients with a human epidermal growth factor receptor 2 (*HER2*) mutation, who received neratinib (Nerlynx). Cohorts C and D included patients with a serine/threonine-specific protein kinase B mutation (*AKT*), who received capivasertib plus fulvestrant or capivasertib monotherapy, respectively. Cohort E recruited patients with no targetable mutation, and they received olaparib (Lynparza) plus ceralasertib. Umbrella trials can be complicated due to use of multiple cohorts, but they provide the advantage of being able to simultaneously research multiple interventions within the same disease state.

PLATFORM TRIALS

Platform trials differ from basket and umbrella trials in that they evaluate multiple hypotheses in a single protocol, and the specific design of a platform trial can vary significantly (Fountzilas et al., 2022). These trials are often adaptive in nature and may incorporate Bayesian algorithms to expand or close treatment study arms while the trial is actively being conducted (Figure 1; Barker et al., 2009). (Bayesian algorithms are a type of statistical inference that updates hypotheses as more evidence becomes available during the course of data collection.)

An example of a platform trial is the Targeted Agent and Profiling Utilization Registry (TAPUR) study (Mangat et al., 2018). Launched in 2016, TAPUR represents the first precision oncology trial conducted by the American Society of Clinical Oncology (ASCO). This large, multicenter, nonrandomized platform trial is currently evaluating the efficacy and safety of many FDA-approved targeted therapies in tumor types for which they are not yet currently indicated. TAPUR includes a wide variety of tumor types including advanced or metastatic solid tumors, multiple myeloma, and B-cell non-Hodgkin lymphomas (Mangat et al., 2018). Results from several different arms and baskets of the TAPUR study have recently been published (Ahn et al., 2020; Al Baghdadi et al., 2020; Al Baghdadi et al., 2019; Alva et al., 2021; Fisher et al., 2020; Gupta et al., 2022; Klute et al., 2022).

PROS, CONS, AND CONSIDERATIONS OF MASTER TRIALS IN PRECISION ONCOLOGY

Each type of master trial has its own pros and cons, so advanced practitioners involved in the care of patients participating in these trials or those utilizing therapies based on the results of these studies should be familiar with the advantages and disadvantages of these novel clinical trial designs.

Basket trials are primarily single-arm trials that usually serve as hypothesis-generating or discovery trials, and thus often still require confirmation of drug efficacy in a larger clinical trial. Strengths of basket trials include utilizing prior knowledge of targetable mutations, and this can help determine the potential drug efficacy of a targeted therapy in several different cancer types all in one trial. Basket trials also can enable the inclusion of rare cancer types for which a single clinical trial would otherwise be difficult to perform (Janiaud et al., 2019). Some of the downsides of basket trials include slow enrollment of subjects if the mutation is rare, risk of type I errors with small sample sizes in different baskets, and the possibility that different tumor types may respond differently to targeted therapies.

Advantages of umbrella trials include the improvement of subject screening rates and improving patient eligibility due to including an array of biomarkers that may be present in any given disease state, rather than enriching or limiting to one biomarker (Janiaud et al., 2019). Umbrella trials also increase the possibility that subjects will benefit from targeted therapy (Awada et al., 2016). Disadvantages of umbrella trials are the requirement for several study arms, the need for inclusion of more subjects, and a requirement for active trial follow-up.

Platform trials can lead to more rapid evaluation of a drug, and can also provide needed modification of drug dosage and sample size based on the ongoing results due to the adaptive design of these studies (Awada et al., 2016). However, there can be substantial difficulties in performing these trials since active and dynamic follow-up is necessary. Additionally, clinicians participating in or evaluating these trials may not be familiar with the complex statistical analyses required to conduct these trials with an adaptive clinical trial design.

CONCLUSION

The increase in targeted, biomarker-driven therapeutics in cancer care has also given rise to novel and unique clinical trial designs that are leading to drug evaluations and approvals beyond traditional phase I, II, and III clinical trials focused on one primary tumor type defined by site of origin. As master protocols become more prevalent in drug development and advanced practitioners become ever more involved with every facet of clinical research (Braun-Inglis et al., 2022), it is imperative that advanced practitioners understand and interpret the design, rationale, and results of these unique and often complex precision medicine trial designs.

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