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Oncologic Precision Medicine and the Use of Basket and Umbrella Clinical Trials

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Introduction

The revolution in cancer biology, which became manifest in clinical oncologic practice approximately twenty years ago,¹ was made possible, in part, by remarkable technological innovations in DNA and RNA sequencing, proteomics, and epigenetics. These innovations have permitted the examination of surgical tissues, ever smaller tumor biopsies, as well as blood specimens for the presence of pathogenic mutations and/or the expression of other molecular characteristics that can guide the usage of systemic cancer therapies with a high level of therapeutic specificity.^{2, 3} In this fashion, the clinical application of molecular tumor characterization has facilitated the introduction of numerous targeted small molecules, as well as a variety of immunomodulators, into clinical oncology for the treatment of a wide range of solid and hematologic malignancies; these agents have dramatically improved the landscape of cancer therapeutics.^{4–6}

It is in this context that the concept of precision oncology, amplified by a report from the National Academy of Medicine,⁷ defined this approach as: “an intervention to prevent, diagnose, or treat cancer that is based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not.”⁸

The first generation of precision oncology trials evaluated the feasibility of matching a cancer therapy to the specific molecular characteristics of a patient’s tumor.^{9, 10} These studies established the feasibility of this approach,¹¹ while demonstrating the complexities associated with the implementation of precision oncology studies,¹² and the initial modest clinical benefit of this clinical trial methodology.^{13, 14} Perhaps the most important contribution of the first generation of clinical trials evaluating ‘molecular matching’ has been to firmly move the cancer drug development paradigm away from that used to discover non-specific cytotoxic agents during the second half of the twentieth century,¹⁵ and toward a focus on the application of innovative molecular tools to both assess the mechanism of

action of new molecules in the clinic, as well as to predict which agents are most likely to convey clinical benefit to the patient.⁸

Precision oncology clinical trial designs have evolved considerably over the past decade. Most such studies can now be subcategorized as some type of “Master Protocol”—a concept that includes basket, umbrella, or platform trials.¹⁶ Master protocols provide an administrative and investigational framework for both organizing and providing quality control for the molecular characterization studies of patient materials that can systematize a variety of different therapeutic approaches for individual histology-specific or histology-agnostic patient subgroups. In the face of the increased effort involved in coordinating the operational aspects of the laboratory-based clinical trial components of a Master Protocol, the real potential benefit of these studies is to improve the efficiency of identifying biomarker-selected drugs with enhanced effectiveness for molecularly-defined patient populations.

This issue of *The Cancer Journal* examines the current state of precision oncology clinical trials, from their humble beginnings as multi-histology phase II studies, to the wide variety of molecular matching approaches ongoing worldwide. The articles in this issue evaluate how molecular characterization studies can be validated across multiple laboratories to enhance the enrollment of patients on national trials, the biostatistical considerations that underpin the use of Master Protocol designs, and ongoing precision oncology trials supported by the NCI as well as the institutional approach to such studies at the M.D. Anderson Cancer Center. In addition, papers in this issue discuss novel considerations for the conduct of histology-agnostic studies as well as the so-called N of 1 approach for individual treatment programs that have led to an exploration of the molecular basis for exceptional responses to both cytotoxic and targeted cancer therapeutics. Finally, as this approach becomes more highly integrated into routine clinical oncologic practice, the future investigational landscape for precision oncology trials is envisioned. Reviewing the evolution of precision cancer therapy over the past 75 years, as described in these papers, strongly suggests that the trajectory of therapeutic oncology will, over the next several decades, be dominated by a greater understanding of molecular vulnerabilities in cancers across the oncologic landscape, as well as the ability to target those vulnerabilities pre-emptively. Improved diagnostic technologies and faster development of molecules that can be predicted—based on those technologies—to greatly improve the specificity of systemic treatment suggest a very bright future for cancer therapeutics.

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