Future Clinical Trials
Genetically Driven Trials

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KEYWORDS

• Basket clinical trial • Biomarker • Molecular profiling

KEY POINTS

- Molecular profiling identifies distinct molecular mechanistic classes in major human cancers.
- Therapeutic successes are more likely when matching drugs with biologically relevant cancer mechanisms.
- Molecular profiling of cancers is an essential step in defining therapeutic strategies and clinical trials enrollment.

INTRODUCTION

Rapid incorporation of cost- and time-efficient genomic analysis technologies has been transformative for cancer medicine. Therapy selection on part of treating physicians is progressively shifting from the empirically validated one-size-fits-all chemotherapy or biological agents to tailoring agents to specific molecular features of patients' tumors. It has become even more imperative to identify a drug-amenable mechanism in the setting of clinical trials selection for patients. Again and again, studies have shown that randomly assigned treatments in patients participating in clinical trials are rarely beneficial with response rates less than 5%. Contrastingly, in the matched scenario when a drug is given because of the existence of a mechanism defined by genetic alteration, the likelihood of benefit increases to 20% to 30% range.[1,2] For a physician searching for investigational therapy options, the task of deciphering the actionable cancer mechanism poses an unprecedented challenge previously unknown to cancer medicine. This challenge was nicely formulated by Dr George Sledge[3] in his 2011 American Society for Clinical Oncology (ASCO) presidential address as being "a clinical cancer biologist." In this new reality, we are learning, in real time with the basic science, how cancer is a complex constellation of diseases sharing highly diverse alterations across previously incontestable organ and histologic

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groupings and boundaries. For that reason alone, it has become more common for clinical trials to seek patients based on their tumors' molecular signatures. As a result, molecular profiling is viewed as a critical element in the design and conduct of oncology clinical trials, as it allows investigators to match the biomarkers within an individual's tumor with agents that specifically target those biomarkers. In the context of daily clinical practice, increasing numbers of oncologists are using molecular profiling to obtain insights into the dominant mechanism of their patients' cancers to find appropriate anticancer therapies, either through clinical trials or through off-label use of a growing number of the Food and Drug Administration (FDA)–approved targeted drugs. Here, the author reviews the successes of such matching exercises on the part of clinical trial investigators and on the part of practicing clinicians whose smartness in choosing the right trial for the right patient oftentimes remains unrecognized and does not earn podium applauses.

Targeting the Oncogenic Driver Mechanism

To date, genetic characterization of most human cancers consistently revealed a high level of diversity of oncogenic mechanisms within each site of origin and histologic subtype.[4–6] To complicate matters more, there is a growing appreciation of the existence of multiple genetically distinct clones within the same tumor that can compete for fitness and survival under selective pressures of anticancer therapies.[7] Monitoring these clonal dynamics becomes a major focus of genetic cancer surveillance, which spurred rapid development of noninvasive approaches of DNA sampling from blood,[7] saliva,[8,9] vaginal swabs,[10] and so forth. Despite the branched genetic phylogeny, some of the critical founding oncogenic lesions are shared between the tumor clones. In this context, molecular profiling can be used to uncover the dominant oncogenic mechanism in a tumor and to select therapies that target the oncogenic driver.[11] Although this approach may seem new, it dates back to 1960, when Nowell and Hungerford[12] described the famous Philadelphia chromosome translocation *t(8,21)* activating the abelson murine leukemia viral oncogene homolog 1 kinase and the malignant transformation in chronic myeloid leukemia. Four decades later, ST1571, later known as imatinib (Gleevec), was used for the first time in humans to suppress the culprit tyrosine kinase and to reverse the cancer process clinically and biologically.[13,14] Since the first validation of the oncogene-targeted therapy with imatinib, it has been appreciated that treating the principal driver oncogene can have a powerful impact. Experimental evidence further suggested that the rapidity of withdrawal of oncogene activity has the greatest impact on the anticancer effect.[15] This finding led to the proposed pulsatile blockade[16] and ideas of synthetic lethality[17] or combination of targeted agents.[18]

The ongoing trials are poised to investigate the efficacy of molecularly targeted treatments for *oncogene-defined* subsets of cancers across different tumor histologies.[19] In addition to the National Cancer Institute (NCI) (United States)–supported Molecular Analysis for Therapy Choice (MATCH) clinical trial, the ASCO launched its own Targeted Agent and Profiling Utilization Registry (TAPUR) trial offering access to the FDA-approved agents to patients with mechanistically relevant and well-defined genetic biomarkers.[20] These efforts require a genomic prescreening study to identify patients whose tumors harbor specific molecular abnormalities that can be matched to the relevant targeted treatments, regardless of tumor histology type. Success of these matching experiments is anxiously awaited. Single-institution pioneering studies[1] have clearly demonstrated that the unmatched cohorts of patients with advanced cancer rarely benefit from these targeted therapies, whereas the patients with a matched drug-to-cancer mutation do substantially better. For clinical practice,