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Commentary

Trailblazing Precision Oncology for Rare Tumor Subtypes

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The rapid evolution of molecular diagnostic techniques, including massively parallel DNA sequencing, transcriptomics, and proteomics, has ushered in the age of precision oncology, which seeks to identify biomarker-based therapeutic vulnerabilities and target them with available drugs on a patient-by-patient basis. These developments have led to the initiation of multidisciplinary Molecular Tumor Boards (MTB), which seek to recommend therapeutics to patients based on varying Levels of Evidence linking specific genetic alterations to treatment response. Several reports have documented MTB experiences, including a study from the Moores Cancer Center at University of California San Diego in which 11/34 evaluable patients received "matched therapy" informed by tumor genetic profiling, leading to partial responses (PR) in 3/11 (27%) patients [1]. In another study from our group at the Norris Cotton Cancer Center, 4/35 evaluable patients received matched therapy; 3/4 patients remained on therapy at the time of reporting, 2 of whom experienced clinical benefit lasting >10 months [2]. In both of these studies, matched therapy informed by tumor genetic profiling led to improved outcomes for patients.

In this issue of *The Oncologist*, Kato and colleagues from the Moores Cancer Center impressively documented the usage of precision medicine approaches in rare and ultra-rare tumor subtypes, defined as those with an incidence of fewer than 15/100,000 or 2/100,000 cases per year, respectively [3]. Of the 40 patients assessed, 37/40 (93%) patients had ≥1 therapeutically targetable alteration detected in their tumor or in circulating tumor DNA (ctDNA) in plasma. Among those patients, 21/37 (57%) received matched therapy; 8 of those 21 patients had stable disease (SD) with <6 months of follow-up, and 11 patients had clinical benefit (as typically defined by SD ≥6 months [$n = 3$], PR [$n = 6$], or complete response [CR; $n = 2$]), yielding a clinical benefit rate of 85% (11/13) and an objective response rate (ORR, defined as PR + CR) of 62% (8/13). Furthermore, matched therapy significantly prolonged progression-free survival compared with last prior (unmatched) therapy. Preliminarily, this study provides strong support for the use of tumor genetic and protein profiling in precision oncology for (ultra-)rare tumor subtypes. For most patients, tumor alterations detected through DNA sequencing or protein analysis led to rational selection of therapeutic strategies based on available preclinical and clinical evidence. This success is especially important because 22%–25% of tumors are of an (ultra-)rare subtype and are often challenging to manage clinically due to a lack of experience. The findings by Kato et al. support the use of precision oncology approaches in (ultra-)rare tumor subtypes, and mark an important evolutionary step for MTBs.

Despite the overall success of the study by Kato et al. and its importance in the clinical management of (ultra-)rare tumors, it remains clear that there is an unmet need to discover effective drugs for tumor subtypes without known targetable genetic alterations. For example, patients treated with a regimen that included nivolumab (anti-PD-1 antibody) or vemurafenib ($BRAF^{V600E}$ inhibitor) showed ORRs of 75% (3/4) and 67% (2/3), respectively. Importantly, 67% (2/3) of responders in the nivolumab group had basal cell carcinomas, which tend to have higher mutational burdens due to skin exposure to ultraviolet radiation. High mutational burden has been associated with improved response to PD-1 inhibitors [4]. Similarly, all three patients in the vemurafenib group had Erdheim-Chester Disease that contained $BRAF^{V600E}$ mutations, and $BRAF^{V600E}$ mutations are typically essential for response to available BRAF inhibitors [5, 6]. In contrast, patients treated with regimens that included trametinib (MEK inhibitor), bevacizumab (anti-vascular endothelial growth factor antibody), or palbociclib (Cyclin-Dependent Kinase 4/6 inhibitor) showed ORRs of 0% (0/4, 0/3, and 0/2, respectively). Despite these being effective agents for other indications, associations between clinical response and specific genetic alterations are lacking. In this study, trametinib was given to 2/3 (67%) patients based on the presence of *KRAS* mutation or amplification; bevacizumab was given to 3/3 (100%) patients based on *TP53* mutation; and palbociclib was given to 2/2 (100%) patients based on *CDKN2A/B* alteration or loss (noted by the authors as not being predictive of response). However, it must be considered that recommendation of treatment with a drug combination, such as in a clinical trial, may be driven by the presence of one gene-drug association, whereas a partnering drug may not be genetically warranted. These findings highlight a dichotomy between effective and ineffective drug-gene pairings, where the 62% of (ultra-)rare tumor patients who experienced objective response may have been the ones with clinically proven targetable genetic alterations.

The findings of Kato et al. present several interesting opportunities for precision oncology research; we discuss four opportunities here. (a) Levels of Evidence: a solution employed by MTBs is to assign "Levels of Evidence" to drug recommendations. For example, Levels ranging from 1 to 4 can be assigned to each recommendation to describe the strength of clinical and preclinical

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supporting evidence, ranging from U.S. Food and Drug Administration approval for a given indication (Level 1) to preclinical evidence or hypothesis (Level 4) [2]. For (ultra-)rare tumor subtypes, a "Levels of Evidence" scale could be modified and validated using clinical and preclinical data from common tumor subtypes as a surrogate. (b) Matching Score: the authors hypothesized that a high patient Matching Score (calculated as number of alterations matched with a targeted therapy divided by number of total alterations) may be associated with clinical benefit. We propose to expand the Matching Score to assign weights based on Levels of Evidence for the proposed matched therapies, which may strengthen the ability to predict clinical benefit. (c) Tumor DNA versus ctDNA: there are some patients for whom the results of DNA sequencing from tumors and plasma did not align; it will be important to determine whether such differences are clinically meaningful. Although these differences may just be due to technical limitations, there are currently limited comparative data regarding the relative predictive performance of tumor DNA sequencing versus ctDNA biomarkers. (d) Integrating DNA, RNA, and protein biomarkers: biomarkers are currently used as independent predictors of treatment response. However, as technologies evolve and become more cost-effective, patients' tissues may be more regularly profiled at the DNA, RNA, and protein levels. Rational integration of these results, such as via combined pathway analysis tools, may increase confidence in matching patients to therapies.

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Editor's Note:
See the related article, "Rare Tumor Clinic: The University of California San Diego Moores Cancer Center Experience with a Precision Therapy Approach," by Razelle Kurzrock et al. on page 171 of this issue.