VIEWPOINT

Is Precision Medicine an Oxymoron?

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The initial results of the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) trial were presented at the 2018 American Society of Clinical Oncology Annual Meeting. The NCI-MATCH trial is an ongoing phase 2 trial that seeks to determine whether targeted therapies for specific gene mutations will lead to objective responses agnostic to the primary cancer type. The trial features nearly 40 treatment arms, each of which aims to enroll at least 35 patients whose tumors have a specific genetic alteration. Individual arms rely on objective response as the primary end point, which also drives decisions about expansion beyond the first stage of accrual. Additional arms in the NCI-MATCH trial are currently enrolling, and several are in development.

Three cohorts from the NCI-MATCH trial were reported; patients with tumors harboring *ERRB2*/*HER2* amplification, *FGFR* alterations, or *PIK3CA* mutations were treated with T-DM1, AZD4547, or taselisib, respectively. Objective response rates were low across all arms, ranging from 0% to 9.5%, with no agent reaching the prespecified threshold of notable clinical activity.[1-3] Although there were patients with prolonged stable disease, this finding should be interpreted with caution because these were nonrandomized trials of patients with widely disparate prior therapy. Valid concerns raised by the investigators and discussants included the extensive prior therapy of many of the enrolled patients as well as co-occurring mutations, each of which could have limited the impact of targeted single-agent therapy.

The modest results reported for these NCI-MATCH arms stand in contrast to those of the neurotrophic tropomyosin receptor kinase (TRK) inhibitor, larotrectinib, which was associated with durable objective responses across a wide range of malignant neoplasms (75%) independent of their histologic features.[4] In this case, fusions involving tropomyosin receptor kinase genes lead to chimeric proteins with constitutively activated or overexpressed kinase function conferring dominant oncogenic potential, similar to EML4-ALK (the fusion between echinoderm microtubule associated protein-like 4 and anaplastic lymphoma kinase) in non–small cell lung adenocarcinoma. However, unlike gene fusion events, the presence of other genetic alterations has not reliably led to tissue-agnostic activity, which may be due to differences in pathway activation and dependence among tumors, indicating that context may be important for some oncogenic pathways. This is exemplified by *BRAF* V600E mutations in melanoma compared with colorectal cancer. While vemurafenib demonstrated significant activity in *BRAF* V600E–mutated melanoma, similar response rates were not observed in colorectal cancer owing to feedback activation of epidermal growth factor receptor.[5] Discordant results have also been observed in *ERBB2*/*HER2*-amplified breast and gastric cancer treated with trastuzumab and pertuzumab. In fact, taken as a whole, targeting receptors of the epidermal growth factor receptor family has taught us that patient selection is necessary but not sufficient to reliably predict tumor regression even in patients with similar histologies.

Perhaps unsurprisingly, the NCI-MATCH trial screened more than 6000 patients in a roughly 2-year period, highlighting the broad interest of patients and clinicians in the promise of molecularly driven studies. Unfortunately, this robust interest has not yielded globally robust results, in part because of the imprecision of precision medicine and biological naivete driving catchy phrases that oversimplify the malignant process. Nonetheless, the ability to engage a large population of patients and clinicians in the clinical trials process is encouraging and provides a valuable framework for future patient-selective trials. Regarding how tissue-agnostic results are then further tested and evaluated, an open forum is needed to discuss and develop clinical activity thresholds that are linked to clinical development algorithms. These must be developed within the context of other single-agent and combination strategies, including immunotherapy, so that we prioritize testing of the most promising approaches regardless of whether these approaches are labeled "precision medicine." The upper and lower extremes of responses are easy to act on, whereas there is a tendency to ascribe more significance to a few durable responses with molecularly targeted agents, although a similar percentage could be observed with unselected chemotherapy or immunotherapy.

The preliminary results from the NCI-MATCH trial highlight a critical biological reality that has been known for some time: that genomic alterations do not always lead to oncogenic pathway activation or addiction and that targeting multiple driver and/or resistance pathways may be required for optimal antitumor efficacy. In fact, as we consider how to prioritize strategies for further testing, a better understanding of cancer biology is needed to optimize and define context-dependent oncogenic mutations and resistance mechanisms. There is no one-size-fits-all approach, but preclinical models, such as patient-derived xenografts and organoids, may help elucidate potential codrivers and resistance mechanisms so that rational combinations can be designed and tested to support clinical deployment. Tissue acquisition during a study, such as biopsy specimens harvested after disease progression, which were obtained in a subset of patients enrolled in the MATCH trial, are instrumental in characterizing changes associated with adaptive resistance. Overall, this strategy will require greater investment in systems biology to select patients and derive combinations based on a more informed signature while still acknowledging the inher-

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ent imprecision. Analyses of circulating tumor DNA may also provide insights regarding dynamic changes that correspond to drug response or resistance as has been observed with RAS mutations in patients with colorectal cancer treated with epidermal growth factor receptor inhibitors.6 The field of oncology drug development has witnessed immense progress based on the elegant science of many, and now is the time to minimize dogma and bias and tackle the complexity of preclinical and clinical drug development. This must be done to prioritize clinical trials in this notable era or risk launching poorly founded trials that preclude enrollment to studies of greater impact.

Do these MATCH results indicate that a molecularly driven agnostic approach is a failure? The answer is a qualified yes and no. There is no question that a higher efficacy rate was anticipated in these arms, but the trial does represent an initial step in attempting to leverage the knowledge of cancer biology to affect treatment across tumor types. The negative data presented signify a critical step in drug development and molecularly targeted approaches. The lack of single-agent activity is important to define and guide the next steps for target inhibition and highlights the importance of robust correlative studies on available samples. Negative trial data are most helpful when correlative studies generate data that lead to alternative hypotheses. When such correlative studies are not incorporated, essential information is lost, and we lose the iterative process of investigation—bench to bedside and back—that has resulted in major therapeutic advances in the field.

How do we view these results within the context of immunotherapy? The first-ever tissue- or site-agnostic US Food and Drug Administration approval was for pembrolizumab for tumors displaying high microsatellite instability or deficient mismatch repair. However, these results are parallel to those of molecularly targeted agents that regress tumors harboring oncogenic fusion proteins. Both approaches represent the extreme extent to which tumors may respond to molecular or immune blockade. These are the exemplars of biologically driven anticancer agents; however, lest one imagine that immunotherapy is going to be a better substrate for precision medicine approaches, the same challenges have been observed in terms of optimizing patient selection.[7]

In conclusion, there is no doubt that these MATCH results represent a well-intentioned and coordinated attempt to deploy precision medicine in oncology. These results, along with others, represent the continual evolution of imprecise cancer biology and thus should drive us toward integrative and iterative strategies that improve the outcomes for our patients.

ARTICLE INFORMATION

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