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Editorial

Optimizing Precision Oncology and Immunotherapy Strategies: Moving into the Next Stage of Cancer Medicine

Phoebe Lewis[1], Timothy A Yap[1,2,3,4]

Departments of [1]Investigational Cancer Therapeutics (Phase I Program) and [2]Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, [3]Khalifa Institute for Personalized Cancer Therapy, The University of Texas MD Anderson Cancer Center, [4]The Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Approved therapeutic options in cancer medicine have moved from traditional one-size-fits-all approaches with chemotherapy and radiation to now include precision medicine strategies utilizing molecularly targeted therapies and immunotherapy approaches.[1] The archetypal example of a successful biomarker-driven targeted agent often cited is the human epidermal growth factor receptor-2 (HER-2) monoclonal antibody trastuzumab, which has demonstrated antitumor efficacy in the setting of HER-2$^+$ breast cancer.[2-4] Similarly, three generations of tyrosine kinase inhibitors that inhibit the epidermal growth factor receptor (EGFR) signaling with different potencies and selectivity have demonstrated patient benefit in EGFR-mutant nonsmall cell lung cancer (NSCLC).[5] In the setting of melanoma, nearly 50% of patients harbor an activating *BRAF* V6600E mutation, which results in constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway.[6] Vemurafenib is a small molecule that specifically inhibits mutant *BRAF* and has demonstrated improved overall survival in patients with melanoma harboring activating *BRAF* mutations.[7,8] These successes in precision medicine have now obtained Food and Drug Administration (FDA) approval and are well-established in the patient management guidelines. Numerous targeted therapy drugs are now incorporated into first-line therapies for cancer treatment, and research in evaluating rational combinations of such therapies with chemotherapy and/or immunotherapy are being investigated.[4,5] We now need to ensure as a community that patients with cancers around the globe have equal access to such effective therapies and companion diagnostics. In this issue, Jazieh et al. determined the pattern of testing and mutation prevalence of patients with NSCLC in the Middle East and North Africa populations.[9] They show that only a small fraction of these patients with NSCLC are tested for druggable targets despite harboring a higher prevalence of EGFR mutations than Western populations. Overcoming such challenges of molecular testing will require systematic plans to address both education and resource allocation.

More recently, novel targeted therapies directed against oncogenic fusion proteins have also demonstrated unprecedented success in clinical trials.[10] Translocations in neurotrophic tropomyosin receptor kinase (TRK) genes that code for TRKs may lead to constitutively active TRK fusion proteins that are oncogenic drivers across cancer types.[11] For example, the TRK inhibitor, larotrectinib, has demonstrated high-durable response rates across a variety of cancers in both pediatric and adult patients.[10] These TRK fusions appear to be found commonly in rare tumors such as mammary analog secretory carcinoma, and rarely in common tumors, including colorectal cancers. Another promising targeted approach is the use of potent and selective RET inhibitors, such as BLU-667[12] and LOXO-292[13] in tumors that harbor an oncogenic *RET* aberration, such as NSCLC, medullary thyroid cancer, and papillary thyroid cancer. These RET inhibitors have produced durable clinical responses in early clinical trials, in patients with *RET*-altered tumors, thereby clinically validating selective RET targeting. In this issue, Chin et al. reviewed the development of selective extracellular signal-regulated kinase inhibitors, which have demonstrated preliminary antitumor activity in clinical trials involving patients with advanced cancers harboring RAS, RAF, or MAPK pathway alterations.[14]

As with molecularly targeted agents, immunotherapy represents a paradigm-shifting cornerstone of today's cancer treatment and research. The recent award of the Nobel Prize in Physiology or Medicine to Drs. James Allison and Tasuku Honjo highlights the importance of this class of therapies and its impact on the field. Monoclonal antibodies that block immune checkpoint receptors, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD)-1/PD-ligand-1 (PD-L1), result in the activation and reinvigoration of cytotoxic responses that can reverse anergic and exhausted immune cells to fight cancer.[15-17] Melanoma, renal cell carcinoma, and NSCLC are associated with high-response rates to immunotherapy with anti-CTLA-4 and anti-PD-1 inhibitors in different combinations, and these agents are now FDA approved for use in these indications.[18] High mutational burden, defective mismatch repair, and microsatellite instability-high) are associated with higher responses to immunotherapy and are likely to be due to the association with higher levels of neoantigens.[17] Understanding the characteristics of the patient populations that will respond (or not respond) to immunotherapy continues to be critical for treatment decisions and is an active area of research. Investigating the mechanisms of the underlying biology that dictate immunotherapy responses will be

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critical for designing clinical trial strategies that impact patient benefit across cancer types.

While molecularly targeted agents and immunotherapies are now well-established as cornerstones in cancer medicine, with many of these therapeutic agents leading to improved clinical outcomes in subsets of patients, a major challenge is the management of intrinsic and acquired resistance to these agents, likely occurring due to tumor heterogeneity, as well as compensatory signaling and other pathways.[18,19] For example, a limitation with molecularly targeted therapy approaches is the disappointing efficacy observed in the majority of clinical trials involving such agents.[20] While trastuzumab and imatinib increased the overall survival by years in HER2$^+$ breast cancer and chronic myeloid leukemia, respectively, the vast majority of targeted agents have failed to show any improvement in survival or have only modestly improved survival.[18,19] Combination strategies utilizing multiple agents are being investigated to circumvent this, but such approaches may exacerbate toxicities already observed with single agents.[20,21] We, therefore, need to scale up our efforts in improving our understanding of the underlying mechanisms and developing better strategies to manage immune-related adverse events-associated with the wide range of immunotherapies available in the clinic, both as single agents and in combination regimens. In this issue, Tran et al. described a case study where the gastrointestinal (GI) targeting anti-integrin antibody vedolizumab provided a steroid-sparing therapeutic effect to achieve remission of the upper GI immune-related toxicities, even in cases where multiple steroid courses have failed.[22]

Another challenge we face is that despite immunotherapy demonstrating therapeutic benefit in certain cancer types, the proportion of patients who benefit is largely modest. Strategies to induce sensitivity to immunotherapy agents through combinations with targeted therapies and other classes of agents are also under investigation. Immune checkpoint inhibitors are still a relatively novel class of agents in oncology, and consensus must be made on how to accurately interpret clinical responses in the setting of immunotherapy. Delineating patterns in pseudoprogression, true progression, and hyperprogression across cancer types in the setting of treatment with immunotherapy agents is critical to accurately evaluate responses and to determine if it is appropriate to continue patients on treatment. It will also be important to understand if these patterns in clinical responses differ when immunotherapy is combined with other agents and how their safety profile changes.

We are currently at the crossroads of drug development with both targeted agents and immunotherapy. We appear to have hit a plateau with both precision medicine targeted therapy strategies and also single-agent immunotherapy approaches, so we need to rethink how we optimize such therapies moving forward into the next phase of cancer medicine. Ultimately, a better understanding of the underlying biology of treatment resistance and responses will be the first step to improving the design of rational combinations of both targeted therapy and immunotherapy. Future research will also be necessary to understand the evolving cancer biology that occurs during different sequential therapies. Obtaining tumor biopsies and serial blood sampling for circulating-tumor DNA analysis or for immune monitoring from patients, and fully utilizing these samples to inform further laboratory studies in a reverse translational manner, may yield vital information for the identification of novel biomarkers of response and resistance. Tumor biopsies may also be used in patient-derived xenograft and organoid models, which allow preclinical testing of rational combinations in parallel to assessments in the clinic.[23,24] Subjecting patients to multiple tumor biopsies is a continuous challenge in clinical research, but obtaining such tissue will be critical to improving our understanding of cancer biology. Investigating how anticancer therapy influences the tumor and its microenvironment in the setting of primary cancer and metastatic disease over the course of treatment is a critical gap in knowledge that needs to be addressed. Novel study designs, involving umbrella, basket, or even a combination of such approaches, termed "um basket" studies, will help answer some of these questions directly in the clinic by rationally pairing patients with actionable aberrations with appropriate targeted therapies.[25] We are cautiously optimistic that these examples of antitumor strategies, among other modern and rational approaches, hold great promise to provide the necessary impetus needed to impact patient care and ultimately move us into the next stage of cancer medicine.

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Address for correspondence:
Dr. Timothy A Yap,
The University of Texas MD Anderson Cancer Center,
Mendelsohn Faculty Center, FC8.3022, 1400 Holcombe Blvd.
Unit 455, Houston, Texas 77030, USA.
E-mail: tyap@mdanderson.org

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