Personalized Medicine and Clinical Trials: A Q&A With Apostolia M. Tsimberidou, MD, PhD

APOSTOLIA M. TSIMBERIDOU, MD, PHD, *tenured professor at the University of Texas, MD Anderson, has been practicing medicine at The University of Texas MD Anderson Cancer Center for almost 2 decades. Tsimberidou's research focuses on the use of personalized medicine to treat patients with advanced metastatic cancer. In 2007, she started IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy), the first precision medicine program in oncology at MD Anderson. Since then, Tsimberidou has focused on treating patients with advanced metastatic cancer using the latest technology, taking into consideration the specific biologic characteristics of every patient's tumor. Her clinical trials include targeted therapy, immunotherapy, a combination of these agents, and other treatment approaches.*

***AJMC®*: In your view, what does personalized medicine encompass, and what does this mean for managed care?**

TSIMBERIDOU: In recent years, the term *personalized* (individualized or precision) *medicine* includes the identification of the complex mechanisms of carcinogenesis in individual patients (using advanced/evolving technology for tumor molecular profiling, transcriptomic, proteomic, immune marker analysis, circulating tumor DNA analysis, and others) as well as the use of strategies to inhibit the function of the key drivers of carcinogenesis. These strategies include targeted agents and immunotherapy.

To improve patient care, treatment selection should be dynamic and adaptive, taking into consideration the changing biologic landscape of patients' tumor profiles in time and metastatic sites and patients' comorbidities. The ultimate goal should be to eliminate minimal residual disease and significant subclones conferring tumor resistance to treatment.

***AJMC®*: How does personalized medicine have the potential to revolutionize medicine, and how is next-generation sequencing important to this shift?**

TSIMBERIDOU: In my opinion, personalized medicine has optimized the selection of treatment. In 2007, before we started the personalized medicine program IMPACT in the phase I clinical trials program, selection of clinical trials and novel agents across all tumor types was random and not based on specific patient tumor biologic abnormalities. Since the implementation of molecular profiling and immune markers, we have been able to select the treatment that is more likely to benefit our patients. Over the years, I have ordered, collected, or reviewed data from more than 5000 patients who were treated in my department using the personalized medicine approach (mostly for the IMPACT-1 and IMPACT-2 protocols). The complexity of available biologic data is increasing over time because of the continued breakthroughs in technology to understand carcinogenesis, enabling the identification of multiple abnormalities in each patient. The number of identifiable molecular abnormalities in tumor tissue, blood, immune markers, or other biologic features is increasing. Although the FDA has approved several drugs, including the most recent accelerated approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with microsatellite instability-high or mismatch repair deficient, there is still a large gap between the large number of driver biologic abnormalities we detect in individual patients and the limited availability of drugs that would inhibit the function of these abnormalities to offer our patients the best treatment outcomes possible.

***AJMC®*: Recently, adaptive studies have been an area of interest for the FDA and for researchers. Is adaptive patient selection for trials currently possible using next-generation sequencing? How do you see next-generation sequencing and adaptive studies changing the way clinical trials are done?**

TSIMBERIDOU: We are conducting a randomized trial in precision medicine, IMPACT 2, which is a randomized study evaluating molecular profiling and targeted agents in advanced cancer [ClinicalTrials.gov identifier: NCT02152254]. It is sponsored in part by Foundation Medicine. In theory, innovative study design, including adaptive randomization is considered by statisticians a strategy to overcome the challenge of multiple new tests and too few patients (with identical profiles) to analyze. In practice, given the complexity of interpretation of molecular profiles and immune markers to select treatment, in my opinion, no design can optimally address the challenge of evaluating biologic profiling and treatment selection.

The reasons are that every patient has a unique molecular profile, has frequently multiple molecular abnormalities that evidently cannot be inhibited by single agents or combinations of a few drugs, various comorbidities, and differences in tumor microenvironment. Therefore, we should not anticipate that the randomized trials will optimally answer the scientific questions; ie, that by stratifying them in 2 or more groups, there will be a robust conclusion that 1 therapeutic strategy is superior to the other(s). In addition, adaptive designs are cumbersome and expensive and require a multidisciplinary approach (including oncologists, molecular biologists, and statisticians) to draw meaningful and accurate conclusions.

What appears to be very informative is the so-called N-of-1 databases, which enable learning from each patient to inform the treatment of the next patient with a similar tumor type and biologic disease. Most clinical trials with novel therapeutic strategies focus on specific tumor types with specific biologic markers. Some studies select patients with alteration(s) detected using circulating tumor DNA analysis. At the present time, we should continue collecting these data and analyze them systematically. A few clinical trials with adaptive design have as an end point to expedite the FDA approval of investigational drugs. Overall, caution should be exercised on the interpretation of the results of randomized trials. The emphasis should be on complete understanding of a tumor's biology in-depth and discovery of new drugs that will eliminate cancer.

***AJMC®*: How do you believe managed care needs to approach next-generation sequencing genetic panel testing? How is that likely to enter clinical practice and, perhaps, supplant the current paradigm of having a single genetic test approved alongside each new product?**

TSIMBERIDOU: The recent approval of pembrolizumab by the FDA has stimulated a lot of enthusiasm among physicians, as well as patients, and provides access to immunotherapy to patients who can benefit from this treatment. Next-generation sequencing genetic panel testing holds the promise of improving patient care. However, the implementation of this approach is limited, mostly because of the cost of the drugs. Immunotherapeutic approaches are significantly more expensive than targeted therapies and require close monitoring for short- and long-term adverse events. For certain indications and drugs, improved clinical outcomes justify the increased cost. Ongoing economic studies are challenging, as the interpretation of tumor biologic data, the baseline characteristics, treatment, and their association with clinical outcomes are crucial to draw precise and robust conclusions.

> **"We should strive to have more complete assessments of tumor biology and more careful selection of treatments."**

***AJMC®*: If the cost of next-generation sequencing goes down, how would that change clinical practice and the response of managed care?**

TSIMBERIDOU: Based on historical data, the cost of next-generation sequencing is expected to decrease with mathematical precision. To implement precision medicine, driver marker or markers need to be identified, and effective anticancer agents or strategies must be available. I hope that we will continue to discover and develop new effective drugs. The question is how these drugs will become available to individual patients who are expected to benefit from these drugs but have no access to clinical trials or the drugs that are not FDA approved for their indication. The current system of drug development from preclinical data to FDA approval is not efficient. For instance, the role of contract research organizations (CROs), which were initially designed to be independent entities, assessing the integrity of the data and improving the quality of the trial should be reevaluated. Nowadays, several CROs represent a major barrier in clinical trials because of their slow and inadequate procedures, high turnover of employees, inefficient performance, and the disproportionally significantly high cost associated with the relatively limited service they provide to the drug development. These challenges make the process of study drug development very difficult and the studies significantly more expensive and subsequently lead to delays and increased cost of drug approvals. In addition, the regulatory aspects of new drug development are inefficient and should be decreased to the minimum to ensure patient safety, scientific rigor, and integrity of the »

clinical trials. Very few of the drugs with promising preclinical data that enter clinical trials lead to improved outcomes and are eventually approved by the FDA. Perhaps more extensive preclinical work and improved screening of trials that are investigated in phase 1, 2, or 3 clinical trials will make the process of drug development more efficient and cost-effective.

In many academic institutions, the success of the drug development programs is measured by the number of patients entered in trials and the dollar amount associated with the research. There is no emphasis on quality metrics; ie, whether a drug or strategy improves patient outcomes. This is an area that needs improvement. Novel drug development should be patient centered, and it should reflect improvements in clinical outcomes—not merely assessed by the number of patients entered in clinical trials but by the quality of research, the quality of trials, and the quality of drugs.

***AJMC®*: Unfortunately, it sounds like there are some disincentives to doing certain types of research, motivated by financial reasons. From the perspective of managed care, would there be any opportunities for personalized medicine to help reduce costs and create incentives to help reduce the cost of care ultimately by selecting the right patients for the right therapies?**

TSIMBERIDOU: Definitely, yes. I think personalized medicine holds this promise of understanding tumor biology, offering patients the drugs or the strategies that are more likely to benefit them rather than randomly selecting treatment. Currently, for instance, some clinical trials with immunotherapy require markers, but the vast majority do not, and historically the success rate is 10% to 30% across tumor types. We should continue to evaluate markers of response and markers of severe toxicity associated with these treatments; moreover, many patients who have progressive disease continue to be treated on immunotherapy protocols, although their disease is progressing. These patients should be monitored very closely during therapy. It is important to look at the patients' tumor biology not only at the time of diagnosis but also during treatment to monitor their molecular abnormalities, using next-generation sequencing or hopefully one day through circulating tumor DNA analysis, in combination with other markers, to determine the next therapeutic strategy.

***AJMC®*: How is the clonal nature of cancer a challenge when implementing precision medicine, and how is this being addressed in the research setting?**

TSIMBERIDOU: The clonal nature of cancer is very important. Published articles have demonstrated the role of a significant subclone in patients' adverse outcomes. Even in the most expensive sponsored clinical trials, there is limited interest in understanding tumor biology and understanding the mechanism of action of the drug in development. There is no strong interest in understanding why the patients have progressive disease or toxicity. We should aim to obtain and interpret the next-generation sequencing data and other biologic markers before the initiation of treatment, during treatment, and at the time of disease progression.

***AJMC®*: What are some of the milestones that you have seen in personalized medicine over the past several years? What do you see for the next several years in terms of personalized medicine? There are so many emerging technologies and medications now that it can be difficult for managed care organizations to keep up. How can they better assess technologies?**

TSIMBERIDOU: We had several breakthroughs and milestones over the past few years. For example, in 2011, the FDA approved vemurafenib and several other targeted therapies for patients with metastatic melanoma. In the past 3 years, the FDA approval of several immunotherapeutic agents and strategies has improved patient outcomes.

As for future milestones, the drug development process should become concise and efficient. The current system of new drug development should be carefully reviewed, and the dysfunctional components should be eliminated. The focus of clinical research should become patient centered, and it should encourage innovative research that is promising to improve patient care.

The main focus should be on prevention of diseases, including cancer; implementing lifestyle modification, starting from raising awareness about obesity, hypertension, diabetes, and hyperlipidemia; encouraging physical activity and stress management; and emphasizing screening tests following the standard guidelines.

Moving forward, we should strive to have more complete assessments of tumor biology and more careful selection of treatments. At this time, insurance companies determine patient care, based on the drugs that are FDA approved. In the next few years, if we focus our energy and efforts on the discovery of new and effective targeted agents, optimize the treatment selection process based on patients' characteristics, expedite the drug-approval process, and eliminate inefficient processes and unnecessary costs of drug development (associated with CROs and administrative costs), we will accelerate the implementation of precision medicine. We need to continue to explore novel therapeutic strategies, illuminating the complex mechanisms of tumor biology and combining these novel approaches with the existing drugs to cure cancer. ■