Embarking on the next era of precision medicine

Angela Qu, M.D., Ph.D., Vice President, Biomarkers and Genomic Medicine, Translational Medicine
Parexel®

The American Society of Clinical Oncology defines tumor-agnostic therapy as a type of therapy that uses drugs or other substances to treat cancer-based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy, sometimes referred as tissue-agnostic therapy, uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug.

"This is an expansion from the current precision medicine model that primarily targets one tumor type guided by a biomarker," explained Angela Qu, M.D., Ph.D., Vice President, Biomarkers and Genomic Medicine, Translational Medicine, Parexel. "Moving into and across multiple tumor types, a so-called pan-cancer drug development approach guided by biomarkers is a game changer. This is a dream field for both drug developers and patients."

Patients with multiple tumor types are already seeing the benefits as evidenced by the four pan-cancer drug approvals in the past four years. In May 2017, the FDA approved Merck's Keytruda (pembrolizumab) for patients with unresectable or metastatic solid tumors carrying microsatellite instability-high or mismatch repair deficient biomarkers, making it the first drug to receive tumor-agnostic approval in oncology — a watershed in the history of precision medicine. Keytruda received a second approval in June 2020 to include expanded cancers with a high tumor mutational burden (TMB-H). Experts credit Keytruda's approval as revolutionary not only because of the mechanism of action, but also because the FDA approved it for the treatment for site/tissue-agnostic tumors based on their biomarker status. In essence, the FDA approved the biomarker as the indication rather than approving the drug for a particular tumor

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The global liquid biopsy market size is expected to reach $5.96 billion by 2030, exhibiting a CAGR of 13.4% during the forecast period. Enhanced view of tumor provided by liquid biopsy technology is estimated to augment the market in coming years.

Source: Grand View Research, Inc.

type. For the first time ever, as long as a tumor had the biomarker, it didn't matter where the tumor was in the body; Keytruda may be considered as a treatment option.

In 2018, U.S. regulators approved Bayer's Vitrakvi (larotrectinib) for cancer patients carrying NTRK fusion (a specific genetic defect of neurotrophic tyrosine receptor kinase gene). In 2019, the FDA approved Roche's Rozlytrek (entrectinib), a treatment for adult and adolescent patients whose cancers have NTRK fusion, and for whom there are no effective treatments. At least 10 additional tumor-agnostic therapies are in development, based on a range of genetic mutations, including mutations in the RET gene, found in 2.21% of all cancers, and mutations in the neuregulin 1 gene (NRG1), which is found across solid tumors including lung, pancreas, and breast tissue. [Cancer World]

With cancer being the second leading cause of death in the United States, preceded only by heart disease, and estimates suggesting that almost 40% of Americans will be diagnosed with cancer at some point in their lives, there is a real need for new research innovation. While tumor-agnostic patient inclusion in clinical trials is not a novel concept, what is new is the ability to enroll molecularly enriched patients as part of basket or platform trials for cancers that have one or more molecular alterations, where these alterations have a reasonable likelihood of predicting response to a particular therapy based on preclinical and/or computational modeling, and these alterations are found across a variety of cancers. Dr. Qu expressed excitement by the prospect of taking a transformative approach to developing precision medicines based on tumor-agnostic trial designs, which can be conducted in different ways but under an overarching master protocol, often with specific treatment arms or baskets for cancers of different origins.

One of the innovations needed to develop tumor-agnostic drugs are clinical trials that are designed to span multiple histologies, which is made possible by an increased scientific understanding of disease mechanisms. "Advances from a drug development perspective are also being driven by scientists and

Precision medicine leverages one or more biomarkers, often genetic or genomic in nature, to guide therapy decisions. A biomarker is a defined and measurable characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions. The biomarkers are indicators of how the drug will be metabolized in the body, who is most likely to benefit, or who may be at risk of side effects.

Source: Parexel

medical researchers who are able to dive deeper into the data and leverage genomic technology to understand the link between the underlying biology and the association with the tumor types or other disease conditions."

Dr. Qu credited regulatory bodies, which have made significant strides in supporting and advancing precision medicine and genomic biomarker development, for applying scientific rigor to come to a greater understanding of the demonstrated efficacy and safety of these new therapies that meet such huge unmet medical needs. Dr. Qu was honored to provide feedback as an invited panelist on a recent U.S. Food and Drug Administration and American Association of Clinical Research initiative in advancing precision medicine development in multiple melanoma. "We should be working together from a regulatory and an industry perspective to navigate this cutting edge space," she said.

Parexel is well-positioned to lead the transformation in this area. Dr. Qu noted that the company has deep subject matter expertise in regulatory, technology, data, and clinical trial innovation. "We

have designated teams in all of the innovation areas, ranging from translational medicine, which allows us to establish the connectivity between genomic/biomarker data to identify the targeted patients, to teams that are experts in adaptive trial design and modeling/simulation innovation, to determining the right dosing and improving trial efficiency," she said.

If the ultimate goal for precision medicine is to get the targeted therapy to the right patient population, then determining the right dosing is one of the keys to success. Not all patients can take the same dosage of the same drug and receive the same benefits. From a trial design perspective, dosing based on genetic or genomic makeup should be factored in so as to account for the variance in how patients process different drugs. "A drug that may be beneficial to you might be toxic to me because the dose is too high as I may carry a genetic variation," Dr. Qu said.

While initial success has been in the area of oncology, Dr. Qu said other areas such as rare disease, could benefit from the advances being made in precision medicine. There are more than 7,000 distinct types of rare and genetic diseases impacting more than 400 million people globally. And eight out of 10 of these diseases are caused by a faulty gene.

"We are already seeing an uptake from FDA in regard to the drug approvals from precision medicine in rare disease areas, including the spinal muscular atrophy, for example, and Duchenne's muscular dystrophy," she said.

Another area of innovation that excites Dr. Qu is the field of liquid biopsy. Liquid biopsies, unlike tissue biopsies, which despite their highly invasive nature have been the standard for cancer diagnosis for several years, offer a less invasive methodology along with high effectiveness.

"We can use this noninvasive approach for genomic biomarker interrogation, which allows for patient selection from a diagnostic perspective and give

Cancer biomarkers are molecules or specific processes that signal the presence of cancer. Biomarkers can be proteins, genes or gene mutations, molecular modifications, or microenvironmental changes. Generally, biomarkers are disease or process specific. For example, breast cancer biomarkers allow sub-typing based on hormone receptor status (e.g., estrogen-receptor positive, HER2-positive, and triple negative). In lung cancer, various mutations such as EGFR, ALK, ROS-1, and BRAF are biomarkers used to subtype non-small cell lung cancer (NSCLC).

us the ability to dynamically monitor the treatment response during a clinical trial," Dr. Qu said.

Dr. Qu is optimistic about the future and the role that Parexel will play in advancing precision medicine, expanding beyond high throughput genomic technologies and big data generation into the next generation of omics, which she has coined as "clinico-omics: clinical data plus real-world genomics data or real-world evidence."

Dr. Qu continued, "At Parexel, we are pioneers in this space; we are developing and refining genomic and biomarker strategies, applications, and innovative approaches to help us generate insights in the precision medicine space. This is a very exciting time."

With Heart

Parexel International Corporation
275 Grove Street, Suite 101C, Newton, MA 02466, USA
+1 617 454 9300
info@parexel.com

Offices across Europe, Asia, and the Americas

www.parexel.com

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