New Study Tracks Accelerating Use of Biomarkers in Cancer Clinical Trials

BY PEGGY EASTMAN

Individualized biomarker-based cancer therapies rooted in clinical trial results are growing rapidly, according to a new study published by the Personalized Medicine Coalition (PMC). The study, done by the global management consulting firm L.E.K. Consulting, shows that 55 percent of clinical trials for cancer treatments in 2018 involved the use of biomarkers, compared to just 15 percent in 2000—a 17 percent compound annual growth rate.

The study is the first comprehensive quantitative examination of a cancer biomarker database, noted PMC President Edward Abrahams, PhD. The study, which was released at PMC's annual conference at Harvard Medical School, used automated analytical techniques and manual curation to examine all oncology trials registered on ClinicalTrials.gov for the inclusion of biomarkers. The biomarkers most commonly investigated in trials conducted between 2016 and 2018 include immune-related biomarkers such as CD19, CD4, and PD-1/PD-L1, along with genetic drivers of cancer such as *KRAS*, *ROS1*, and *FGRF*.

The accelerating shift in drug development toward biomarker-based therapies documented in the new study "has profound implications for key stakeholders across the health care spectrum," stated Abrahams in his foreword to the study. These stakeholders include the pharmaceutical and diagnostic industries, oncologists and other health care providers, payers, and cancer patients who stand to benefit from earlier detection and more effective treatments based on their individual biomarkers. Validated biomarkers can lead to approved companion diagnostics for cancer drugs.

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Growth in the use of biomarkers will affect the biopharmaceutical industry's research and commercial decision-making; oncologists and other health care providers' capabilities to build expertise in precision medicine; payers who will be called on to enable broad coverage for biomarker profiling; diagnostic laboratories and test developers; and most important of all, cancer patients, whose care will be based on effective treatments tailored to their individual medical needs.

In its recent AACR Cancer Progress Report 2019, the American Association for Cancer Research (AACR) states that the greater precision of molecularly targeted therapeutics is a boon to patients because these drugs tend to be more effective and less toxic than cytotoxic chemotherapeutics.

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"As a result, they are not only saving the lives of patients with cancer, but also allowing these individuals to have a higher quality of life," the new AACR report noted. Like the PMC, the AACR hails "an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the individual patient and the characteristics of his or her cancer dictates the best treatment option for the patient."

The new PMC study points out that biomarker trial strategy has become more complex over time, and that more than 50 percent of biomarker trials now examine two or more biomarkers per trial.

> Oncologists and other health care providers will need to prioritize their capabilities for precision medicine, including biomarker profiling, as well as data management and interpretation infrastructure, to enable precision medicine care delivery.

"Biomarkers are critical in the development of personalized medicines and have added more complexity to clinical trial design, execution, and data analysis," the study stated.

Overall, biomarkers are being explored across all cancers, the study shows. The most common tumors being studied for biomarkers are breast (69%), lung (66%), leukemia (64%), lymphoma (57%), melanoma (74%), and prostate (86%). In the past 4 years, biomarkers such as PD-1/PD-L1/2, ALK, TIL, CD4, MRD, and BRAF have shown the fastest growth in clinical trial exploration, the analysis showed.

There is also a growing emergence of trials for pan-tumor biomarkers such as MSI and NTRK. In November 2018, the FDA approved larotrectinib for children and adults who have solid tumors that test positive for the *NTRK* gene fusion biomarker. "The approval of larotrectinib for use in a tissue-agnostic way followed several decades of basic, translational, and clinical research," as noted in the AACR progress report.

"These trends clearly reflect advances in the use of biomarkers to guide personalized drug development independent of the more traditional organ-specific clinical trial approaches," stated the PMC biomarker study's co-authors, Alex Vadas, PhD, Managing Director in L.E.K.'s Life Sciences and Biopharma practice; T.J. Bilodeau, principal in the Healthcare and Life Sciences practice and Director of the L.E.K. Healthcare Insights Center; and Chintan Oza, PhD, Senior Consultant in the Life Sciences and Biopharma practice.

As previously reported in *Oncology Times,* the NCI recently released its Annual Plan & Budget Proposal for Fiscal Year 2021. That plan, which will mark the 50th anniversary of the National Cancer Act, states that one of NCI's scientific priorities is an understanding of the mechanisms of cancer. This growing understanding serves as a catalyst that leads to new ways of diagnosing and treating cancer, including biomarker-based therapies.

Abrahams noted that the development of personalized cancer therapies based on biomarkers has been a somewhat rocky road.

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He stated in his foreword to the new study that, when the PMC first published *The Case for Personalized Medicine* in 2006, the pharmaceutical industry was skeptical about developing drugs for subpopulations of patients based on biomarkers. Back in 2005, biomarker-based medicines represented just 5 percent of new molecular entities (NDEs) approved by the FDA; in 2018, that figure had risen to 42 percent, with the majority of new NDEs in oncology. In 2005, with the exception of a few scientists specializing in molecular biology, Abrahams commented that "personalized medicine was a daunting concept, especially for those in the industry with a more commercial focus."

Indeed there were clear challenges, he stated, including a limited appreciation of human heterogeneity at the molecular level; a business model based on developing drugs for "all comers"; an unclear regulatory system that inhibited integrating diagnostics into health care; an overtaxed reimbursement system slow to comprehend the value of diagnostics and the need to charge higher prices for targeted drugs for smaller populations; and the fact that most health care providers were trained before the human genome was mapped. (An initial rough draft of the human genome was made available in June 2000; the Human Genome Project was declared complete in April 2003.) Mapping the human genome led to pharmacogenetics, the study of human genetics and drug response.

While back then the concept of personalized medicine seemed daunting, Abrahams noted that Janet Woodcock, MD, Director of the FDA's Center for Drug Evaluation and Research, saw the potential for biomarkers in drug development based on human molecular heterogeneity. "She was not wrong," he wrote.

Based on their new analysis, the L.E.K. study authors drew the following conclusions about biomarker-based cancer drug development.

- In oncology, biomarkers have become highly valuable in driving research and development and the commercialization of targeted therapies. This favorable stance toward biomarker development for innovative oncology therapies is becoming the norm rather than the exception, and the industry will have to adapt to this evolving paradigm of personalized medicine.
- Biopharmaceutical companies have incorporated biomarker strategies to drive their research and commercial operations. Biomarkers are used to make their targeted therapy portfolios optimal; make clinical development decisions; access and preserve biospecimens; build and mine scaled clinico-genomic datasets; segment commercial markets; develop market access and pricing strategies for biomarker-driven targeted therapies; and pursue broader collaborations with academic and diagnostic partners.
- Oncologists and other health care providers will need to prioritize their capabilities for precision medicine, including biomarker profiling, as well as data management and interpretation infrastructure, to enable precision medicine care delivery.
- Diagnostic companies will play a major role in actively collaborating with biopharmaceutical companies and providers. Multiplexing, sample-sparing, and liquid biopsy techniques that enable broader testing from smaller amounts of tissue or plasma samples may play a prominent role.
- Payers will need to enable reimbursement that includes broader coverage of biomarker testing. Reimbursement policies will need to ensure sustainable access to biomarker-based cancer therapies, which can be costly. Some of these provide dramatic clinical benefits but require increased manufacturing costs because of the need to develop a personalized therapy for each cancer patient by genetically re-engineering that patient's cells.
- Regulators will need to provide comprehensive guidance on sample quality and testing, further simplify the process for companion diagnostics, and standardize guidance relating to the use of personal data for research purposes. OT

Peggy Eastman is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Assess the implications of the current shift in drug development toward biomarker-based therapies. 2. Analyze the challenges of personalized cancer therapies that are based on biomarkers.

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