Upping the Ante in the Fight Against Cancer

by Kim Ribbink

In 2015, PharmaVOICE conducted a year-long series into the oncology market and the latest developments in cancer research. Since then, cancer R&D has advanced by leaps and bounds, with some significant breakthroughs. In this update on the cancer market, we look at some of the most important advances now and into the future.

The battle to address one of the most deadly and pervasive sets of diseases has been making significant strides. While cancer — as a group of diseases — remains the second-largest killer in the United States, claiming more than 600,000 lives a year, there are a growing number of therapies and treatment modalities to tackle different types of cancer.

The oncology drug market is growing rapidly and is expected to reach $200 billion a year, according to a report by the IQVIA Institute for Human Data Science. FDA approvals of oncology therapies has accelerated, with 13 new drugs approved in 2017 and more than 15 approvals that expanded the labels of drugs for use in additional patient populations, other indications, and in combination with other drugs, says Rachel Webster, D.Phil., principal director, oncology lead at Decision Resources Group.

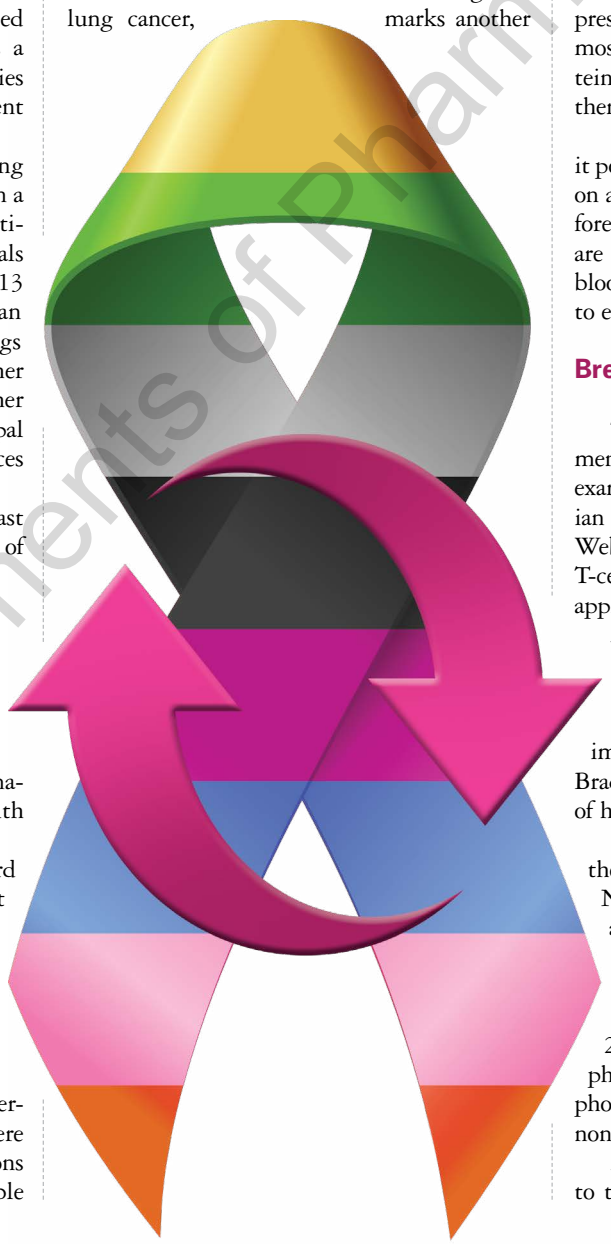
The plethora of drug approvals in the last 18 months correlates with the dynamism of the oncology landscape, Dr. Webster says.

The Changing Face of Cancer Treatment

Oncology practice has dramatically changed in the last decade, says Ute Berger, M.D., senior VP, medical affairs, pharmacovigilance and patient safety, PRA Health Sciences.

"There has been a paradigm shift toward the use of targeted therapies directed against the specific molecular drivers of tumors in individual patients where possible," Dr. Berger says. "Lung cancer is one of the tumor types where the standard of care for patients has significantly changed over the last couple of years.

"A huge paradigm shift occurred when certain mutations such as EGFR and ALK were discovered and as a result, several generations of targeted therapy options are now available for these subpopulation patients," she says. "The introduction of immunotherapy in 2015, followed by approvals of several checkpoint immune inhibitors for different stages in lung cancer, marks another paradigm shift with significant impact on delaying disease progression and prolonging overall survival of lung cancer patients."



One of the areas that Kevin Hrusovsky, president, chairman, and CEO, Quanterix, is most excited about is using blood-based protein biomarkers to advance early detection and therapeutic monitoring of disease.

"Advances in protein detection are making it possible to determine which genes are turned on and may allow early detection of cancer before symptoms appear," he says. "Researchers are also monitoring specific biomarkers in the blood to see how they develop and change due to exposure to environmental factors."

Breakthrough Developments

There have been breakthroughs in treatment for a range of oncology indications, for example urothelial carcinoma, NSCLC, ovarian cancer, and hepatocellular carcinoma, Dr. Webster says. Two, however, stand out: CAR T-cell therapy and the first tumor agnostic approval.

Adoptive cell immunotherapy boosts the body's immune defenses against cancer in a completely different way — by genetically re-engineering a patient's own immune T cells, known as CAR T-cells, says Brad Sanderson, senior scientific advisor, head of health outcomes, CRF Health.

The FDA approved the first CAR T-cell therapy tisagenlecleucel-T (Kymriah from Novartis) in August 2017 for pediatric and young adults with acute lymphoblastic leukemia (ALL), and then a second, axicabtagene ciloleucel (Yescarta from Gilead/Kite), was approved in October 2017 for adults with aggressive B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin's lymphoma, Dr. Webster says.

In May 2018, Kymriah was approved to treat heavily-pretreated DLBCL, achieving

We are close to being able to use biomarkers to determine which medications have the greatest impact on disease treatment on an individualized level.

KEVIN HRUSOVSKY
Quanterix

rates of remission that are comparable with Yescarta, providing a second CAR T-cell therapy option for DLBCL.

Another CAR T-cell therapy directed to B-cell maturation antigen (BCMA) for treating multiple myeloma has been hitting the headlines in the last year, Dr. Webster says. Multiple myeloma remains an incurable disease, but BCMA-targeted bb2121 (Bluebird bio/Celgene) has achieved response rates of 95% (complete remission rates of 50%) — impressive data given patients were heavily pretreated (median of eight prior regimens).

Nevertheless, she notes that the potential for severe and life-threatening sides effects, namely cytokine release syndrome and neurological toxicity, restricts their use, while the high cost — $475,000 and $373,000 for Kymriah in ALL and Yescarta in DLBCL, respectively — underscores the ongoing issue of the high cost of treating cancer.

The PD-1 inhibitor pembrolizumab, Keytruda from Merck, became the first cancer treatment to be FDA approved for any solid tumor with a specific genetic feature, Dr. Webster continues. The tumor agnostic approval was granted for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors if patients have progressed from prior treatments and have no other treatment options and for colorectal cancer patients who carry these genetic features if they have progress following certain chemotherapy treatments.

"Keytruda's approval represents a breakthrough because it is the first time that a cancer drug has been approved based on a biomarker that is common to multiple tumor types, moving away from approval being defined by the anatomical location or organ where the tumor originates or by the pathological diagnosis; it is the biomarker defining the disease rather than the site of tumor origin defining the disease," she says.

The evolution of the FDA's understanding of how biomarkers can be used to monitor drug trials has the potential to lead to accelerated approvals and lower costs to develop effective drugs, Mr. Hrusovsky says.

He adds that the FDA's recognition of biomarkers as viable tools to advance clinical trials is especially important given the promise to accelerate the development of drugs and treatments for oncology and neurology, and for ensuring drug efficacy.

Other breakthroughs include new innovations in treatment of early stage breast cancer. Quantum Leap Healthcare Collaborative, a nonprofit organization and sponsor of the I-SPY 2 trial, has presented significant progress made in the trial in improving the outcomes of early stage breast cancer patients. The I-SPY 2 trial features an innovative adaptive statistical design where every patient's data contributes to a learning system and is performed through an FDA master.

I-SPY 2 has enrolled more than 1,300 patients at 16 U.S. sites, and by the end of 2018 around 17 drugs will have entered the trial and 12 will have completed evaluation. To date, seven drugs have graduated from the trial, with two receiving accelerated approval and one gaining breakthrough designation by FDA.

In recent years, immunotherapy has dramatically changed the way oncology patients are treated, and the FDA is approving immunotherapy drugs for more therapeutic indications.

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Decision Resources Group

The Future of Cancer Treatment

The use for immune checkpoint inhibitors will continue to expand to more cancer types, and particularly agents that target the PD-1/PD-L1 checkpoint in cancer treatment, Mr. Sanderson says.

"However, one of the challenges to overcome if this type of therapy is to succeed will be the identification/selection of patients who have a physiological profile that is likely to benefit from that specific treatment," he says.

At present, only 20% of proteins in cancer cells can be targeted by currently available medicines but Mr. Sanderson says a new class of drugs, known as stapled peptides, has emerged as a promising way to target protein-protein interactions.

"These small proteins have an artificial chemical bridge that holds them in a shape that allows them to penetrate the cell, interfering with the proliferation pathway," he says.

While it is early days, Dr. Berger believes deployment of CRISPR technology in cancer has the potential to change the landscape in the future.

Dr. Webster sees the approval of tumor-agnostic therapies as establishing a new paradigm for cancer drug development, and notes that before the end of 2018 there may be a second tumor-agnostic approval — larotrectinib (Loxo Oncology) — for locally advanced or metastatic adult and pediatric patients with tumor types harboring a tropomyosin receptor kinase (TRK) gene fusion, a rare genomic abnormality.

In addition, continued identification and validation of diagnostic, prognostic, predictive, and therapeutic biomarkers will impact patient outcomes as they will allow early detection of tumors and guide the choice of a targeted therapy based on specific molecular features of the cancer, Dr. Berger says.

Another development will be drug combinations with an objective of achieving synergistic or greater efficacy than single agents.

"We are witnessing a plethora of drug combinations being evaluated in multi-arm, multi-cohort, and other novel Phase I/II trial designs that could expedite drug development," Dr. Webster says. "The approach to cancer treatment is now about finding the optimal drug combination and how best to integrate these combinations into complex oncology treatment algorithms in terms of timing, sequencing, and dosing."

Mr. Hrusovsky says scientific research and evidence supporting precision health is moving healthcare toward cancer prevention, giving the medical community the ability to stop the spread of cancer earlier and begin treatment when it's most effective.

"In the next five years, I believe we will see a growing understanding of baseline levels for a number of protein biomarkers on an individual basis," he says. "With a baseline biomarker reading early in life followed by annual or bi-annual testing, patients will be able to track incremental changes to their health. This will be one of the first major steps in transforming sick care to preventive healthcare."

These biomarkers could replace other methods to detect disease, such as CT scans, which don't provide the sensitivity necessary to see brain cancer until it has progressed, or mammograms, which provide false positives up to 10% of the time. Biomarkers will also be important for determining drug efficacy, Mr. Hrusovsky says.

"The potential for biomarkers to continue influencing precision health across a broader set of therapeutic areas is most exciting," he says. "We are on the cusp of major breakthroughs in science and medicine, and for that reason it is an amazing time to be in healthcare."

While future developments hold much promise, Dr. Berger says it's as important to strengthen prevention strategies, including cancer screening, vaccination, tobacco control, healthy eating, and physical activity.

"Researchers estimate that about 50% of cancer cases and deaths in the United States could be prevented if people adopted healthy lifestyle choices," she says. "We know cervical cancer is largely preventable now through vaccination. Incidence of other cancer types such as colon cancer can be significantly lowered by lifestyle changes and screening. Safe sun exposure practices and avoidance of indoor tanning can lower the risk for melanoma." PV

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